THE JOURNAL OF
SEXUAL MEDICINE

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, MD[3]

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.

J Sex Med 2017;14:27−35.

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, intracorporal 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 al[6] 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]

Received June 29, 2016. Accepted November 1, 2016.

[1]Department of Urology, University of California, Los Angeles, CA, USA;
[2]Baylor College of Medicine, Houston, TX, USA;
[3]Department of Urology, Miller School of Medicine, University of Miami, Miami, FL, USA
*Equivalent contribution.

http://dx.doi.org/10.1016/j.jsxm.2016.11.001

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 ED[6]) through March 2016 that reported on using the IIEF-EF sore 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.

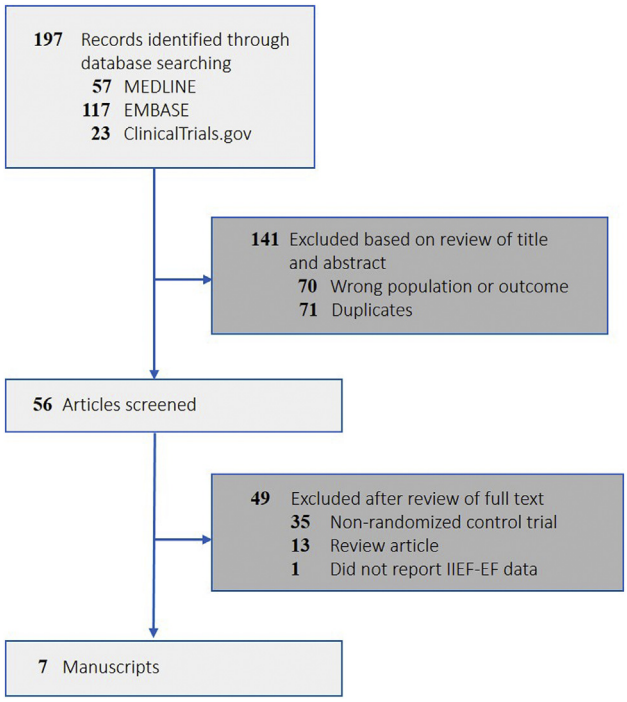

Figure 1. Flow diagram for study selection.

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 regiments 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/mm^2. 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 Osther[10] and Sirini et al[11]) 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	Duration of follow-up (wk)	Weeks of treatment	Treatments/ wk	Shocks per treatment	Total treatment 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
Fojecki and Osther[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	Duration of follow-up (wk)	Weeks of treatment	Treatments/ wk	Shocks per treatment	Total treatment 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		
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.

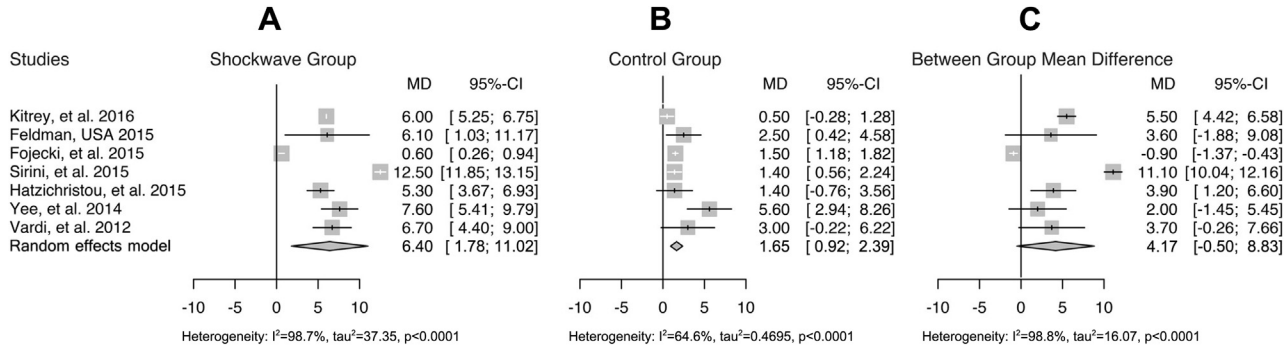

Figure 2. Forest plot of change in International Index of Erectile Function erectile function score for men undergoing low-intensity extracorporeal shockwave therapy vs sham therapy.

