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ORIGINAL ARTICLE

Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study

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Abstract

Objective. The aim of this study was to investigate whether low-intensity extracorporeal shockwave therapy (LI-ESWT) can be used as a treatment for men with erectile dysfunction of organic origin. **Materials and methods.** This prospective, randomized, blinded, placebo-controlled study included 112 men unable to have intercourse either with or without medication. Erectile dysfunction was assessed at screening and 5, 12 and 24 weeks after treatment. Assessment was performed by interview and using the Erection Hardness Scale (EHS) and the International Index of Erectile Function (IIEF-15) questionnaire. The men were randomly assigned either to LI-ESWT ($n = 51$, active group) or placebo ($n = 54$, placebo group). They received five treatments over 5 weeks. Both the participants and the doctors were blinded to the treatment. After 10 weeks, the placebo group received active treatment (active placebo group). **Results.** Twenty-nine men (57%, active group) were able to obtain an erection after treatment and to have sexual intercourse without the use of medication. In the placebo group, only five men (9%) showed similar results ($p = 0.0001$). The EHS after 5 weeks showed that men in the active group experienced a significant improvement in their erectile dysfunction, but no significant result was found with the use of the IIEF – Erectile Function domain. **Conclusions.** This placebo-controlled study over 5 weeks shows that 57% of the men who suffered from erectile dysfunction had an effect from LI-ESWT. After 24 weeks, seven (19%, active group) and nine (23%, active placebo group) men were still able to have intercourse without medication. This study shows a possible cure in some patients, but more research, longer follow-up in the placebo group and an international multicentre randomized study are needed.

Keywords:

Erectile dysfunction, extracorporeal shockwave, penis

HistoryReceived 26 January 2014
Revised 31 July 2014
Accepted 30 October 2014**Introduction**

Erectile dysfunction is a male sexual dysfunction defined as a consistent or recurrent inability to attain or maintain an erection sufficient for sexual intercourse [1,2]. Erectile dysfunction is a common disorder of middle-aged men that profoundly affects their quality of life [3,4]. For the past 15 years, oral treatment with phosphodiesterase-5 (PDE-5) inhibitors or intracavernosal injection therapy with vasodilating agents has been the preferred treatment for erectile dysfunction [2].

Extracorporeal shockwave therapy (ESWT) has been used for many years in different fields. In 1980, the clinical use of extracorporeal shockwave lithotripsy as a treatment for stone disease in the upper urinary tract began and proved effective [5–7]. Throughout the years, ESWT has been modified for use in other specialities, such as in the treatment of gallstones, sialolithiasis and Peyronie's disease [8–10]. Animal studies have demonstrated neoangiogenesis in myocardial

tissue and skin flaps [11,12], which invites the hypothesis that erectile dysfunction of vascular origin could be treated by ESWT [11–14].

Recent studies have shown promising results of low-intensity extracorporeal shockwave therapy (LI-ESWT) on patients suffering from mild to severe erectile dysfunction [15–17]. A randomized, double-blind, controlled study of men allocated in a two-to-one ratio to LI-ESWT or sham operation showed positive short-term clinical and physiological effects of LI-ESWT on erectile function in PDE-5 inhibitor responders [17].

The aim of the present study was to evaluate LI-ESWT given to men with erectile dysfunction in a one-to-one ratio, and then to investigate and monitor the effects of treatment on erectile function.

Materials and methods**Study population**

During the period 2012–2013, 112 men with erectile dysfunction of organic origin who had responded to PDE-5 inhibitors were included in this prospective, randomized, blinded, placebo-controlled study and followed for 5 weeks.

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They had all been referred from general practitioners, were recruited from all over Denmark and participated at their own expense. The inclusion criteria were erectile dysfunction for more than 6 months, an Erection Hardness Score (EHS) less than 2 and an Index of Erectile Function (IIEF-15) score less than 20, age 18–80 years and having been in a stable relationship for more than 3 months. Men with psychogenic erectile dysfunction, neurological pathology, prior radical prostatectomy, rectal extirpation, radiation therapy to the pelvic area and recovery from any cancer within the past 5 years were excluded. Patients with heart disease prohibiting sexual activity or taking medication with antiandrogens were also excluded.

The randomization was done using a computer-generated list with random numbers.

Clinical information

The study was approved by the National Committee on Health Research Ethics and the Danish National Data Protection Agency. All men who met the criteria for participation gave written informed consent before receiving LI-ESWT. Before the first visit, all participants had answered questions about their medical and sexual history. All men were informed that the use of PDE-5 inhibitors was prohibited during the study. There was no washout period before the start of the study. At the first visit, the head urologist went through the IIEF-15 questionnaire and the EHS with every single man to ensure that all participants understood the questionnaires which would be used for later follow-up.

The IIEF-15 patient questionnaire was used to assess the severity of erectile dysfunction. For the calculation, only questions 1, 2, 3, 4, 5 and 15, also known as the International Index of Erectile Function – Erectile Function domain (IIEF-ef domain), were used. A high EHS and a high IIEF-ef domain indicate good erectile function. The treatment success threshold was primarily set at EHS 3–4, which indicated that the men could have intercourse without medication. Furthermore, an increase in IIEF-ef domain score of at least 5 points was used. Assessment of erectile function was performed by interview at screening and thereafter by mail.

Study design

After ensuring that the inclusion criteria had been fulfilled, the men were randomly assigned to either active LI-ESWT treatment (active group) or placebo (placebo group) based on a randomization list that was stored in a sealed envelope. Both the men and the physicians were blinded to the allocation. Knowledge of the contents of the envelope and group assignment was available only to the Head of the Department of Urology, who was responsible for the randomization.

The participants were assessed by EHS and IIEF-ef domain at baseline and at 5 weeks. Ten weeks after study start, men in the placebo group were offered LI-ESWT and the blinded part of the study was terminated. The active placebo group were assessed at 5, 12 and 24 weeks after their treatment.

Treatments took place over a 5 week period and were carried out using a handheld Duolith® SD1 machine (Storz,

Tägerwil, Switzerland) set at 0.15 mJ/mm², 5 Hz, with a total of 3000 impulses, and a total energy of 12.8 J per treatment. LI-ESWT was performed in six positions on the penis (distal, centre and proximal part of each corpus cavernosum) and given by a doctor. The cap used to prevent LI-ESWT in the placebo group was positioned by the Head of the Department to ensure blinding. The machine and noise from the machine were the same in the two groups, so that neither the doctor nor the patients would know whether they received active or inactive treatment.

After the treatment each participant was asked about the effects and side-effects.

This set-up had previously demonstrated its effectiveness in a pilot study [18], where 11 (73%) out of 15 men who were treated achieved an effect. The success rate in this study and other studies [15–17] was used to calculate the power and the number of patients needed to treat in order to prove an effect in the present study. With a success rate of 60%, it was calculated that the study needed the inclusion of 80 men with no dropouts and 100 men with a dropout rate of 15% (= 2.4% one-sided, = 20%). The dropout rate in the present study was 6% (seven patients).

Data analysis

The chi-squared test was used to analyse the differences between patient groups. The level of significance for all analyses was $p < 0.05$.

Results

Baseline

In total, 112 participants were enrolled in the study. Seven of these were excluded; three owing to illness which prevented them from receiving treatment and four because they failed to return the questionnaires. After the first 5 weeks two participants from the placebo group stopped because of travel costs.

The median age was 60 years (range 37–80 years). The active group and the placebo group were similar in terms of comorbidities and use of PDE-5 inhibitors, as assessed by the questionnaires ($p = 0.56$) (Table 1).

All patients completed the treatment and none of them had any significant side-effects. In both groups, some patients reported a slight burning sensation shortly after treatment. No skin rashes or haematomas were reported during or after the treatment.

Follow-up

The EHS and the IIEF-ef domain were used to evaluate the participants after they had completed five treatments. In the active group, 29 men (57%) had an EHS of 3–4, which made it possible for them to have full sexual intercourse at 5 weeks of follow-up. Three men (6%) had an EHS of 1–2, and 19 (37%) showed no change in erectile dysfunction. In the placebo group, five men (9%) had an EHS of 3–4, seven (13%) an EHS of 1–2 and 42 (78%) had experienced no change. The difference between the two groups was

Table 1. Patient demographics and comorbidities.

	Active (ESWT) group	Placebo group	p
No. of patients (%)	51 (49)	54 (51)	0.7
Age (years), median (range)	59 (41–80)	60 (37–79)	
ED duration (months), mean (range)	57 (9–240)	64 (12–240)	
Comorbidity ^a , n (%)	22 (43)	27 (50)	0.56
Diabetes	9 (18)	7 (13)	
Hypertension	17 (33)	20 (37)	
Heart disease	2 (4)	6 (11)	
Alcohol (units/week)	8	9	1.0
Smoker	5	9	0.39
Oral medication for ED (%)	44	47	
Good effect	25 (49)	23 (43)	0.53
Varying effect	9 (18)	9 (17)	1.0
Poor effect	8 (16)	13 (24)	0.33
Side-effects	2 (4)	2 (4)	1.0
No present medication	7 (14)	7 (13)	1.0

ESWT = extracorporeal shockwave therapy; ED = erectile dysfunction.

^aSome of the patients had more than one comorbidity.

statistically significant at the EHS levels 0 and 3–4 ($p = 0.0001$), but not at the EHS level 1–2 (Table 2).

In the active group, the EHS response rate was 80% at week 12 and 70% at week 24. In the active placebo group, the EHS response rate was 85% at week 12 and 75% at week 24. In the period between weeks 12 and 24, the number of men who achieved an EHS score of 3–4 declined in both groups, from 12 (28%) to seven (19%) in the active group and from 12 (28%) to nine (23%) in the active placebo group (Table 3). There was no significant difference between the two groups in terms of IIEF-ef domain after week 5. The IIEF domain score improved by at least 5 points in 19 men (43.2%) in the active group and in 19 men (37.1%) in the placebo group (Table 2). Compared with baseline IIEF-ef domain scores, 13 men (22%) in the active group had achieved an increase of 5 or more points and 10 men (28%) had achieved an increase of more than 10 points at 12 weeks. At week 24, 12 (32%) still showed scores of 5 or above and six (15%) still showed scores greater than 10 (Table 3). In the active placebo group, a trend towards better results after active treatment was observed at the follow-up in week 5; thus, 14 men (33%) had scores greater than or equal to 5 and 14 men (33%) had achieved an increase of more than 10 points. At week 24, 15 (38%) still showed scores of 5 or above and seven (17%) still showed scores above 10 (Table 3).

