Does Low Intensity Extracorporeal Shock Wave Therapy Have a Physiological Effect on Erectile Function? Short-Term Results of a Randomized, Double-Blind, Sham Controlled Study

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Purpose: We investigated the clinical and physiological effect of low intensity extracorporeal shock wave therapy on men with organic erectile dysfunction who are phosphodiesterase type 5 inhibitor responders.

Materials and Methods: After a 1-month phosphodiesterase type 5 inhibitor washout period, 67 men were randomized in a 2:1 ratio to receive 12 sessions of low intensity extracorporeal shock wave therapy or sham therapy. Erectile function and penile hemodynamics were assessed before the first treatment (visit 1) and 1 month after the final treatment (followup 1) using validated sexual function questionnaires and venoocclusive strain gauge plethysmography.

Results: Clinically we found a significantly greater increase in the International Index of Erectile Function-Erectile Function domain score from visit 1 to followup 1 in the treated group than in the sham treated group (mean ± SEM 6.7 ± 0.9 vs 3.0 ± 1.4, $p = 0.0322$). There were 19 men in the treated group who were initially unable to achieve erections hard enough for penetration (Erection Hardness Score 2 or less) who were able to achieve erections sufficiently firm for penetration (Erection Hardness Score 3 or greater) after low intensity extracorporeal shock wave therapy, compared to none in the sham group. Physiologically penile hemodynamics significantly improved in the treated group but not in the sham group (maximal post-ischemic penile blood flow 8.2 vs 0.1 ml per minute per dl, $p < 0.0001$). None of the men experienced discomfort or reported any adverse effects from the treatment.

Conclusions: This is the first randomized, double-blind, sham controlled study to our knowledge that shows that low intensity extracorporeal shock wave therapy has a positive short-term clinical and physiological effect on the erectile function of men who respond to oral phosphodiesterase type 5 inhibitor therapy. The feasibility and tolerability of this treatment, coupled with its potential rehabilitative characteristics, make it an attractive new therapeutic option for men with erectile dysfunction.

Key Words: erectile dysfunction, high-energy shock waves, penis, hemodynamics

Abbreviations and Acronyms

ED = erectile dysfunction
EHS = Erection Hardness Score
FMD = flow mediated dilatation
FU1 = followup 1
FU2 = followup 2
IIEF = International Index of Erectile Function
IIEF-EF = International Index of Erectile Function-Erectile Function domain score
LI-ESWT = low intensity extracorporeal shock wave therapy
PDE5i = phosphodiesterase type 5 inhibitors
V1 = visit 1

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For another article on a related topic see page 1903.

NUMEROUS therapeutic strategies exist for improving erectile function. While these therapies have been proven to be safe and effective, they are limited for use before the sexual act and do not modify the physiological mechanism of penile erection.[1] Gene and stem cell therapies are current examples of treatment strategies whose therapeutic goals are to restore erec-

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tile function as part of the present trend to shift the field of ED treatments away from on demand palliative treatments.[2,3]

Adopting this new treatment strategy we began exploring the use of LI-ESWT to achieve this goal.[4,5] Using LI-ESWT as a treatment modality is not new. In 1990 Young and Dyson discovered that therapeutic ultrasound encourages angiogenesis by enhancing the expression of vascular endothelial growth factor.[6–8] This finding led clinicians to begin using shock wave therapy in the treatment of coronary artery disease,[9] bone fractures,[10] calcifying tendonitis[11] and diabetic foot ulcers.[12]

The results of our pioneer pilot study demonstrated that LI-ESWT improved erectile function and penile hemodynamics in men with ED who respond to pharmacotherapy.[4] We also reported that LI-ESWT effectively converted PDE5i nonresponders to responders.[5] While these results were encouraging, our studies were limited by the small sample size and lack of an appropriate control group. To validate our previously published results and to demonstrate whether LI-ESWT has a true physiological effect on the erectile mechanism, we conducted a larger, randomized, double-blind, sham controlled study in men with ED and cardiovascular risk factors who responded to PDE5i.

MATERIALS AND METHODS

The study protocol was reviewed and approved by our institution's Ethics Review Board. All participants gave written informed consent before entering the study.

Screening, Inclusion and Exclusion Criteria

We recruited men with a history of ED for at least 6 months who were already responding to PDE5i from our outpatient ED clinic between July 2009 and October 2010. A total of 77 men underwent an initial screening, including a complete medical history and physical examination (fig. 1). For study inclusion each man had to have an IIEF-EF of 19 or greater while on PDE5i and had to be in a stable heterosexual relationship for more than 3 months. Each man also had to agree to discontinue PDE5i during the entire study period. Men were excluded from analysis if they had undergone radical prostatectomy, received pelvic radiotherapy or hormonal therapy, were receiving ongoing treatment for a psychiatric condition, or had any anatomical, neurological or hormonal abnormalities. Ultimately 10 men met the exclusion criteria.

Study Protocol

The 67 participants who met the inclusion criteria underwent a 4-week PDE5i washout period. At V1 the men were assigned into 2 groups of those who received LI-ESWT (treated group) and those who were given sham therapy (sham group) in a 2:1 ratio using a computer generated table of random numbers. At the same visit each man completed a full IIEF and EHS questionnaire while not on PDE5i. The penile hemodynamics of each man was also evaluated at V1 using our previously described FMD technique in which penile blood flow is measured at rest and after a 5-minute ischemic period using venoocclusive strain gauge plethysmography.[13,14] Each subject then began the 9-week treatment period, which was comprised of 2 treatment sessions per week for 3 weeks that were repeated after a 3-week no treatment interval. A month after the final treatment session (FU1) erectile function and penile hemodynamics were reassessed while the men were still not taking PDE5i (fig. 2).

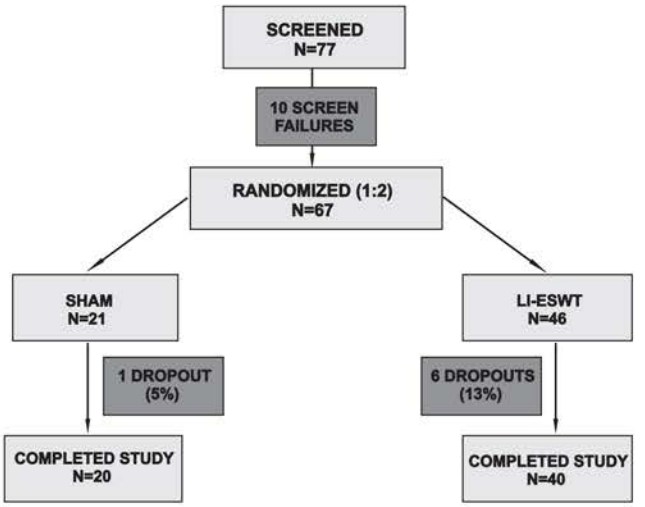

Figure 1. Patient screening and randomization flowchart

Specifics of LI-ESWT

We applied a standard commercial gel normally used for sonography to the penis. The shock waves were delivered to the distal, mid and proximal penile shaft, and the left and right crura using a specialized focused shock wave probe (Omnispec ED1000, Medispec Ltd., Yehud, Israel) as described in our previous studies (fig. 3).[4,5] Since the depth of the shock waves reached both corpora, treatment was delivered on 1 side of the penile shaft only. The 300 shocks at an energy density of 0.09 mJ/mm^2 and a frequency of 120 shocks per minute were delivered at each of the 5 treatment points. Each treatment session was 15 minutes. Due to the low energy density, no local or systemic analgesia was needed.

Followup

To improve the recruitment and compliance rates, all men were eligible to receive an additional treatment course if they were unsatisfied with the initial outcome and had an IIEF-EF of less than 25 at FU1 without PDE5i, regardless of the group to which they were originally assigned. The IIEF of the men who did not undergo additional treatment was reevaluated after 3 months (FU2).

Randomization and Sham Treatment

At randomization each man received a numeric identifier code that was paired to a treatment or sham probe supplied by the manufacturer. The sham probe looked identical to and made the same noise as the treatment probe, but contained a metal plate that prevented the shock wave energy from being applied to the penis. Since the noise and vibration of the probes used in both groups were

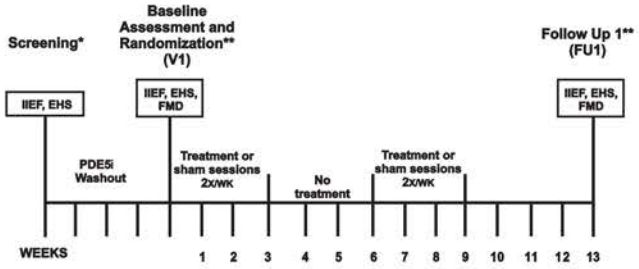

Figure 2. Study flowchart. Single asterisk indicates with PDE5i. Double asterisk indicates without PDE5i.

similar, and the treatment was painless, the operator and subject were blind to the treatment type.

Main Outcome Measures

We used the IIEF-EF to evaluate erectile function. Treatment success was defined as a 5-point or greater improvement in the IIEF-EF between V1 and FU1 because this value indicates an improvement of erectile function by at least 1 severity category. The secondary outcome measures were defined as significant increases in the IIEF subcategories, an increase in EHS from 2 or less at V1 to 3 or more at FU1, and an improvement in penile blood flow.

Statistical Analysis

The data were analyzed using statistical software (JMP®, SAS), and the data are expressed as median and range or mean ± SEM. The values of the study parameters from the 2 study groups were compared by Student's t test with pooled variances or the Wilcoxon signed rank test as appropriate. The linear relationship between changes in the IIEF-EF and changes in penile blood flow at FU1 was assessed by Spearman's rank order correlation. A chi-square contingency analysis was used to examine the relationship between the IIEF-EF and penile hemodynamics, with statistical significance set at 5%.

RESULTS

The baseline characteristics of the 2 study groups were similar (table 1). Six (13%) men in the treated group and 1 (5%) man in the sham group did not complete the study protocol (fig. 1). Of these men 3 took PDE5i, 2 could not meet the necessary time commitments, 1 separated from his wife and 1 had a prolonged hospitalization.

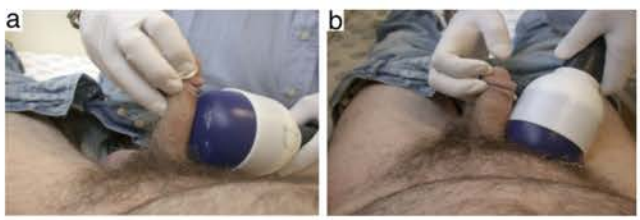

Figure 3. Application of shock wave probe to penile shaft (*a*) and crura (*b*).

Table 1. *Baseline characteristics of the study population at randomization while off PDE5i therapy*

	Sham	Treatment
No. men	20	40
Median age (range)	57 (35–77)	58 (27–72)
Median mos ED (range)	60 (6–240)	42 (6–240)
Concomitant condition (% of men):		
Cardiovascular risk factors*	60	75
Coronary artery disease	10	20
Diabetes mellitus	30	30
Mean ± SEM IIEF-EF domain scores	11.5 ± 0.86	12.6 ± 0.75
Median IIEF-EF domain scores (range)	12.5 (6–17)	13.5 (6–19)
Disease stratification (% of men):†		
Severe dysfunction (IIEF-EF 0–6)	20	12.5
Moderate dysfunction (IIEF-EF 7–12)	30	32.5
Mild to moderate dysfunction (IIEF-EF 13–18)	50	42.5
Mild dysfunction (IIEF-EF 19–24)	0	12.5

All values not significant ($p > 0.05$).

* Including at least 1 of cigarette smoking, hypercholesterolemia, hypertension or obesity.

† Statistical assessment of possible treatment group differences in disease severity distributions of patients could not be performed due to the small numbers in some subgroups.

Efficacy

At FU1 the mean IIEF-EF in the treated group increased by 6.7 points while the score in the sham group increased by 3.0 points ($p = 0.0322$, fig. 4). There were 26 (65%) men in the treated group and 4 (20%) in the sham group who had a 5-point or greater increase in IIEF-EF ($p = 0.0001$). The treated men had significantly improved mean scores in the IIEF subcategories of Sexual Desire ($p = 0.0348$) and Overall Satisfaction ($p = 0.0054$, fig. 4). Of 28 men in the treated group who had an EHS of 2 or less at V1, 19 reported an increase in EHS to 3 or greater at FU1 vs no men in the sham group (fig. 5).

Penile hemodynamics were assessed in 59 of the 60 men who presented at FU1 (1 man in the treated group refused this assessment after treatment). Penile hemodynamics improved significantly in the treated group (table 2, $p < 0.0001$). Furthermore, we noted a strong positive correlation between changes in the IIEF-EF and changes in the resting and maximal post-ischemic penile blood flow at FU1 ($p < 0.0001$). The IIEF-EF and the post-ischemic maximal blood flow improved ($p < 0.001$) in 22 (56%) men in the treated group and 1 (5%) man in the sham group.

Adverse Events

Unlike painful higher intensity shock wave energy used to treat nephrolithiasis and Peyronie disease (0.2 to 1.1 mJ/mm^2), the low intensity shock wave energy (0.09 mJ/mm^2) used in this study was not associated with any pain or side effects such as ecchymoses or hematuria.

Post-Study Followup

A total of 23 men including 16 (80%) from the sham group opted to receive a second series of treatments

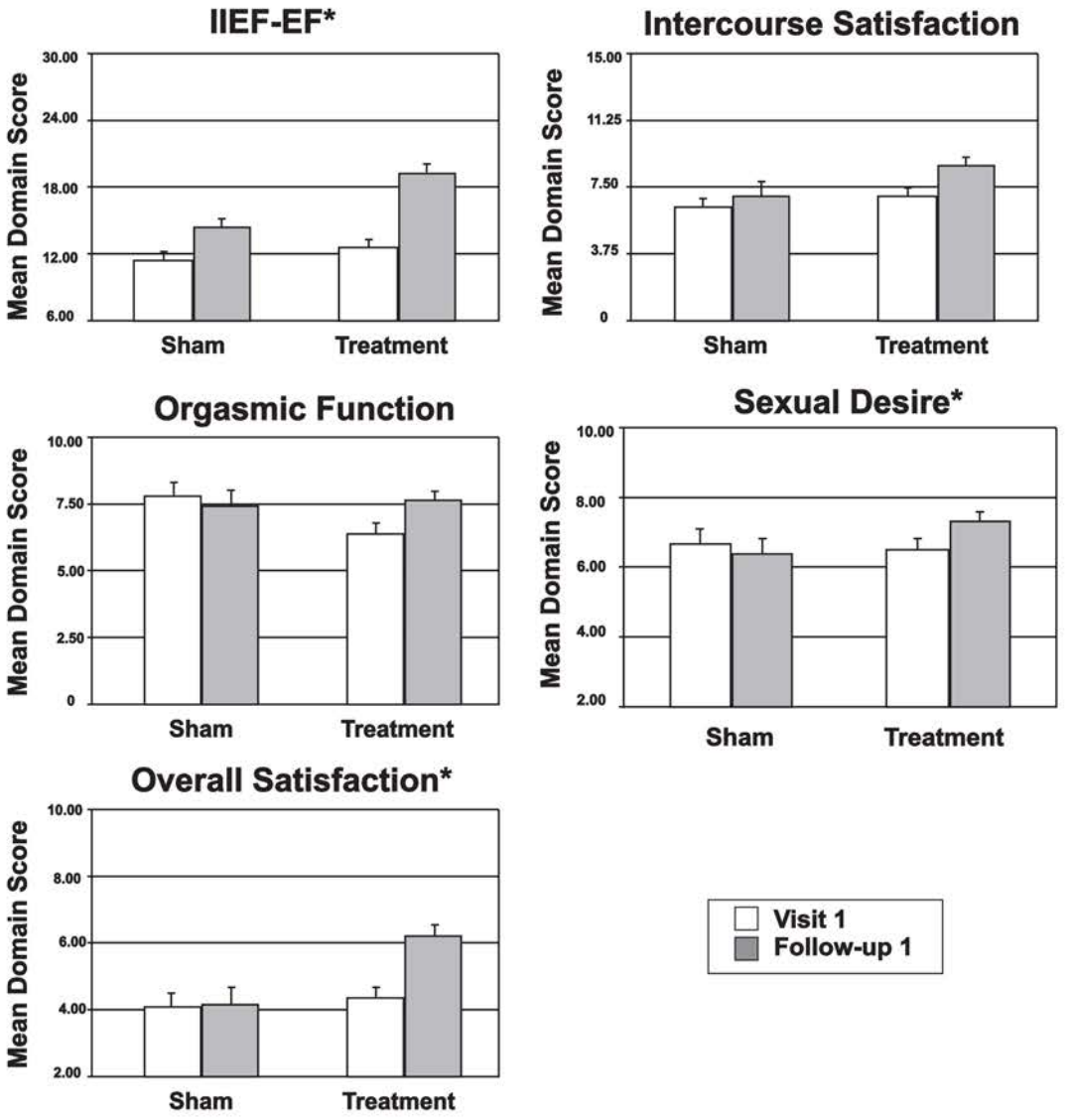

Figure 4. IIEF domain scores (mean ± SEM) for men treated with LI-ESWT or sham therapy at V1 or FU1. Asterisk indicates $p < 0.05$ and represents significance of difference between 2 groups.

without knowing their original group (fig. 6). Mean IIEF-EF of men continuing on to a second round of treatments was 12.2 at FU1, while the remaining 36 men who had followup at 3 months had an additional increase in mean IIEF-EF from 20.7 at FU1 to 22.1 at FU2.

DISCUSSION

Due to the skepticism surrounding this novel treatment, insufficient scientific background and disappointing results of penile shock wave therapy in Peyronie disease, it was crucial to further establish the validity of LI-ESWT by conducting a randomized, double-blind, sham controlled study. We chose to use measurement tools that are validated and widely accepted such as the IIEF and EHS. While validated in men receiving on demand PDE5i, these questionnaires have a high degree of sensitivity and specificity for detecting treatment related changes in the erectile mechanism.[15–17] Since LI-ESWT is a nonpharmacological intervention whose effect is not defined per sexual encounter but during a prolonged period, questionnaires such as the sexual encounter profile were not used.

We postulated that the underlying mechanism of LI-ESWT action is to improve penile hemodynamics. To confirm this hypothesis, objective and quantifiable measures of penile hemodynamics are required. Our experience with nocturnal penile tumescence testing in our first pilot study led us to conclude that nocturnal penile tumescence is not suitable to be used as an investigative tool due to difficulties in interpreting the results in terms of meaningful pa-

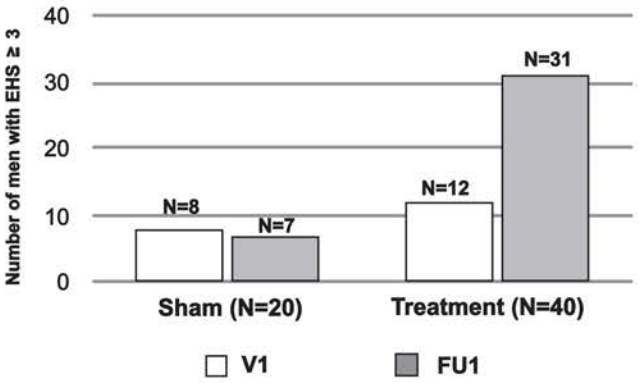

Figure 5. Number of men with EHS 3 or greater at V1 and FU1. For EHS clinical interpretation, grade definitions characterizing penis are grade 1—larger but not hard, grade 2—hard but not hard enough for penetration, grade 3—hard enough for penetration but not completely hard, grade 4—completely hard and fully rigid.

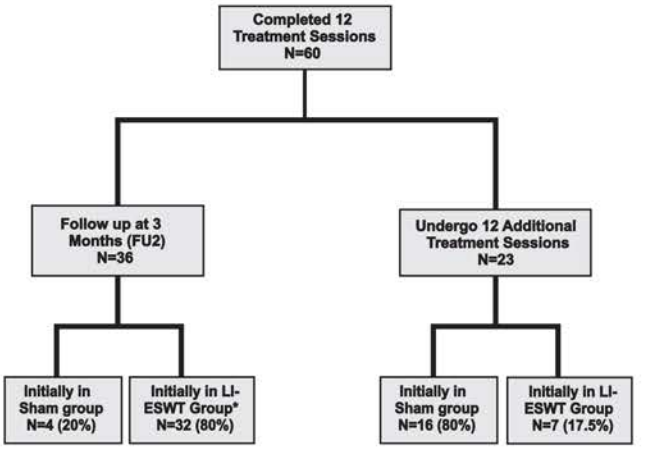

Figure 6. Patient followup after 12 treatment sessions. Asterisk indicates 1 patient (2.5%) was lost to FU2.

rameter changes and changes in penile hemodynamics. We did not use duplex ultrasonography because it mainly measures cavernous artery flow, is operator dependent, and is reliant on the timely response of injected vasoactive agents and patient disposition. Although it is an excellent test to evaluate penile vascular status, duplex ultrasonography may be problematic for the comparison of changes in penile hemodynamics before and after intervention. We used venoocclusive plethysmography to measure penile hemodynamics because it can objectively assess penile perfusion in the flaccid state in a simple and reproducible fashion, it is not operator dependent and it has previously been proven to reflect changes in erectile function after intervention.[13,14] Furthermore, while our group was the first to describe the FMD technique in the penis, it is not principally different from the widely used FMD technique to assess endothelial function in the brachial artery.

The IIEF-EF of the treated men significantly improved at FU1. The increase was not as great as the increases in the IIEF-EF that were reported in studies that introduced the therapeutic effects of PDE5i.[18–20] Admittedly, comparing the efficacies of an on demand treatment to a nonpharmacological rehabilitative intervention that is unrelated to the sexual act is inherently problematic. Unlike the ED naive cases in the first sildenafil studies that had not previously experienced treatment success, those in our study had a different definition of therapeutic success because they already had a positive experience with PDE5i. Furthermore, many of the original PDE5i studies included a mixed ED population, as opposed to our group of men with similar ED risk factors. Our exclusion criteria may also account for the 25% sham effect seen in our study compared to a placebo effect as high as 46% reported in the original PDE5i studies.[21] The results of later studies that excluded patients with psychogenic ED, and examined the effect of PDE5i on men with organic ED and cardiovascular risk factors, are comparable to the results of our study.[22,23] Nevertheless, it is possible that our empirical LI-ESWT protocol is less effective than PDE5i therapy.

Table 2. *Changes in penile blood flow at FU1*

	Resting Blood Flow (ml/min/dl)	Max Blood Flow (ml/min/dl)
Sham:		
Median	0.2	−0.1
Min	−6.7	−9.2
Max	7.6	18.5
Treatment:		
Median	4.6	8.2
Min	−15.5	−17.0
Max	80.2	124.8

All values $p < 0.0001$.

An unexpected finding was the significant improvement in the IIEF Sexual Desire domain scores of the treated men, a finding that has been reported in at least 1 of the previous studies that evaluated pharmacotherapy.[19] While our finding was statistically significant, the clinical importance of a 1-point increase in this score remains unclear.

We did not find statistically significant improvement in the IIEF Sexual Satisfaction domain score. We attribute this lack of improvement to our subjects' previous positive experience with PDE5i. Nevertheless, the IIEF Overall Satisfaction domain score did increase significantly after treatment, indicating a beneficial effect of LI-ESWT.

The EHS data also revealed that more men in the treated group than in the sham group were able to achieve erections sufficiently hard for penetration.

Ease of definition and applicability make the EHS a valuable tool for simple clinical assessment. However, it is statistically ill suited for pre-post and 2-group study designs such as ours.

Physiological evidence that LI-ESWT improves penile hemodynamics comes from the finding that the 2 measures of penile blood flow improved significantly in the treated group and were positively correlated with the increases in IIEF-EF. Moreover, in seeking a success criteria based on clinical and physiological outcomes, we found that of the patients who had a 5-point or greater improvement in the IIEF-EF and improved penile hemodynamics all but 1 came from the treated group. Further supporting our contention that LI-ESWT improves penile hemodynamics is our finding that most of the treated men reported improvement in erectile function between treatment sessions 6 and 8, which is probably the time needed for LI-ESWT to induce the physiological changes.

While the purpose of this study was to evaluate the physiological effects of LI-ESWT on the penis, our finding that the IIEF-EF remained increased 3 months after the final treatment suggests that the positive physiological effect is preserved. This finding is similar to that of our previous study demonstrating that the subjects' IIEF-EF remained high at the 3 and 6-month followup.[4]

The treatment protocol that we used in all our studies to date was based on that described in the cardiology literature.[24,25] This empirical protocol had not been previously tested in animal or human penile tissue and, therefore, will likely change as more protocols are examined.

Although our final study population was comprised of only 60 men, this number of participants was sufficient to achieve our main goal of determining whether our treatment protocol could yield a genuine physiological effect on cavernous tissue.

To date, no deleterious side effects have been reported in the long-term followup of patients undergoing high intensity penile shock wave therapy for the treatment of Peyronie disease,[26,27] despite findings that such shock waves may lead to the collagenization of corporal smooth muscle in the rat.[28] While our subjects did not report any adverse effects to the treatment, the long-term risk of LI-ESWT on penile tissue has yet to be fully elucidated.