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

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.

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 al[8] was the only one in which patients used PDE5i during the SWT phase. Our study also had

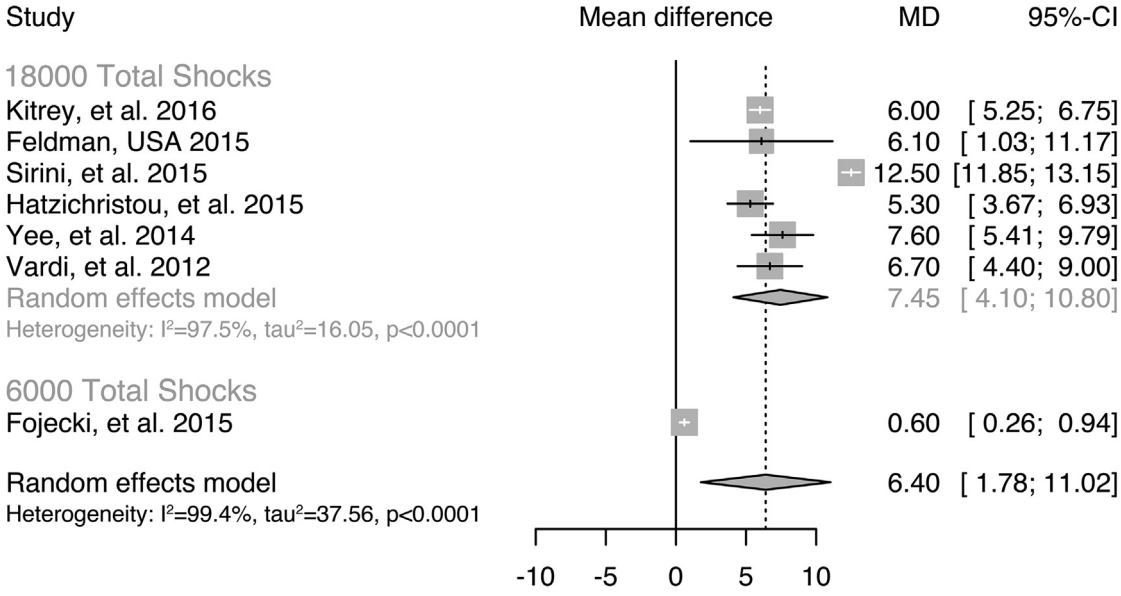

Figure 3. Sub-analyses by total treatment shocks.

increased heterogeneity ($I^2 = 99.4\%$), which can be attributed to two studies (Fojecki and Osther[10] and Sirini et al[11]) 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.

Corresponding Author: Ranjith Ramasamy, MD, University of Miami, 1150 NW 14th Street, Suite 309, Miami, FL 33136, USA; E-mail: ramasamy@miami.edu

Conflicts of Interest: The authors report no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy

(b) Acquisition of Data
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn

(c) Analysis and Interpretation of Data
Raul I. Clavijo; Taylor P. Kohn; Ranjith Ramasamy

Category 2

(a) Drafting the Article
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy

(b) Revising It for Intellectual Content
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy

Category 3

(a) Final Approval of the Completed Article
Raul I. Clavijo; Taylor P. Kohn; Jaden R. Kohn; Ranjith Ramasamy