Discussion

In this 5 week placebo-controlled study, LI-ESWT helped 57% of patients with erectile dysfunction of organic origin to have intercourse without medication. Worldwide, growing numbers of men are suffering from diseases such as diabetes, hypertension and heart disease, which contribute to the development of erectile dysfunction [4]. For many years, oral treatment with PDE-5 inhibitors, injection therapy with alprostadil, vacuum constriction devices and surgical

Table 2. Effect of LI-ESWT based on EHS and IIEF-ef domain between the active group and the placebo group at the 5 week follow-up.

	Active (ESWT) group	Placebo group	p
Number of patients (%)	51 (49)	54 (51)	
EHS at 5 weeks, response rate (%)	51 (100)	54 (100)	
0	19 (37)	42 (78)	0.0001
1–2	3 (6)	7 (13)	0.53
3–4	29 (57)	5 (9)	0.0001
IIEF-ef domain score change at 5 weeks (%)	44 (86)	51 (94)	
<5 points	25 (57)	32 (63)	
≥5 points	15 (34)	11 (22)	0.67
≥10 points	4 (9)	8 (16)	

LI-ESWT = low-intensity extracorporeal shockwave therapy; EHS = Erection Hardness Score; IIEF-ef domain = International Index of Erectile Function – Erectile Function domain.

treatment have been the available treatment methods for erectile dysfunction [1]. However, these treatments do not help patients to achieve spontaneous erection, and the medications are contraindicated in some conditions and may have side-effects. Several studies have therefore investigated other

Table 3. Follow-up data in the active group and the placebo group after both had received extracorporeal shockwave therapy (ESWT).

	Active (ESWT) group	Active placebo group
No. of patients	51	52 ^a
EHS at 5 weeks, response rate (%)	51 (100)	52 (100)
0	19 (37)	6 (11)
1–2	3 (6)	18 (35)
3–4	29 (57)	28 (54)
EHS at 12 weeks, response rate (%)	41 (80)	44 (85)
0	7 (18)	5 (11)
1–2	22 (54)	27 (61)
3–4	12 (28)	12 (28)
EHS at 24 weeks, response rate (%)	36 (70)	39 (75)
0	6 (17)	8 (21)
1–2	23 (64)	22 (56)
3–4	7 (19)	9 (23)
IIEF-ef domain score change at 5 weeks, response rate (%)	44 (86)	42 (81)
<5 points	25 (57)	14 (33)
≥5 points	15 (34)	14 (33)
≥10 points	4 (9)	14 (33)
IIEF-ef domain score change at 12 weeks, response rate (%)	46 (90)	45 (86)
<5 points	23 (50)	20 (44)
≥5 points	13 (28)	16 (36)
≥10 points	10 (22)	9 (20)
IIEF-ef domain score change at 24 weeks, response rate (%)	38 (75)	40 (77)
<5 points	20 (53)	18 (45)
≥5 points	12 (32)	15 (38)
≥10 points	6 (15)	7 (17)

Data are shown as n (%).

EHS = Erection Hardness Score; ESWT = extracorporeal shockwave treatment; IIEF-ef domain = International Index of Erectile Function – Erectile Function domain.

^aTwo dropouts due to travel costs.

treatment modalities for erectile dysfunction, such as LI-ESWT, which is a promising new, minimally invasive method with almost no side-effects [14–19].

Before the present study was undertaken, a pilot study was performed in which a group of 15 men followed the same protocol. After treatment, 11 of these men (73%) were able to have intercourse without medication [18]. In four men (27%), the improvement in erectile function was maintained after 24 months. The benefit of LI-ESWT has previously been demonstrated in a randomized, double-blind, sham-controlled study which, however, used another machine and treatment interval [15]. The present study used shockwaves generated electromagnetically and the men attended one session per week for 5 weeks. The Vardi group [15] used shockwaves generated by an electrohydraulic unit, and the waves were delivered using a broader probe than the one used in the present study. In the study by Vardi, two treatment sessions were given per week for 3 weeks, the treatments were repeated after a 3 week treatment-free interval, and the probe was applied to the same places on the penis as well as to the crura [15]. In an open-label, single-arm prospective study, Vardi and co-workers [16] showed a 50% improvement in achieving erection without any PDE-5 inhibitors at 6 months of follow-up. The present study and the studies by Vardi [15,16] are not completely comparable owing to differences in the number of patients, treatment sites (Vardi includes treatment of the crura), probe sizes (much larger probe used by the Vardi group), total number of treatments (the Vardi group used 12 treatments) and machines, as explained above.

The outcome was determined by the use of the IIEF-ef domain and EHS. The IIEF-15 has been validated in Denmark but the EHS has not. At the 5 week follow-up, 57% of the patients receiving ESWT had an EHS greater than 2, which is sufficient for full sexual intercourse ($p < 0.05$). However, there was a fall in EHS at the 24 week follow-up, where 28% still had a score greater than 2. This could indicate a need for possible follow-up treatments. Some of the patients improved their score, but not enough for full sexual intercourse. It is likely that some patients require a larger number of treatments, possibly a higher dose of therapy or a combination with medication to achieve sufficient results. Further studies are needed in this field. Unfortunately, this study did not demonstrate a treatment benefit as expressed in a higher IIEF-ef domain score. Considering the treatment success threshold, the results are not significant. However, a positive effect was found in about 20% of the treated men over the 24 weeks of follow-up. The participants seemed to have some problems understanding the questionnaires, even after being instructed by a doctor on the first day of inclusion. It was the IIEF-15 that caused problems, which became clear when the researchers calculated the results and talked to the participants. However, when seeing the results of the EHS, which clearly show EHS 3–4 in 57% of the active group at week 5 and 19% at week 24, and knowing that the starting values of EHS were below 0–2, something had clearly changed for these men. Further randomized, placebo-controlled studies are needed in this area, and attention should be given to the questionnaires and the interviews to ensure that the results reflect the participants' outcomes in their most accurate forms.

One limitation of this study is the lack of penile haemodynamic or other objective measurements, but another study has shown that ESWT exerts a genuine effect on the erectile mechanism by improving penile blood flow [17]. Another limitation is the lack of a fully blinded 24 week follow-up. However, previous studies have shown that there was no change in the placebo group in terms of clinical situation or questionnaire scores [17]. When an interim analysis was performed after 10 weeks, men in the placebo group were promised that if there was an effect in the active treatment group, they would also be offered active treatment.

The strength of the present study is that it is a prospective, randomized study for which motivated men were recruited from different social strata with no racial variation.

The effect of LI-ESWT on erectile dysfunction has not been clearly determined. The basis for its use as a treatment for erectile dysfunction is the notion that it could induce the release of endothelial nitric oxide synthase, vascular endothelial growth factors and proliferating cell nuclear antigen and thus enhance neovascularization. Research suggests that neovascularization has been achieved within the field of cardiology [19]. Studies of these factors in erectile dysfunction are still pending. Studies have shown partial improvement of erectile dysfunction in a diabetic rat model treated with ESWT or stem cells [13,20], and neoangiogenesis in corpora cavernosa in normal rats and diabetic rats treated with ESWT compared with controls [13].

In conclusion, this study has shown that 57% of patients with erectile dysfunction of organic origin had an effect from LI-ESWT after 5 weeks. After 24 weeks, seven men (19%) in the active group and nine (23%) in the active placebo group were still able to have intercourse without medication. The study showed the same response in the placebo group when this group was treated with active LI-ESWT. The treatment is patient friendly, has no side-effects requiring treatment and can be used for all patients. The present study underlines that there is a need for further research and randomized, international and multicentre studies in this area.

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Men's Power-Pressure Wave Erectile Regeneration-Therapy: an Early Assessment

Abstract

Introduction: Low intensity extracorporeal shockwave therapy for erectile dysfunction (LISWT) has been well researched as a treatment for Erectile Dysfunction (ED) and used as a first line treatment in many parts of the world as a viable alternative to oral, on-demand, phosphodiesterase type 5 inhibitors (PDE5i). Though effective, these drugs have limitations and are associated with significant non-compliance, side effects and do not reverse the underlying pathology [1-3]. Non-invasive low intensity shockwave therapy (LISWT) has been shown to significantly improve erectile function in men previously PDE5i dependent.

Materials and Methods: Vaughan Medical LLC based in Fort Lauderdale, USA purchased the STORZ Medical D-ACTOR 100 to treat patients with ED with the C-15 Ceramic Grey Tip at 15 Hertz and 2.6 Bar with 500 pulses per 1.5 cm on top of the shaft and 1,000 pulses right side then 1,000 left side just below the shaft on the pelvis/corporal bundle. Each patient had 6 treatments either two treatments per week for three weeks or one treatment per week for six weeks randomized by patient preference and/or to fit in with clinic schedules [4-7].

Results: Men's PoWER Therapy using the STORZ Medical D-ACTOR 100 (LISWT) has shown in this early experience to be an effective treatment paradigm for erectile dysfunction. All patients completed the treatment regime and all gained an improvement in their SHIM score with an average improvement from Moderate ED to Mild-Moderate after 6 treatments. It appears from this early experience that the optimal treatment regime is six (6) treatments at two treatments per week for three weeks [8-11]. The same energy settings were used for all patients of 15 Hertz and 2.6 bars with 500 pulses per 1.5 cm on top of the shaft and 1,000 pulses right side then 1,000 left sides just below the shaft on the pelvis/corporal bundle.

Conclusion: The early experience of LISWT has shown an improvement in the sexual function of patients and a treatment regime of two treatments per week for three weeks appears optimal but further research is required [12-15].