CONCLUSIONS

This is the first randomized, double-blind, sham controlled study in which LI-ESWT has been shown to have a beneficial effect on erectile function in men with ED and cardiovascular risk factors. While we do not know the precise mechanism of action of LI-ESWT, our objective measures lead us to presume that this therapy works by improving penile hemodynamics. We also found that this treatment is feasible and tolerable, and is unique in that it has rehabilitative characteristics. Additional studies with long-term followup are now needed to fully evaluate the efficacy of this new therapy and confirm our findings. These studies must be backed by basic science research whose aims are to fully understand the mechanism of action of this energy. With this additional knowledge, our hope is that LI-ESWT will make its way into the armamentarium of treatment options currently being used in the long-term clinical management of ED.

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Editorial by Konstantinos Hatzimouratidis on pp. 249–250 of this issue

Can Low-Intensity Extracorporeal Shockwave Therapy Improve Erectile Function? A 6-Month Follow-up Pilot Study in Patients with Organic Erectile Dysfunction

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Abstract

Background: Low-intensity extracorporeal shockwave therapy (LI-ESWT) is currently under investigation regarding its ability to promote neovascularization in different organs.
Objective: To evaluate the effect of LI-ESWT on men with erectile dysfunction (ED) who have previously responded to oral phosphodiesterase type 5 inhibitors (PDE5-I).
Design, setting, and participants: We screened 20 men with vasculogenic ED who had International Index of Erectile Function ED (IIEF-ED) domain scores between 5–19 (average: 13.5) and abnormal nocturnal penile tumescence (NPT) parameters. Shockwave therapy comprised two treatment sessions per week for 3 wk, which were repeated after a 3-wk no-treatment interval.
Intervention: LI-ESWT was applied to the penile shaft and crura at five different sites.
Measurements: Assessment of erectile function was performed at screening and at 1 mo after the end of the two treatment sessions using validated sexual function questionnaires, NPT parameters, and penile and systemic endothelial function testing. The IIEF-ED questionnaire was answered at the 3- and 6-mo follow-up examinations.
Results and limitations: We treated 20 middle-aged men (average age: 56.1 yr) with vasculogenic ED (mean duration: 34.7 mo). Eighteen had cardiovascular risk factors. At 1 mo follow-up, significant increases in IIEF-ED domain scores were recorded in all men (20.9 ± 5.8 vs 13.5 ± 4.1, $p < 0.001$); these remained unchanged at 6 mo. Moreover, significant increases in the duration of erection and penile rigidity, and significant improvement in penile endothelial function were demonstrated. Ten men did not require any PDE5-I therapy after 6-mo follow-up. No pain was reported from the treatment and no adverse events were noted during follow-up.
Conclusions: This is the first study that assessed the efficacy of LI-ESWT for ED. This approach was tolerable and effective, suggesting a physiologic impact on cavernosal hemodynamics. Its main advantages are the potential to improve erectile function and to contribute to penile rehabilitation without pharmacotherapy. The short-term results are promising, yet demand further evaluation with larger sham-control cohorts and longer follow-up.

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1. Introduction

In the past decade, phosphodiesterase 5 inhibitors (PDE5-Is) have become available for the treatment of erectile dysfunction (ED). However, their effect is still limited to the sexual act and probably do not improve spontaneous erections. These limitations are probably due to their inability to improve penile blood flow for a time period that is sufficient to allow optimal oxygenation and recovery of cavernosal vasculature. Recently, the effect of long-term daily use of PDE5-Is on endothelial function (EnF) has been shown to induce a short-term improvement in erectile function (EF) but probably not a longstanding one [1–3].

In the search for a new treatment modality that would provide a rehabilitative or curative effect for ED, we looked into technologies that could potentially affect endothelial function and improve penile hemodynamics. We came across some related preliminary publications, particularly from the cardiovascular literature, showing that in vitro as well as in vivo (porcine model) low-intensity extracorporeal shockwave therapy (LI-ESWT) could enhance the expression of vascular endothelial growth factor (VEGF) and its receptor Flt-1 [4,5], and could induce neovascularization and improve myocardial ischemia [6]. Newer studies further demonstrated this hemodynamic effect in humans [7,11,12]. Moreover, LI-ESWT was found to be effective not only in the myocardium, but also in other organs with impaired vascularity. Recently, this treatment modality using LI-ESWT was found effective in the treatment of chronic diabetic foot ulcers as compared with hyperbaric oxygen therapy, showing better clinical results and local perfusion [8]. In a prospective randomized trial, LI-ESWT was also effective in improving wound healing after vein harvesting for coronary artery bypass graft surgery [9].

The mechanism of action of LI-ESWT is still unclear. It has been shown that this low intensity energy induces non-enzymatic production of physiologic amounts of nitric oxide [10] and activates a cascade of intracellular signaling pathways that lead to the release of angiogenic factors. These encouraging experimental and clinical outcomes provided the theoretic basis for applying this treatment modality to cavernosal tissue in order to improve penile vascular supply and EnF in men with longstanding vasculogenic ED.

2. Patients and methods

The study protocol was reviewed and approved by the local institutional review board and each participant gave his written informed consent.

The methodology used was based on the clinical trials performed in patients with cardiovascular disease using LI-ESWT [11,12]. We adapted the treatment protocol and the probe that was used in these studies for the penis in order to account for the superficial location of the corpora cavernosa and the need to cover the entire corporal surface as well as the crura. Our treatment protocol consisted of two treatment sessions per week for 3 wk, which were repeated after a 3-wk no-treatment interval (Fig. 1).

Shockwaves were delivered by a special probe that was attached to a compact electrohydraulic unit with a focused shockwave source (Omnispec ED1000, Medispec Ltd, Germantown, MD, USA). We applied a standard commercial gel normally used for sonography without any local anesthetic effect on the penis and perineum. The penis was manually stretched; the shockwaves were delivered to the distal, mid, and proximal penile shaft, and the left and right crura. The duration of each LI-ESWT session was about 20 min, and each session comprised 300 shocks per treatment point (1500 per session) at an energy density of 0.09 mJ/mm^2 and a frequency of 120/min. The volume of penile tissue that was exposed to shockwaves at each site was cylindrical (diameter: 18 mm; height: 100 mm). During the treatment period, no psychologic intervention or support was provided and patients were required to maintain their normal sexual habits.

2.1. Inclusion/exclusion criteria

We recruited men with a history of ED for at least 6 mo from our outpatient clinic. Each study patient had abnormal 2-night nocturnal penile tumescence (NPT) parameters at screening, had responded positively to PDE5-I therapy (were able to penetrate during sexual intercourse while on on-demand PDE5-I treatment), and had an International Index of Erectile Function ED (IIEF-ED) domain score between 5–19. Each patient agreed to discontinue PDE5-I therapy until the first 1-mo follow-up examination. The exclusion criteria were psychogenic ED (normal NPT parameters), any neurologic pathology, prior radical prostatectomy, and recovery from any cancer within the past 5 yr.

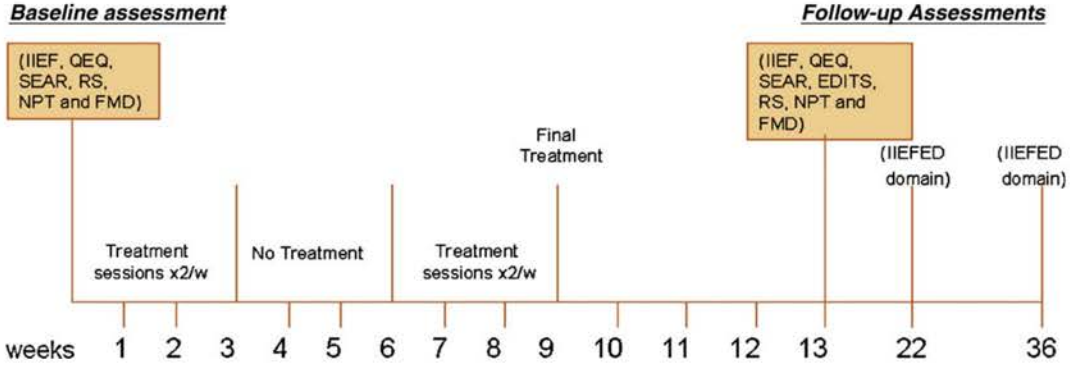

Fig. 1 – Study flow chart.
IIEF = International Index of Erectile Function; QEQ = Quality of Erection Questionnaire; SEAR = Self-Esteem and Relationship Questionnaire; RS = rigidity score; NPT = nocturnal penile tumescence; FMD = flow-mediated dilatation; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction.

2.2. Study protocol

Upon inclusion (visit 1), after a 4-wk PDE5-I washout period, each participant completed several validated sexual function questionnaires: IIEF, rigidity score (RS), Quality of Erection Questionnaire (QEQ), and the Self-Esteem and Relationship Questionnaire (SEAR). Additionally, penile and forearm EnF testing was done in the last 14 enrolled men using our already-described flow-mediated dilatation (FMD) technique [13,14]. This method uses veno-occlusive strain gauge plethysmography to measure penile and forearm blood flow after a 5-min ischemic period. We used this technique to establish changes in penile EnF by measuring specific indices of endothelial parameters: basal blood flow (P-base), and the maximal postischemic flow. Efficacy was evaluated at 1 mo after end of treatment by completing sexual function questionnaires, determining NPT parameters, EnF testing, and completing an Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire. For long-term evaluation, we used the IIEF-ED domain score at the 3- and 6-mo follow-up examinations. A change in the IIEF-ED domain score of >5 points was used as the main measure of treatment success.

2.3. Statistical analysis

Paired student *t* tests and nonparametric Wilcoxon sign-rank tests were used to examine differences within subjects. Pearson correlation that took into account the changes in systemic EnF was used to examine the relationship between the change in the IIEF-ED scores and the changes in penile EnF at the 1-mo follow-up examination. To this end, we first constructed indices of FMD change using forearm EnF as the reference value before calculating the correlation. The indices were calculated from the difference between the values of the 1-mo and the baseline penile FMD indices, divided by the difference between the 1-mo and the baseline forearm FMD indices. Pearson correlation was also used to examine the degree to which other study parameters or derived indices were related. Lines of best fit were determined and plotted for all correlation analyses. The level of significance for all analyses was set at 5%.

3. Results

This protocol was applied to 20 middle-aged men (mean: 56.1 ± 10.7 yr, range: 33–73 yr) with vasculogenic ED for a mean of 34.7 mo. Eighteen men had one or more cardiovascular risk factors.

Table 1 summarizes the pre- and post-therapy scores of all sexual function questionnaires in all study participants. The characteristics of each study participant and the effect

Table 1 – Results of sexual function questionnaires before and 1 month after low-intensity extracorporeal shockwave therapy

Test score	Baseline score ± SD	Score 1 mo after treatment ± SD	% change	*p* value
IIEF ED domain	13.5 ± 4.1	20.9 ± 5.8	55	<0.001
Total IIEF	39.3 ± 8.7	54.7 ± 11.7	39	<0.001
QEQ	32.9 ± 18.2	61.4 ± 25.8	83	<0.001
RS	1.45 ± 1.0	2.7 ± 1.1	86	<0.001
SEAR	36.0 ± 10.4	46.5 ± 11.3	32	<0.001

IIEF = International Index of Erectile Dysfunction; ED = erectile dysfunction; QEQ = Quality of Erection Questionnaire; RS = rigidity score; SEAR = Self-Esteem and Relationship Questionnaire.

Table 2 – Patient characteristics and the effect of low-intensity extracorporeal shockwave therapy on the International Index of Erectile Function score for each subject from baseline to 6 months after end of treatment

Patient number	Age	ED duration (mo)	ED risk factors*	IIEF-ED baseline	Δ IIEF-ED at 1 mo	Δ IIEF-ED at 3 mo	Δ IIEF-ED at 6 mo	IIEF-ED 6 mo
1	47	6	3	18	3	6	5	23**
2	47	24	1	16	7	9	12	28**
3	62	36	3 + 4 + 5	11	12	10	13	24**
4	68	60	3	13	8	8	7	21**
5	54	18	3 + 4 + 5	19	−6	−2	−2	17
6	59	24	3	7	3	6	6	13
7	61	60	3 + 4 + 5	16	11	9	9	25**
8	58	24	2	13	2	2	4	17
9	33	144	1	17	6	6	7	24**
10	54	12	2 + 3	16	1	1	0	16
11	65	24	3	5	22	19	18	23
12	62	12	3 + 4	13	14	16	16	29**
13	59	36	3	13	13	10	10	23
14	46	24	3	5	6	6	6	11
15	33	100	2	11	6	6	10	21
16	73	20	3 + 4	11	−3	−3	−3	8
17	68	24	3 + 5	17	11	11	11	28**
18	63	8	3 + 5	16	9	2	2	18
19	58	15	2 + 3	15	12	9	9	24**
20	53	24	2	17	6	7	7	24**

ED = erectile dysfunction; IIEF-ED = International Index of Erectile Function – Erectile Dysfunction;
* 1 = no risk factors; 2 = miscellaneous risk factors (eg, smoking, medications, surgical procedures); 3 = cardiovascular risk factors (eg, hypertension, hypercholesterolemia, hypertriglyceridemia); 4 = coronary disease; 5 = diabetes mellitus.
** Patients with spontaneous erections who did not require phosphodiesterase type 5 inhibitor therapy.

Table 3 – Changes in nocturnal penile tumescence parameters before and 1 month after low-intensity extracorporeal shockwave therapy ($n = 18$)

Parameter	Baseline (mean ± SD)	1 mo after treatment (mean ± SD)
Total number of erection	3.9 ± 2.2	4.6 ± 2.3
Total erection time, h	1.3 ± 1.3	1.4 ± 0.9
Average tip rigidity	37.2 ± 18.9	42.1 ± 22.8
Average base rigidity	47.5 ± 18.1	52.5 ± 22.0
Max rigidity best event, tip	52.6 ± 20.7	61.0 ± 29.6
Max rigidity best event, base	66.9 ± 16.5	68.6 ± 26.6

of LI-ESWT on their IIEF-ED during the study period are presented in Table 2.

At the 1-mo follow-up examination, the IIEF-ED domain scores significantly increased from 13.5 ± 4.1 to 20.9 ± 5.8 ($p < 0.001$). The scores of 14 men increased by >5 points and of 7 men by >10 points. The treatment satisfaction scores were also high at the 1-mo follow-up examination (mean score: 23.2). At the 3- and 6-mo follow-up examinations, the improved IIEF-ED domain scores were maintained, and the average increase at the 6-mo follow-up was 7.1 ($p = 0.001$). A significant improvement in EF was recorded in six men with severe ED at baseline (IIEF-ED domain scores <12); their average IIEF-ED domain score rose from 8.3 to 16.6 at the 6-mo follow-up examination.

Pre- and post-treatment NPT parameters were collected from 18 men (2 patients refused to perform the second NPT). All NPT parameters improved at the 1-mo examination, especially the rigidity parameters (Table 3).

Penile EnF improved significantly after LI-ESWT (Table 4): basal flow (7.3 ml/min per deciliter vs 17.8 ml/min per deciliter; $p < 0.001$) and post-ischemic maximal flow (12.0 ml/min per deciliter vs 28.9 ml/min per deciliter, $p < 0.001$). No significant changes were measured in forearm EnF (Table 4). A strong correlation was found between the changes in the IIEF-ED scores and the changes in EnF parameters at the 1-mo follow-up examination (Fig. 2).

At the 3- and 6-mo follow-up examinations, 10 men reported that they had spontaneous erections that were sufficient for penetration and did not require PDE5-I support before sexual intercourse.

None of the study participants reported any pain during the treatment and follow-up periods, and no adverse effects were recorded.

4. Discussion

All currently available treatments for ED enhance sexual function by improving the quality of erections, yet none are curative. The search for an ED cure is the next step, and should be the goal of this coming decade. Examples of the different therapeutic targets and strategies for curing ED include the Rho/Rho-kinase signaling pathway [15], gene therapy [16], and stem cell regeneration [17]. Advanced treatment protocols for rehabilitating or preserving EnF in men with ED using chronic PDE5-Is have been proposed and are currently undergoing evaluation [1,2,18]. To date, data on the therapeutic benefits of these treatment protocols to restore spontaneous EF are still scarce.

High-intensity ESWT (lithotripsy) is a well-established treatment for kidney stones. The results of attempts to destroy the fibrotic plaques of Peyronie's disease using this high energy have been published with debatable success, except for pain relief [19,20]. Beneficial therapeutic effects of moderate intensity also have been reported in certain orthopedic conditions, such as plantar fasciitis, Achilles tendonitis, and tennis elbow, probably due to the attenuating action on inflammatory processes [21–24]. More

Table 4 – Changes in flow-mediated dilatation parameters in both penile and forearm blood flow before and 1 month after treatment

Location		Baseline	1 mo	% change	p value
Forearm	Baseline flow (ml/min/dl)	4.0 ± 2.2	4.8 ± 3.3	19	0.258
	Maximal flow (ml/min/dl)	12.0 ± 9.0	10.6 ± 7.4	−12	0.544
Penis	Baseline flow (ml/min/dl)	7.3 ± 4.7	17.8 ± 11.0	145	0.004
	Maximal flow (ml/min/dl)	12.0 ± 8.3	28.9 ± 15.2	140	<0.001

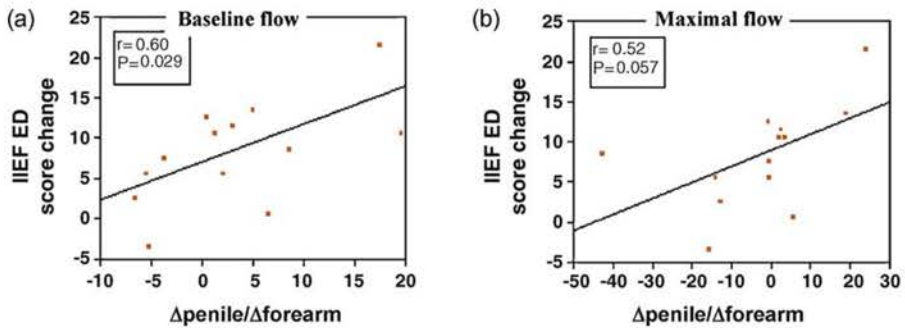

Fig. 2 – Correlation between the adjusted flow-mediated dilatation indices for (a) baseline and (b) maximal flow and the changes in the International Index of Erectile Function erectile dysfunction score 1 mo after treatment.
IIEF ED = International Index of Erectile Function—Erectile Dysfunction domain.

recently, the potential efficacy of LI-ESWT has been investigated in other clinical conditions [6,8,9]. It has been demonstrated that this form of energy triggers the activation of various intracellular signaling pathways and causes upregulation of numerous angiogenic factors to promote neovascularization [4]. In a porcine model of myocardial ischemia, Nishida et al demonstrated that cardiac LI-ESWT induces angiogenesis and markedly ameliorates myocardial ischemia without any adverse effects [5]. In another series of studies, Wang et al. [25,26] demonstrated similar processes in other animal models. The above scientific research led to the assumption that LI-ESWT also might be beneficial in enhancing blood flow in the corpora cavernosa of vasculogenic ED patients.

We structured our treatment protocol on what has been previously used in cardiology for achieving neovascularization. The rationale for including a no-treatment interval in our protocol is based on the finding that biologic responses to LI-ESWT appear to be time-dependent as the peak expression of the neovascularization response occurs 4 wk after treatment [27].

We initially started this investigation as a pilot study in patients with vasculogenic ED. After analyzing the results of the first six men, we were surprised by the positive responses. We decided to increase the number of participants and to include measurements of EnF into our protocol. Another reason for adding EnF was to overcome the problems of comparing pre- and post-therapy NPT parameters and to gain some insight into the underlying hemodynamic mechanism induced by this treatment.

For this purpose, we decided to use our FMD methodology, and not Doppler sonography; we wanted to obtain objective, measurable, and comparable hemodynamic results that did not require a pharmacologically-induced vasoactive intervention and to eliminate any operator-dependent bias. Our results show impressive objective data that confirm the beneficial effect of LI-ESWT on penile hemodynamics and its correlation with an improved clinical response, as demonstrated by an increase in the IIEF-ED scores 1 mo after LI-ESWT.

Although a considerable placebo effect can be expected with our treatment protocol, our high response rate (>70%) is substantially higher than that of any previously published placebo-controlled trial in men with ED. Moreover, the fact that this effect was maintained without any additional active intervention 6 mo after treatment provides additional evidence that LI-ESWT exerts a genuine physiologic effect on cavernosal tissue.

Although our positive results were obtained using validated scientific instruments, we would like to emphasize that the most striking clinical observation was that almost every participant gave a highly positive feedback, sometimes as early as the second treatment session, with the efficacy still present 6 mo later.

This is a proof-of-concept study that was performed to demonstrate the clinical efficacy of LI-ESWT in a small number of highly selected patients with a relatively short follow-up using an adapted empirical protocol. For LI-ESWT to become a recognized curative treatment in patients with ED, large multicenter, long-term, randomized and sham-controlled studies should now be performed. Moreover, other LI-ESWT protocols need to be evaluated, and there is a need to better define those patients who respond to this type of treatment and evaluate the duration of its effect. More data also are needed with regard to the possible long-term impact of shockwaves on penile tissue.

5. Conclusions

The results of this pilot study emphasize the efficacy and tolerability of penile LI-ESWT in ED. Our short-term results are extremely encouraging, but demand further evaluation. In the future, this could be one of the few nonpharmacologic treatment modalities that are able to improve EF without any adverse effects. Based on our results, LI-ESWT appears to have the potential to be a rapid and curative therapy for ED. Even if the therapeutic effect will be short-lasting, it can be easily repeated. The promising results of this pilot study will hopefully encourage basic research to explore and understand the mechanism of action of this energy on biologic systems, as well as assist in finding further applications of this novel therapeutic modality in other fields of medicine.

Author contributions: Yoram Vardi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gruenwald, Vardi.
Acquisition of data: Gruenwald, Vardi, Appel, Massarwi.
Analysis and interpretation of data: Gruenwald, Vardi, Appel, Jacob.
Drafting of the manuscript: Gruenwald, Vardi.
Critical revision of the manuscript for important intellectual content: Gruenwald, Vardi.
Statistical analysis: Gruenwald, Vardi.
Obtaining funding: Vardi.
Administrative, technical, or material support: Gruenwald, Vardi, Appel.
Supervision: Gruenwald, Vardi.
Other (specify): None.

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ORIGINAL RESEARCH—ERECTILE DYSFUNCTION

Low-Intensity Extracorporeal Shock Wave Therapy—A Novel Effective Treatment for Erectile Dysfunction in Severe ED Patients Who Respond Poorly to PDE5 Inhibitor Therapy

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ABSTRACT

Introduction. Low-intensity shock wave therapy (LI-ESWT) has been reported as an effective treatment in men with mild and moderate erectile dysfunction (ED).

Aim. The aim of this study is to determine the efficacy of LI-ESWT in severe ED patients who were poor responders to phosphodiesterase type 5 inhibitor (PDE5i) therapy.

Methods. This was an open-label single-arm prospective study on ED patients with an erection hardness score (EHS) ≤ 2 at baseline. The protocol comprised two treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. Patients were followed at 1 month (FU1), and only then an active PDE5i medication was provided for an additional month until final follow-up visit (FU2).

At each treatment session, LI-ESWT was applied on the penile shaft and crus at five different anatomical sites (300 shocks, 0.09 mJ/mm^2 intensity at120 shocks/min).

Each subject underwent a full baseline assessment of erectile function using validated questionnaires and objective penile hemodynamic testing before and after LI-ESWT.

Main Outcome Measures. Outcome measures used are changes in the International Index of Erectile Function-erectile function domain (IIEF-ED) scores, the EHS measurement, and the three parameters of penile hemodynamics and endothelial function.

Results. Twenty-nine men (mean age of 61.3) completed the study. Their mean IIEF-ED scores increased from 8.8 ± 1 (baseline) to 12.3 ± 1 at FU1 ($P = 0.035$). At FU2 (on active PDE5i treatment), their IIEF-ED further increased to 18.8 ± 1 ($P < 0.0001$), and 72.4% ($P < 0.0001$) reached an EHS of ≥ 3 (allowing full sexual intercourse). A significant improvement ($P = 0.0001$) in penile hemodynamics was detected after treatment and this improvement significantly correlated with increases in the IIEF-ED ($P < 0.05$). No noteworthy adverse events were reported.

Conclusions. Penile LI-ESWT is a new modality that has the potential to treat a subgroup of severe ED patients. These preliminary data need to be reconfirmed by multicenter sham control studies in a larger group of ED patients.

Gruenwald I, Appel B, and Vardi Y. Low-intensity extracorporeal shock wave therapy—A novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med 2012;9:259–264.

Key Words. Low Intensity Extracorporeal Shock Wave Therapy; Erectile Dysfunction; Penis

Introduction

Erectile dysfunction (ED) is one of the most common disorders of middle-aged men that profoundly affect their quality of life [1]. Although tremendous advances for treating this disorder have been made in the past decade, most currently available treatment modalities still rely on an "on demand" regime, of which up to 35% are unsuccessful [2–4]. From our experience, ED patients who were treated with a phosphodiesterase type 5 inhibitor (PDE5i) tend to search for an alternative

treatment modality that would ameliorate their ED. Hence, there is a need for an effective new treatment concept that would have a durable effect on the spontaneous improvement of erectile function.