REFERENCES

1. Wessells H, Joyce GF, Wise M, Wilt TJ. Erectile dysfunction. **J Urol 2007;177:1675-1681.**
2. Smith WB II, McCaslin IR, Gokce A, et al. PDE5 inhibitors: considerations for preference and long-term adherence. **Int J Clin Pract 2013;67:768-780.**
3. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. **Eur Urol 2010;57:804-814.**
4. Mulhall JP, Jahoda AE, Cairney M, et al. The causes of patient dropout from penile self-injection therapy for impotence. **J Urol 1999;162:1291-1294.**
5. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. **J Urol 1994;151:54-61.**
6. Vardi Y, Appel B, Jacob G, et al. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. **Eur Urol 2010;58:243-248.**
7. Qiu X, Lin G, Xin Z, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. **J Sex Med 2013;10:738-746.**
8. Kitrey ND, Gruenwald I, Appel B, et al. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. **J Urol 2016;195:1550-1555.**
9. Feldman R, Denes B, Appel B, et al. The safety and efficacy of Li-ESWT in 604 patients for erectile dysfunction: summary of current and evolving evidence. **J Urol 2015;193:e905-e906.**
10. Fojecki GT, Osther P. Low-energy linear extracorporeal shock wave therapy for erectile dysfunction. Poster presented at: 17th Congress of European Society of Sexual Medicine. December 2015; København.
11. Srini VS, Reddy RK, Shultz T, et al. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. **Can J Urol 2015;22:7614-7622.**
12. Hatzichristou DG, Kalyvianakis DE: Erectile dysfunction shock wave therapy (EDSWT) improves hemodynamic parameters in patients with vasculogenic erectile dysfunction (ED): a triplex-based sham-controlled trial. Presented at annual congress of European Association of Urology, Madrid, Spain, March 20-24, 2015, abstract 124.
13. Yee CH, Chan ESY, Hou S-M, et al. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. **Int J Urol 2014;10:1041-1045.**
14. Vardi Y, Appel B, Kilchevsky A, et al. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. **J Urol 2012;187:1769-1775.**
15. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. **Ann Intern Med 2009;151:264-269; w64.**
16. Rosen RC, Riley A, Wagner G, et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. **Urology 1997;49:822-830.**
17. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org.
18. Review Manager (RevMan). 5.3 ed. Copenhagen: Nordic Cochrane Centre, Cochrane Collaboration; 2014.
19. Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. **Research Synth Methods 2010;1:97-111.**
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. **Stat Med 2002;21:1539-1558.**
21. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. **BMJ 2003;327:557-560.**
22. Sterne JA, Juni P, Schulz KF, et al. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. **Stat Med 2002;21:1513-1524.**
23. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. **Stat Med 2002;21:589-624.**

24. Viechtbauer W. Conducting Meta-Analyses in R with the metafor package. **J Stat Softw 2010;36:1-48**.

25. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. **BMJ 1997; 315:629-634**.

26. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. **J Clin Epidemiol 2001; 54:1046-1055**.

27. R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at http://www.R-project.org. Accessed December 8, 2016.

28. Rosen RC, Allen KR, Ni X, et al. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. **Eur Urol 2011;60:1010-1016**.

29. Olsen AB, Persiani M, Boie S, et al. Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. **Scand J Urol 2015;49:329-333**.

30. Holfeld J, Zimpfer D, Albrecht-Schgoer K, et al, Epicardial shock-wave therapy improves ventricular function in a porcine model of ischaemic heart disease. J Tissue Eng Regen Med http://dx.doi.org/10.1002/term.1890. E-pub ahead of print.

31. Wang CJ, Wang FS, Yang KD, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. **J Orthop Res 2003;21:984-989**.

32. Yan X, Zeng B, Chai Y, et al. Improvement of blood flow, expression of nitric oxide, and vascular endothelial growth factor by low-energy shockwave therapy in random-pattern skin flap model. **Ann Plast Surg 2008;61:646-653**.

33. Liu J, Zhou F, Li GY, et al. Evaluation of the effect of different doses of low energy shock wave therapy on the erectile function of streptozotocin (STZ)-induced diabetic rats. **Int J Mol Sci 2013;14:10661-10673**.

34. Gruenwald IE, Appel B, Vardi Y. The effect of a second course of low intensity shock waves for ED in partial or non-responders to one treatment course. **J Sex Med 2012;9:315**.

35. Assaly-Kaddoum R, Giuliano F, Laurin M, et al. Low intensity extracorporeal shockwave therapy (Li-ESWT) improves erectile function in a model of type II diabetes independently of NO/cGMP pathway. **J Urol 2016;196:950-956**.