Keywords: Men's PoWER Therapy; Low intensity extracorporeal shockwave therapy; Erectile Dysfunction

Review Article

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Abbreviations: LISWT: Low Intensity Extracorporeal Shockwave Therapy for Erectile Dysfunction; ED: Erectile Dysfunction; PDE5i: Phosphodiesterase Type 5 Inhibitors; PDE5: Phosphodiesterase Type 5

Introduction

Used in medicine since the 1980s, shockwave therapy involves the aiming of shockwaves-energy waves that travel faster than the speed of sound-toward treatment areas from outside the body. The approach is sometimes used to break up kidney stones and treat conditions like joint pain, bursitis, and tendinitis. More recently, scientists have examined its use in the treatment of ED, with encouraging results. Low-intensity extracorporeal shock wave therapy (LIESWT) to the penis has recently emerged as a new and promising modality in the treatment of erectile

dysfunction (ED). Shock waves are acoustic waves that generate a pressure impulse and that carry energy when propagating through a medium [16,17]. The degree of focus can be modulated noninvasively, resulting in variable concentration of energy at a desired location. When shock waves are applied to an organ, the focused waves interact with the targeted deep tissues and act as transient micromechanical forces that initiate several biological changes [18].

This initial study focused on the first initial experience of the LISWT procedure known under the name Men's PoWER Therapy with 22 patients with ED who did not have success with phosphodiesterase type 5 (PDE5) inhibitors or required spontaneous erections. Many patients found the medications are not suitable and some they don't respond to them. Some participants also had vascular risk factors that could contribute

to ED, such as diabetes, high lipid levels, high blood pressure, and possible coronary artery disease. For three to six weeks, the men participated in either twice weekly or once weekly PoWER Therapy sessions lasting just a few minutes [19-21]. Six sessions in all with the STORZ Medical D-ACTOR 100 D with the C-15 Ceramic Grey Tip at 15 Hertz and 2.6 Bar with 500 pulses per 1.5 cm on top of the shaft and 1,000 pulses right side then 1,000 left side just below the shaft on the pelvis/corporal bundle with topical Lidocaine offered and used at patient discretion. At each appointment, shockwaves were applied to the penis and the perineum (the area between the anus and the scrotum). The men completed a SHIM score at start and post last treatment [22,23].

Before treatment, and again at last treatment point, the men's erectile function was assessed using the SHIM score measurements, which is often used in medical studies of ED. The patients were all treated by one of two practitioners. All twenty two (22) of the men (average age: 57.78 years) completed the treatment regime so we calculated the results based on data from this group. We found that 95% of the men had improved erections based on the SHIM Score measurement tool at last treatment. None of the men had side effects from treatment. The men's age and the length of time with ED did not affect the results. We acknowledge several limitations, including the lack of a placebo group and to date no long term follow up [23-25].

We stress the need for further research to determine long term benefit and how many LISWT sessions would be most effective and over what period of time (treatment regime) and which men are the best candidates for this therapy. The patients (Table 1) were selected randomly into two groups by patient preference and/or to fit in with clinic schedules between two treatments per week and one treatment session per week. In the two treatment sessions a week group an 8 point average increase in SHIM score was noted from 9.17 to 17.17 average with an average age of 63.33 years (Table 2) where in the one treatment per week group an average increase on 3 point score was noted from 7.5 to 10.5

with an average age of 55.69 years (Table 3). It is worth noting that the ED score was severe in the one treatment per week group and only moderate in the two treatment sessions a week group (Figure 1-3) [26-31].

Table 1: Patient group-an early assessment.

N = 22	Median	Range
Age Years	40.5	(39 – 80)
IIEF-5 Questionnaire (SHIM) at start	7.05	3 - 20
IIEF-5 Questionnaire (SHIM) after last treatment	10.5	5 - 22

Table 2: Two treatments per week cohort.

N = 6	Median	Range
Age Years	63.33	(53 – 75)
IIEF-5 Questionnaire (SHIM) at start	9.17	5 - 18
IIEF-5 Questionnaire (SHIM) after last treatment	17.17	6 - 22

Table 3: One treatment per week cohort.

N = 16	Median	Range
Age Years	55.69	(39 – 80)
IIEF-5 Questionnaire (SHIM) at start	7.05	3 - 20
IIEF-5 Questionnaire (SHIM) after last treatment	10.5	5 - 22



Figure 1: The D-ACTOR 100.



Figure 2: The treatment head.

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

Figure 3: SHIM Score Form.

Total score: _____

1-7: Severe ED 8-11: Moderate ED 12-16: Mild-moderate ED 17-21: Mild ED 22-25: No ED

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Shockwave treatment of erectile dysfunction

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Abstract

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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

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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

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

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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

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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-ESWT was applied.

LI-ESWT for ED

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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 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).



[Table 1.](#)

The clinical studies included in the paper.

Discussion

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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

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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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Footnotes

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Sexual Medicine

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 corporeal 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 induces neovascularization and improves 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/mm² 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.

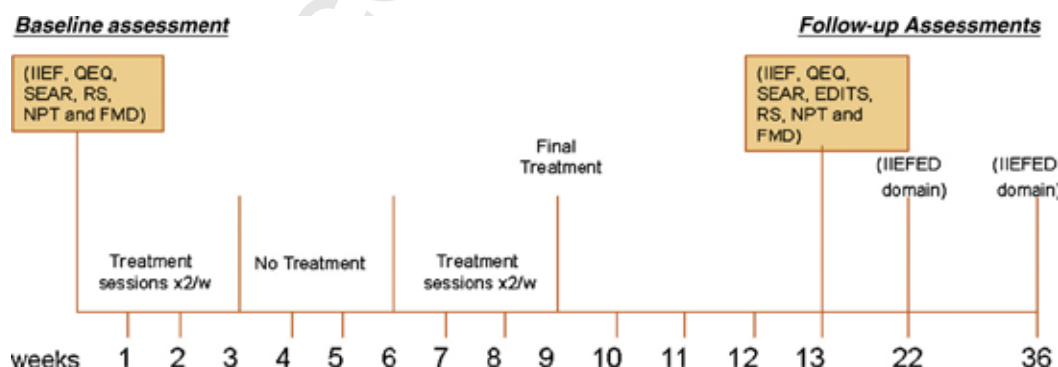


Fig. 1 – Study flow chart.

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 shock-wave therapy

Test score	Baseline score \pm SD	Score 1 mo after treatment \pm SD	% change	<i>p</i> 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 ^a	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;

^a 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

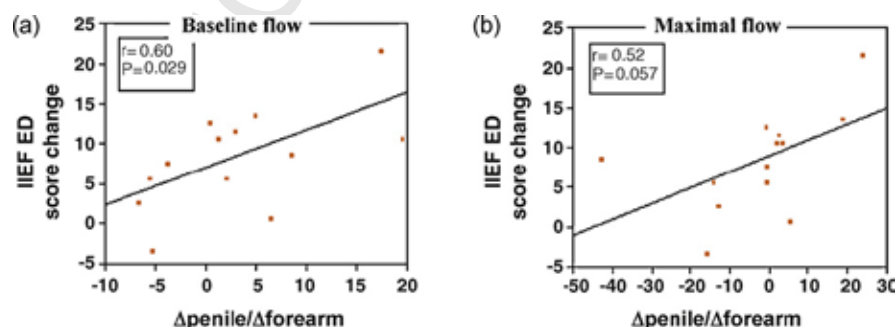


Fig. 2 – Correlation between the adjusted flow-mediated dilatation indices for (a) baseline and (b) maximal flow and the changes in the International Index of Erectile Function erectile dysfunction score 1 mo after treatment. IIEF ED = International Index of Erectile Function–Erectile Dysfunction domain.

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.

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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 \pm 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

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 mecha-

nism of penile erection.¹ Gene and stem cell therapies are current examples of treatment strategies whose therapeutic goals are to restore erectile function as part of the present trend to shift the field of ED treat-

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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ments 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 tendonitis¹¹ 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

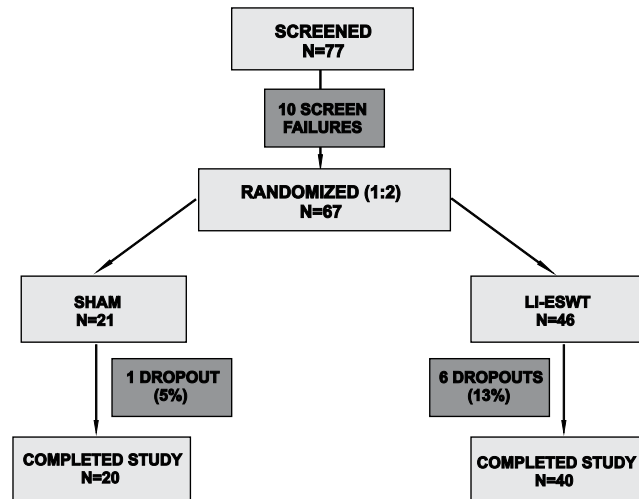


Figure 1. Patient screening and randomization flowchart

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).

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/mm² 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

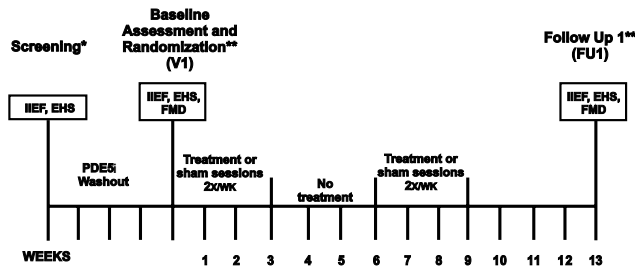


Figure 2. Study flowchart. Single asterisk indicates with PDE5i. Double asterisk indicates without PDE5i.