We recently reported on the efficacy of a novel therapy, namely, applying low-intensity extracorporeal shock wave therapy (LI-ESWT) to the penis of patients with vasculogenic ED [5]. Results from in vitro and in vivo studies have shown that LI-ESWT induces neovascularization [6–8], and this finding was the theoretical basis for initiating studies on using LI-ESWT for treating ED. The results of our first preliminary research on ED patients who were responsive to PDE5i therapy showed that this treatment modality enhances penile perfusion and substantially improves erectile function [5].

A number of studies have been published on improving efficacy of PDE5i in men who do not respond or respond poorly to PDE5i therapy [9,10], suggesting potential ways to increase the efficacy of PDE5i therapy but not proposing any innovative treatments. Today, patients unsatisfied with response to oral therapy are candidates for either intracavernosal injections or penile implants. As most responders to PDE5i are usually managed by general practitioners in the primary health care setting, poor responders or severe ED patients are mainly referred to urologists and are managed in ED clinics. If LI-ESWT would be proved to be effective in these more severe ED patients, such a unique modality could expand our urological treatment armamentarium in the management of ED. It is against this background that we undertook the current study in which we evaluated the efficacy of LI-ESWT in severe ED men who were poor responders to PDE5i therapy.

Materials and Methods

This was an open-label single-arm prospective pilot study approved by the local ethics committee. The study had a screening phase, a 12-week LI-ESWT phase, applied to the patient's genital area, and a 2-month evaluation phase (Figure 1). Only men over 40 in a stable relationship (>3 months), who were previously diagnosed with ED at our outpatient clinic and were registered as poor responders to PDE5i therapy, were eligible for screening. In order to ensure that these men were poor responders, they were thoroughly questioned in regard to the dosage of the PDE5i, the timing of its intake, and the concomitant sexual stimulation. Men who could not provide definite answers were given four tablets of PDE5i and then asked to return for follow-up after they had completed their treatment. At this follow-up examination, the severe ED and poor responders were identified and then recruited for the study. Our key inclusion criterion was a low erection hardness score (EHS) of zero to two during PDE5i therapy. We excluded men (i) with an unstable medical or psychiatric condition, (ii) with a previous history of a neurological pathology, and (iii) after radical pelvic surgery, irradiations, or hormonal therapy.

At screening, written informed consent and demographic data were obtained from each participant. Assessment of erectile and sexual function during PDE5i treatment was determined using the International Index of Erectile Function-erectile

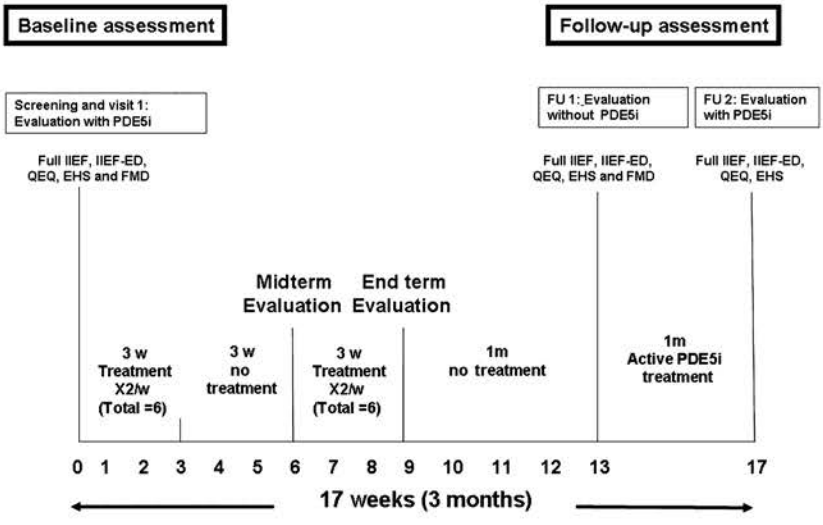

Figure 1 Study flow chart. EHS, erection hardness score; FMD, flow mediated dilatation; FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; PDE5i, phosphodiesterase type 5 inhibitor; QEQ, Quality of Erection Questionnaire.

function domain (IIEF-ED) score, the Quality of Erection Questionnaire (QEQ), and determination of the EHS. We used the flow mediated dilatation (FMD) technique for objective evaluation of the participant's penile hemodynamics and endothelial function [11,12]. After completion of the assessments, the first of the 12 LI-ESWTs was then administered. In the treatment phase, we used the identical treatment protocol that we used in our first study [5]. The treatment protocol consisted of two treatment sessions per week for 3 weeks, which were repeated after a 3-week no-treatment interval. At each treatment session, LI-ESWT was applied on the penile shaft and crus for 3 minutes at five different penile anatomical sites. Each LI-ESWT comprised 300 shocks per treatment point at an energy density of 0.09 mJ/mm^2 and a frequency of 120/min. One month after the end of treatment (FU1), the results of LI-ESWT without PDE5i therapy were evaluated using the identical methods that were used at screening. As the main aim of this study was to assess the effect and benefit of LI-ESWT on this specific population of poor responders, we then provided an active PDE5i medication regime to each study participant, which comprised four tablets of a PDE5i that each man selected according to his best personal experience. One month later (FU2), we reassessed erectile function using the identical methods that were used at screening. The main outcome measures for success were changes in the IIEF-ED, the EHS measurement, and the three parameters of penile hemodynamics and endothelial function.

Statistical Analysis

A repeated-measures analysis of variance (ANOVA) was used to investigate the overall effects of treatment by comparing the effect of LI-ESWT on the study parameters at visit 1 to those from FU1 (net effect without PDE5i therapy) and at visit 1 to those from FU2 (under PDE5i treatment). The Tukey test was used to investigate the specific pairwise differences in the IIEF-ED, the QEQ scores, and the maximum FMD values. ANOVA results are reported as least squares mean ± the pooled standard error of the least squares mean (sem).

The binomial test was used to determine the proportion of treatment successes after treatment at FU1 and FU2 and the significance of the difference between the two proportions.

The changes in the EHS values for each study participant were compared by Bowker's test. For this purpose, the study group was divided into two subgroups: those who achieved a score of three to four on each follow-up visit and those who did not, and then comparing their scores with those that were determined at baseline, where none had scored three or four.

Spearman rank correlation was used to establish the relationship between the changes in the penile hemodynamics and endothelial function and the changes in the IIEF-ED from visit 1 to FU1.

All data were statistically analyzed using JMP Discovery Software (SAS Institute, NC, USA); statistical significance was at 5%.

Results

Thirty-three men entered the study after screening. Four men discontinued due to study noncompliance [2] and protocol violation [2]. The remaining 29 men who met the inclusion–exclusion had a mean IIEF-ED of 8.8 and a median ED duration of 60 months. Other detailed baseline characteristics are displayed in Table 1. The men were middle-aged with coronary heart disease, diabetes mellitus, or cardiovascular risk factors, had severe ED for more than a year, and were incapable of full sexual intercourse.

At FU1, subjects reported improved erectile function, as measured by significantly increased ($P = 0.035$) IIEF-ED (Figure 2), and 10 (34.5%) also reported increased penile rigidity (Figure 3).

Two months after end of the treatment (FU2), while on PDE5i therapy, the mean IIEF-ED increased by 10 points (18.8 ± 1 [standard deviation], $P < 0.0001$) (graph 1). In fact, eight men (27.6%) were normalized according to the IIEF-ED (≥25), and the IIEF-ED domain scores improved in 22 men (75.9%) by at least five points. Twenty-one men (72.4%) reported an EHS value ≥3 ($P < 0.0001$; see Figure 3). On average, the men noted some improvement in their erectile function, 3 weeks after the start of LI-ESWT, which was usually between the sixth and eighth treatment sessions.

Table 1 Baseline patient characteristics

Mean age (years)		61.3	
Age range (years)		41–79	
Cardiovascular risk factors		N	Percent
	Hypertension	24	83.7%
	Hypercholesterolemia	27	93.1%
	Heavy smoker	12	41.4%
	Obesity	8	27.5%
Coronary artery disease		16	55.1%
Diabetes mellitus		21	72.4%

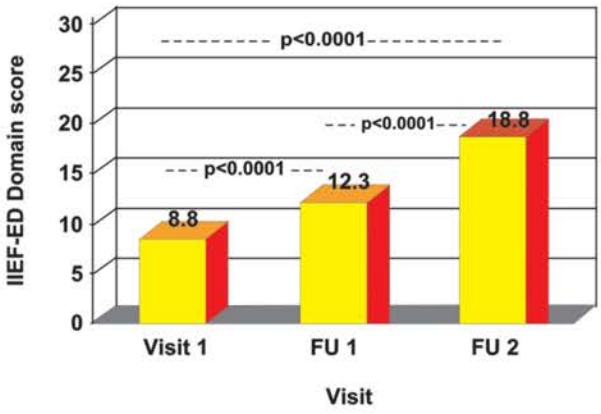

Figure 2 Mean IIEF-ED scores before and after LI-ESWT. FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; LI-ESWT, low-intensity extracorporeal shock wave therapy.

The secondary outcome measures that were used to assess the effect of LI-ESWT on erectile function were the total IIEF and the QEQ scores. Both scores increased significantly from baseline to FU2 (IIEF 30.6 vs. 48.9; QEQ scores: 12.2 vs. 45.5, $P < 0.0001$ for both).

Penile endothelial function improved significantly ($P = 0.0001$) after LI-ESWT, as assessed by the three parameters of penile hemodynamics and endothelial function, namely, maximal postischemic blood flow (Figure 4), basal blood flow, and the area under the flow-time curve (AUC).

We noted a strong correlation between the changes in the IIEF-ED and the changes in those three parameters at baseline and FU1, namely, maximal postischemic blood flow ($P = 0.0087$; Figure 5), basal blood flow ($P = 0.0448$), and AUC ($P = 0.0109$).

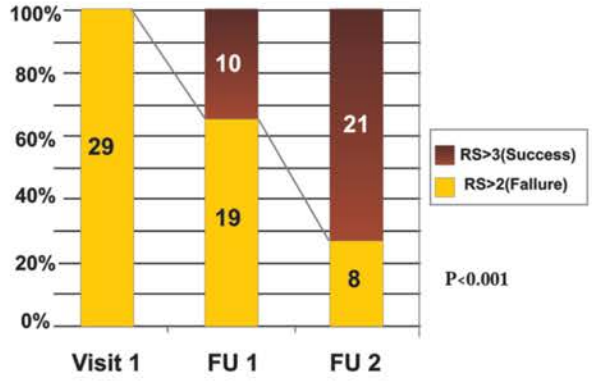

Figure 3 Changes in rigidity scales according to visit. RS, rigidity scale.

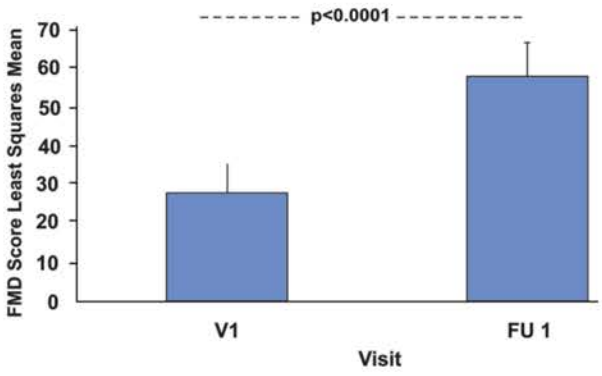

Figure 4 Maximal postischemic blood flow measured at the penis level per visit. FU, follow-up.

None of the men reported pain or any adverse events due to or after the treatment. In fact, the only adverse event was a mild transient allergic reaction to the gel in one man when it was applied at treatment session 2.

Discussion

This is our second report on the effect of LI-ESWT in ED patients. The results of our first

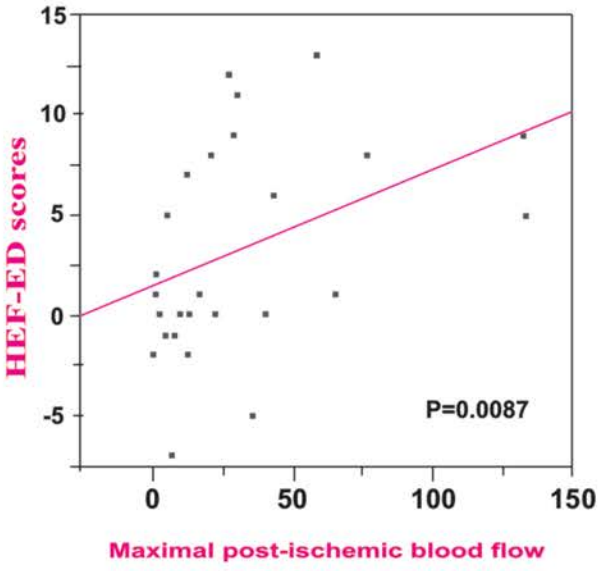

Figure 5 Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED domain scores. Graph 4: Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED score. IIEF-ED, International Index of Erectile Function-erectile function domain.

study showed that this treatment exerts a beneficial effect on 20 ED men who were responders to PDE5is. Here, we report that LI-ESWT is also beneficial when given to 29 poor responders with severe ED and significant cardiovascular risk factors. These results also confirm that this modality exerts a genuine physiological effect on the erectile mechanism when applied directly to the cavernosal tissue.

For this study, we used the identical protocol from our first trial of which the obtained good results did not justify any modification at this time. This does not mean that this treatment protocol is optimal. Hence, additional studies using different protocols need to be done in order to reach the desired clinical outcome.

We recruited men that were already on routine follow-up at our outpatient ED clinic.

Seven were on injection therapy and two were candidates for a penile implant. The others were relatively new patients who were poor or nonresponders to PDE5is and had been referred to our clinic for further treatment. At screening, we interviewed each man using a detailed intake sheet, documented their sexual difficulties in real-life situations, and compared the data with their IIEF-ED. This way, we assured that the study population consisted of true poor or nonresponders and allowed us to simplify the protocol and to assure patient compliance.

Our primary end points were the change in IIEF-ED and in the EHS value. We selected the IIEF-ED as it is the "gold standard" and the most commonly used instrument for evaluating ED. The EHS value was selected as it can precisely make a distinction between those who are able to penetrate and achieve full sexual intercourse from those who are unable to do so. We believe that the EHS value is a reliable measure of the functional capability of our study participants, and because of its simplicity, it should be used more frequently in other ED trials.

The results of the current study showed that the EHS value was three or more in 72.4% of the men after LI-ESWT. This result is remarkable as LI-ESWT significantly improved their response to PDE5i therapy and enabled these nonsexually functioning men to now achieve vaginal penetration and full sexual intercourse. This achievement is also noteworthy because it enabled 34% of these men to function sexually without using any medication. These results are supported by the corresponding improvement in their penile hemodynamics. Both the subjective and objective measurements of erectile function coincide, emphasizing that LI-ESWT exerts a genuine effect on the erectile mechanism by improving penile blood flow.

We noticed that most men feel some initial improvement between the sixth and eighth treatment sessions and sometimes a later effect is reported even after the end of treatment.

Limitations of this study are the lack of a sham-controlled arm and the relatively low number of participants. Despite these weaknesses, the substantial changes in the IIEF–ED and the EHS values, as well as the clinically significant effect that was achieved in this group of severe ED patients, cannot be undervalued.

Our finding that this emerging new and exciting treatment modality exerts a beneficial effect in men with severe ED suggests that LI-ESWT could be used as an alternative treatment or as an addition to PDE5i therapy. Noteworthy is our finding that the 21 diabetic patients in our study responded to this energy. As such men are considered a difficult to treat population for ED, this finding raises the question whether LI-ESWT is specifically effective in diabetic ED. Evaluation of the efficacy of LI-ESWT in such men using randomized, double-blind, sham-controlled studies is now needed, and we are in the midst of performing such a study. There is also a need for studies whose aim is to define the optimal treatment protocol in order to be able to offer the best results when using LI-ESWT in ED patients.

Conclusions

These preliminary results of the effect of LI-ESWT in a group of men with severe ED who were nonresponders to PDE5is suggest that LI-ESWT probably has a physiologic effect on the erectile mechanism, a fact that still needs to be reconfirmed in a placebo-controlled manner.

The fact that the magnitude of response is impressive and the objective hemodynamic data showed significant changes posttreatment drives us to believe that there is more than just a placebo effect, especially due to the severity of this study group.

We are aware of the skepticism that this new therapeutic approach may arouse but hope that the data provided in this preliminary study will persuade the reader to at least remain open-minded to this optional treatment strategy. This will probably happen only after better understanding of the

basic physiological effect that this energy has on the cavernosal tissue and the availability of multicenter clinical data.

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Conflict of Interest: None.

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ORIGINAL RESEARCH

ERECTILE FUNCTION

Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial

Dimitrios Kalyvianakis, MD, FECSM, and Dimitrios Hatzichristou, MD, PhD, FECSM

ABSTRACT

Background: Although several reports have documented the subjective improvement of erectile function after low-intensity extracorporeal shockwave therapy (LI-ESWT) in patients with vasculogenic erectile dysfunction (ED), objective assessment data of penile hemodynamics are lacking.

Aim: To assess penile hemodynamics before and 3 months after LI-ESWT in a group of patients with documented vasculogenic ED.

Methods: This was a double-blinded, randomized, sham-controlled trial. Forty-six patients with ED were randomized; 30 underwent LI-ESWT and 16 had a sham procedure in double-blinded fashion. All patients underwent penile triplex ultrasonography by the same investigator immediately before and 3 months after treatment. Patient demographics, International Index of Erectile Function erectile function domain (IIEF-ED) score, and minimal clinically important difference were assessed at baseline and 1, 3, 6, 9, and 12 months after treatment.

Outcomes: Changes in peak systolic velocity and resistance index as measured by triplex ultrasonography at baseline and 3 months after treatment were the main outcomes of the study. Secondary outcomes were changes in the IIEF-EF score from baseline to 1, 3, 6, 9, and 12 months after treatment and the percentage of patients reaching a minimal clinically important difference during the same period for the two groups.

Results: IIEF-EF minimal clinically important differences for the active vs sham group were observed for 56.7% vs 12.5% ($P = .005$) at 1 month, 56.7% vs 12.5% ($P = .003$) at 3 months, 63.3% vs 18.8% ($P = .006$) at 6 months, 66.7% vs 31.3% ($P = .022$) at 9 months, and 75% vs 25% ($P = .008$) at 12 months. Mean peak systolic velocity increased by 4.5 and 0.6 cm/s in the LI-ESWT and sham groups, respectively ($P < .001$).

Clinical Implications: Such results offer objective and subjective documentation of the value of this novel treatment modality for men with vasculogenic ED.

Strengths and Limitations: Strengths include the prospective, randomized, sham-controlled type of study and the assessment of penile hemodynamics. Limitations include the small sample and strict inclusion criteria that do not reflect everyday clinical practice.

Conclusion: The present study confirms the beneficial effect of LI-ESWT on penile hemodynamics and the beneficial effect of this treatment up to 12 months. **Kalyvianakis D, Hatzichristou D. Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial. J Sex Med 2017;14:891−897.**

Key Words: Low-Intensity Shockwave Therapy; Erectile Dysfunction; Peak Systolic Velocity; Penile Doppler

INTRODUCTION

Several treatment effective options are available for vasculogenic erectile dysfunction (ED); phosphodiesterase type 5 (PDE5) inhibitors and intracavernosal injections are effective and safe vasodilating agents.[1] The main disadvantage of currently available pharmacotherapy is the inability to alter the underlying predominant pathology in patients with vasculogenic ED (eg, cavernosal artery insufficiency). Furthermore, PDE5 inhibitors might be contraindicated or should be used with caution in some patients.[2]

Low-intensity extracorporeal shockwave therapy (LI-ESWT) has shown encouraging results for patients with ischemic heart

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disease,[3] chronic diabetic foot ulcers, or wound healing.[4,5] Basic research has shown that low-intensity shockwaves act by provoking microtrauma in the endothelium of the helicine arteries, leading to the release of angiogenic factors, such as nitric oxide synthase and vascular endothelial growth factor, and endothelial cell proliferation factors, such as proliferating cell nuclear antigen.[6,7]

Recent sham-controlled clinical trials have reported subjective improvement in erectile function and systemic endothelial function measured by nocturnal penile tumescence and flow-mediated dilatation, respectively.[8–10] However, most of the published studies did not assess penile hemodynamics. The purpose of the study was to assess penile hemodynamics before and after LI-ESWT and subjective long-term improvement of erectile function.

METHODS

We recruited men who a history of vasculogenic ED for at least 6 months. Diagnosis was based on sexual and medical history, clinical examination, and laboratory test results. Eligible subjects were at least 18 years old, had ED for at least 6 months, and were at least partial responders to PDE5 inhibitors (able to penetrate at least half the time while taking a PDE5 inhibitor). For inclusion in the study, after a 4-week washout period, the baseline International Index of Erectile Function erectile function domain (IIEF-EF) score had to be at least 6 (mild to moderate ED) to 21 (moderate and severe ED). Patients with no ED or with mild ED were excluded. All subjects had been in a stable heterosexual relationship with the same partner for more than 3 months. The exclusion criteria were radical prostatectomy; psychogenic ED; penile anatomic abnormalities; neurogenic ED; hormonal abnormalities; antiandrogen therapy; history of heart attack, stroke, or life-threatening arrhythmia within 6 months before enrollment in the study; and recovery from any cancer within the past 5 years. All patients accepted and signed the informed consent form for the study, which was approved by the institutional review board.

Study Sample

Sample size calculation was based on a difference of at least 3.5 in changes from baseline to month 12 in IIEF-EF score between the study groups, with 80% power and 5% statistical significance. The calculation assumes a common SD of the change of 3.5 and a ratio of 2:1 between the groups. A two-group t-test with a 0.05 two-sided significance level would have 80% power to detect the difference of at least 3.5 in IIEF-EF score between groups when the sample sizes were 15 for the sham group and 30 for the active treatment group.

Study Protocol

The study consisted of the following phases. The screening phase included a 4-week run-in phase of using PDE5 inhibitors to identify at least partial response to PDE5 inhibitors. Subjects who met the inclusion criteria underwent a 4-week PDE5 inhibitor washout period and completed the IIEF questionnaire, and data were selected by a research assistant. At the end of the washout phase, eligible patients underwent triplex ultrasonography of the cavernosal arteries by the same investigator to assess penile hemodynamics.[11] All patients were blindly randomized to one of two active treatment groups or to a sham control group. The groups were marked as A, B, and C, two of which indicated active treatment groups and one of which indicated a sham control group. The treatment protocol was applied by two investigators in double-blinded fashion and included biweekly treatment sessions at the first, second, third, seventh, eighth, and ninth weeks after the washout period, for a total of 12 treatments (sessions). All patients underwent penile triplex ultrasonography by the same investigator at baseline and 3 months after treatment. Side effect profile was assessed at every visit during the treatment period, and the IIEF score was assessed before and at 1, 3, 6, 9, and 12 months after treatment (Figure 1).

Blinding and Randomization

Study procedures were identical for the active treatment and sham control groups, but the sham treatment was conducted using a distinctively designed shockwave applicator. The sham shockwave applicator contained an element that blocked delivery of shockwaves. The two types of shockwave applicator (active and sham) looked identical. All patients were blindly randomized using specific computer software into one of two active treatment groups or into a sham control group in a 2:1 ratio, respectively.

LI-ESWT Methodology

We applied a standard commercial gel normally used for sonography on the subject's penis and on the membrane of the shockwave applicator. The treatment included a standard protocol of 300 shocks to each treatment location (three locations on the penile shaft and two locations on the penile crura for a total of 1,500 shocks) using a specialized focused shockwave probe (Omnispec ED1000, Medispec Ltd, Yehud, Israel) as described in previous studies.[9,10] The treatment was performed at an energy intensity of 0.09 mJ/mm^2; the energy level was automatically predetermined by the device. The treatment was performed at an energy intensity of 0.09 mJ/mm^2 and frequency of 160 pulses/min. Each treatment session lasted approximately 20 minutes without local or systemic analgesia.

Penile Triplex Ultrasonography Protocol

Penile triplex ultrasonography was performed (BK Flex Focus 400, BK Ultrasound, Peabody, MA, USA) to assess penile hemodynamics at baseline and 3 months after the final LI-ESWT treatment. The test was performed as follows: 0.5 mL of vasoactive agent (tri-mix solution) was injected into the corpus cavernosum and the time of injection was recorded. Then, the ultrasound B-mode probe was placed on the left and right

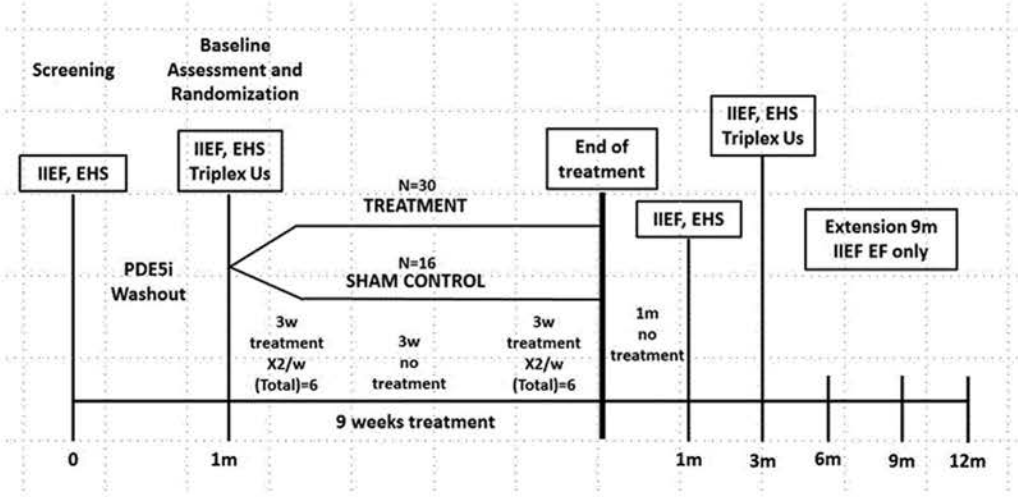

Figure 1. Study flowchart. EHS = Erection Hardness Scale; IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function erectile function domain; m = months; PDE5i = phosphodiesterase type 5 inhibitor; Us = ultrasonography.

cavernous arteries. By shifting to Doppler mode, focusing the cursor, and adapting a right angle at 60°, the systolic and end-diastolic velocities (centimeters per second) were determined. Doppler angle was not changed during the evaluation. An evaluation of peak systolic velocity (PSV) to end-diastolic velocity blood flow with automatic calculation of the resistance index (RI) at various time points was followed for up to 30 minutes. Flow measurements were performed at 5, 10, 15, and 20 minutes, reserving a measurement at 30 minutes for patients who did not achieve adequate penile hardness or a purely erectile response; in such cases, re-dosing with 0.5 mL of tri-mix solution was followed and all measurements were repeated. The highest values achieved were reported.