36. Lu Z, Lin G, Reed-Maldonado A, et al. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol http://dx.doi.org/10.1016/j.eururo.2016.05.050. E-pub ahead of print.

37. Hisasue S, China T, Ide H, et al. Initial experience of low-intensity shock wave therapy for the treatment of erectile dysfunction in teikyo University Hospital, Japan. **Urology 2012;80:S313-S314**.

38. Reisman Y, Hind A, Varaneckas A, et al. Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-up pilot study. **Int J Impot Res 2014; 27:108-112**.

39. Bechara A, Casabe A, De Bonis W, et al. Effectiveness of low-intensity extracorporeal shock wave therapy on patients with erectile dysfunction (ED) who have failed to respond to PDE5i therapy. A pilot study. **Arch Esp Urol 2015;68:152-160**.

40. Pelayo-Nieto M, Linden-Castro E, Alias-Melgar A, et al. Linear shock wave therapy in the treatment of erectile dysfunction. **Actas Urol Esp 2015;39:456-459**.

SUPPLEMENTARY DATA

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

THE JOURNAL OF
SEXUAL MEDICINE

ORIGINAL RESEARCH

ERECTILE FUNCTION

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

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

ABSTRACT

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

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

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

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

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

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

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

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

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

INTRODUCTION

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

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

Received December 13, 2016. Accepted May 19, 2017.

Center for Sexual and Reproductive Health, Aristotle University of Thessaloniki Greece, Thessaloniki, Greece

http://dx.doi.org/10.1016/j.jsxm.2017.05.012

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

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

METHODS

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

Study Sample

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

Study Protocol

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

Blinding and Randomization

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

LI-ESWT Methodology

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

Penile Triplex Ultrasonography Protocol

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

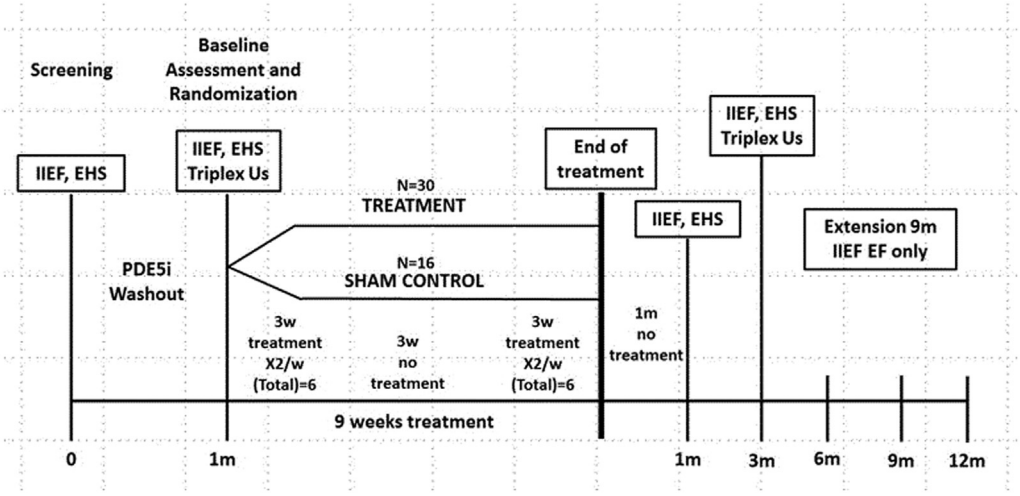

Figure 1. Study flowchart. EHS = Erection Hardness Scale; IIEF = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function erectile function domain; m = months; PDE5i = phosphodiesterase type 5 inhibitor; Us = ultrasonography.