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 \pm 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 \pm SEM IIEF-EF domain scores	11.5 \pm 0.86	12.6 \pm 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/mm²), the low intensity shock wave energy (0.09 mJ/mm²) 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

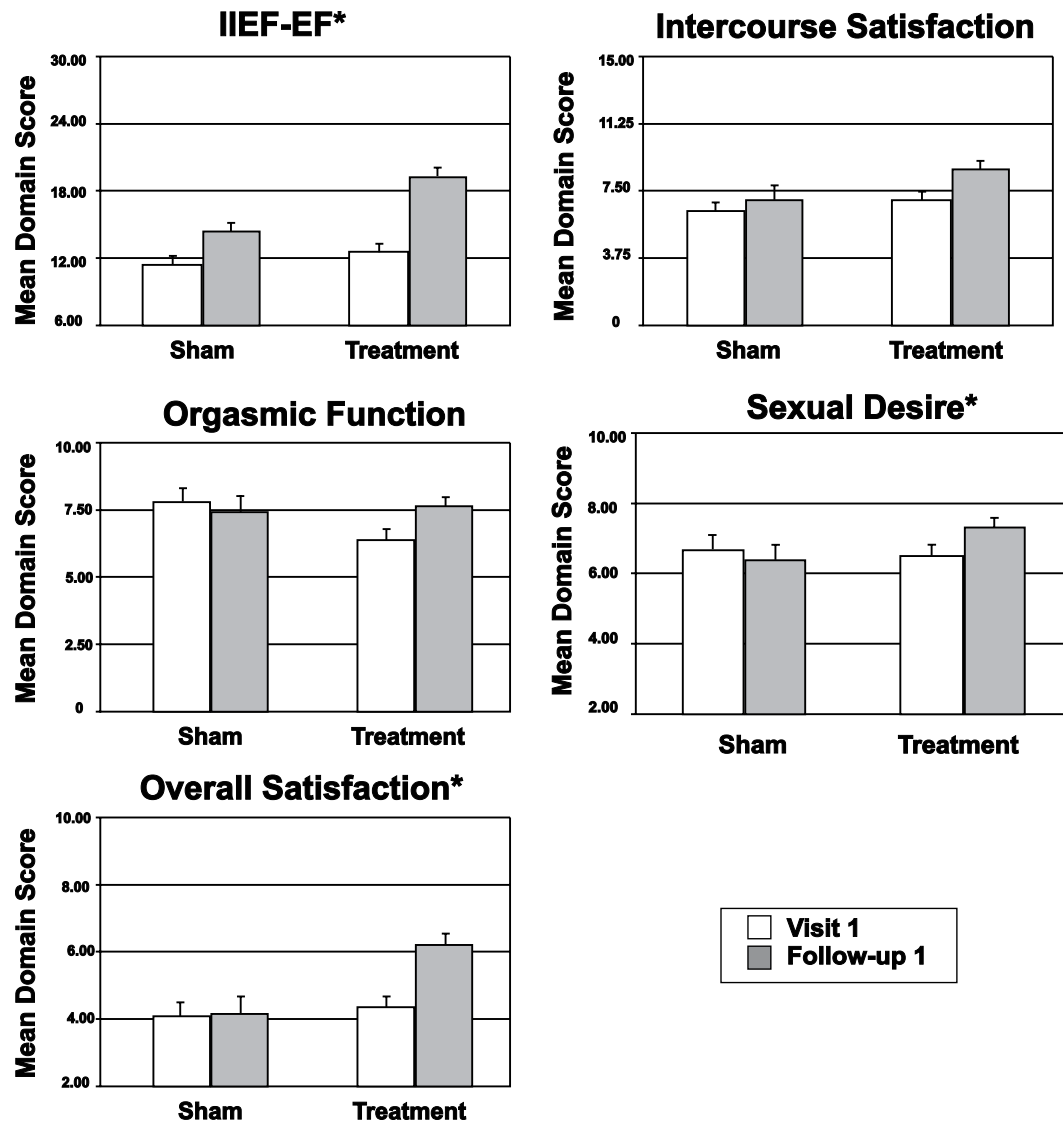


Figure 4. IIEF domain scores (mean \pm SEM) for men treated with LI-ESWT or sham therapy at V1 or FU1. Asterisk indicates $p < 0.05$ and represents significance of difference between 2 groups.

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-

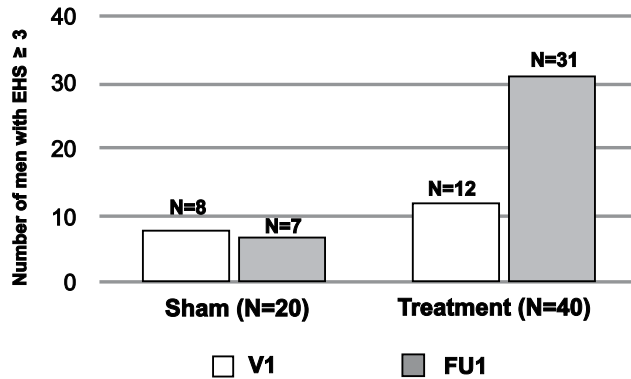


Figure 5. Number of men with EHS 3 or greater at V1 and FU1. For EHS clinical interpretation, grade definitions characterizing penis are grade 1—larger but not hard, grade 2—hard but not hard enough for penetration, grade 3—hard enough for penetration but not completely hard, grade 4—completely hard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

parameter 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

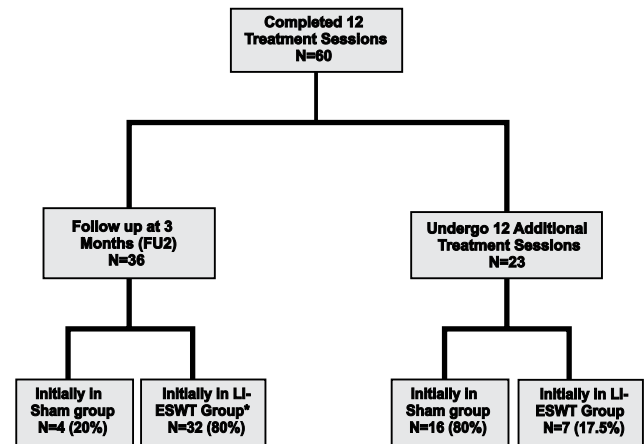


Figure 6. Patient followup after 12 treatment sessions. Asterisk indicates 1 patient (2.5%) was lost to FU2.

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.

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.

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 $p < 0.0001$.

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 determin-

ing 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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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/mm² intensity at 120 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 **;:**_**.**

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

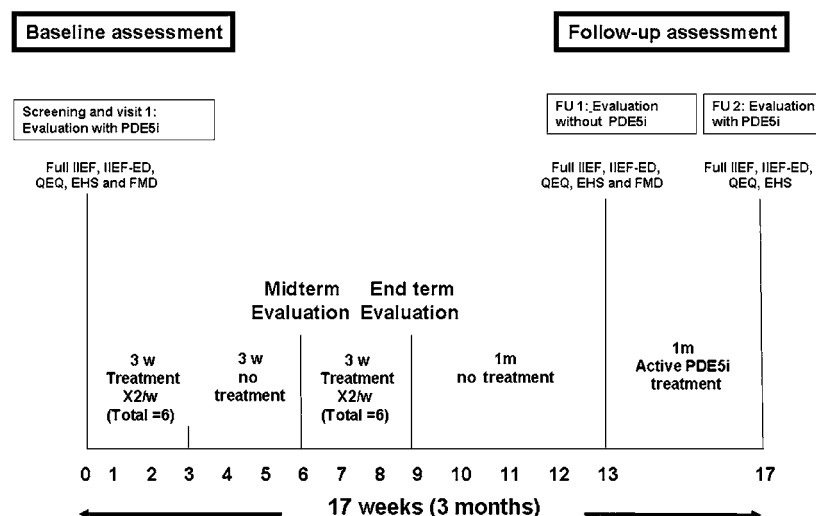


Figure 1 Study flow chart. EHS, erection hardness score; FMD, flow mediated dilatation; FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; PDE5i, phosphodiesterase type 5 inhibitor; QEQ, Quality of Erection Questionnaire.

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/mm² 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 \pm 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 non-compliance [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%

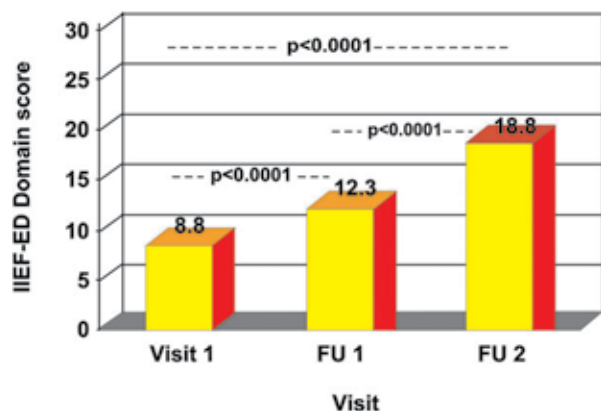


Figure 2 Mean IIEF-ED scores before and after LI-ESWT. FU, follow-up; IIEF-ED, International Index of Erectile Function-erectile function domain; LI-ESWT, low-intensity extracorporeal shock wave therapy.

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 ($P = 0.0109$).

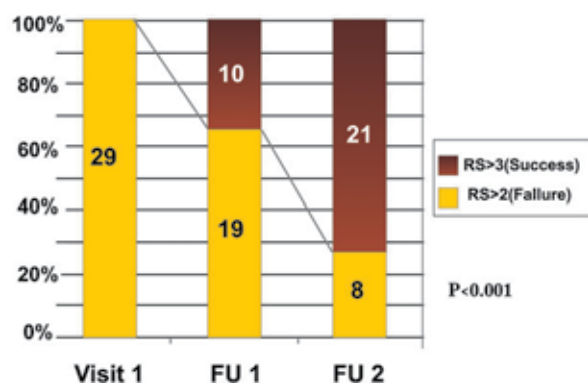


Figure 3 Changes in rigidity scales according to visit. RS, rigidity scale.

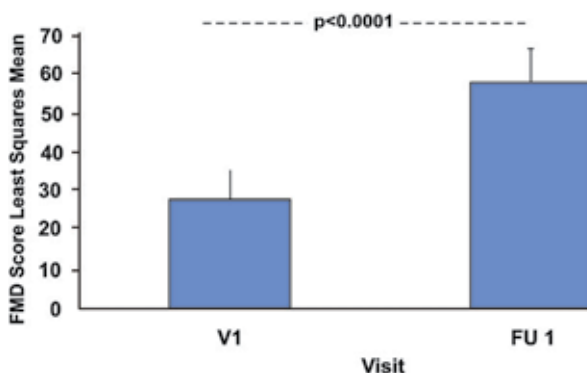


Figure 4 Maximal postischemic blood flow measured at the penis level per visit. FU, follow-up.