Main Outcome Measures

Changes in PSV and RI as measured by triplex ultrasonography at baseline and 3 month after treatment were the main outcomes of the study. The IIEF-EF score was used to evaluate erectile function. Improvement in IIEF-EF score from baseline to 12-month follow-up; the minimal clinically important difference in IIEF-EF score; and a change in IIEF-EF score equal to or greater than 2, 5, and 7 points for mild, moderate, and severe ED, respectively, were measured.[12]

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 20.0 (IBM Corp, Armonk, NY, USA). Normality of measurements for PSV, RI, and IIEF-EF score was tested using the Shapiro-Wilk test to establish that normality was not violated in most cases. Parametric tests and models were used for analyses of the data. Study parameters were summarized in tables by treatment and presented as mean ± SD, median ± range, or frequency (percentage) according to the distribution of the parameter. Comparative analysis of baseline characteristics was applied using the two-sample t-test or median test for quantitative parameters and the χ^2 test for categorical parameters. The repeated measures general linear model was applied for analyzing the difference in IIEF-EF scores and changes from baseline between treatments. Changes from baseline in PSV and RI were analyzed within each treatment using paired-samples t-test. The level of significance for all analyses was set at 5%.

RESULTS

Fifty-nine patients were screened; 46 who met the inclusion criteria were randomized into groups. All 46 patients completed the study; the sham control group and the active treatment group consisted of 16 and 30 randomly assigned patients, respectively. Table 1 presents the baseline characteristics of the two study groups.

IIEF-EF Score Changes

At baseline and 1, 3, 6, 9, and 12 months after the last treatment, the IIEF-EF scores in the active treated group were 13.8 ± 3.6, 18.46 ± 3.6, 18.46 ± 3.5, 19.0 ± 3.3, 18.63 ± 3.0 and 19.1 ± 2.8, respectively. The IIEF-EF scores in the sham group were 14.6 ± 3.4, 16.43 ± 3.5, 15.93 ± 3.6, 16.12 ± 2.6, 16.00 ± 3.0, and 16.00 ± 2.8 (Figure 2). One patient achieved an IIEF-EF score of 26 (no ED). We tested whether there were significant differences among the six repeated measurements of IIEF-EF score over time. The model showed no difference for the pretreatment measurement between the two groups ($P = .475$). In addition, the difference in the mean IIEF-EF score the first month after treatment showed a tendency toward significance ($P = .072$) but became significant between the two groups after month 3 ($P = .02$), whereas after months 6, 9, and 12 months the differences were highly statistically significant ($P < .01$ for all comparisons).

A minimal clinically important difference of the IIEF-EF score for the active treatment vs sham group was 56.7% vs 12.5%

Table 1. Baseline characteristics of study population at randomization (no phosphodiesterase type 5 inhibitor use)

	Sham	Treatment	*P* value
Men, n	16	30	
Age (y), median (range)	55.1 (38–72)	53.0 (31–72)	.52†
ED (y), median (range)	5.5 (1–15)	5.5 (1–20)	.99†
Concomitant condition, %			
Cardiovascular risk factors*	56.3	50	.69§
Diabetes mellitus	37.5	26.7	.45§
IIEF-EF domain score, mean ± SD	14.6 ± 3.4	13.8 ± 3.6	.47‡
EHSG score, mean ± SD	2.75 ± 0.45	2.95 ± 0.41	.70‡
PSV (cm/s), mean ± SD	30.7 ± 3.55	31.1 ± 3.23	.70‡
EDV (cm/s), mean ± SD	5.95 ± 1.87	5.86 ± 1.65	.86‡
RI, mean ± SD	0.81 ± 0.07	0.80 ± 0.05	.53‡

ED = erectile dysfunction; EDV = end-diastolic velocity; EHSG = Erection Hardness Grading Scale; IIEF-EF = International Index of Erectile Function erectile function domain; PSV = peak systolic velocity; RI = resistance index.
*Including at least one of the following: hypertension, metabolic syndrome, obesity, smoking, and hypercholesterolemia.
†By median test.
‡By Student t-test.
§By χ^2 test

(P = .005) at 1 month, 56.7% vs 12.5% (P = .003) at 3 months, 63.3% vs 18.8% (P = .006) at 6 months, 66.7% vs 31.3% (P = .022) at 9 months, and 75% vs 25% (P = .008) at 12 months (Figure 3).

Penile Hemodynamics Changes

Penile triplex ultrasonographic measurements were used as an objective method to assess penile hemodynamics before and 3 months after treatment. The mean change of PSV was 4.5 and 0.6 for the treatment and sham-control groups, respectively, from baseline to 3 months after the last treatment (Table 2). The mean change of the RI was 0.04 and −0.01 for the treatment and placebo groups, respectively, from baseline to 3 months after treatment. We tested whether there was a significant difference between baseline and post-treatment PSV and RI. P values were greater than .05 for the sham control group and less than 0.001 for the active group. Individual plots describing maximal PSV at baseline and at 3-month follow-up clearly showed an

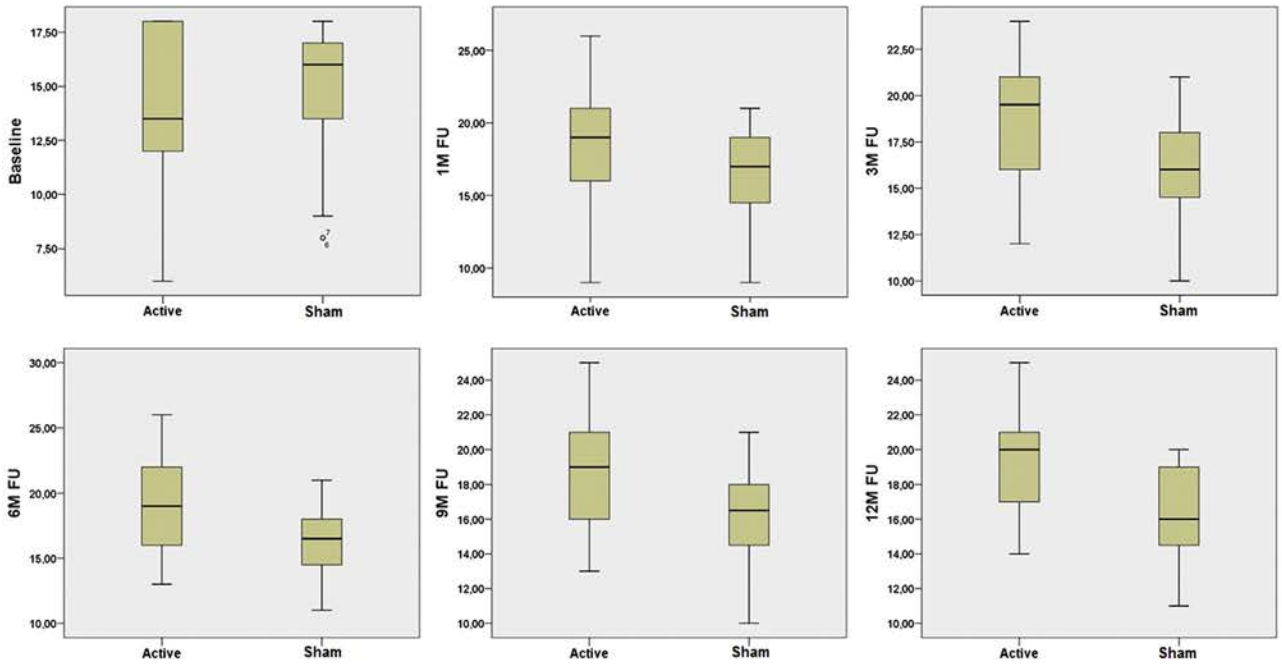

Figure 2. Twelve-month FU of International Index of Erectile Function erectile function score. All analyses were done using Student t-test. FU = follow-up; M = month. Figure 2 is available online at www.jsm.jsexmed.org.

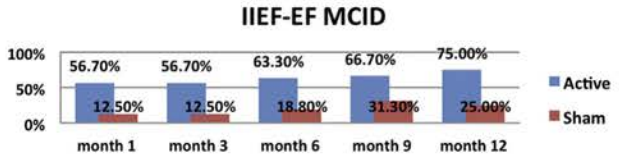

Figure 3. IIEF-EF score MCID in active and sham groups at 1-, 3-, 6-, 9-, and 12-month follow-up visits ($P < .02$ by χ^2 test). IIEF-EF = International Index of Erectile Function erectile function domain; MCID = minimal clinically important difference. Figure 3 is available online at www.jsm.jsexmed.org.

improvement in arterial inflow in all but one patient in the active treatment group (Figure 4). No pain or any other side effect was observed in any patient.

DISCUSSION

During the past decade, the use of LI-ESWT has been added as novel therapy to the treatment algorithm of ED. The increased reports and clinical studies of this therapy have emphasized LI-ESWT as a therapeutic method for ED with great acceptance by the research community and patients. The positive treatment effect of LI-ESWT in patients with ED has been confirmed recently by the first meta-analyses on this method.[13,14] Nevertheless, in all studies included in these meta-analyses, the treatment benefit of LI-ESWT was evaluated mainly by improvement in IIEF score, a patient-reported assessment that is purely subjective.

The present study clearly demonstrated the beneficial effects of LI-ESWT on penile hemodynamics as measured by the most commonly performed diagnostic test for the diagnosis of vasculogenic ED. Our finding that PSV increased in all but one patient in the active group strengthens the clinical evidence that LI-ESWT improves penile hemodynamics. The main disadvantages of penile duplex ultrasonography include operator dependence and inadequate smooth muscle relaxation; all hemodynamic assessments were performed by the same experienced investigator using a standardized protocol[11] and adapting the re-dosing principle to achieve maximum smooth muscle relaxation. The scheme of the shockwave therapy was the same as that used in cardiology[15] and that used in all published randomized control trials for the treatment of ED. Such methodology allows comparison of the present data with previously published data. The present results were consistent with those of previous studies for changes in IIEF-EF score.[11] An important finding of our study is that IIEF score and PSV increased significantly at 3 months in a linear fashion. Patients with no improvement in IIEF score had no improvement in PSV. The increase in IIEF-ED score remained statistically significant even at 12-month follow-up in the active treatment group, clearly showing the long-term benefit of LI-ESWT.

The concept of improving endothelial function and neovascularization using low-intensity shockwave energy is not new.[16] Well-established therapeutic protocols have been established in cardiology and diabetology to exploit this application.[15,17,18] In sexual medicine, the application of LI-SWT is a novelty and emerged by the unmet need for a non-pharmaceutical therapy that could be used to supplement existing modalities.[10] Unfortunately, existing treatments for ED offer only temporary symptomatic relief and none are curative. Targeting the etiology of ED is an extremely demanding clinical feat that appears to be served satisfactorily by LI-ESWT. In particular, clinical researchers have shown an overall improvement in IIEF score and a very high rate of conversion of non-responders to PDE5 inhibitors after application of LI-ESWT.[8,10] Although the exact mode of action of LI-ESWT is not known, it appears to be mediated by a local induction of neoangiogenesis and endothelial repair[19,20] by stimulating the expression of angiogenesis-related growth factors (nitric oxide synthase and vascular endothelial growth factor) and endothelial cell proliferation factors(proliferating cell nuclear antigen).[21,22] Further basic research is urgently needed to gain insight into the mechanism of action of LI-ESWT on cavernosal structures.

Our findings further support the growing evidence for the clinical use of LI-ESWT in patients with vasculogenic ED. The prospective, randomized, sham-controlled study, the assessment of penile hemodynamics, and the report of patients who achieved a minimal clinically important difference are the strengths of this study. Limitations include the small sample and strict inclusion criteria that do not reflect everyday clinical practice; however, such criteria strengthen the results of this triplex-based study. Future randomized clinical trials are important to identify the best treatment protocol for each patient (timeframe and need for maintenance therapy) depending on the severity of ED (patients

Table 2. Change from baseline in PSV and RI at 3-Month FU

	Sham group	*P* value	Active group	*P* value
PSV (cm/s)		0.45		<.001*
Baseline	30.7 ± 3.55		31.1 ± 3.23	
3-mo FU	31.1 ± 3.50		35.5 ± 3.60	
RI		0.75		<.001*
Baseline	0.81 ± 0.07		0.80 ± 0.05	
3-mo FU	0.80 ± 0.05		0.84 ± 0.04	

FU = follow-up; PSV = peak systolic velocity; RI = resistance index.
*By paired-samples t-test.

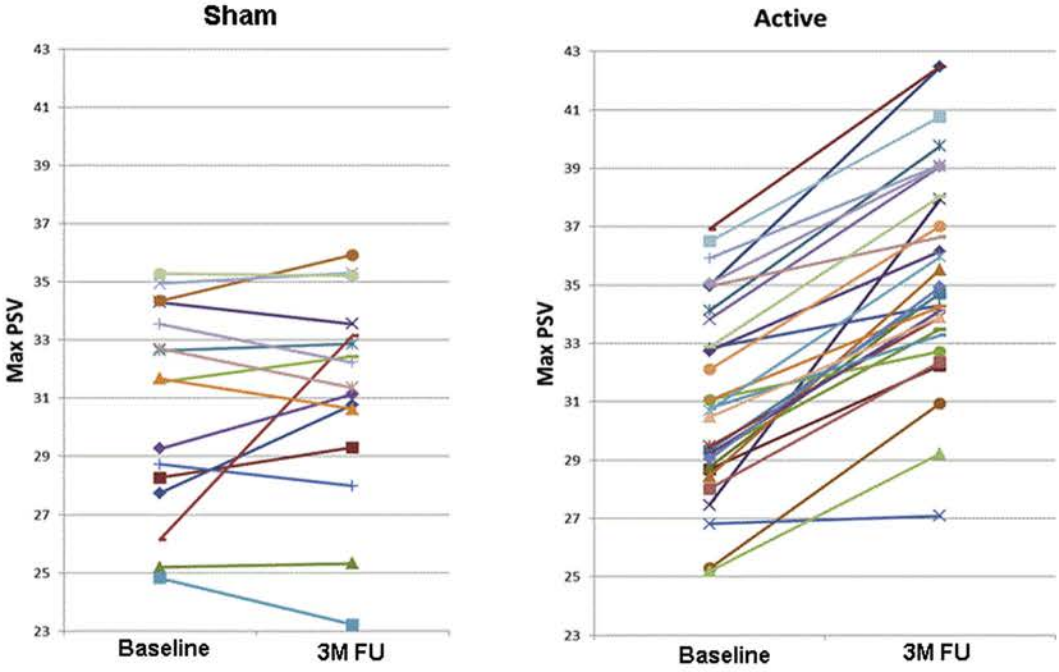

Figure 4. Individual plots of maximum PSV at baseline and at 3 months after low-intensity shockwave therapy. All but one patient showed an increase in PSV in the active group. 3M FU = 3-month follow-up; Max PSV = maximum peak systolic velocity. Figure 4 is available online at www.jsm.jsexmed.org.

with mild or moderate ED might need fewer treatment sessions) and specific subpopulations such as those with diabetes and different age groups. Such research will identify those who could really benefit from this revolutionary therapy and make the indications of this novel treatment modality more accurate.[23,24]

CONCLUSIONS

The present study demonstrated the beneficial effect of LI-ESWT on penile hemodynamics. Also, the study confirmed previous findings that application of LI-ESWT to the penile shaft is safe and effective for the treatment of vasculogenic ED.

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Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population

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Introduction: *Erectile dysfunction (ED) has been shown to be associated with a number of physical conditions and affects not only physical but also psychosocial health. Currently oral, on-demand phosphodiesterase type 5 inhibitors (PDE5i) are preferred first line treatment. Though effective, these drugs have limitations and are associated with significant non-compliance, side effects and do not reverse the underlying pathology. Non-invasive low intensity shockwave therapy (LISWT) has been shown to significantly improve erectile function in men previously PDE5i dependent. We describe our experience and results with this therapy in an Indian population of men with ED. This study assessed the efficacy of low intensity extracorporeal shockwave therapy (LI-ESWT) on Indian men with organic ED who had previously responded to PDE5i.*

Materials and methods: *All the patients underwent a 1 month PDE5i washout period. Men were randomized to receive either 12 sessions of LI-ESWT (n = 95) or placebo/sham therapy (n = 40). Before the first treatment, erectile function and penile hemodynamics were assessed to substantiate a vascular etiology for the ED. Outcomes were assessed using Erection Hardness Score (EHS), International Index of Erectile Function-Erectile Function Domain (IIEF-EF domain) and Clinical Global Impression of Change (CGIC) scores at 1, 3, 6, 9 and 12 months post-treatment.*

Results: *We found a significant increase in the EHS and IIEF-EF Domain scores from visit 1 to follow up 5 (12 months) in the treated group compared to the placebo group. By 1 month after treatment there were highly significant differences between the LI-ESWT and placebo groups ($p < 0.0001$). Out of 60 men in the LI-ESWT group who completed the study, 47 (78%) men at FU1 and 43 (71%) at FU5 who were initially unable to achieve spontaneous erections hard enough for penetration (EHS ≤ 2) were able to do so (EHS ≥ 3) compared to none in the placebo group. The treatment was well tolerated and none of the men experienced treatment related discomfort or reported any adverse effects from the treatment.*

Conclusions: *In this double-blind, placebo-controlled study, LI-ESWT demonstrated a positive long term clinical effect with improvement in erectile function of Indian men with vasculogenic ED who were prior responders to PDE5i therapy. The efficacy and tolerability of this treatment, coupled with its long term benefits and rehabilitative characteristics, make it an attractive new therapeutic option for men with vasculogenic erectile dysfunction.*

Key Words: erectile dysfunction, low intensity, penis, hemodynamics, shockwaves

Introduction

There are several therapeutic options available for treating men with erectile dysfunction (ED) with phosphodiesterase type 5 inhibitors (PDE5i) currently first line therapy for men with vasculogenic ED. While these have proven to be safe and effective, they have limited utility as most need to be dosed on demand in close proximity to sexual activity and do not provide long term benefit.[1] Gene and stem cell therapies are examples of treatment strategies with the potential to address the underlying pathophysiology with the goal of restoring spontaneous erectile function, rather than provide on-demand palliative treatment.[2,3]

Low intensity extracorporeal shockwave therapy (LI-ESWT) has recently been introduced as a treatment

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modality for ED. In 1990 Young and Dyson demonstrated that therapeutic ultrasound could promote angiogenesis by enhancing the expression of vascular endothelial growth factor.[4-6] That finding led to the investigation of low intensity or low energy shockwaves in the treatment of coronary artery disease,[7] non-healing bone fractures,[8] calcifying tendonitis[9] and diabetic foot ulcers.[10] Vardi in 2010 demonstrated that LI-ESWT treatment to be an effective treatment strategy for ED in a mostly European population of men with vasculogenic ED.[11,12] Recently, Qiu et al investigated the effect of LI-ESWT on ED of streptozotocin (STZ) induced diabetes mellitus rat model. The researchers found out that LI-ESWT can partially ameliorate DM-associated ED by promoting regeneration of neuronal nitric oxide synthase (nNOS)-positive nerves, endothelium, and smooth muscle in the penis. These beneficial effects are thought to be mediated by recruitment of endogenous MSCs.[13]

As it has been reported that there are differences between Asian and European men in penile length and the underlying etiologies of ED,[14] we report herein our initial experience on the efficacy and safety of LI-ESWT for the treatment of ED in an Asian population.

Materials and methods

Screening, inclusion and exclusion criteria

We screened men in our ED outpatient clinic between September 2009 and September 2011who had a history of ED for at least 6 months and who were responders to PDE5is. A total of 165 men underwent screening, which included a complete medical history and physical examination, penile Doppler, nocturnal penile tumescence (NPT), International Index of Erectile Function (IIEF), International Index of Erectile Function-Erectile Function Domain Score (IIEF-EF domain) and erection hardness score (EHS). All subjects were required to discontinue PDE5i during the study period. For study inclusion each participant had to have an IIEF-EF domain score of < 18 following a 4 week PDE5i washout period (time V1 = baseline taken just before the first visit). Written informed consent was obtained before entering the study. The study protocol was reviewed and approved by our institution's ethics review board. Men were excluded if they had undergone radical prostatectomy, received pelvic radiotherapy or hormonal therapy, were receiving treatment for a psychiatric condition, or had any anatomical, neurological or hormonal abnormalities.

Since the mean age for men presenting with ED in the Indian population tends to be younger than in the West, and psychogenic causes for ED are more common than in younger than older patients, to ensure that our study group did not include men with psychogenic ED, we used penile Doppler to confirm an underlying organic basis for the ED at study entry.

Based on Doppler findings 30 patients were excluded, leaving 135 enrolled in the study. Inclusion and exclusion criteria are summarized in Table 1.

Study protocol

Substantiation of non-psychogenic ED

At the screening visit (Sx) the penile hemodynamics of each male were evaluated with real time ultrasonographic color Doppler (GE LOGIQ P6 machine) using a high frequency transducer (8 MHz linear vascular probe.[15,16] In the flaccid state, cavernosal diameter, cavernosal

TABLE 1. **Study selection criteria**

Inclusion criteria	**Exclusion criteria**
ED of more than 6 months.	Prior history of prostatectomy or pelvic radiotherapy.
Positive response to PDE5i.	Any cause of ED other than vascular-related.
IIEF-EF domain score of 6 ≤ 18.	Any unstable medical, psychiatric, spinal cord injury, penile anatomical abnormalities.
Non-neurological pathology.	Clinically significant chronic hematological disease.
Stable heterosexual relationship for more than 3 months.	Cardiovascular conditions that prevent sexual activity. H/o heart attack, stroke or life-threatening arrhythmia within the previous 6 months. Cancer within the past 5 years. Anti-androgen treatment (oral or injectable). Use of any treatment for ED within 7 days of screening.

ED = erectile dysfunction; PDE5i = phosphodiesterase type-5 inhibitors, IIEF-EF =International Index of Erectile Function – Erectile Function

arteries, deep dorsal vein and their flow velocities were measured using an 8 MHz GE LOGIQ P6 linear probe, with Doppler frequencies of 4.4 MHz and a CW Doppler with transmitting frequencies of 8-10 MHz. The patients were given oral sildenafil 100 mg, and 60 minutes later the cavernosal diameter, cavernosal arteries, deep dorsal vein were assessed and their flow velocities measured. The patients were than provided with visual sexual stimulation for 10 minutes to achieve a full or maximum erection. The above measurements were then repeated 70 and 80 minutes post-sildenafil. Patients were considered eligible to participate in the study if peak systolic velocity (PSV) was < 30 cm.

Randomization

All 135 participants underwent a 4 week PDE5i washout period. At baseline, prior to first visit (study time V1), the men were randomized 3:1 into two groups: those randomized to LI-ESWT (treatment group) and those randomized to sham therapy (placebo group).

Treatment and follow up periods

Each subject then began the 9 week treatment period which involved two LI-SWT treatment sessions per week for 3 weeks, repeated after a 3 week no treatment interval. Four outcome evaluation measures were examined, each in a separate analysis. Two separate analyses were performed assessing change in IIEF-EF domain scores, as follows:

1) IIEF-EF domain score change: these were evaluated as change of scores against V1 (baseline) for each of the six succeeding visits, and directly across all seven visits.
2) Total IIEF score change: these were evaluated across visits Sx, V1, V7 and FU1.
3) EHS score: these were evaluated across all seven visits.
4) CGIC score: these were evaluated across the six post-baseline visits.

The details of the changes in IIEF-EF domain scores, the erection hardness scores and the clinical global improvement change scale (CGICS) are shown in Table 2.

LI-ESWT procedure in treatment group

Standard commercial ultrasound gel was applied to the penis. The penis was stretched manually and the shockwaves were delivered to the distal, mid and proximal penile shaft, and to the left and right crura using a specialized focused shockwave probe Omnispec ED1000 (Medispec Ltd., Yehud, Israel).[4,5] As the depth of the shockwaves reaches both corpora, treatment was applied to only one side of the penile shaft. Three hundred shocks at an energy density of 0.09 mJ/mm^2 and a frequency of 120 shocks per minute were delivered at each of the five treatment points. Each treatment session lasted approximately 15 minutes. No, topical, local or systemic analgesia was administered.

