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

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Abstract

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

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

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

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

2. Patients and methods

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

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

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

2.1. Inclusion/exclusion criteria

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

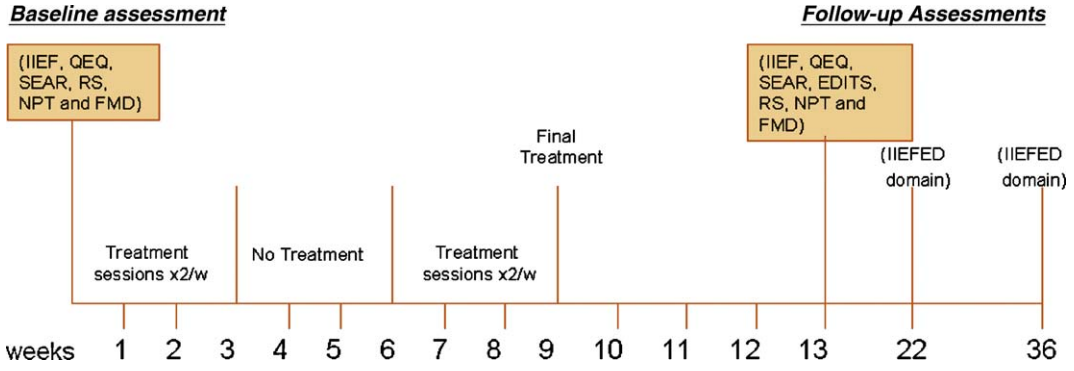


Fig. 1 – Study flow chart.
IIEF = International Index of Erectile Function; QEQ = Quality of Erection Questionnaire; SEAR = Self-Esteem and Relationship Questionnaire; RS = rigidity score; NPT = nocturnal penile tumescence; FMD = flow-mediated dilatation; ED = erectile dysfunction; EDITS = Erectile Dysfunction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

2.2. Study protocol

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

2.3. Statistical analysis

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

3. Results

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4. Discussion

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

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

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

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

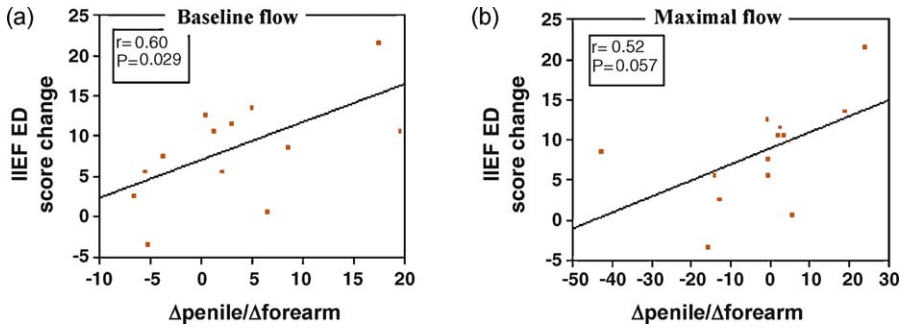


Fig. 2 – Correlation between the adjusted flow-mediated dilatation indices for (a) baseline and (b) maximal flow and the changes in the International Index of Erectile Function erectile dysfunction score 1 mo after treatment.
IIEF ED = International Index of Erectile Function—Erectile Dysfunction domain.

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

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

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

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

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

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

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

5. Conclusions

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

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

Study concept and design: Gruenwald, Vardi.
Acquisition of data: Gruenwald, Vardi, Appel, Massarwi.
Analysis and interpretation of data: Gruenwald, Vardi, Appel, Jacob.
Drafting of the manuscript: Gruenwald, Vardi.
Critical revision of the manuscript for important intellectual content: Gruenwald, Vardi.
Statistical analysis: Gruenwald, Vardi.
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Supervision: Gruenwald, Vardi.
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