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

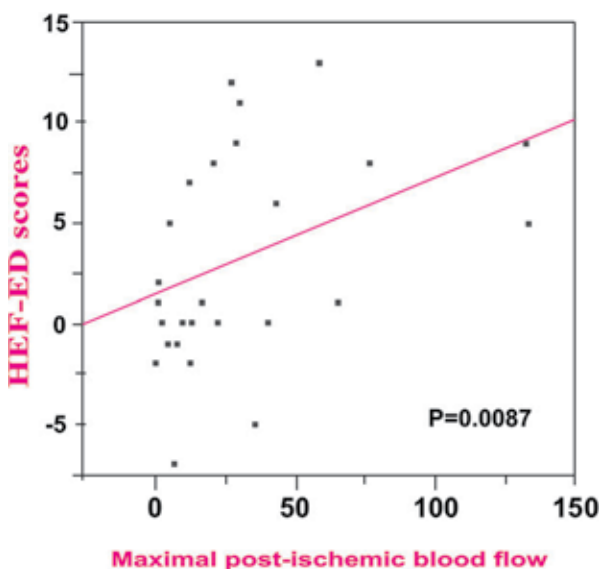


Figure 5 Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED domain scores. Graph 4: Spearman rank correlation between the changes in the maximal postischemic blood flow parameter and changes in IIEF-ED score. IIEF-ED, International Index 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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Category 3

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Pro: does shockwave therapy have a place in the treatment of Peyronie's disease?

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Introduction

Peyronie's disease (PD) is an often debilitating psychosexual condition characterized by the presence of penile pain, deformity and plaque(s), with ensuing erectile dysfunction (ED) (1). While the natural history of PD remains controversial, and no one truly knows the underlying pathophysiology of PD (2,3), it is accepted that in 50% of men with PD, the disorder is progressive (1,4).

The PD process is divided into two distinct phases, an initial acute (inflammatory) response and the subsequent chronic fibrotic stage with the formation of a penile plaque that signifies a stable disease (2). Patients usually describes a new onset of penile pain in the acute phase of PD, and penile deformities such as curvature, indentation, hinge effect or hourglass deformity may not be fully developed at the initial stage (2). It is possible that the optimal time to intervene is during the active disease phase when the inflammatory plaque is treatable (1). Surgery should be reserved in men who do not respond to conservative treatment, have a stable disease (at least 6 to 12 months of onset) or want the most definitive clinical outcome (1).

Why low intensity extracorporeal shock wave therapy (LiESWT) in PD?

The use of extracorporeal-generated electrohydraulic, electromagnetic or piezoelectric shock waves for the treatment of renal calculi has fundamentally changed the way urinary stones is managed (5). Since shock wave technology has become established in the field of urology, the modification to a lower energy source, that of LiESWT, soon

has come to be of use in the orthopaedic field for treating degenerative and painful joint conditions (6). Furthermore, positive results have been achieved, particularly for the treatment of pain and wound healing (7). The application of LiESWT to target organs can induce a cascade of biological reactions that promote angiogenesis and tissue revascularisation (8,9).

Given that LiESWT has been established as an effective treatment option in various calcified and non-calcified orthopaedic disease, it is therefore possible that LiESWT could be effective in treating Peyronie's plaque. Since the PD process continues to evolve in the early phase, it is likely that the use of non-invasive therapy to halt and/or alter disease progression may be effective and appealing to many patients. Furthermore, when the remodelling of the plaque becomes complete, pain also tends to disappear. The dissolution of the plaque may result in resolution of penile curvature and/or deformity.

In fact, the use of LiESWT in PD has been reported since the late 1980s (10). Electron microscopy study demonstrated actual histological changes within the Peyronie's plaque following LiESWT (11). While clinical outcomes of LiESWT for the treatment of PD has been mixed, in recent years there has been a renewed interest in its use (1,12-18). Published studies also found that LiESWT generates a significant improvement in erectile function and penile hemodynamics without any adverse effect (19,20).

Penile pain

The initial exploratory meta-analysis showed a decrease

in penile pain from 56% to 100% following LiESWT in men with PD (12). Palmieri reported that a significantly lower pain score based on the visual analog scale (VAS) in those who received LiESWT compared to placebo group with pain disappearance (53% *vs.* 7%) and pain reduction (30% *vs.* 36%) (16). The mean VAS score was significantly lower when compared with baseline values in the LiESWT, while no statistically significant differences were found in the placebo group. Similarly, Hatzichristodoulou reported an 85% reduction in penile pain in the LiESWT group compared to 48% in the placebo group ($P=0.013$) with 4% of patients actually reporting worsening of penile pain in the placebo group. Importantly no patient received analgesia at the time of LiESWT administration (14).

Penile pain is frequently regarded as indicative of an active, inflammatory stage of PD. While pain seems to resolve faster with LiESWT than during the natural disease course, the question arises whether penile pain should be treated, as most patients will experience spontaneous improvement with time (4). In some instances, pain can be effectively treated with anti-inflammatory or intralesional therapy (1,2).

Nonetheless the consensus from the 3rd and 4th International Consultation of Sexual Medicine (ICSM) (1) stated that LiESWT provided greater pain reduction in the LiESWT group compared to placebo. Possible therapeutic mechanisms of action of LiESWT include direct disturbance of pain receptors and hyperstimulation analgesia (21), as well as direct plaque damage and heat-induced increased vascularity of the area, leading to the induction of an inflammatory reaction with lysis of the plaque, calcification resorption, and removal of macrophages (22).

Penile curvature and plaque size

Early published literature reported that the decrease in penile curvature varies between 21% and 74%; with a reduction in plaque size between 0% to 68% among men who received LiESWT (12,13). However, the clinical outcomes in recent randomised controlled trials showed an actual change of less than 10° compared to the control group (14,15). Hatzichristodoulou reported an increase in penile deviation in 40% of patients following LiESWT although only five (10.9%) patients showed an increase in plaque size in this group (14). Similarly, Chitale reported deterioration in dorsal and lateral angle in LiESWT compared to control group, with no change in plaque size in most of the patients from both groups (15). In fact, most

patients who showed an increased penile deviation after LiESWT also showed an increase in plaque size confirming that an increase in plaque size correlates with worsening of penile deviation.

On the other hand, Palmieri found that the mean plaque size and mean curvature degree were decreased in the LiESWT but increased in the placebo group (16). After 24 weeks, the mean plaque size and curvature degree were significantly higher in the placebo group when compared with both baseline and LiESWT values, leading to the assumption that LiESWT may have a protective effect on disease progression by stabilizing the deviation and plaques. In another recent single-arm, open-label prospective study, Chung reported that an improvement in penile curvature by more than 15° was observed in 33% of men with a corresponding decrease in penile plaque hardness in 60% of men, and a reduction in penile plaque by 2 cm² in 27% of men (23). There was correspondingly softening and reduction in penile plaque size in this successful group of LiESWT men. This change in penile plaque density is consistent with a previous study where electron microscopy of penile plaque tissue in patients with PD following LiESWT demonstrated a reduction in packing and clumping of the collagen fibres (11).

Sexual (erectile) function

In contrast to the published literature supporting the role of LiESWT in men with ED (17,18), the reported changes in erectile function following LiESWT for the treatment of PD has been mixed. While International Index of Erectile Function-5 (IIEF-5) score is frequently used to evaluate sexual function in men with PD, it has never been specifically validated for use in this disease state. Published meta-analysis in 2004 reported that the improvement in sexual function varies from 12% to 80% (12). However more recent studies have found no significant difference between LiESWT and control group (14-16).

Chitale did not identify any beneficial effect of LiESWT compared to placebo in terms of quality of erections based on the Global Assessment Questionnaire for the effect of penile deformity on quality of sexual life (15). Hatzichristodoulou reported no significant difference in successful intercourse between the LiESWT and control groups. He also reported that, in patients who were unable to perform intercourse before treatment, 61.5% of the LiESWT group reported an improvement, compared to 38.5% in placebo group (14). In contrast, Palmieri found a significant difference in terms

of men IIEF-5 score reported in the LiESWT group when compared with baseline values with no significant differences found in the placebo group (16). Chung also reported an increase in erectile function (23). This improvement in IIEF score, especially in men who reported mild to moderate ED prior to LiESWT, highlighted that the improvement in penile curvature resulted in easier sexual penetration. Perhaps an underlying neovascularization induced by LiESWT might play a role in the greater erectile function.

Controversy and unresolved issues

Despite the cellular basis of PD that points to distinct alterations in wound healing and propagation of fibrotic process as the underlying cause, PD remains a therapeutic challenge due to the lack of knowledge on the exact pathophysiology and the unpredictable natural course of the disease (1). Nonetheless, it is likely that treatment instituted during the active phase of PD will have the greatest impact and may alter the disease process.

Any treatment modality for PD should primarily focus on the reduction of penile curvature as this is the most important and bothersome symptom in affected patients and often leads to the inability of sexual intercourse and negative psychological effect. At present, Xiaflex is the only Food and Drug Administration-approved medical treatment for PD and can be associated with serious penile complications such as penile hematoma and fracture. While surgical therapy remains as the most effective treatment option in men with PD, it is associated with significant risks such as penile length loss, sensory alteration and ED. Among the minimally invasive therapies, LiESWT has been employed for treating symptomatic plaques in patients with PD, with controversial results (1,12-18,23). While the initial exploratory meta-analysis in the early 2000s showed that LiESWT could exert beneficial effects on painful erections and on sexual function with some effects on penile plaque size and curvature (12), recent published literature has largely failed to demonstrate a significant benefit in the use of LiESWT to treat both plaque size and penile curvature (14-16). In fact, the 3rd and 4th ICSM (1) stated that while there is evidence to support that LiESWT will improve penile pain, there is currently no strong evidence to suggest that its use will decrease penile curvature or plaque volume.

While existing literature has largely failed to demonstrate any significant benefit in the use of LiESWT to treat penile curvature (1,12-18), these outcomes should be interpreted with some caution due to underlying methodological flaws

(12-18,23) and perhaps the inappropriate use of shock wave energy flow density (12-18,23). At present, there is no agreeable treatment template and the existing treatment protocol is often based on manufacturer's guidelines and is likely derived from previous orthopedic literature. The conflicting study outcomes with regards to the change in penile curvature and plaque size may be attributed to several factors, such as inclusion of patients with complex PD: the presence of more than 1 axis of penile curvature, curvature greater than 90°, presence of hour-glass deformity, and men with two or more palpable Peyronie's plaques as well as longer duration of PD.