TABLE 2. **Scoring details**

IIEF-EF domain score	
≤ 5	no attempts at intercourse
6-10	severe ED
11-16	moderate ED
17-21	mild to moderate ED
22-25	mild ED
≥ 26	"normal" erectile function
Erection hardness score	
Grade 1 – tumescence but no rigidity	
Grade 2 – tumescence with minimal rigidity	
Grade 3 – rigidity sufficient for sexual intercourse	
Grade 4 – fully rigid erection	
Clinical global improvement – change scale	
1 – very much improved	
2 – much improved	
3 – minimally improved	
4 – no change	
5 – minimally worse	
6 – much worse	
7 – very much worse	

ED = erectile dysfunction

Placebo treatment

Patients allocated to the placebo group were treated with a placebo probe supplied by the manufacturer. The placebo probe was identical in appearance and made the same sound as the treatment probe, but contained a metal plate to block the transmission of the shockwave energy from being applied to the penis. Since the appearance, sound and vibration of the probes used in both groups were similar, and the treatment is painless, both the operator and the subject were blinded to treatment randomization.

Follow up

We characterized seven distinct phases of the treatment course, Figures 1a and 1b: Sx is the first (screening) visit at which the patient undergoes penile Doppler, NPT, IIEF score, IIEF-EF domain and EHS. Visit 1 (V1) is the randomization visit where baseline IIEF score, IIEF-EF

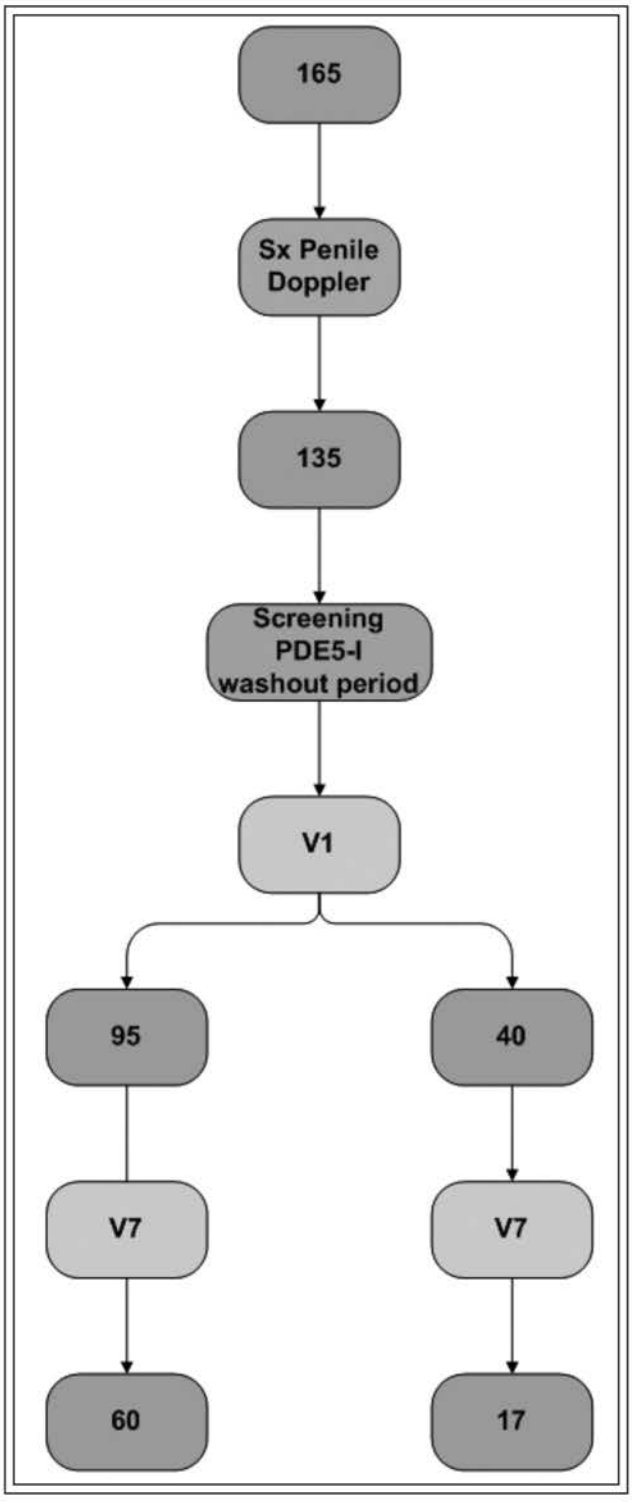

Figure 1a. Trail screen failure and dropout flowchart.

domain and EHS were assessed and the patients were randomly allocated to either the treatment or placebo groups. Visit 7 (V7) occurs after six treatment sessions and a 3 week no-treatment interval period when the patient presents for the seventh session visit. Follow up 1 (FU1) is the first follow up which is carried out 1 month after the last treatment session. FU2, FU3, FU4 and FU5 are follow-ups after 3, 6, 9 and 12 months after the 12th session.

Main outcome measures (primary end point)

We used the IIEF-EF domain to assess erectile function. Treatment success was defined as a 5-point or greater improvement in the IIEF-EF domain between V1 and FU1 (also FU5), as this correlates with an improvement in erectile function by at least one severity category. The secondary outcome measures were defined as significant increases in the CGIC and an increase in EHS from ≤ 2 at V1 to ≥ 3 at FU1 and FU5.

Results

Statistical analysis

JMP (SAS Institute, Cary, NC, USA) and R statistical software were employed for analyses. Specifically for Friedman's test and associated post-hocs, Galili's R program[17] was employed. Patients in the placebo-treated went through only three phases of the study and followed for 3 months, (V7, FU1, FU2). Comparisons with the shockwave-treated group at later time points were thus limited.

The demographic and medical characteristics of the treatment and placebo groups are shown in Table 3.

For IIEF-EF domain and total IIEF statistics, change scores were constructed for each patient for each stage, with reference to V1, i.e. Delta IIEF-EF domain V7 is the change score at V7 minus V1, and Delta IIEF-EF domain FU1 is FU1-V1.

The distributions of the data indicated the use of non-parametric statistics, therefore, separate Wilcoxon tests were performed at each stage. Summarized inference from one way ANOVA, Wilcoxon test and 2 sample test – normal approximation, Table 4.

Besides basic distributional analysis of demographic and outcome factors, we conducted longitudinal analyses of four outcome parameters over either six or seven visits. The non-parametric distributions of the total IIEF and IIEF-EF domain change scores, and the ordinal scales used for RS and GCI necessitated the use of Friedman's ANOVA, a rank-based non-parametric procedure for repeated measures, along with multiplicity-corrected, pairwise (between all stage pairs) post-hoc tests. Friedman's test does not allow for missing data, and imputation, LOCF, or other data "recovery" strategies are not appropriate for this study. Box plots and parallel coordinate plots (individual response plots) were also produced.

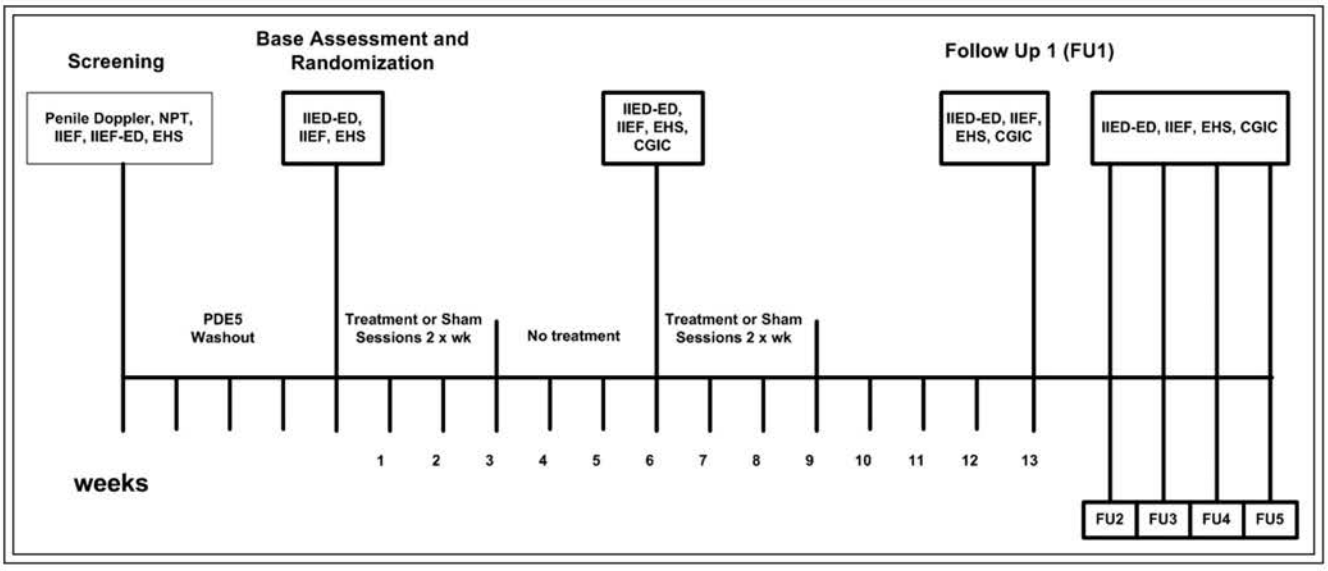

Figure 1b. Study flowchart.

TABLE 3. **Demographic and medical characteristics of treatment and placebo groups**

Item	Finding
PME	There are no differences in the degree of premature ejaculation (PME) in either group, p = 1.00.
DM	There are no differences in rates of diabetes mellitus (DM) in the two groups, p = 0.276.
HTN	There is significantly more hypertension (HTN) in the shockwave-treated group (21/95, or 22.11%) than in the placebo-treated group (2/40, or 5%), p = 0.0219.
IHD	There is significantly more ischemic heart disease (IHD) in the placebo-treated group (10/40, or 25%) than in the shockwave-treated group (3/95, or 3.16%), p = 0.0003.
SMOKING	There are no differences in smoking between the groups, p = 0.18.
ALCOHOL	There are more drinkers of alcohol in the placebo-treated group (19/40, or 47.5%) than in the shockwave-treated group (22/95, or 23.16%), p = 0.0074.
LIPIDS	There are more lipid patients in the placebo-treated group (19/40, or 47.5%) than in the shockwave-treated group (19/95, or 20%), p = 0.0017.

TABLE 4. **Summary of changes between baseline, visit 7 and follow up 1**

Item analyzed	Inference
DELTA IIEF-EF DOMAIN Between V7 and V1	Greater changes for shockwave treatment than for placebo treatment at stage1, p < 0.0001. Multiplying the p value by two still yields a highly significant difference, p < 0.0001.
DELTA IIEF-EF domain between FU1 and V1	Greater changes for shockwave treatment than for placebo treatment at stage 1, p < 0.0001. Multiplying the p value by two still yields a highly significant difference, p < 0.0001.

A. Shockwave group

IIEF-EF domain change scores relative to V1 baseline scores (n = 60)

Friedman's test indicated overall differences between change scores, $p < 0.0001$. Protected pairwise comparisons indicate many differences between change scores at different stages. A trend for good significance was evidenced at $p < 0.10$, Figure 2a.

IIEF-EF scores over all seven stages (n = 60)

In order to allow direct comparisons with the baseline (V1) level, raw IIEF-EF domain scores were compared across all seven phases of the study. Friedman's test indicated overall differences between changes scores, $p < 0.0001$. Protected pairwise comparisons indicate many changes were noted at $p < 0.10$, Figure 2b.

EHS score over all seven stages (n = 60)

EHS scores, an ordinal assessment measure, were compared across all seven stages. Friedman's test indicated overall differences between erection hardness scores, $p < 0.0001$. Protected pairwise comparisons indicate many differences between scores at different stages. A trend for significance was evidenced at $p < 0.10$, Figure 3a.

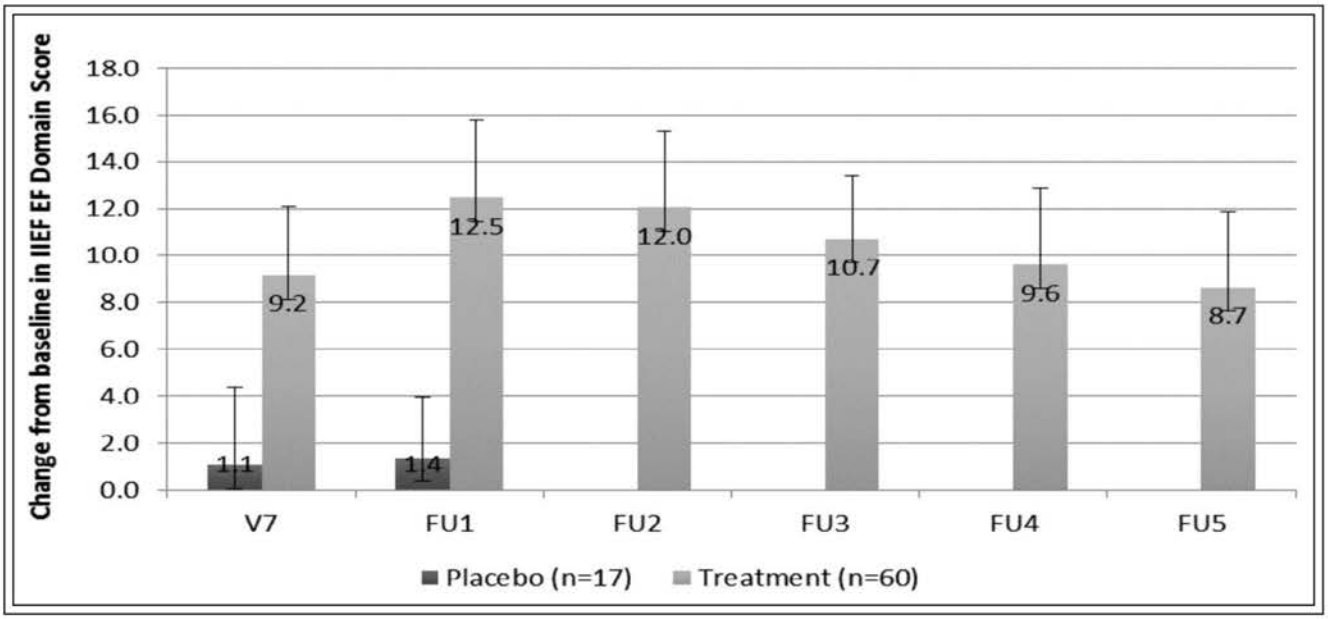

Figure 2a. Improvement of IIEF-EF domain change scores from baseline.

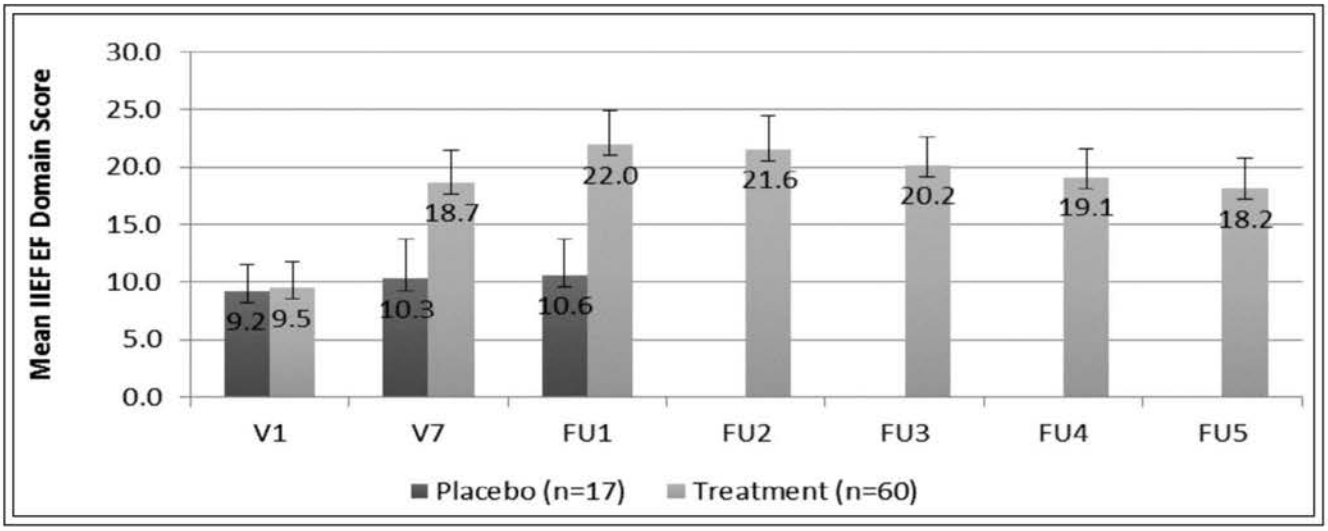

Figure 2b. IIEF-EF domain scores.

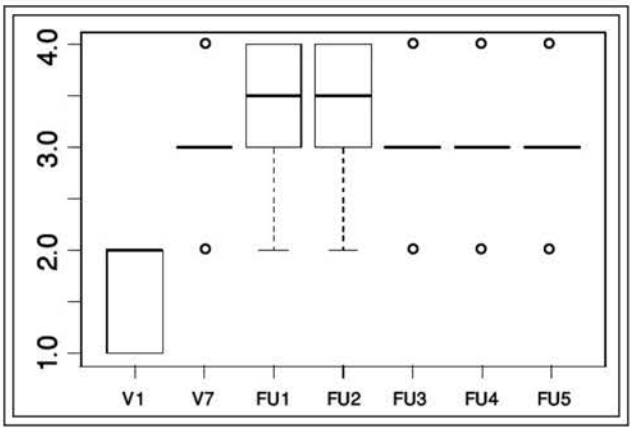

Figure 3a. EHS score over six post-baseline stages.

GCI score over six post-baseline stages

GCI scores, an ordinal assessment measure, were compared across six post baseline phases. Friedman's test indicated overall differences between GCI scores, $p < 0.0001$ (data not shown).

B. Comparisons between shockwave and placebo-treated groups

Contingency table/Fischer's exact probability test was applied between treated group and placebo.

Patient characteristics

Of 135 patients 95 received shockwave treatment and 40 were subjected to sham treatment (placebo group). Their characteristics are shown in Table 3, which shows the age comparison.

Efficacy – IIEF-EF domain change scores

Improvement as measured by IIEF was greater in men with severe ED than in men with moderate ED at all time-points, except at FU3, where there was a numerical trend but did not reach significance. Both the moderate and severe ED groups improved by an average of at least 7 points at 1 year follow up (FU5) compared to baseline values (V1). Improvement at 12 months follow up was smaller than at first month after treatment (FU1) but similar to visit seven – V7 (no statistically significant difference).

In the placebo group there was no statistical improvement – either when comparing the moderate with the severe group, or with the severe group compared to baseline. No placebo effect was observed, which may be a reelection of the strict selection and rigorous screening to exclude men with psychogenic etiology (57% were screened out or dropped-out before visit 1). For screen failure and dropout rate please refer to Figure 1a. The placebo group (n = 17 and n = 14 / 40 followed / recruited) was followed only until FU-1 (6 months post-last treatment).

Efficacy – Erection hardness change score, Figure 3b

All of the patients in the treatment group had EHS ≤ 2 at visit 1. At FU1 (1 month post-final treatment) 90% of the treated patients (54/60) reported functional erections defined as EHS ≥ 3 and were able to achieve vaginal penetration. At FU1, 100% of the patients in the treatment group had an improvement in their EHS by at least one grade. At FU1 all patients reported an EHS ≥ 2. Fifty percent of the patients achieved EHS of 4 (fully rigid), 40% had EHS = 3 (penile rigidity

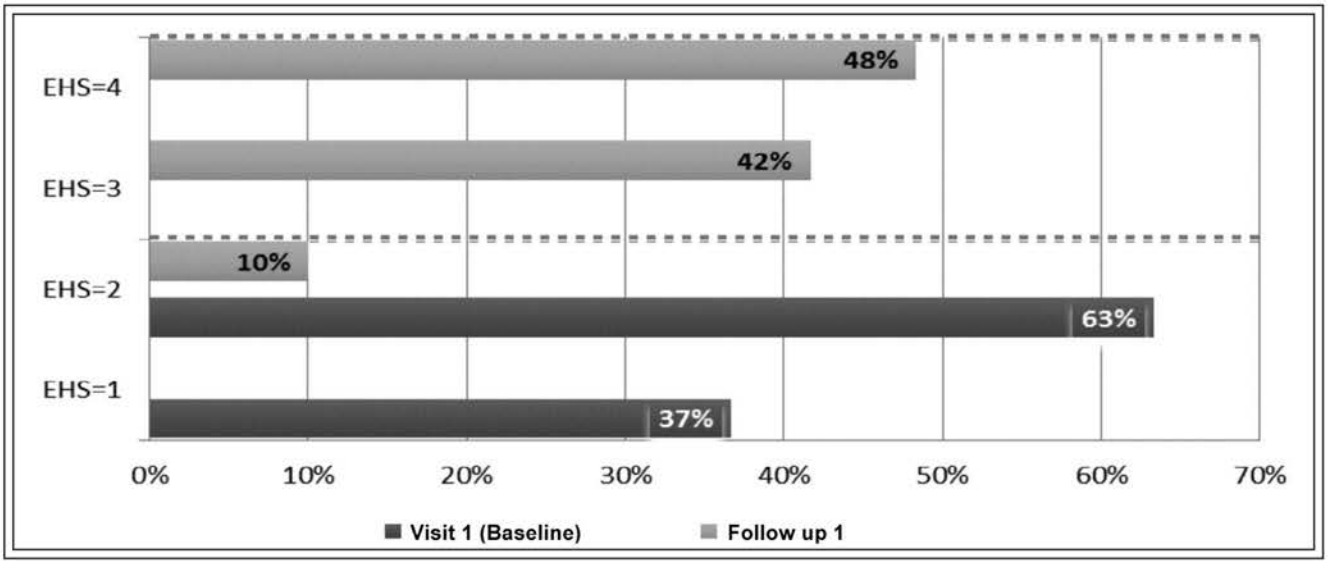

Figure 3b. Erection hardness scores.

that allowed vaginal penetration but not completion of successful intercourse); only 10% improved by only one grade (EHS 1 to EHS 2); 73% (44/60) improved EHS by two grades. In the placebo group there was a slight decrease in EHS at the follow ups. At FU5, four patients from the treatment group regressed to EHS ≤ 2, however, 83% (50/60) reported EHS ≥ 3 erections. This correlated with the regression seen both in IIEF-EF domain and CGIC. This regression or loss of efficacy was minimal and not significant.

Adverse events

The low intensity shockwave energy used in this study (0.09 mJ/mm^2) was not associated with any reported pain or discomfort. There were no reports of ecchymoses or hematuria.

Discussion

Recently, the European Association of Urology issued the updated Male Sexual Dysfunction guidelines 2013, and included LI-ESWT as a possible modality for treating ED. The authors based their recommendation on animal study conducted on diabetic rat model[13] as well as reports of the clinical experience conducted on European males.[11,12] As there is some skepticism surrounding this treatment approach and the supporting scientific data is limited , we felt it was important to assess the efficacy and safety of LI-ESWT by conducting a randomized, double-blind, placebo-controlled study on an Indian population.

We chose to use assessment tools that are validated and widely accepted, including the IIEF and EHS. While validated in men receiving on demand PDE5i, these questionnaires have a high degree of sensitivity and specificity for detecting treatment related changes in the erectile function.[18-22] Since LI-ESWT is a non-pharmacological intervention whose effect is not related to the timing of the sexual encounter, we chose not to use questionnaires such as the sexual encounter profile.

The IIEF-EF domain scores of the treated men showed significant improved as early as FU1. Although significant, the improvement was not as great as the increases reported in the IIEF-EF domain scores that was reported for PDE5i.[23-28] However, these were not head to head studies and were conducted in different populations and this study made a rigorous attempt to exclude men with psychogenic ED. Unlike the initial sildenafil studies, which involved naïve cases, in our study required men to be PDE5i experienced with a positive response. Additionally, many of the original PDE5i studies included a mixed ED population, in contrast to our group of men who were restricted to have vasculogenic risk factors only. Our strict inclusion and exclusion criteria may also account for the lower (14%) placebo effect seen in this study compared to reported placebo effects as high as 45% in the initial PDE5i studies.[26] Later studies that excluded patients with psychogenic ED, and examined the effect of PDE5i on men with organic ED and cardiovascular risk factors, report placebo response rates comparable to what we report here.[26] It is possible that our empirical LI-ESWT protocol may not be ideal, and improved outcomes may be achieved by protocol modifications in the future.

Ease of definition and applicability make the EHS a valuable tool for simple clinical assessment. The EHS were consistent with IIEF scores and confirmed that more men in the treated group than in the placebo group were able to achieve erections sufficiently hard for penetration. However, the EHS is statistically ill suited for pre-post and two-group study designs such as ours. Further supporting our hypothesis that LI-ESWT improves penile hemodynamics is our finding that most of the treated men reported improvement in erectile function between treatment sessions 6 and 8, which should correspond to the time needed for LI-ESWT to induce the physiological changes. While the purpose of this study was to evaluate the early physiological effects of LI-ESWT on erectile function in men with vasculogenic ED our finding that the reported improvements in the IIEF-EF domain were maintained 3 months after the final treatment suggests that the physiological effect is maintained. This study is the first study to report detailed 1 year follow up results for men with vasculogenic ED undergoing LI-ESWT. We believe that future studies should include long term follow up to study and evaluate the durability of the effects of LI-ESWT on erectile function in men with ED.