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

Main Outcome Measures

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

Statistical Analysis

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

RESULTS

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

IIEF-EF Score Changes

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

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

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

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

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

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

Penile Hemodynamics Changes

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

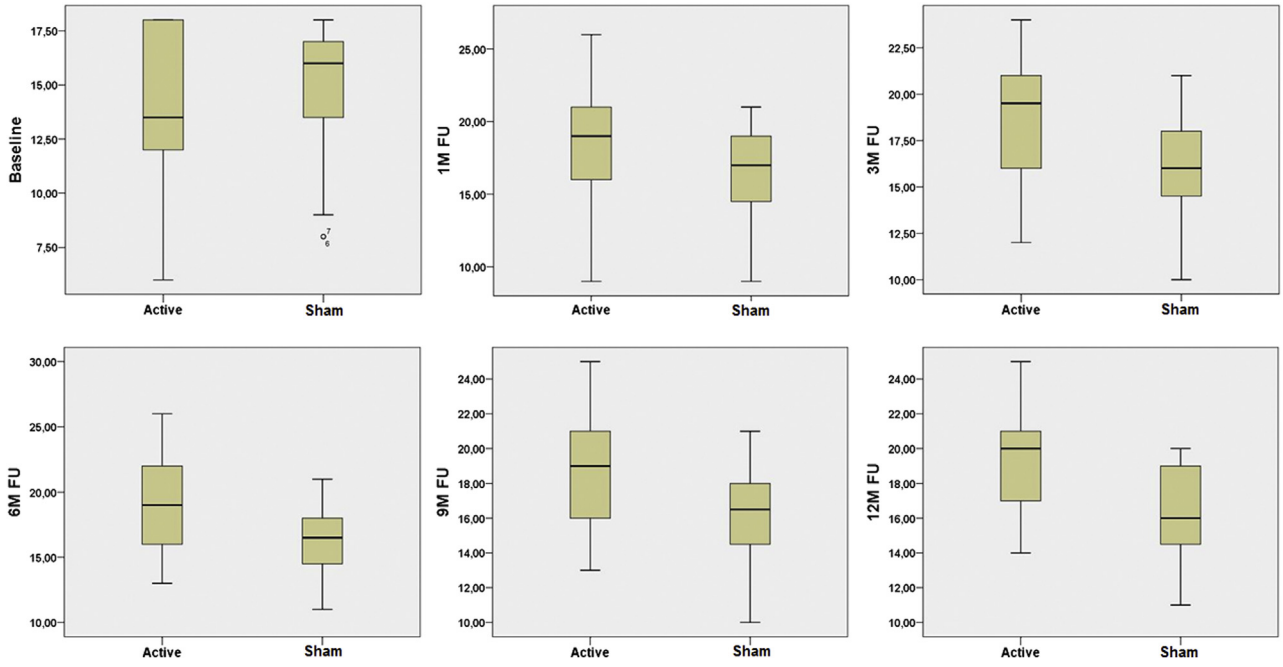

Figure 2. Twelve-month FU of International Index of Erectile Function erectile function score. All analyses were done using Student t-test. FU = follow-up; M = month. Figure 2 is available online at www.jsm.jsexmed.org.

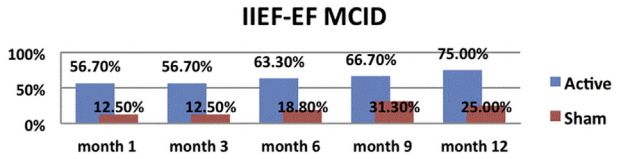

Figure 3. IIEF-EF score MCID in active and sham groups at 1-, 3-, 6-, 9-, and 12-month follow-up visits ($P < .02$ by χ^2 test). IIEF-EF = International Index of Erectile Function erectile function domain; MCID = minimal clinically important difference. Figure 3 is available online at www.jsm.jsexmed.org.