A variety of contributing factors will likely influence the outcome of LiESWT for PD. Prolonged history of PD and presence of plaque calcification, as a marker of chronicity, indicates unlikely history of spontaneous regression. It is also more likely that men who reported improvement in penile curvature had a PD history of less than 12 months, indicating likely active disease process, which is more susceptible to a mechanical effect. Furthermore, subgroup analysis of patients in the LiESWT group showed an overall better outcome in younger patients with a relatively milder degree of curvature (15,17). Comparative studies between LiESWT with other treatment modality showed that LiESWT is not superior to other options (1,11,12) and when used in combination with other therapeutic options such as intralesional injection or tadalafil for men with PD and ED, there were improvements in erectile function score and quality of life score while the plaque size and curvature were unchanged (24).

Published literature showed that LiESWT is safe and well tolerated in an outpatient setting without the need for anesthesia. In fact, most patients are satisfied and would recommend this treatment to other men, even when they did not obtain significant improvement in penile curvature and plaque size following LiESWT.

Conclusions

The current literature on the use of LiESWT in the PD population remains controversial. It may be possible that the newer generation of shock wave lithotripter has an improved technology that disrupts the tunical plaque without inducing further plaque formation or injuring the underlying cavernosal tissue. While the exact therapeutic mechanism remains unclear, it is postulated that LiESWT may play a role in plaque remodelling and improvement in consecutive resorption of calcification (12), resulting in

softer plaque and further correction and/or resolution of the penile curvature. Furthermore, LiESWT may have a protective effect on disease progression by stabilizing penile deviation and PD plaques (16). Therefore, it appears that LiESWT should ideally be offered and utilized in younger men during the active phase of PD, i.e., less than 6 months and with a milder degree of curvature and softer non-calcified plaque, and in the absence of hour-glass deformity. In a carefully selected group of men with PD, LiESWT appears to be safe, reduces penile pain, and has some efficacy in improving penile curvature and plaque, with high patient satisfaction rate. Many men are keen to pursue minimal invasive therapy such as LiESWT to preserve penile length, as the current surgical intervention is invariably associated with loss of penile length. Nonetheless, there is a need to define which subgroup of PD population is best suited, the LiESWT protocols (modality of shock wave energy, emission frequency and total energy delivery) and the role of combination therapy in PD such as concurrent penile remodelling and the use of penile traction device or intralesional therapy. Other important factors such as the actual physiological changes in the penile tissues and the long-term risk of shock waves have yet to be fully elucidated.

LiESWT remains a useful and valid minimally invasive treatment option for men with PD who have failed conventional medical therapy and are not keen to undergo surgical intervention. In a carefully selected group of men with PD, LiESWT appears to be safe, has moderate efficacy in improving penile curvature and pain, and is associated with high level of acceptance and patient satisfaction rate.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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SHOCK-WAVE THERAPY APPLICATION IN CLINICAL PRACTICE (REVIEW).

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Abstract

The article presents literature review on the use of extracorporeal **shock-wave therapy** in physiotherapeutic practice. The basic mechanisms of **shock** waves influence on the organism are spotlighted. Studies proving high efficacy of the method in treatment of wide variety of inflammatory diseases and traumatic genesis are presented. The data on comparative assessment of **shock-wave therapy** efficacy, and results of researches on possibility of extracorporeal **shock-wave therapy** effect potentiating in combination with other therapeutic methods are reflected. Recent years, the range of indications for **shock-wave therapy** application had been significantly widened. However, further study of the method is still relevant because mechanisms of action of the factor are studied insufficiently; methods of **therapy** parameters selection (energy flux density, number of pulses per treatment, duration of a course) are either advisory or empirical.

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Effects of Low-Intensity Extracorporeal Shockwave Therapy on Erectile Dysfunction: A Systematic Review and Meta-Analysis



Raul I. Clavijo, MD,^{1*} Taylor P. Kohn, MD,^{2*} Jaden R. Kohn, BS,² and Ranjith Ramasamy, MD³

ABSTRACT

Introduction: Low-intensity extracorporeal shock wave therapy (Li-ESWT) has been proposed as an effective non-invasive treatment option for erectile dysfunction (ED).

Aim: To use systematic review and meta-analysis to assess the efficacy of Li-ESWT by comparing change in erectile function as assessed by the erectile function domain of the International Index of Erectile Function (IIEF-EF) in men undergoing Li-ESWT vs sham therapy for the treatment of ED.

Methods: Systematic search was conducted of MEDLINE, EMBASE, and ClinicalTrials.gov for randomized controlled trials that were published in peer-reviewed journals or presented in abstract form of Li-ESWT used for the treatment of ED from January 2010 through March 2016. Randomized controlled trials were eligible for inclusion if they were published in the peer-reviewed literature and assessed erectile function outcomes using the IIEF-EF score. Estimates were pooled using random-effects meta-analysis.

Main Outcome Measures: Change in IIEF-EF score after treatment with Li-ESWT in patients treated with active treatment vs sham Li-ESWT probes.

Results: Data were extracted from seven trials involving 602 participants. The average age was 60.7 years and the average follow-up was 19.8 weeks. There was a statistically significant improvement in pooled change in IIEF-EF score from baseline to follow-up in men undergoing Li-ESWT vs those undergoing sham therapy (6.40 points; 95% CI = 1.78–11.02; $I^2 = 98.7\%$; $P < .0001$ vs 1.65 points; 95% CI = 0.92–2.39; $I^2 = 64.6\%$; $P < .0001$; between-group difference, $P = .047$). Significant between-group differences were found for total treatment shocks received by patients ($P < .0001$).

Conclusion: In this meta-analysis of seven randomized controlled trials, treatment of ED with Li-ESWT resulted in a significant increase in IIEF-EF scores.

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Key Words: Erectile Dysfunction; Shock Waves; Randomized Controlled Trial; Meta-Analysis

INTRODUCTION

Erectile dysfunction (ED) is when a man is unable to achieve or maintain an erection for satisfactory sexual performance. ED is estimated to affect one in every five men and, given the aging male population and increasing prevalence of comorbid conditions, it is likely to become even more prevalent.¹ Phosphodiesterase type 5 inhibitors (PDE5is) are often

effective in treating patients with ED and are associated with few side effects; however, a significant proportion of men do not respond to therapy.² In men who do not respond to PDE5is or cannot tolerate them because of side effects, options such as medicated urethral suppositories for erection, intracorporeal injections, and penile prostheses are available.³ Although these treatment options can be effective, long-term usage rates are hindered by side effects and potential complications.⁴ Furthermore, these treatments attempt to improve erectile function without treating the underlying pathophysiology of ED.⁵

Low-intensity extracorporeal shockwave therapy (Li-ESWT) has been proposed as a treatment option for ED with minimal side effects. Vardi et al⁶ first reported on the use of Li-ESWT for ED; their rationale was extrapolated from cardiac literature reporting improvements in neovascularization. Recent studies of a diabetic rat model have recently supported the notion that Li-ESWT indeed might induce structural changes that regenerate penile tissue.⁷

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AIMS

Given the availability of several randomized sham-treatment-controlled trials studying the effects of Li-ESWT in the treatment of ED, we performed a meta-analysis to determine whether this novel treatment improves erectile function in men with ED when assessed by the International Index of Erectile Function erectile function domain (IIEF-EF) compared with men undergoing sham therapy.^{8–14} In addition, from our review of the literature, we sought to provide formal recommendations for future randomized controlled trials.

METHODS

Search Strategy

Randomized controlled trials published from January 2010 (the year that SWT was first used as a treatment for ED⁶) through March 2016 that reported on using the IIEF-EF score for men with ED receiving Li-ESWT were identified using electronic searches of MEDLINE, EMBASE, and ClinicalTrials.gov. Additional studies were identified by scanning the reference lists of articles identified, searching relevant conference abstracts, and corresponding with study investigators using the approach recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁵ A flow diagram for study selection is presented in [Figure 1](#). The computer-based searches combined terms: “[(shockwave) OR (shock wave) AND erectile dysfunction].”

Inclusion Criteria and Trial Selection

Studies were included if they were randomized controlled trials of Li-ESWT for ED that reported on the use of the IIEF-EF, a validated six-question questionnaire that assesses erection frequency, erection firmness, penetration ability, maintenance frequency, maintenance ability, and erection confidence on a scale of 0 to 5.¹⁶ The most comprehensive publication was used when there were several involving the same study population. Abstracts of randomized controlled trials from relevant conferences were included in this analysis in accordance with recommendations of the Cochrane Handbook for Systematic Reviews section 6.2.2.4.¹⁷

Data Extraction

The following information was extracted independently by two trained investigators using a standardized form: authors and publication year, year of study, publication type, practice setting, duration of follow-up, population, SWT regimen, IIEF-EF (six-question form), participant inclusion and exclusion criteria, sample size, geographic locale in which the study took place, mean or median participant age, and model of Li-ESWT machine. All discrepancies were resolved by discussion and adjudication of a third reviewer. Study investigators from most studies were contacted to obtain further information.

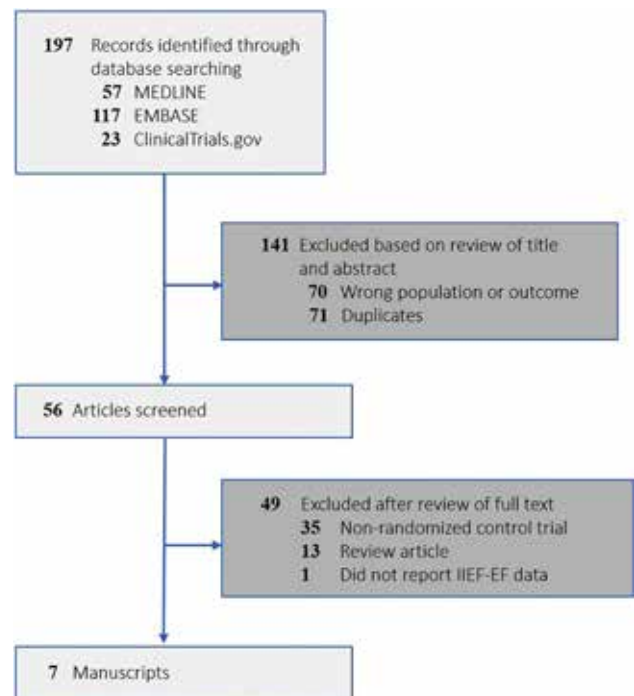


Figure 1. Flow diagram for study selection.