The treatment protocol that was used in our current study and by others[12,13] to date is based on that described in the cardiology literature.[29,30] This is an empirical treatment protocol that has not been previously tested in pre-clinical animal models or human erectile tissue and, therefore, may eventually be modified as more protocols are studied. Although our final study population included only 60 men, it was sufficient to achieve our main goal of demonstrating the beneficial effect of LI-ESWT on erectile function. The dropout rate was high in the treatment group and not unexpectedly higher in the placebo group. We suspect that the length of the treatment (12 sessions), and the fact that in the treatment group subjects reported sufficient change only at visit 7-8, may have contributed to 37% (35/95) dropout rate. This was even more pronounced in the placebo group with 58% (23/40) dropout rate. This lack of patients' compliance to the protocol underscores the need to evaluate shorter protocols with perhaps fewer treatment sessions.

To date, adverse side effects have not been reported by others in patients undergoing high intensity penile shockwave therapy for the treatment of Peyronie's disease,[31-33] and while our subjects did not report any adverse effects to the treatment, the long term safety of LI-ESWT on penile tissues needs further investigation.

Conclusions

This is the first randomized, double-blind, placebo controlled study of the safety and efficacy of LI-ESWT on erectile function in men with ED in an Asian population. While the precise mechanism of action of LI-ESWT has not been established, our objective measurements suggest that this therapy works by improving penile hemodynamics. We also speculate that this treatment is unique in that it appears to provide long term rehabilitative benefits. Additional studies with long term follow up and modified treatment protocols are now needed to fully evaluate the efficacy of this new therapy and confirm our findings. We also encourage ongoing and additional basic science research to provide an understanding of the underlying mechanism of action. Our hope is that LI-ESWT will be incorporated as an effective and well tolerated non-invasive option into the armamentarium of treatments currently being used in the clinical management of men suffering from ED. □

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Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough?

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Abstract | Erectile dysfunction (ED) affects ~30% of all men above the age of 40 years and its prevalence steadily increases with age. Current nonsurgical treatment options, including phosphodiesterase type 5 inhibitors (PDE5I), provide temporary relief but have failed to provide a permanent improvement of the condition. Low-intensity extracorporeal shockwave therapy (Li-ESWT) is noninvasive and uses acoustic waves, which can pass through tissue and be focussed to target specific areas or organs to induce the desired effects. The use of Li-ESWT has previously been described in other disease contexts, such as ischaemic heart disease, bone fractures, and burns, in which it improves neoangiogenesis; similar principles seem to apply in the erectile tissue. The major potential advantage of the treatment, therefore, is the possibility to restore natural erectile function. Thus, Li-ESWT is the only currently marketed treatment for ED that might offer a cure, which is the most desired outcome for most men with ED. Li-ESWT has also been suggested to improve the effect of PDE5I in nonresponders, reducing the need for more invasive treatments. Several single-arm trials have shown benefit of Li-ESWT on patient-reported erectile function scores, but data from randomized trials are conflicting, and many questions remain to be answered before we can routinely offer this treatment to patients. Thus, the search for the true clinical value of Li-ESWT for ED represents a dynamic and continuing field of enquiry.

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Approximately 30% of all men >40 years experience erectile dysfunction (ED) and the prevalence of ED increases with age[1]. The condition can have considerable negative effects on quality of life for both the men and their partners[2]. Several treatments are available, including oral phosphodiesterase type 5 inhibitors (PDE5I), vacuum pumps, intraurethral medications, penile injection therapy, and — as a last resort — penile implants[1]. However, these treatments do not cure the underlying pathology and the results are not always satisfactory. They also carry risks of adverse effects or complications, and most available treatments take the spontaneity out of sex, as intimacy needs to be planned according to application and onset of the effect. This situation can feel unnatural to some patients and their partners and, therefore, curative treatments are highly desirable[3]. Over the past decade, low-intensity extracorporeal shockwave therapy (Li-ESWT) has emerged as a promising option for the treatment of ED[4].

Li-ESWT is a noninvasive technique that uses the targeted passage of acoustic waves through tissues or organs to induce the desired effects. The technology was originally introduced as a noninvasive treatment for kidney stones[4] and has since been used in the management of many other conditions including bone fractures, musculoskeletal disorders, cardiovascular disease, and wound healing[5]. The exact mechanism of action of Li-ESWT in ED is unknown, but energy from the acoustic waves is hypothesized to activate cellular pathways that increase the expression of local growth factors, improving endothelial function, angiogenesis, and perhaps even regeneration of nerve fibres[6,7].

The major advantage of Li-ESWT treatment is the possibility to restore natural erections; Li-ESWT is the only marketed treatment for ED that has the potential for cure. Li-ESWT has also been suggested to improve the effect of PDE5I in men who have previously not responded to this treatment, negating the need to consider more invasive treatments[8]. Although convincing effects have not been reported in all studies, enthusiasm for using Li-ESWT for ED remains high, and a substantial amount of scientific research on its use has

Key points

- Low-intensity extracorporeal shockwave therapy (Li-ESWT) has emerged and rapidly gained popularity as a treatment option for men with erectile dysfunction (ED)
- The mechanisms by which this therapy enhances erectile function are unclear, but hypotheses include stimulation of neoangiogenesis, recruitment of stem cells and Schwann cell activation leading to nerve regeneration
- Single-arm trials almost unanimously show beneficial effects in patients with vasculogenic ED, even in those who do not respond to phosphodiesterase-5 inhibitors
- Randomized controlled trials (RCTs) have produced conflicting results, and have evaluated erectile function only a short time after treatment; several RCTs are highly biased
- Meta-analyses and systematic reviews conclude that shockwave therapy has an effect, but these analyses are limited by the fact that biased RCTs have been included in these analyses, and some fail to recognize this limitation
- Thus, no high-quality level 1a evidence is available and level 1b evidence is conflicting regarding the use of Li-ESWT for ED treatment

emerged. This Review explores the rationale and mechanisms behind Li-ESWT and considers the data regarding its use in patients with ED in order to provide clinical recommendations and identify future research goals.

Mechanism of action

Shockwaves and their effects on tissues

A shockwave is a longitudinal acoustic wave consisting of a short pulse of about 5 μs duration that is characterized by a near instantaneous jump to a peak positive acoustic pressure, which is referred to as a 'shock', followed by a longer-lasting period of negative pressure[9]. The amplitude of the negative pressure is always much less than that of the peak positive pressure, and no abrupt pressure transition is observed in the negative phase of the waveform[9] (FIG. 1). The shape and amplitude of the waves and their effects on tissues to which they are applied can differ depending on the machine used to generate the waves (electrohydraulic, electromagnetic, piezoelectric or piezomagnetic). Shockwaves exert stress in tissues via two main mechanisms: the first is direct mechanical stress associated with the high-amplitude shockwave itself, and the second is associated with the growth and violent collapse of so-called cavitation bubbles in fluid. Interestingly, cavitation is more likely to result in injury within blood vessels than within the surrounding tissue, as a bubble surrounded by tissue will be constrained and will not be able to go through a violent growth-and-collapse cycle. In a blood vessel, the fluid environment enables the bubbles to grow and collapse. This phenomenon is consistent with the observation that damage occurs first in the capillaries, which, owing to their small size, will be subject to greater stresses than larger vessels during the most explosive part of the growth cycle (FIG. 2), causing shear stress and damage to the endothelium. Shear stress and endothelial damage are well described factors resulting in neovascularization and, indeed, shockwave therapy has been shown to induce the formation of new blood vessels[10,11].

Neoangiogenesis. In 1990, Young and Dyson[12] discovered that therapeutic ultrasonography encourages angiogenesis in superficial wounds in Wistar rats. Using microfocal X-ray techniques, they reported an increase in the number of vessels detected in the wound area after five daily sessions of low-intensity ultrasonography. A 2012 study used intravital fluorescent microscopy to show that the application of shockwaves to full-thickness burns in mice ears reduced the nonperfused area, indicating neoangiogenesis[13]. Similar indications of neovascularization were shown in pigs with chronic myocardial ischaemia and in a rat model of hindlimb ischaemia, both of which were treated with extracorporeal shockwave therapy[14,15]. In healthy rabbits, application of shockwave therapy induced neoangiogenesis at the tendon–bone junction[16,17].

The mechanisms of this observed neoangiogenesis are thought to include upregulation of growth factors, such as vascular endothelial growth factor (VEGF); VEGF protein and mRNA expression were upregulated in shockwave-treated ischaemic pig heart, rat hindlimb, and in a rat osteotomy model[14,15,17]. Supportive of these data, *in vitro* treatment of human umbilical vein endothelial cells (HUVECs) was also shown to upregulate mRNA expression of VEGF and its receptor FLT1 (REF. 14).

Recruitment of progenitor cells. Another putative mechanism by which shockwaves might induce neoangiogenesis is by recruitment of stem cells and progenitor cells, which might have a role in new blood vessel formation. In the rat hindlimb, shockwave preconditioning induced an upregulation of stromal cell-derived factor 1 (SDF-1)[15]. SDF-1 is a specific ligand for CXCR-4, which is strongly expressed on endothelial progenitor cells (EPCs) and in haematopoietic stem cells, and has a crucial role in cell homing and function[18]. Outgrowth endothelial cells are an EPC subtype committed to endothelial cell formation and are involved in neovascularization[19]. In the rat ischaemic hindlimb model, combining shockwave therapy with perfusion of exogenous EPCs showed additive effects in increasing perfusion, indicating that shockwaves enhance neovascularization both by upregulation of angiogenetic factors and by attraction of cells important in the formation of new blood vessels[15].

Modulation of vasodilation. Shockwave therapy has been shown to induce immediate vasodilatation[20], which gives rise to the hypothesis that shockwave treatment could modulate the production of NO or other vasodilators. These effects could be enzymatic or nonenzymatic in nature. Evidence of a nonenzymatic pathway of NO production has been shown by application of high-energy shockwaves to an L-arginine and hydrogen peroxide mixture, which resulted in synthesis of NO[21]. Conversely, shockwaves applied at energy densities compatible with clinical use are able to enhance endothelial nitric oxide synthase (eNOS) enzymatic activity via the PI3K–Akt pathway and can, therefore, stimulate NO production in HUVECs[22]. Furthermore, shockwave therapy has also been shown to stimulate neuronal nitric oxide synthase (nNOS) enzymatic activity and NO production in neuronal cells in a dose-dependent fashion[23].

Electrohydraulic
Shockwaves are generated by high voltage discharging to a spark plug in an underwater source.

Electromagnetic
Electromagnetic shockwave generation is based on the physical principle of electromagnetic induction, as used, for example, in loudspeakers.

Piezoelectric
Piezo elements are arranged on a spherical surface and are synchronously excited by an electrical pulse to emit a pressure wave in the direction of the centre of the spherical surface.

Piezomagnetic
Analogous to the piezoelectric shockwave generator, but instead of an electrical pulse, physical deformation of the piezo elements is achieved by applying a magnetic field.

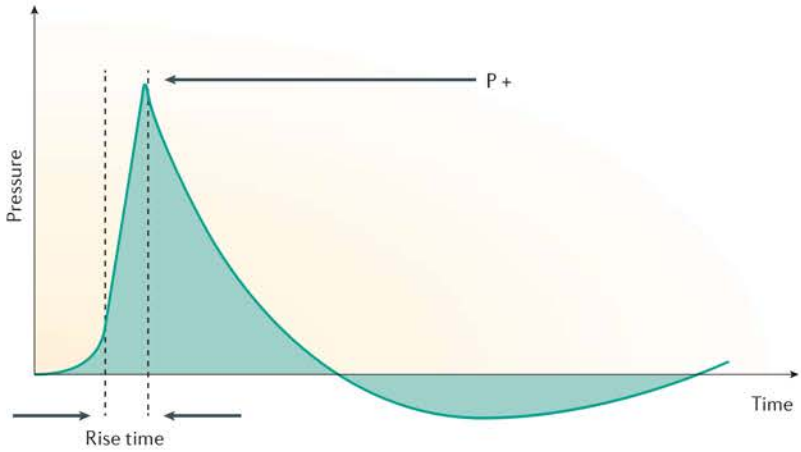

Figure 1 | **Schematic depiction of a shockwave as used in the treatment of erectile dysfunction.** A shockwave is a longitudinal acoustic wave consisting of a short pulse of about 5 µs duration that is characterized by a near instantaneous jump to a peak positive acoustic pressure, which is referred to as a 'shock', followed by a longer-lasting period of negative pressure. The amplitude of the negative pressure is always much less than that of the peak positive pressure, and no abrupt transition is observed in the negative phase of the waveform. Depending on the energy flux density used and the source of the shockwave, variations are seen in the shape and amplitude of the shockwave.

Nerve regeneration. Very few studies have investigated the effects of shockwave therapy on nerve regeneration. Hausner *et al.*[24] showed that shockwave therapy improved functional recovery in Sprague–Dawley rats receiving a homotopic nerve autograft into the right sciatic nerve, compared with controls that received autografts without shockwave therapy. Electron microscopic analysis revealed that debris clearance was faster and scarring reduced in the regenerating nerves of shockwave-treated animals compared with controls, which led the authors to propose that shockwaves ameliorate Wallerian degeneration and improve removal of degenerated axons, increasing the regenerative capacity of the injured axons[24]. Following peripheral nerve injury, Schwann cells alter their phenotype from myelinated to multiplying and activated, and they form the bands of Büngner, which act as a guide for developing axons[25]. Schuh *et al.*[25] investigated the effects of *ex vivo* shockwave treatment of nerves on subsequent Schwann cell cultures from these nerves and found consistently higher purity, proliferation rate, and expression of regenerative phenotype-associated markers (p75 neurotrophic factor receptor, glial fibrillary acidic protein, c-Jun) in pretreated Schwann cell cultures. Hence, these studies suggest an effect of shockwave therapy on nerve regeneration, which could be established by supporting Schwann cell proliferation.

Putative mechanisms in animal models of ED

To date, four studies by three research groups have indicated beneficial effects of shockwave therapy on erectile function in rats with diabetes. The incidence of ED in men with diabetes is threefold that of the general population and erectile difficulties manifest at a younger age. Endothelial dysfunction represents a unifying alteration in the pathogenesis of cardiovascular diseases, diabetes and ED[26], hence, diabetic animal models displaying ED provide a robust means of evaluating novel treatment strategies, particularly those with putative effects on the level of endothelial function and structure[6]. Qiu and co-workers[27] used streptozotocin (STZ) injections to induce type 1 diabetes mellitus in rats and applied 300 shocks to the penis at 0.1 mJ/mm^2 and a frequency of 120 per minute for six sessions, resulting in a partial recovery of the erectile responses of STZ rats to cavernous nerve stimulation. Liu *et al.*[28] used a similar rat model and administered a total of 100, 200, or 300 shocks at 120 per minute for six sessions, with a similar resultant improvement in the highest-dose group and a dose-dependent increase in efficacy of shockwave therapy. Equivalence of low-intensity pulsed ultrasonography (LIPUS) and low-energy shockwave treatment were shown in the same rat model by Lei and co-workers[29]. Using the Goto-Kakizaki (GK) rat, a genetic model for type 2 diabetes, Assaly-Kaddoum[6] and colleagues showed that Li-ESWT significantly improved erectile function to the same extent as sildenafil, and treatment effects were potentiated when combined with sildenafil.

Neoangiogenesis. As in other disease models, the observed functional improvement in ED in the diabetic rat is associated with enhanced expression of endothelial markers, such as eNOS and rat endothelial antigen 1 (RECA-1), as well as elevated VEGF levels[27–29]. These data suggest increased endothelial cell turnover in the corpus cavernosum. As endothelial proliferation is a key event in the formation of new blood vessels, this observation suggests an increase in neoangiogenesis, although quantification of small vessels has not been carried out.

Recruitment of progenitor cells. In a study by Qiu and colleagues[27], newborn pups were injected with the thymidine analogue 5-ethynyl-2′-deoxyuridine (EdU), which is incorporated in the DNA of actively proliferating cells. These label-retaining cells (LRCs) are believed to represent stem cells due to their ability to stay quiescent after a brief period of cellular division, which enables them to retain a higher level of EdU[30]. The concept derives from the observation that stem cells divide only rarely to preserve their proliferative potential and reduce DNA errors that occur during chromosome duplication[31]. Type 1 diabetes was then induced by STZ injection and shockwave therapy was applied to the penis afterwards. The team observed that the number of LRC was about ninefold ($P<0.05$) higher in the shockwave-treated group of rats than in the untreated group, which the authors interpreted as stem cells being recruited to the penis after treatment[27]. This finding was reproduced in a subsequent study by Li *et al.*[32],who also illustrated that shockwave therapy induced the expression of SDF-1 in the corpus cavernosum in a dose-dependent manner, suggesting that SDF-1 might act as a recruitment factor for these EDU$^+$ cells. The authors interpreted the higher number of LRCs observed in the corpus cavernosum as an indication of mesenchymal stem cell recruitment.

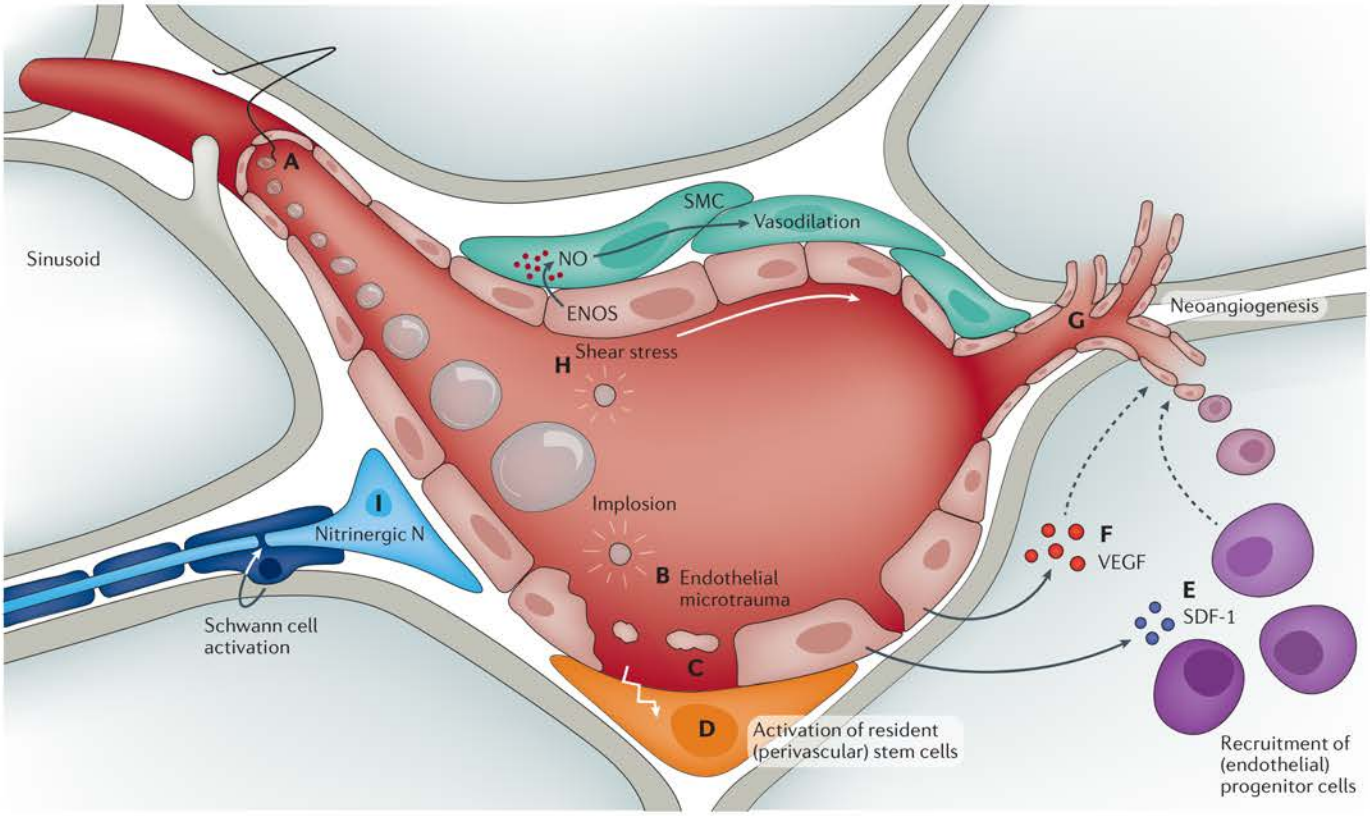

Figure 2 | **Putative mechanisms of action of shockwave therapy for ED.** Shockwaves form microbubbles (A) in the vasculature and tissue that collapse (B) and cause disruption of the endothelium (C). Endothelial disruption might activate resident stem cells (D) and result in chemokine production with attraction of (endothelial) progenitor cells (E) and release of VEGF (F); these factors combine to initiate neoangiogenesis (G). In addition, microbubble collapse induces shear stress and might simulate endothelial NO production (H). Furthermore, shockwave therapy might also enhance Schwann-cell-mediated nitrergic-nerve repair after injury (I).

However, the relevance of this observation has been debated, as in newborn pups, EdU is not only incorporated in stem cells but might also be retained in other cell types with a slow rate of proliferation throughout their lifespan. Furthermore, the ideal time for stem cell labelling with nucleotide analogues — early neonatal, late neonatal, and adult — has never been determined in this context[33]. Thus, the influx of LRCs might indicate influx of other cells types as well as stem cells and, in the context of ED, specific recruitment of stem cells needs to be confirmed, for example by co-staining of the EdU-stained cells with antibodies against stem cell markers such as CD105, CD73 and CD90, and possibly Stro-1 in the corpus cavernosum[34,35].

Modulation of vasodilation. An *ex vivo* study, in which endothelium-dependent and endothelium-independent relaxation of cavernous tissues of shockwave-treated GK rats was tested in an organ bath setting, concluded that shockwave treatment did not improve altered nitrergic relaxations in GK rats versus Wistar rats serving as their healthy controls[6]. The absence of an effect of shockwave therapy on *in vitro* nitrinergic relaxation results suggests that the pro-erectile effect of Li-ESWT might be mediated by a mechanism independent of NO and/or its downstream second messenger cGMP. This conclusion was further supported by treating the tissues with sildenafil, which recruits the NO and/or cGMP pathway, as an additive effect was observed when combined with Li-ESWT[6]. Hence, direct vasodilatatory effects of shockwave therapy have not yet been confirmed in animal models of ED.

Nerve regeneration. Shockwave treatment of the penis in an unvalidated rat model of pelvic neurovascular injury (combined cavernous nerve crush and internal pudendal neurovascular bundle ligation) induced a dose-dependent increase in intracorporeal nNOS levels and p75 neurotrophin receptor, as well as increased levels of S100, a marker for mature Schwann cells in the dorsal penile nerve[32]. According to the study authors, the findings suggested increased nerve regeneration as a result of shockwave application, as Schwann cells are key players in this process. Corresponding *in vitro* studies showed that Li-ESWT treatment of Schwann cells induced Schwann cell proliferation[32]. Thus, Li-ESWT might stimulate neuroregeneration by creating and maintaining an environment amenable to nerve regrowth.

Animal models in summary. Studies in animal and disease models suggest that shockwave therapy is able to stimulate neoangiogenesis, recruit regenerative cells, enhance nerve regeneration via stimulation of Schwann cell proliferation, and might exert direct vasodilatatory effects, potentially as a result of enhanced shear stress caused by shockwave application[20]. Only a very limited number of studies have investigated these effects in rodent models of diabetic and nerve-injury-induced ED, and suggest altered expression of endothelial markers and potential influx of regenerative cells, whereas direct modulation of vasodilatation has not been confirmed. In nerve injury models, effects on neuroregeneration might be achieved via Schwann cell activation, although this effect has only been observed *in vitro*. These studies provide preliminary insights, but no definitive answers, and many questions remain regarding the effects of shockwave therapy outside of the diabetic and neurogenic ED setting.

Clinical data in vascular ED

Focussed Li-ESWT

Based on the fact that a reduction in cavernosal arterial blood flow is one of the hallmarks of ED, Vardi and colleagues[4] hypothesized that effects on neovascularization induced by low-intensity shockwaves in other organ systems might also hold potential for the treatment of ED, by improving arterial blood supply to the erectile tissue in the corpora cavernosa. In 2010, they initiated the first single-arm trial to provide a proof of principle and designed a treatment protocol based on the methodology used in cardiac Li-ESWT and adapted the depth of penetration to fit the cavernosal target tissue[4,5]. As the study used a focussed Li-ESWT device (Omnispec 1000, Medispec), the study protocol included five different target sites in the penis in order to cover the whole corpora cavernosa: three along the penile shaft and two at the crural level. Using the protocol suggested by Vardi and co-workers, four single-arm trials and five randomized controlled trials (RCTs) have since been conducted, using focussed-shockwave machines with electromagnetic or electrohydraulic generated shockwaves (TABLE 1). The treatment protocol for studies using the Omnispec 1000 has been consistent, based on 2 sessions per week consisting of 1,500 shocks with an energy flux density (EFD) of 0.09 mJ/mm^2 for two periods of 3 weeks, intercalated with a 3 week treatment pause. Conversely, studies using the Duolith device (Storz Medical AG) have involved 5–12 weekly sessions of 3,000 shocks each at an EFD of 0.15–0.25 mJ/mm^2 (REF. 4).