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

DISCUSSION

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

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

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

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

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

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

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

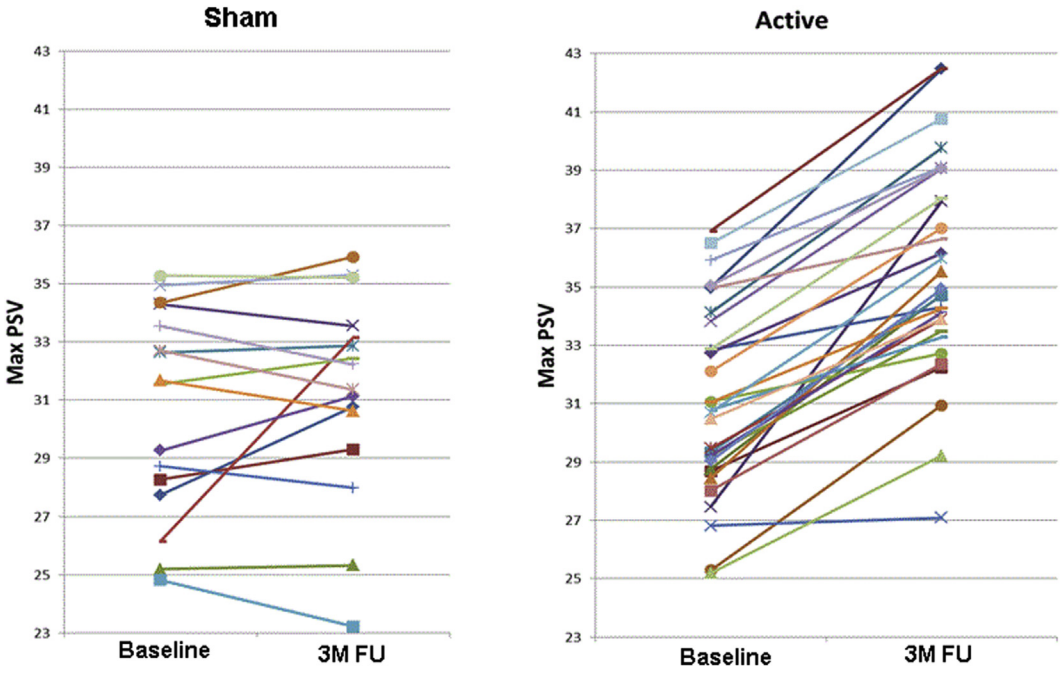

Figure 4. Individual plots of maximum PSV at baseline and at 3 months after low-intensity shockwave therapy. All but one patient showed an increase in PSV in the active group. 3M FU = 3-month follow-up; Max PSV = maximum peak systolic velocity. Figure 4 is available online at www.jsm.jsexmed.org.

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

CONCLUSIONS

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

Corresponding Author: Dimitrios Hatzichristou, MD, PhD, FECSM, Center for Sexual and Reproductive Health, Leoforos Nikis 33, 54622, Thessaloniki, Greece. Tel: 302310228028; Fax: 302310228028; E-mail: hatzichr@med.auth.gr

Conflicts of Interest: D.H. has received speaker honoraria from Medispec, Dornier Med Tech, and Menarini; and has research grants from Medispec and Dornier Med Tech. The other authors report no conflicts of interest.

Funding: Medispec has offered the device and the probes for this study.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Dimitrios Hatzichristou

(b) Acquisition of Data
Dimitrios Kalyvianakis

(c) Analysis and Interpretation of Data
Dimitrios Kalyvianakis; Dimitrios Hatzichristou

Category 2

(a) Drafting the Article
Dimitrios Kalyvianakis; Dimitrios Hatzichristou

(b) Revising It for Intellectual Content
Dimitrios Kalyvianakis; Dimitrios Hatzichristou

Category 3

(a) Final Approval of the Completed Article
Dimitrios Kalyvianakis; Dimitrios Hatzichristou

REFERENCES

1. Hatzimouratidis K, Amar E, Eardley I, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. **Eur Urol 2010;57:804-814.**
2. Hatzimouratidis K, Salonia A, Adaikan G, et al. Pharmacotherapy for erectile dysfunction: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). **J Sex Med 2016;13:465-488.**
3. Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy for ischemic cardiovascular disorders. **Am J Cardiovasc Drugs 2011;11:295-302.**
4. Moretti B, Notarnicola A, Maggio G, et al. The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. **BMC Musculoskelet Disord 2009;10:54.**