Quality Assessment

The risk of bias in the included randomized trials was assessed using the Cochrane Risk of Bias Assessment tool in the domains of randomization, sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other potential sources of bias.¹⁷ Domains were independently assessed by two trained investigators (R.I.C. and T.P.K.). All discrepancies were resolved by discussion and adjudication by a third reviewer (R.R.). A graph and a summary for risk of bias were generated with RevMan 5.2.¹⁸

Data Synthesis and Analysis

The mean differences in IIEF-EF scores measured before initiating and then after treatment with Li-ESWT or placebo were calculated for each study. Overall differences were calculated by pooling the study-specific estimates using random-effects meta-analysis that included between-study heterogeneity.¹⁹ Between-study heterogeneity was assessed by standard χ^2 tests and the I^2 statistic (ie, percentage of variability in prevalence estimates because of heterogeneity rather than sampling error or chance)^{20,21} and by comparing results from studies grouped according to prespecified study-level characteristics (total treatment shocks, mean participant age, baseline IIEF-EF score, and duration of follow up) using stratified meta-analysis and meta-regression.^{22,23} The influence of individual studies on the overall summary estimates was examined by serially excluding each study in a sensitivity analysis.²⁴ Bias secondary to small study effects was investigated using the funnel plot and the Egger test.^{25,26} All analyses were performed using R 3.2.2 (R Foundation for Statistical Computing).²⁷ Statistical

tests were two-sided and used a significance threshold of a P value less than .05.

MAIN OUTCOME MEASURES

Difference in pooled change in IIEF-EF score from baseline to follow-up in men treated with Li-ESWT was compared with that in those treated with sham therapy.

RESULTS

Study Characteristics

Seven randomized controlled trials involving 602 participants were included in this meta-analysis (Table 1). Six studies used the Omnispec ED1000 (Medispec Ltd, Yehud, Israel) and one study used an ESWT device from Richard Wolf GmbH (Knittlingen, Germany). The mean number of participants per study was 86.4 (range = 53–135), the mean age was 60.7 years, mean baseline IIEF-EF score was 9.2, and mean follow-up was 19.8 weeks (range = 13–56). All seven studies used sham therapy for the control group using shockwave probes that looked and sounded similar to the active treatment probe. All seven studies included men with vasculogenic ED and excluded men with neurogenic ED. Four studies included men with mild, mild to moderate, moderate, and severe ED. One study included only men with mild to moderate, moderate, and severe ED. One study included only men with mild ED while on PDE5i. Two studies did not specify the severity of ED for the included patients. Seven studies consisted of regimens of two treatments per week for 3 weeks, then 3 weeks without treatment, followed by 3 weeks of two treatments per week—for a total of 18,000 total treatment shocks. One study had a regimen of one treatment every 5 weeks, 4 weeks without treatment, followed by 5 weeks with one treatment per week—for a total of 6,000 total treatment shocks. All studies included in the present analysis used an energy flux density of 0.09 mJ/mm². Five studies took place in Asia, two in Europe, and one in North America. All seven trials studied IIEF-EF score as a primary outcome. Five studies were published as journal articles and two studies were published as abstracts. Further inclusion and exclusion criteria are listed in Table 1. For most studies, the risk of bias was low. However, the risk of bias was unclear for several domains of published abstracts (eFigures 1 and 2).

Effect of Li-ESWT on Change in IIEF-EF Score

There was a statistically significant improvement in pooled change in IIEF-EF score from baseline to follow-up in men treated with Li-ESWT compared with those receiving sham therapy (6.40 points; 95% CI = 1.78–11.02; $I^2 = 98.7\%$; $P < .0001$ vs 1.65 points; 95% CI = 0.92–2.39; $I^2 = 64.6\%$; $P < .0001$; between-group difference, $P = .047$; Figure 2A, B). For each study the control group was subtracted from the treatment group to determine the between-group mean difference, which was meta-analyzed (4.17 points; 95% CI = –0.5 to

8.3; $I^2 = 98.8\%$; $P < .0001$; Figure 2C). The sensitivity analysis demonstrated that, for the sham treatment group, no individual study affected the overall prevalence estimate by more than an absolute difference of 0.5 point. For the Li-ESWT group, two studies (Fojecki and Osther¹⁰ and Sirini et al¹¹) were found to affect the overall prevalence estimate by an absolute difference of 0.5 point (eTable 1).

Effect of Li-ESWT on Change in IIEF-EF Score According to Study-Level Characteristics

Among the seven studies, no between-group differences were noted in sub-analyses that controlled for the potential confounders of duration of follow-up, age of participant, and baseline IIEF-EF scores ($P > .05$ for all comparisons; Table 2). A significant between-group difference was observed for total treatment shocks when compared by stratified meta-analysis ($P < .001$; Figure 3).

Assessment of Publication Bias

Visual inspection of the funnel plot showed minimal asymmetry for the treatment group, suggesting that the pooled estimates were unlikely to be importantly biased secondary to small study effects (eFigure 3). The Egger regression asymmetry test supported this finding (treatment: $z = 0.14$; $P = .89$). In comparison, visual inspection of the funnel plot showed significant asymmetry for the sham group; the Egger regression asymmetry test supported this (control: $z = 2.11$; $P = .03$). This asymmetry occurs from an increased number of small studies that reported improvement during sham therapy, which is opposite any publication bias.

DISCUSSION

This systematic review and meta-analysis of seven randomized controlled trials involving 691 men demonstrated a statistically significant improvement in IIEF-EF score of men with ED undergoing Li-ESWT compared with men undergoing sham therapy. This positive result suggests that Li-ESWT might clinically improve erectile function in men with ED.

It has been previously determined that a change of four points in the IIEF-EF score is the minimum clinically important difference, which indicates a difference that might be clinically meaningful to patients and potentially change management.²⁸ For the trials included in this study, the combined improvement in IIEF-EF score was 4.17 after treatment with Li-ESWT, which is greater than the minimum clinically important difference. Of note, one randomized controlled trial was not included in the meta-analysis because pre- and post-treatment IIEF-EF scores were not reported and were not available after attempting to contact the investigators.²⁹ This study found no difference between the treatment and control groups at 5 weeks. This study used a different device than the seven included studies

Table 1. Selected characteristics of seven studies included in this systematic review

Study	Year (wk)	Duration of follow-up (wk)	Weeks of treatment wk	Treatments/ treatment	Shocks per treatment	Total shocks	Sample		Baseline IIEF-EF score		Change in IIEF-EF score		Age (y)		Exclusion criteria	Inclusion criteria
							Treatment	Sham	Treatment	Sham	Treatment	Sham	Treatment	Sham		
Kitrey et al ⁸	2016	13	6	2	1,500	18,000	37	16	7.0	8.0	6.0	0.5	60.0	64.0	Penile anatomic abnormality; unstable medical condition; neurologic or hormonal abnormalities; treated for prostate cancer	Previous PDE5i responders; ED > 6 mo; rigidity score < 3 during PDE5i therapy; SHIM < 21 during PDE5i therapy; non-hormonal, neurologic, or psychological pathology; stable heterosexual relationship > 3 mo
Feldman et al ⁹	2015	13	6	2	1,500	18,000	84	40	—	—	6.1	2.5	—	—	—	Responders to PDE5i
Fojacki and Oster ¹⁰	2015	18	10	1	600	6,000	63	63	10.9	11.5	0.6	1.5	65.4	63.3	Prostatectomy; radiotherapy in pelvis; hormonal therapy against prostate cancer; anatomic penis disorder; penile prosthesis; treatment with anticoagulants (except acetylsalicylic acid 75 mg); psychiatric disorder; hypogonadism; IIEF score > 25; pregnant partner or delivered within past 12 mo; critical health disease; neurologic disorders	ED ≥ 6 mo; in relationships; patient accepts not using any other therapy against ED

(continued)

Table 1. Continued

Study	Year (wk)	Duration of follow-up (wk)	Weeks of treatment	Shocks per treatment	Total shocks	Sample	Baseline		Change in		Age (y)	Exclusion criteria	Inclusion criteria			
							IIEF-EF score		IIEF-EF score							
							Treatment	Sham	Treatment	Sham						
Srini et al ¹¹	2015	13	6	2	1,500	18,000	95	40	9.5	9.2	12.5	1.4	40.1	31.8	Radical prostatectomy; pelvic radiotherapy; any cause of ED other than vascular; chronic hematologic disease; cardiovascular condition; cancer in past 5 y; antiandrogen treatment; any anatomic, neurologic, or hormonal abnormalities	IIEF-EF domain score < 18 after 4 wk; PDE5i washout period; peak systolic velocity < 30 cm
Hatzichristou and Kalyvianakis ¹²	2015	56	6	2	1,500	18,000	30	16	13.8	14.6	5.3	1.4	53.0	55.1	—	Vasculogenic ED and positive response to PDE5i treatment
Yee et al ¹³	2014	13	6	2	1,500	18,000	30	28	10.2	10.2	7.6	5.6	58.9	63.3	Known endocrine disease; androgen deprivation therapy; neurologic disease; penile structural abnormality; radical prostatectomy; penile implant	≥18 y old; ≥6-mo history of ED; in heterosexual relationship ≥ 6 mo; SHIM score ≤ 21
Vardi et al ¹⁴	2012	13	6	2	1,500	18,000	40	20	12.6	11.5	6.7	3.0	58.0	57.0	Radical prostatectomy; pelvic radiotherapy or hormonal therapy; psychiatric condition; anatomic, neurologic, or hormonal abnormalities	IIEF-EF score < 19 while on PDE5i; stable heterosexual relationship > 3 mo

ED = erectile dysfunction; IIEF-EF = International Index of Erectile Function erectile function domain; PDE5i = phosphodiesterase type 5 inhibitor; SHIM = Sexual Health Inventory for Men.