Outcomes of shockwave therapy for ED have been measured using the validated erectile hardness score (EHS; a score of 3–4 indicates that penetration is possible)[36], and the validated International Index of Erectile Function (IIEF)-5[37] questionnaire and the IIEF erectile function (IIEF-EF)[38] domain score. After shockwave treatment, the percentage of patients achieving an EHS >3 ranged from 54% in patients who did not respond to treatment with PDE5I to almost 78% in patients with mild-to-moderate vascular ED, whereas IIEF improvements were in the range of +1.5 (IIEF-5) in PDE5I-nonresponders to +10 (IIEF-EF) in patients with vascular ED who also used PDE5I[4,7,8,39–51] (TABLE 1). Notably, three of the five RCTs of focussed-shockwave devices that used these questionnaires met their primary outcome measure[8,39,45], although one had a high risk of bias[45], and the results of two other RCTs were negative for the primary outcome[40,50]. It should be noted however, that in one of these two trials, the depth of penetration was set at skin level according to the manufacturer's instructions[50]. In one of the negative studies, the treatment protocol was identical to the one originally described by Vardi and colleagues[4], indicating that the results of the latter group might not be reproducible[40,41]. A limitation of all these trials is that the follow-up period was short — a maximum of 6 months, with the exception of the one RCT with a high risk of bias, which followed up patients for 12 months[45]. Differences in patient selection and allowance of concomitant PDE5I use might explain these differences, although user-dependency (the shockwave device is hand-held enabling interuser variability in application) and differences in trial design and execution cannot be ruled out. To illustrate the latter, some trials used a cap on the probe to prevent shockwaves from reaching the tissue as the sham treatment, whereas others switched off the device and provided a ticking sound via loudspeakers.

Linear Li-ESWT

Focussed shockwaves provide energy to a very small area at which the probe is aimed. The need to treat different areas of the corpus cavernosum separately might, therefore, limit the treatment effect. Linear distribution of shockwaves might be able to overcome this limitation by providing superior organ coverage of the corpora cavernosa (FIG. 3)[42]. Based on this assumption, treatment protocols using linear shockwaves have reduced the number of sessions to, typically, four once-weekly sessions of 3,600–5,000 shocks (generated by a piezomagnetic or piezoelectric source), although one study mentions ten weekly sessions with only 600 shocks given per session[50]. Results of four single-arm trials show improvements in IIEF-EF scores reaching +7.5 in patients with vasculogenic ED and a somewhat surprising improvement of +9 points in PDE5I nonresponders. Two RCTs have been performed, of which one carried a low risk of bias as it was well designed and executed and adequately powered, which did not show improvement in either IIEF-5 score or in EHS 3–4 rate[50]. Of note, this study was the one trial that used a 10 × 600 shocks schedule. Furthermore, one potential criticism is that a gel pad was used that delivers shockwaves at the skin level. According to the authors, these have a penetration depth of at least 0.5–1 cm, so the use of this pad might or might not be sufficient for the shockwaves to reach the centre of the corpora and crura[50]. The other trial was a multicentre RCT, but this study was poorly conducted, with severe limitations in methodology: the placebo treatment was performed with the device off and a shockwave sound through speakers, and minimal clinical important differences (MCID) that were developed for the six-item IIEF-EF were applied to the five-item IIEF-5 score for which MCIDs have never been validated, potentially

Energy flux density
(EFD). The energy delivered by the shockwave-generating source at the focussed point is called *energy flux density* and is normally recorded in energy per surface area units (mJ/mm^2).

Table 1 | **Original studies of Li-ESWT for erectile function**

Study	Design	Rate EHS 3–4 (%)	IIEF-EF change	IIEF-5 change	Sessions × shocks	EFD (mJ/mm^2)	Risk of bias (RCT only)
Vardi *et al.*[4] (2010)	• Single-arm study • *n* = 20 • Vasculogenic ED • 1–6 months follow-up period • Omnispec ED1000 (focussed)	NA	+7.4 (55%)	NA	12 × 1,500	0.09	NA
Vardi *et al.*[39] (2012)	• Monocentric RCT • *n* = 40 • Vasculogenic ED • 1-month follow-up period • Omnispec ED1000 (focussed)	77.5	+6–7 (56%)	NA	6 × 1,500	0.09	Low risk of bias
Gruenwald *et al.*[7] (2012)	• Single-arm study • *n* = 29 • PDE5I nonresponders • 1-month or 2-month follow-up period • (without and with PDE5I, respectively) • Omnispec ED1000 (focussed)	72.4	• +3.5 (without PDE5i) • +10 (with PDE5i)	NA	12 × 1,500	0.09	NA
Olsen *et al.*[40] (2014)	• Monocentric RCT • *n* = 112 • Vasculogenic ED • 5-week, 3-month, or 6-month follow-up period • Duolith SD1 (focussed)	• 57 (5-weeks) • 28 (3 months) • 19 (6 months)	NA	• (≥5 points change 43%, NS) • (≥5 points change 50%, NS) • (≥5 points change 47%, NS)	5 × 3,000	0.15	Low risk of bias; EHS not validated in Danish
Yee *et al.*[41] (2014)	• Monocentric RCT • *n* = 30 • Vasculogenic ED • 1-month follow-up period • Omnispec ED1000 (focussed)	NA	+2 (NS)	NA	12 × 1,500	0.09	Low risk of bias
Reisman *et al.*[42] (2015)	• Single-arm study • *n* = 58 • Vasculogenic ED • 6-month follow-up period • Renova (linear)	NA	+7.5	NA	4 × 3,600	0.09	NA
Srini *et al.*[45] (2015)	• Monocentric RCT • *n* = 60 • Vasculogenic ED • 12-month follow-up period • Omnispec ED1000 (focussed)	71	+8.7	NA	12 × 1,500	0.09	High risk of bias[‡]; very high drop-out rate, statistically different groups at baseline in terms of ED and comorbidity
Chung *et al.*[43] (2015)	• Single-arm study • *n* = 30 • PDE5I nonresponders • 1.5-month or 4-month follow-up period • Duolith SD1 (focussed)	60	NA	• ±2.5 (≥5 points change (60%)	12 × 3,000	0.25	NA

Table 1 (cont.) | **Original studies of Li-ESWT for erectile function**

Study	Design	Rate EHS 3–4 (%)	IIEF-EF change	IIEF-5 change	Sessions × shocks	EFD (mJ/mm²)	Risk of bias (RCT only)
Pelayo-Nieto *et al.*[44] (2015)	• Single-arm study • *n* = 15 • Vasculogenic ED • 6-month follow-up period • Renova (linear)	NA	+5.46	NA	4 × 5,000	0.09	NA
Ruffo *et al.*[46] (2015)	• Single-arm study • *n* = 31 • Vasculogenic ED and PDE5I nonresponders • 3-month follow-up period • Renova (linear)	NA	+4.49	NA	4 × 3,600	0.09	NA
Frey *et al.*[47] (2016)	• Single-arm study • *n* = 18 • Postprostatectomy ED • 1-month and 12-month follow-up periods • Duolith SD1 (focussed)	NA	NA	• +3.5 (1 month) • +1 (12 months)	6 × 3,000	0.15	NA
Kitrey *et al.*[8] (2016)	• Monocentric RCT • *n* = 37 • PDE5I nonresponders • 1-month follow-up period • Omnispec ED1000 (focussed)	54.1	+5 (MCID 40.5%)	NA	12 × 1,500	0.09	Low risk of bias
Bechara *et al.*[48] (2016)	• Single-arm study • *n* = 40 • PDE5i-nonresponders • 12-month follow-up period • Renova (linear)	60	+9	NA	4 × 5,000	0.09	NA
Hisasue *et al.*[49] (2016)	• Single-arm study • *n* = 57 • Vasculogenic ED • 6-month follow-up period • Omnispec ED1000 (focussed)	57.1	NA	• +5 (with PDE5i, 64.2%) • +4 (without PDE5i)	12 × 1,500	0.09	NA
Fojecki *et al.*[50] (2016)	• Monocentric RCT • *n* = 126 • Vasculogenic ED • 1.75-month and 4.5-month follow-up period • FBL10 (linear)	3.5	• +2.2 (NS) • +0.9 (NS)	NA	10 × 600	0.09	Low risk of bias
Motil *et al.*[51] (2016)	• Multicentric RCT • *n* = 125 • Vasculogenic ED • 1-month follow-up period • Piezowave2 (linear)	NA	NA	+4.2 (81.33%)	4 × 4,000	0.16	High risk of bias[‡]; no statistics applied, used MCID for IIEF-EF applied on IIEF-5, poor description of methodology, placebo group used device off and artificial sound through speakers

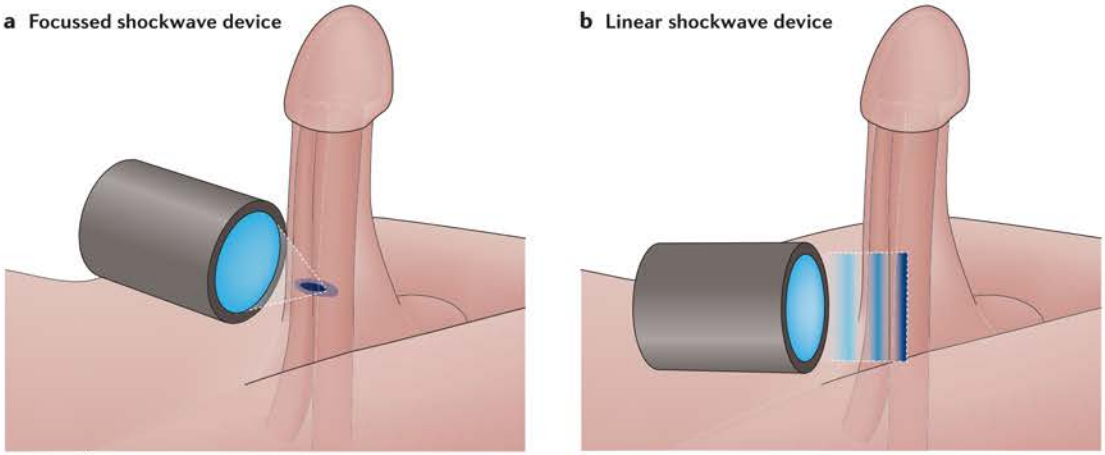

Figure 3 | **Focussed and linear shockwave therapy.** Focussed devices deliver the generated shockwaves to a focussed area at a predetermined tissue depth. Thus, the probe must be moved during the course of a treatment session in order to cover the complete corpora cavernosa including the crura. Linear shockwave devices deliver the generated shockwaves over a larger, linear shaped area at a predefined depth of penetration. Thus, a larger area of corporal tissue is treated simultaneously, limiting the need to move the probe over the penis and crura.

influencing the number of responders to see an improvement. In addition, no statistical analysis was performed, but the study did show an unparalleled response rate of 81.3%[51]. These limitations undoubtedly severely affect the clinical validity of this RCT, nonetheless it has been included in meta-analyses, *vide infra*.

Factors affecting the success of Li-ESWT

Several factors have been hypothesized to influence the final treatment outcome after shockwave therapy for ED. In a meta-analysis[52], patients with mild ED at baseline were shown to benefit most from Li-ESWT, whereas in an RCT performed by Yee and colleagues[41], the only patients to benefit were those with severe ED at baseline. Overall review of the available data suggests that PDE5I nonresponders have lower response rates than those observed in the treatment-naive or PDE5I responders, which might be associated with the fact that they more often have moderate or severe ED (TABLE 1). Reisman and co-workers' multicentre single-arm trial additionally studied the duration of ED and showed that men who had experienced ED for 10–13 years had lower quantitative responses (IIEF-EF) than those with shorter disease duration, and that duration of ED overall was negatively correlated with treatment success[42]. A study of 56 men treated with Li-ESWT showed that age (OR 0.85, 95% CI 0.76–0.95), and the presence of ≥3 comorbidities (OR 0.02, 95% CI 0.00– 0.98) were predictive factors for achieving an EHS of 3–4 at 1 month after completion of the treatment[49]. Whether any differences exist in treatment outcomes between various devices and treatment protocols is unknown, owing to a lack of direct comparison studies. Dose-finding studies — in terms of number of shocks, EFD, or number of sessions — have, surprisingly, never been conducted for any device, so the optimal protocols and dosages for shockwave therapy are currently unknown. Meta-analyses have attempted to address this issue and found that lower EFD, increased number of pulses and shorter treatment courses (<6 weeks) are associated with improved treatment outcomes[52–55]. However, the use of different devices with distinct mechanisms of shockwave generation precludes direct comparison of the outcomes of various energy settings or protocols. Hence, well-designed RCTs with standard treatment protocols and long-term follow-up periods are required in order to demonstrate the actual efficacy of Li-ESWT for the treatment of ED[56].

Postprostatectomy ED

As the cavernous nerves run in close proximity to the prostate gland, radical prostatectomy can be associated with nerve damage and permanent ED. Even if the surgery results in minimal direct nerve damage, heating, stretching, and local inflammation can cause a temporary loss of neural function, resulting in a reduction in erogenic, spontaneous, and nightly erections[57,58]. As erection itself is a prerequisite for sufficient penile blood supply and oxygenation, the resulting reduction in regular penile oxygen supply is thought to lead to smooth muscle apoptosis and, finally, fibrosis in the erectile tissue within the corpora cavernosa[58,59]. This process adds a venogenic component to the mechanism of postprostatectomy ED, making it especially difficult to treat using noninvasive methods[60,61].

Despite this unmet need, only two open-label, single-arm studies have explored Li-ESWT as a treatment option for postprostatectomy ED. Both used the electromagnetic Duolith SD1 for 6 weeks. The first included 30 men with mild-to-moderate or mild ED of mixed aetiologies[43]. Three of these men had undergone radical prostatectomy, but no further details were provided. Overall, the authors reported positive effects, but the specific results from the postprostatectomy group were not clear. The only detail mentioned was a greater improvement in erectile function in men with vasculogenic ED compared with those who had undergone radical prostatectomy. Thus, the study provides insufficient data to

support the use of Li-ESWT in the postprostatectomy setting. The second study included 16 men who had undergone bilateral nerve-sparing robot-assisted radical prostatectomy a minimum of 12 months earlier[47]. The median preoperative IIEF-5 score was 25 (22–25), but at the time of the study (that is, after their surgery), the patients' median IIEF-5 score was reduced to 9.5 (range 5–20). IIEF scores taken 1 month after the last Li-ESWT session showed that 7 of 16 patients (43.8%) had a clinically meaningful improvement in erectile function, defined as an improvement of ≥1 ED category (BOX 1); this improvement was maintained in four of these patients after 1 year. However, the median improvement in IIEF-5 scores was just +3.5 (-1–8) at 1 month and dropped to +1 (-3–14) at 1 year. In addition, the study was confounded by the fact that 12 of 16 participants (75%) used other erectogenic aids during the study, and by the fact that spontaneous improvements in erectile function have been reported up to 36 months after surgery in men who originally reported postprostatectomy ED[62]. Thus, discerning which of these effects represented an endogenous improvement and which is a potential Li-ESWT treatment effect is nearly impossible and, indeed, the study authors commented that high-quality studies, in particular RCTs, are needed. At the time of writing, no such studies have been conducted and none are ongoing, so conclusions regarding the effect of Li-ESWT on erectile function following radical prostatectomy cannot be drawn.

Box 1 | **Patient-reported outcomes in erectile dysfunction studies**

The international index of erectile function (IIEF), developed by Rosen *et al.*[38] in 1997, is often used in two abridged forms for evaluating outcomes in studies investigating treatment for ED.

IIEF-5

- An abridged version of the IIEF consisting of five questions[37]
- The possible scores for the IIEF-5 range from 5 to 25, and ED is classified into five categories based on the scores
- Severe ED (5–7), moderate ED (8–11), mild-to-moderate ED (12–16), mild ED (17–21), and no ED (22–25)

Erectile function domain score of the IIEF (IIEF-EF)

- Consists of six questions
- Possible scores range from 6 to 30
- Classified as severe ED (EF scores 6–10), moderate ED (11–16), mild-to-moderate ED (17–21), mild ED (22–25) and no ED (26–30)[85]
- Minimal clinically important differences (MCID) have been defined as the minimal amount of change needed in the EF domain to be clinically meaningful to patients
- MCID were defined according to baseline ED severity — mild: 2; moderate: 5; severe: 7 — by Rosen *et al.*[77]
- If no specific severity category is considered, the MCID for the IIEF-EF is 4 (REFS 78,79)

Erection hardness score (EHS)

- A single-item assessment of rigidity developed in the clinical trials programme for the marketing of sildenafil, which was validated by Mulhall and colleagues[36] in 2007
- Classified in five categories: penis does not enlarge (0); penis is larger, but not hard (1); penis is hard, but not hard enough for penetration (2); penis is hard enough for penetration, but not completely hard (3); penis is completely hard and fully rigid (4)
- In most studies investigating the effects of shockwave therapy on ED, achieving an EHS of 3–4 is defined as successful treatment

Peyronie's-related ED

Since Bellorofonte *et al.*[63] first described ESWT as a potential treatment for Peyronie's disease in 1989, it has been widely used for this indication. Many early studies reported positive results on pain reduction, but reductions in penile deviation or improvements in erectile function have been infrequently observed[64–68]. Importantly, most studies were not randomized and the protocols were not standardized, making interpretation and recommendations difficult. To date, only three sham-controlled trials have been published and these show minimal, if any, benefit of ESWT on ED associated with Peyronie's disease[69–71], and no effect on penile curvature, although pain seemed to resolve faster in patients treated with ESWT than during the natural disease course of Peyronie's disease. Visual Analogue Scale (VAS, on a 10-point scale) scores dropped by 1.05–4.73 in patients treated with ESWT versus 0.8–2.89 in sham-treated patients. In two of the three studies, this drop in pain reporting was statistically significant[69,70], whereas it did not reach significance in the other[71]. However, whether pain should be treated with ESWT is questionable, because 89% of patients with Peyronie's disease will be pain-free after a mean of 18 months, even without any treatment[72]. In addition, ESWT requires multiple visits to treatment facilities, which are associated with costs to the patient and the health-care system. In this context, treating pain with on-demand oral pain medications is probably more reasonable[73,74].

Early studies of ESWT in patients with Peyronie's disease focussed mainly on reduction of penile deviation and improvement of penile pain, with little emphasis on ED[64,70,75]. Thus, these studies cannot be compared with subsequent trials, which have only investigated the effect of Li-ESWT in patients with ED, and not those who also had Peyronie's disease. Even if the use of ESWT to treat Peyronie's disease seems similar to the use of Li-ESWT for the treatment of ED, some fundamental differences must be considered. One important aspect is the EFD, which is set at 0.09 mJ/mm^2 in the majority of studies of Li-ESWT for the treatment of ED (TABLE 1). This dose is much lower than the usual EFD implemented the trials focusing on Peyronie's disease, as these mostly use doses >0.15 mJ/mm^2 (REFS 64,70). Thus, many studies investigating the effects of shockwaves in Peyronie's disease have not strictly applied Li-ESWT, but have actually used medium-intensity or high-intensity shockwaves. Another consideration is that trials of ESWT for Peyronie's disease applied the shockwaves on the Peyronie's plaques of the tunica albuginea, without involving the underlying erectile tissue within the cavernous bodies[64,70,75]. This protocol is in contrast to Li-ESWT for ED treatment, in which the shockwaves are applied at different sites along the penile shaft and the primary target is the erectile tissue, not the tunica albuginea[70,71,75,76]. One nonrandomized study investigating ESWT in patients with Peyronie's disease included patients with Peyronie's disease with or without associated ED[64]. The EFD of 0.07–0.17 mJ/mm^2 is in the mid-range between the doses of ESWT used for Peyronie's disease and the EFD used in Li-ESWT to treat ED. No statistically significant improvement in ED

(assessed by the IIEF-5 score) was observed in this study: the mean IIEF-5 score went from 11 at baseline to 12 at the end of the study in treated patients and from 10 to 12 in untreated patients. Even in the subgroup of patients who had Peyronie's disease and concomitant ED ($n = 18$; 34% of the study cohort), a substantial improvement in erectile function was noted in only five patients (28%). At the end of treatment, 60% of the patients in ESWT group reported that the results were not what they desired and requested another type of treatment. This early study is limited by its retrospective nature and the lack of a real placebo group (the authors used a nontreated cohort of 15 matched patients as controls), but it indicates that ESWT does not improve erectile function in the majority of patients with Peyronie's disease and ED.

Only one randomized study has investigated the use of ESWT in patients with ED and simultaneous Peyronie's disease[75]. In this study, 100 patients with ED and Peyronie's disease were randomized to receive either ESWT alone or in combination with tadalafil 5 mg daily. The authors applied 2,000 shockwaves each session, which was conducted once weekly for 4 consecutive weeks with EFD set at 0.25 mJ/mm^2 to multiple target points on the penis. After a 24-week follow-up period, the IIEF-5 score significantly improved in both groups, with the effect being stronger in the combination group: Li-ESWT: +6.2 points, Li-ESWT combined with tadalafil: 9.92 points ($P > 0.05$). The authors concluded that combining ESWT and tadalafil 5 mg daily might present a valid conservative treatment strategy in patients who suffer from both ED and Peyronie's disease. However, this study was limited by the absence of a placebo group, and the short follow-up duration. Overall, no convincing evidence is available to show that Li-ESWT has a place in the treatment of men with concomitant Peyronie's disease and ED, and trials using energy settings at low intensity are yet to be conducted.

Quality of evidence

The literature uniformly finds that Li-ESWT is safe and single-arm studies investigating the efficacy of Li-ESWT in ED have been encouraging. However, although some studies include objective parameters such as penile duplex ultrasonography or nocturnal penile tumescence measurements[4], the main outcome measure is always a subjective patient-reported outcome expressed through validated questionnaires (BOX 1). The use of patient-reported outcomes means that the potential for placebo responses is high, so randomized trials are needed to truly evaluate the effects of Li-ESWT in ED. Seven such trials have been published to date (TABLE 1). All these trials were conducted in men with vascular pathology as the most likely aetiology of ED. One of the randomized trials, conducted by Srini and colleagues[45], should be interpreted with caution owing to an unusually high drop-out rate of 58% in the placebo group and 42% in the active treatment group[45]. The authors do not provide any reason for this high drop-out rate. A drop-out rate >20% is generally considered to seriously limit study validity[77]. Another trial, by Motil and colleagues[51], is also to be interpreted with caution owing to a lack of statistical analysis and a poor description of methodology, resulting in a high risk of bias. Of the remaining five studies, two, both by the same group, reported that Li-ESWT was efficacious in the treatment of ED[8,39], whereas the other two did not show a benefit over sham treatment[41,50]. The last study, carried out by Olsen and co-workers, showed that Li-ESWT improved the EHS but not the IIEF-5 score[40]. No clear explanation for this inconsistency was offered, but one can speculate that EHS is a more robust tool, whereas the IIEF-5 is able to detect more subtle differences. However, it is important to note that IIEF-5 was stated as the main outcome measure of the study and that the EHS is not validated in the relevant language, which was considered a limitation by the authors, and should indeed be regarded as a possible source of bias.

In 2016–2017, four systematic reviews of Li-ESWT for ED have been published[52–55] (TABLE 2). The first, by Fojecki and colleagues[53] evaluated Li-ESWT in urological disorders including pelvic pain and Peyronie's disease and did not include a meta-analysis. In this study, effects on IIEF scores were inconsistent, whereas EHS data implied that the treatment might be beneficial in PDE5I responders. Again, this outcome might indicate that EHS is a robust tool aimed at the evaluation of penile rigidity only and IIEF might detect more subtle differences, for example, changes in intercourse satisfaction. The authors of this systematic review did not discuss the risk of bias in the individual studies included, and the conclusion failed to take into consideration the limitations of the studies by Srini[33] and Olsen[30], which are the studies to have reported the largest positive effects on the EHS.

The second systematic review, by Lu *et al.*[52] did include a meta-analysis of Li-ESWT in ED, and their main conclusion was that Li-ESWT improved IIEF by an average of 2.00 points compared with sham treatment. Importantly, this improvement is below the minimal clinically important difference, which is accepted as 4 points over all categories of the IIEF-EF[78,79] (BOX 1). Subgroup analyses implied that statistically significant effects were only seen in men with mild ED. Furthermore, several methodological flaws limit the analyses of the Lu *et al.*[52] paper. Firstly, the authors neglected to exclude studies at high risk of bias even though this parameter had been previously noted. Secondly, studies that included ED as a secondary outcome were included on equal terms in the analysis as those that evaluated ED as the primary outcome, and the authors even included a nonrandomized trial that used control data from 15 previous patients[64]. Thirdly, the authors report the meta-analysis results in terms of IIEF score, while the original studies included report on either IIEF-5 or IIEF-EF scores, which cannot be used interchangeably, and they used crude pretreatment and post-treatment scores rather than analysing the change in validated erectile function scores. Finally, the results of some of the cited studies have been erroneously quoted[80].

The third systematic review, by Angulo and colleagues[54] also contained a meta-analysis, but was limited

Table 2 | **Systematic reviews and meta-analyses of Li-ESWT for ED**

Study	Design	IIEF improvement	EHS improvement	Limitations
Fojecki *et al.*[53] (2016)	• Systematic review (PROSPERO: CRD42015015665) • Vardi *et al.*[39] • Olsen *et al.*[40] • Srini *et al.*[45] • Yee *et al.*[41] • *n* = 337 • Vasculogenic ED	"Effects of ESWT on IIEF in ED patients are inconsistent…"	"…data on EHS does imply that the treatment potentially may recover natural erection in PDE5I responders."	• No meta-analysis • No assessment of biases
Lu *et al.*[52] (2016)	• Systematic review and meta-analyses of RCTs only • Vardi *et al.*[39] • Olsen *et al.*[40] • Srini *et al.*[45] • Yee *et al.*[41] • Chitale *et al.*[71] Poulakis *et al.*[64] • Zimmermann *et al.*[87] • *n* = 501 (from meta-analysis only) • All ED aetiologies	2.00 (95% CI 0.99–3.00); *P* <0.0001 compared with placebo	0.16 (95% CI, 0.04–0.29) *P* = 0.01 compared with placebo	• Inclusion of studies at high risk of bias and with ED as a secondary end point (Peyronie's disease, pelvic pain) • Inclusion of nonrandomized trial in meta-analysis (Poulakis *et al.*[64]) • Inclusion of trials on Peyronie's disease with ESWT directed at plaque only, not corpora • Incorrect citation of IIEF data
Angulo *et al.*[54] (2016)	• Systematic review and meta-analyses • Vardi *et al.*[39] • Olsen *et al.*[40] • Srini *et al.*[45] • Yee *et al.*[41] • *n* = 337 • Vasculogenic ED	2.54 (95% CI 2.12–2.95); *P* <0.0001 compared with placebo	NA	No assessment of biases
Clavijo *et al.*[55] (2017)	• Systematic review and meta-analyses • Vardi *et al.*[38] • Srini *et al.*[44] • Yee *et al.*[40] • Hatzichristou & Kalyvianakis (abstract)[80] • Fojecki *et al.* (abstract)[82] • Feldman *et al.* (abstract)[81] • Kitrey *et al.*[8] • *n* = 602 • Vasculogenic ED	4.17 (95% CI -0.5–8.3); *P* <0.0001 compared with placebo	NA	• Inclusion of studies at high risk of bias or with inadequate assessment of bias • Use of unpublished data (quality assessment virtually impossible in abstract versus published full text) and unclear whether overlap exists between the "Israel" groups in Feldman *et al.*[81] and previous trials

to truly randomized trials focussing on ED as the primary end point. In this study, the authors reported that Li-ESWT improved IIEF-EF by an average of 2.54 points compared with sham treatment at 1 month, but that the data were insufficient to evaluate long-term results. As in the meta-analysis conducted by Lu and colleagues[52], this change is below the threshold to be considered a clinically important difference and again, the authors have neglected to account for potential biases within individual studies[52].

The most recent systematic review and meta-analysis was published in 2017 by Clavijo *et al.*[55] In this report, the data are very encouraging, showing an overall improvement of 4.17 points on the IIEF-EF scale compared with placebo. Furthermore, the authors have included an assessment of biases in the supplementary material. However, the study by Srini *et al.*[45] is included even though it is considered to be at high risk of bias owing to the high drop-out rate and unequal groups at baseline. Furthermore, this latest systematic review includes three conference abstracts[81–83] in which the potential risk of bias is unclear, as detailed information is lacking and the data have not been thoroughly peer reviewed[55]. These limitations might be the reason why the outcome is so much higher than in previous meta-analyses. To date, only one of these studies has been published in its entirety[50]. When considering the combined results of the meta-analysis, readers must keep in mind that the Srini study[45] and the two unpublished studies[81,82] all contributed data showing positive effects of Li-ESWT[55]. A further consideration, which applies to all three meta-analyses, is that the study by Olsen and co-workers[40], which failed to show an IIEF-5 improvement compared with placebo, was excluded. This omission is likely due to the fact that Olsen and colleagues did not report raw IIEF data, only the percentage of patients that demonstrated an improvement ≥5 points. Thus, although this study was negative in terms of IIEF data, only the EHS data — which were statistically significant — are included. This discrepancy is a source of potential bias in all three meta-analyses, as positive studies were included but negative studies were excluded, and Olsen and co-workers were not contacted for provision of the raw data.

Overall, these limitations mean that the three currently available meta-analyses cannot be considered to provide level 1 evidence for a clinically meaningful effect of Li-ESWT for ED, and that they should not form the basis of clinical decision-making. Adding to the uncertainty surrounding the use of Li-ESWT is that all the meta-analyses pooled data from studies using different machines, different treatment protocols, and different follow-up durations. To further complicate matters, five different devices are commercially available and these all have differences in both technical specifications and suggested treatment protocols. These inconsistencies mean that data from one device cannot simply be extrapolated to another, and randomized trials have been conducted for only three of these devices, with conflicting results. Moreover, effects of Li-ESWT might differ in different subpopulations and the ideal patient for Li-ESWT still remains to be defined; studies designed to optimize the treatment protocol are lacking.

Future prospects and medical need

To date, all available options for ED treatment act only as symptomatic therapies aimed to relieve the lack of an erection sufficient to complete a satisfactory sexual intercourse. Although PDE5I revolutionized the therapeutic management of men with ED, an unmet medical need remains for cure and restoration of natural erections. In difficult-to-treat populations, in which an underlying condition impairs the erectile response (such as diabetes mellitus, endothelial dysfunction in the context of a metabolic syndrome, or postsurgical erectile impairment), converting PDE5I-nonresponders into responders would be a major advance.

With these goals in mind, as the only available therapeutic option to cure ED and restore natural erectile function, Li-ESWT has rapidly gained popularity, even though the scientific evidence is not robust enough to recommend this approach for routine clinical application. In an editorial, Hatzichristou[84] elegantly raised the point that opportunistic physicians might offer this novel therapy to patients with psychogenic ED or even to men without ED, in a preventive setting. Publicity in the British lay press, regarding a retired England cricketer who claimed that he had Li-ESWT treatment done to prevent future erectile difficulties, is indicative of this concern[85]. Such claims must be strongly condemned by the medical community, rather than being used by doctors to achieve personal gain at the cost of patient care. Although Li-ESWT has been characterized by a low incidence of serious adverse effects, practices like these could be considered no less than quackery. Multiple companies are now promoting their devices based on evidence gained using different machines with different mechanisms of action, and claiming efficacy in the absence of robust RCTs. Both the scientific community and the companies promoting this technology must take responsibility to speed up and improve research in order to produce and publish robust evidence on Li-ESWT for ED.

The available systematic reviews suggest the presence of level 1 evidence; however, the quality of a systematic review is largely dependent on the quality of data acquisition, data uniformity, and the quality of studies included in these reviews. If researchers continue to include positive trials with a drop-out rate of 42–58%, the real efficacy of Li-ESWT for ED will never be revealed. Similarly, these trials include a multitude of studies with large differences in treatment protocols, devices employed, and follow-up durations and methods. The lack of high-quality evidence is perhaps best illustrated by the fact that the FDA has not approved any Li-ESWT device for clinical use in the USA. In light of the above discussion, the fundamental goal in this field should be the careful assessment of the real clinical benefits of Li-ESWT, as the scientific debate thus far has provided more questions than answers. The only way to overcome this limitation will be a large multicentre RCT for each device using a standard protocol, long (>12 months) follow-up period, and including multiple subgroups of ED aetiology enabling preplanned subanalyses of the efficacy in these designated groups[56]. Furthermore, many concerns remain to be addressed regarding the optimal therapeutic protocol, and whether a given protocol is feasible for any Li-ESWT device, or whether protocols should be device-specific. In addition, the long-term effects of Li-ESWT treatment are still not understood — in particular, any harmful effects of Li-ESWT, such as fibrosis, or development of Peyronie's disease due to repeated microtrauma, must be assessed. Finally, we need to better understand the mechanics of the therapy itself, for example, the need for repeated treatment in order to maintain a sustained effect and whether one Li-ESWT device or technology (focussed versus linear, and mechanism of shockwave generation) is superior in terms of both cost and benefit. Additionally, the ideal patient profile for Li-ESWT, in terms of ED severity and aetiology, must also be determined. These questions do not necessarily have to be completely answered before we start routinely applying this treatment, but a minimum level of evidence will be needed to adequately counsel our patients.

Conclusions

Li-ESWT is the first treatment option for ED that has the potential to improve pharmacologically unassisted erectile function. The concept is unprecedented and revolutionary, and the effects at molecular and tissue level are largely unknown, although neoangiogenesis might have a key role. Following a series of single-arm trials, which almost unanimously show a benefit, several monocentric RCTs have now been published with mixed results. The results of these trials are compromized by uncertain or high risks of bias, and systematic reviews and meta-analyses based on these trials carry similar risks. Thus, no level 1 evidence is available to support the use of Li-ESWT in any population of patients with ED, and its use should, therefore, be limited to clinical trials until large multicentric RCTs have provided the necessary data to recommend the routine use of this promising novel technology as a first-line treatment.

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ToC blurb

000 **Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough?**

Mikkel Fode, Georgios Hatzichristodoulou, Ege Can Serefoglu, Paolo Verze and Maarten Albersen on behalf of the Young Academic Urologists Men's Health Group

Low-intensity extracorporeal shockwave therapy (Li-ESWT) has gained popularity as a noninvasive treatment for erectile dysfunction (ED), with the potential to cure, rather than simply provide symptomatic relief. However, the quality of data regarding this treatment option is variable, and drawing conclusions is a challenge. In this Review, a team of expert authors describe the rationale and potential mechanisms of Li-ESWT for ED and discuss the available evidence for its clinical use.

Shockwave treatment of erectile dysfunction

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Abstract: Low-intensity extracorporeal shock wave therapy (LI-ESWT) is a novel modality that has recently been developed for treating erectile dysfunction (ED). Unlike other current treatment options for ED, all of which are palliative in nature, LI-ESWT is unique in that it aims to restore the erectile mechanism in order to enable natural or spontaneous erections. Results from basic science experiments have provided evidence that LI-ESWT induces cellular microtrauma, which in turn stimulates the release of angiogenic factors and the subsequent neovascularization of the treated tissue. Extracorporeal shock wave therapy (ESWT) has been clinically investigated and applied in several medical fields with various degrees of success. High-intensity shock wave therapy is used for lithotripsy because of its focused mechanical destructive nature, and medium-intensity shock waves have been shown to have anti-inflammatory properties and are used for treating a wide array of orthopedic conditions, such as non-union fractures, tendonitis, and bursitis. In contrast, LI-ESWT has angiogenetic properties and is therefore used in the management of chronic wounds, peripheral neuropathy, and in cardiac neovascularization. As a result of these characteristics we initiated a series of experiments evaluating the effect of LI-ESWT on the cavernosal tissue of patients with vasculogenic ED. The results of our studies, which also included a double-blind randomized control trial, confirm that LI-ESWT generates a significant clinical improvement of erectile function and a significant improvement in penile hemodynamics without any adverse effects. Although further extensive research is needed, LI-ESWT may create a new standard of care for men with vasculogenic ED.

Keywords: erectile dysfunction, male impotence, shockwaves, therapy

Introduction

The current nonsurgical treatment modalities in the management of erectile dysfunction (ED) mainly consist of oral phosphodiesterase type 5 inhibitors (PDE5is) and/or intracavernosal injections of vasodilating agents. These treatments are very effective and are reasonably safe with rare unwanted or adverse effects. However, they all share the same major drawback: they do not alter the underlying pathophysiology of the erectile mechanism. These treatments are usually taken on demand, prior to the sexual act, and their effect is essentially time limited. Although daily administration of a PDE5i instead of on-demand treatment does address some of these problems, it still does not modify the pathophysiology of the erectile process. Moreover, the evidence that its effect on the erectile tissue is long-lasting is very limited. Presently, only a small number of men with ED can be offered treatment that would restore their spontaneous erectile function. This group includes those who would benefit from various lifestyle or drug regimen modifications, those who can be treated for relevant endocrine disorders, or those with vasculogenic ED who would benefit from microvascular surgery. Most patients with ED rely on their treatment in order to maintain their sexual function; providing a treatment for men with ED that is rehabilitative or even curative and enables them to regain spontaneous sexual activity with normal intimacy and without adverse effects is an unmet medical goal. Recently, data from several studies have accumulated that this goal could probably be met by low-intensity extracorporeal shockwave therapy (LI-ESWT) of the corpora cavernosa. This review intends to summarize the scientific background underlying the effect of this energy as well as recent clinical evidence of its effect in patients with vasculogenic ED.

Background

Shockwaves (SWs) are acoustic waves that carry energy and when propagating through a medium,

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can be targeted and focused noninvasively to affect a distant selected anatomical region.

When LI-ESWT is applied to an organ, the relatively weak yet focused SWs interact with the targeted deep tissues where they cause mechanical stress and microtrauma. This stress and microtrauma (also known as shear stress) induces a cascade of biological reactions that result in the release of angiogenic factors which in turn triggers neovascularization of the tissue with subsequent improvement of the blood supply.

LI-ESWT in vitro and animal studies

Research on the biological effects of LI-ESWT has mainly been focused on vasculogenesis and local neovascularization. Wang and colleagues [Wang *et al.* 2003] discovered that LI-ESWT stimulates the expression of angiogenesis-related growth factors, such as endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF), and endothelial cell proliferation factors, such as proliferating cell nuclear antigen (PCNA). They also reported that LI-ESWT induces neovascularization, and consequently improves blood supply. Interestingly, they found that 1 week after LI-ESWT, the angiogenic marker levels rose significantly and this effect lasted for approximately 8 weeks. They also showed that neovascularization and cell proliferation were evident 4 weeks after LI-ESWT and persisted for more than 12 weeks. The same group [Wang *et al.* 2003] investigated the effect of LI-ESWT on neovascularization of the tendon-bone junction. For this purpose, LI-ESWT was applied to the Achilles tendon junction of 50 New Zealand rabbits. The extent of neovascularization was determined from the expression of VEGF, eNOS, and PCNA. They found that the number of neovessels and the expressions of the angiogenic markers and PCNA were substantially increased by LI-ESWT. This group previously reported similar findings in a smaller canine study [Wang *et al.* 2002] on the effect of this energy on bone–tendon junction in eight dogs: new capillaries and muscularized vessels were seen in obtained specimens 4 and 8 weeks after local LI-ESWT, with no change in the untreated sites.

The effect of LI-ESWT on intracellular VEGF levels has also been reported by Gutersohn and colleagues [Gutersohn *et al.* 1999] in human umbilical vein endothelial cells (HUVECs). They found that levels of VEGF mRNA in the LI-ESWT-treated cells were significantly greater than those in the untreated controls. The effect of LI-ESWT on intracellular VEGF levels in HUVECs has also been reported by Nishida and colleagues [Nishida *et al.* 2004], who found that LI-ESWT significantly increased the expression of VEGF mRNA and its receptor, Flt-1. Their investigations on the effects of LI-ESWT on a porcine model of chronic myocardial ischemia also showed that VEGF expression was significantly upregulated in the ischemic myocardial cells after treatment [Nishida *et al.* 2004].

Progenitor cell therapy has recently been suggested as a new approach to boost neovascularization of ischemic tissues. During acute ischemia, the release of chemo-attractant factors (i.e. VEGF) act as homing factors for circulating progenitor cells (CPCs). Aicher and colleagues [Aicher *et al.* 2006] investigated the effect of LI-ESWT on homing of infused human CPCs in rats with chronic hind limb ischemia. For this purpose, they applied LI-ESWT (500 hits) to the adductor muscles of the right hind limb of rats (the left hind limbs were used as the controls). Twenty-four hours after LI-ESWT, labeled CPCs were then injected. Forty-eight hours following labeled human CPC injection to the rats. They found a substantially higher number of CPCs in the SW-treated *versus* the untreated adductor muscles. A significant increase in blood flow was also documented following CPC treatment and LI-ESWT. From these results, Aicher and colleagues concluded that LI-ESWT may improve the efficacy of CPC treatment in chronic ischemia.

LI-ESWT for cardiac disease

The effect of LI-ESWT on the myocardium has also been intensively studied in recent years. In a porcine model of ischemia-induced myocardial dysfunction, Nishida and colleagues [Nishida *et al.* 2004] applied LI-ESWT to chronic ischemic hearts of 28 domestic pigs. They found that LI-ESWT improved regional myocardial blood flow and the wall thickening fraction, and even brought about complete recovery of the left ventricular (LV) ejection fraction. In contrast, sustained myocardial dysfunction was found in the pigs which did not receive LI-ESWT. No complications, including arrhythmias, were observed during or after the treatment. In another study in pigs with an acute myocardial infarction, Uwatoku and colleagues [Uwatoku *et al.* 2007] demonstrated that LI-ESWT has a positive effect on LV remodeling. Finally, Ito and colleagues [Ito *et al.* 2010] showed that LI-ESWT also improved LV remodeling after the myocardial ischemia-reperfusion injury.

Clinically, the effect of LI-ESWT on the heart has also been investigated in a double-blind sham-controlled study in eight human patients with severe ischemic heart disease [Kikuchi *et al.* 2010]. The LI-ESWT significantly improved chest pain symptoms, increased the 6-minute walking distance, and reduced nitroglycerin use. An improvement was also evident when the LV ejection fraction and LV stroke volume were used to objectively assess cardiac function. Importantly, they reported that LI-ESWT was safe without any complications or adverse effects.

Yang and colleagues [Yang *et al.* 2012], in a randomized, double-blind, controlled study, also investigated the effects of LI-ESWT in 25 patients with ischemic heart disease in which angina severity scales and questionnaires were used to measure the response. Their results were similar to those that were reported by Kikuchi and colleagues [Kikuchi *et al*, 2010]. None of the patients in the control group reported improvements after treatment. Comparable results have also been reported by Vasyuk and colleagues [Vasyuk *et al.* 2010] and Wang and colleagues [Wang *et al.* 2012] in patients with severe coronary artery disease and refractory angina to whom LI-EWST was applied.

LI-ESWT for ED

Since one of the underlying functional causes of ED is poor cavernosal arterial blood flow, we hypothesized that inducing neovascularization by LI-ESWT could potentially improve cavernosal arterial flow which in turn would improve erectile function. If this hypothesis could be proved, LI-ESWT could then become an effective and noninvasive treatment for ED.

The purpose of our first study was to evaluate the feasibility, efficacy, and safety of LI-ESWT in 20 men, aged 56.1 ± 10.7 years, with mild to moderate ED due to cardiovascular disease and without any neurogenic etiology [Vardi *et al.* 2010]. These patients had ED for almost 3 years (average), and all were able to function sexually with the use of PDE5i (i.e. PDE5i responders). Our treatment protocol was based on the described methodology used in cardiac LI-ESWT [Kikuchi *et al.* 2010], with modifications according to the depth of the target tissue (corpora) and to anatomical differences. We applied 300 SWs (energy intensity of 0.09 mJ/mm^2) to each of five different sites: three along the penile shaft and two at the crural level. The protocol consisted of two treatment sessions per week for 3 weeks, a 3-week no-treatment interval, and a second 3-week treatment period of two treatment sessions per week.

One month after LI-ESWT, the erectile function in 15 men improved. An increase by more than five points in the International Index of Erectile Function - Erectile Function (IIEF-EF) domain score was noted in 14 men, and by more than 10 points in 7 men. Five men did not respond to LI-ESWT. Overall, the average increase in the IIEF-EF domain scores was 7.4 points (13.5–20.9, $p = 0.001$). Furthermore, erectile function and penile blood flow were measured using nocturnal penile tumescence (NPT) and venous occlusion plethysmography of the penis, respectively. LI-ESWT improved all NPT parameters, especially in the 15 men who responded to LI-ESWT, where significant increases in the duration of the erections and penile rigidity were recorded. Penile blood flow also improved significantly and a strong correlation was found between the increase in the IIEF-EF domain scores and the improvement in penile blood flow at the 1-month follow-up examination. At the 6-month follow-up visit, 10 men reported that they still had spontaneous erections that were sufficient for penetration and did not require PDE5i support.

In view of these very successful preliminary results, the effect of LI-ESWT was further investigated in a group of men whose ED was more severe than that of the first group of study patients [Gruenwald *et al.* 2012]. The average initial IIEF-EF domain score of the 29 men who were recruited for this second study was 8.8 ± 1. All 29 men had not responded to oral PDE5i therapy, and had multiple cardiovascular risk factors (23), cardiovascular disease (11), and diabetes mellitus (14). The specific aim of this second study was to investigate the ability of LI-ESWT to convert nonresponders to PDE5i therapy to PDE5i responders, so that they were able to achieve vaginal penetration with oral PDE5i therapy. The results were comparable to the first study. Three months after the completion of the LI-ESWT protocol, the IIEF-EF domain scores improved by at least five points in 22 men (76%) and the mean IIEF-EF domain score increased by 10 points (to 18.8 ± 1, $p < 0.0001$). At the end of the study, eight men (28%) achieved normal erections (IIEF-EF domain score greater than 25) and 21 of the 29 men were able to achieve vaginal penetration with oral PDE5i therapy. Overall, 21 men (72%) were converted to PDE5i responders. Cavernosal blood flow and penile endothelial function, as measured again by venous occlusion

Table 1. The clinical studies included in the paper.

Gruenwald, I., Appel, B. and Vardi, Y. (2012) Low-intensity extracorporeal shock wave therapy - a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. *J Sexual Med* 9: 259-264.
Vardi, Y., Appel, B., Kilchevsky, A. and Gruenwald, I. (2012) Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. *J Urol* 187: 1769-1775.
Vardi, Y., Appel, B., Jacob, G., Massarwi, O. and Gruenwald, I. (2010) Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. *Eur Urol* 58: 243-248.

plethysmography of the penis (flow-mediated dilatation techniques [FMDs]), were both found to be significantly improved ($p = 0.0001$) in the men who responded to LI-ESWT.

In both studies, a strong and significant correlation between the subjective assessment of sexual function using validated sexual function questionnaires and the objective results of penile blood flow and erectile function was found. Moreover, none of the men in both studies reported treatment-associated pain or any adverse events during or after the treatment.

The encouraging results from these two studies led us to conduct a prospective, randomized, double-blind, sham-controlled study on 60 men with ED [Vardi *et al.* 2012]. In this study, we investigated the effects of LI-ESWT on erectile function and penile blood flow using the identical treatment protocol and study parameters that were used in our previous two studies. For the sham-treatment, we used a probe which did not produce any SW energy but looked identical to the treatment probe and produced the same noise and feeling of a 'hit'. The demographic characteristics and the baseline mean IIEF-EF scores of the treated and sham-treated patients of this third study were similar. We found that mean IIEF-EF domain scores of the treated men were significantly higher than those of the sham-treated men. This increase in the IIEF-EF domain scores was also accompanied by improvements in cavernosal blood flows and penile endothelial function, as measured by venous occlusion plethysmography of the penis (FMD). We have been following most of these men for more than 2 years and they all report that the beneficial response that was achieved immediately after therapy has not waned (Table 1).

Discussion

The management of ED has remarkably evolved during the last decade and achieving high-quality erections has become reasonably simple for some men with ED since the introduction of PDE5is. Nevertheless, all current available treatment modalities for ED are basically 'on-demand' therapies and their mechanism of action is to improve a single sexual encounter. One of the main research goals of this coming decade is finding a cure for ED. The current lines of investigation into new ED therapies are based on the Rho-kinase pathway, as well as exploring the feasibility of gene therapy through intracorporeal injections of plasmids and stem cell regenerative therapy. The introduction of a new therapeutic modality for ED whose underlying mechanism of action is unclear or unproven certainly warrants skepticism and criticism. Hence, there are more questions than answers regarding the therapeutic use of LI-ESWT for ED. On the other hand, our consistent and repeatable results withstand these doubts because the results from our three different studies not only confirm each other, but also demonstrate that LI-ESWT has a genuine physiological effect on the erectile mechanism. Although our results are promising, they are still limited. More double-blind, randomized, controlled trials and long-term follow-up studies to confirm our findings are essential. There is also still much to investigate about the effect of LI-ESWT on the various types of ED, and the clinical parameters that could be used to predict who would benefit from LI-ESWT and who would not still require clarification, definition, and validation. There is also a need to determine the treatment protocols of LI-ESWT in order to establish the optimal protocol, in which the number of treatments and the number of penile sites to expose to LI-ESWT are defined. In this regard, we are already investigating different protocols and are offering a second 9-week treatment course for those who responded only partially to the first treatment course. Other studies are crucial for determining the optimal treatment protocol that will provide the best clinical outcome. Basic research is unquestionably required in order to explore and understand the mechanism of action of LI-ESWT on erectile tissue, as well as on other biologic systems.

Conclusions

LI-ESWT is a revolutionary treatment of ED, and probably possesses unprecedented qualities that can rehabilitate erectile tissue. The clinical improvement in subjective erectile function together with the significant improvement in penile hemodynamics following LI-ESWT confirm that LI-ESWT has unique properties that may create a new standard of care for men with ED. LI-ESWT is both feasible and tolerable and without any adverse or unwanted effects. Its main advantage is its ability to improve and potentially restore erectile function in men with ED without additional pharmacotherapy. Hence, LI-ESWT is an appealing addition to the armamentarium of existing treatment options for ED. In the near future we hope that LI-ESWT will be used for the long-term clinical management of ED either as an alternative or as an enhancer to the current treatments of ED.

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Conflict of interest statement

Professor Y. Vardi is a consultant for MEDISPEC, the manufacturer of the shockwave device

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