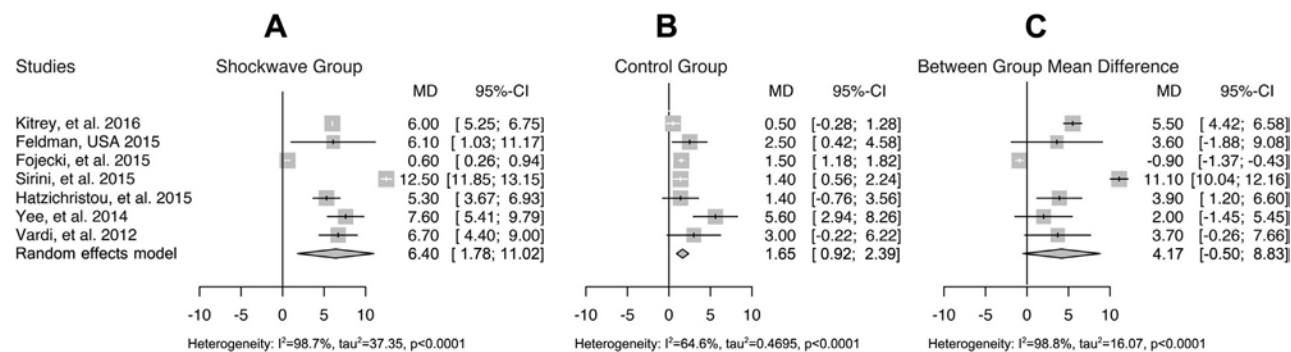


Figure 2. Forest plot of change in International Index of Erectile Function erectile function score for men undergoing low-intensity extracorporeal shockwave therapy vs sham therapy.

(Duolith SD1, Storz, Switzerland) and had a longer follow-up time of 24 months.

The mechanism of action that leads to improvement in IIEF scores in men treated with Li-ESWT has not been elucidated completely. In vitro and animal studies have shown that SWT can promote neovascularization and expression of pro-angiogenesis markers resulting in remodeling of tissue.^{30–32} Studies on the effect of SWT on penile tissue in rats have shown improvement in erectile function and regeneration of endothelium, smooth muscle, and nerves expressing neuronal nitric oxide synthase.^{7,33} Although no histologic or gene expression studies have been carried out in human tissue, using an established protocol, several groups have reported a statistically significant improvement in flow-mediated dilatation in patients treated with Li-ESWT, indicating improvement in penile hemodynamics and endothelial function.^{8,14,34} A recent study of mice as a model of type 2 diabetes treated with Li-ESWT found that Li-ESWT improved erectile function, but not through the expected mechanism dependent on nitric oxide and cyclic guanosine monophosphate.³⁵ Thus, currently, Li-ESWT is believed to be effective primarily by regenerating microvasculature and improving penile hemodynamics; this

Table 2. Meta-regression by age and total shock energy

Meta-regression	Slope	Lower CI	Upper CI	Q	P value
Control arm					
Duration of follow-up	−0.01	−0.07	0.06	0.080	.78
Age (y)	−0.04	−0.37	0.30	0.05	.83
Baseline IIEF-EF score	0.15	−0.31	0.60	0.39	.53
Treatment arm					
Duration of follow-up	−0.05	−0.36	0.26	0.10	.75
Age (y)	−0.41	−0.95	0.14	2.16	.14
Baseline IIEF-EF score	−0.37	−2.80	2.07	0.09	.77

IIEF-EF = International Index of Erectile Function erectile function domain.

could explain why it has been studied mainly in men with vasculogenic ED and not in men with neurogenic ED.

This study is not the first meta-analysis to publish on Li-ESWT and ED.³⁶ In a meta-analysis published by Lu et al,³⁶ men with ED, Peyronie’s disease, and chronic pelvic pain were included. With this heterogeneous population, they found the average IIEF-EF score difference between the treatment group and the control group was 2.00. In the present study, the average IIEF-EF score difference was 4.17, a clinically significant improvement. In addition, Lu et al included randomized controlled trials and cohort studies. With the inclusion of cohort studies, Lu et al presented their meta-analytic findings at a level of evidence of 2a. Although we emphasize that we are not the first to report a systematic review and meta-analysis on the use of Li-ESWT in the treatment of ED, our study differs in that it is the first to publish on a homogenous population of men with only ED. Furthermore, our meta-analysis includes only randomized controlled trials and thus can be regarded as level 1a evidence.

Our study has important strengths and limitations. This is the first meta-analysis published on Li-ESWT that specifically reports on only men with ED, demonstrating a significant clinical and statistical improvement. All seven trials included were randomized controlled trials with sham therapy. However, most included trials had small samples; the largest study included in our meta-analysis had only 135 men.¹¹ Two studies were published as abstracts. Study investigators for the abstracts were contacted for further information, and we received, for our review, a prepared report for one and a study protocol for the other. Although we are uncertain of the current publication status of these two abstracts, we are confident after thorough review of the data presented that the quality of evidence presented is similar to those presented in the peer-reviewed articles. Follow-up was limited to approximately 1 year in most studies and only one study provided follow-up data beyond 1 year.¹² Data on the use of PDE5i during Li-ESWT treatment were available in five studies; the remainder did not report these data. The study by Kitrey et al⁸ was the only one in which patients used PDE5i during the SWT phase. Our study also had

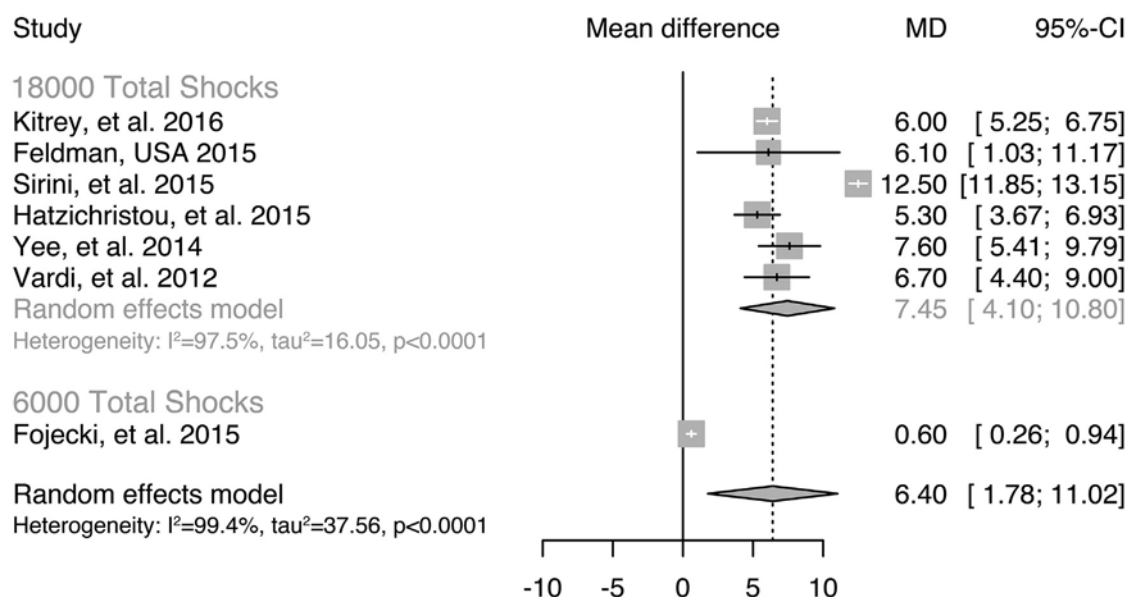


Figure 3. Sub-analyses by total treatment shocks.

increased heterogeneity ($I^2 = 99.4\%$), which can be attributed to two studies (Fojecki and Osther¹⁰ and Sirini et al¹¹) that, when systematically omitted from the sensitivity analysis, caused the overall effect to change by more than 0.5. One possible cause for this heterogeneity could be treatment regimen and subject selection. The study published by Fojecki and Osther showed minimal difference between the treatment and sham groups, which can be explained by the variation in treatment protocol. Fojecki and Osther used a total of 6,000 treatment shocks over 10 weeks, whereas all other studies used 18,000 treatment shocks over 9 weeks. Conversely, Sirini et al described a greater average treatment effect compared with all other treatment groups, which might be explained by their subject selection. The study by Sirini et al is the only one that screened men by ultrasound for vasculogenic ED; thus, they might have selected study participants who were more apt to respond to Li-ESWT. When these two trials are omitted, the heterogeneity significantly decreases ($I^2 = 0\%$) and the total treatment effect is 6.17, very similar to the original calculated treatment effect of 6.40.

Currently, it is unclear where Li-ESWT fits in the current treatment algorithm for ED. The most recent update to the European Association of Urology guidelines on male sexual dysfunction lists SWT as a potential treatment option for ED, but the association refrains from giving any recommendations at this time because of the immaturity of available data.³ The American Urological Association currently does not include SWT in its guideline on management of ED. Because no prior meta-analysis has been performed synthesizing only randomized controlled trials, this study sheds light on the effectiveness of Li-ESWT in treating ED.

However, as with many therapies, patient selection is likely to be crucial in maximizing the benefits of Li-ESWT. Results of

the two randomized controlled trials in this study and the single-arm studies show that factors such as older age, several comorbidities, longer duration of ED,^{37,38} lower baseline IIEF-EF score, and poor initial response to PDE5i can undermine the overall effect of Li-ESWT in the improvement of the IIEF-EF score.^{8,13,39,40} Although our findings indicate an improvement for those undergoing Li-ESWT, more randomized controlled trials are warranted before the acceptance of this treatment becomes widespread. From our review of the literature, we put forth these recommendations for future studies: future studies should be randomized; subjects should be screened by penile Doppler ultrasound and nocturnal penile tumescence to ensure only men with vascular ED are included; the duration of follow-up should be longer than 3 months; other treatment schedules ought to be trialed to determine optimum effect; control groups should undergo sham treatment; PDE5is should be stopped completely and with appropriate washout periods; all studies should be registered on trial registry sites; and all studies should report all adverse events. It seems reasonable that future trials should start with using 18,000 shocks. Because no significant adverse effects have been reported, a more condensed protocol shorter than 6 weeks could be attempted. However, spacing out treatments could end up being more beneficial because of some yet unknown effect on penile physiology.

CONCLUSION

In this meta-analysis of randomized controlled trials evaluating the effect of Li-ESWT on ED, the improvement in IIEF-EF scores was statistically significant for men who underwent Li-ESWT compared with those who underwent sham therapy.

However, more stringent randomized controlled trials are warranted before there is widespread acceptance of this treatment.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jsxm.2016.11.001>.