5. Aschermann I, Noor S, Venturelli S, et al. Extracorporal shock waves activate migration, proliferation and inflammatory pathways in fibroblasts and keratinocytes, and improve wound healing in an open-label, single-arm study in patients with therapy-refractory chronic leg ulcers. **Cell Physiol Biochem 2017;41:890-906.**
6. Lei H, Xin H, Guan R, et al. Low-intensity pulsed ultrasound improves erectile function in streptozotocin-induced type I diabetic rats. **Urology 2015;86:1241.e11-1241.e18.**
7. Li H, Matheu MP, Sun F, et al. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. **J Sex Med 2016;13:22-32.**
8. Gruenwald I, Appel B, Kitrey ND, et al. Shockwave treatment of erectile dysfunction. **Ther Adv Urol 2013;5:95-99.**
9. Vardi Y, Appel B, Jacob G, et al. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. **Eur Urol 2010;58:243-248.**
10. Vardi Y, Appel B, Kilchevsky A, et al. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. **J Urol 2012;187:1769-1775.**
11. Sikka SC, Hellstrom WJ, Brock G, et al. Standardization of vascular assessment of erectile dysfunction: standard operating procedures for duplex ultrasound. **J Sex Med 2013;10:120-129.**
12. Rosen RC, Allen KR, Ni X, et al. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. **Eur Urol 2011;60:1010-1016.**
13. Lu Z, Lin G, Reed-Maldonado A, et al. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. **Eur Urol 2017;71:223-233.**
14. Clavijo RI, Kohn TP, Kohn JR, et al. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. **J Sex Med 2017;14:27-35.**
15. Kikuchi Y, Ito K, Ito Y, et al. Double-blind and placebo-controlled study of the effectiveness and safety of extracorporeal cardiac shock wave therapy for severe angina pectoris. **Circ J 2010;74:589-591.**
16. Nishida T, Shimokawa H, Oi K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. **Circulation 2004;110:3055-3061.**
17. Wang CJ, Chen HS. Shock wave therapy for patients with lateral epicondylitis of the elbow: a one- to two-year follow-up study. **Am J Sports Med 2002;30:422-425.**
18. Wang CJ, Wang FS, Yang KD, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. **J Orthop Res 2003;21:984-989.**
19. Yan X, Zeng B, Chai Y, et al. Improvement of blood flow, expression of nitric oxide, and vascular endothelial growth factor by low-energy shockwave therapy in random-pattern skin flap model. **Ann Plast Surg 2008;61:646-653.**
20. Tepekoylu C, Wang FS, Kozaryn R, et al. Shock wave treatment induces angiogenesis and mobilizes endogenous CD31/CD34-positive endothelial cells in a hindlimb ischemia model: implications for angiogenesis and vasculogenesis. **J Thorac Cardiovasc Surg 2013;146:971-978.**
21. Nurzynska D, Di Meglio F, Castaldo C, et al. Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. **Ultrasound Med Biol 2008;34:334-342.**
22. Zhang H, Albersen M, Jin X, et al. Stem cells: novel players in the treatment of erectile dysfunction. **Asian J Androl 2012;14:145-155.**
23. Lu Z, Lin G, Reed-Maldonado A, et al. Reply to Zi-Jun Zou, Jia-Yu Liang, Yi-Ping Lu's Letter to the Editor re: Zhihua Lu, Guiting Lin, Amanda Reed-Maldonado, Chunxi Wang, Yung-Chin Lee, Tom F. Lue. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol 2017;71:223-33. **Eur Urol 2017;71:e59-e60.**
24. Hatzichristou D. Low-intensity extracorporeal shock waves therapy (LI-ESWT) for the treatment of erectile dysfunction: where do we stand? **Eur Urol 2017;71:234-236.**

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Andrology

Editorial by XXX on pp. x–y of this issue

Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis

Zhihua vLu [a,b], *vGuiting Lin* [a], *Amanda Reed-Maldonado* [a], *Chunxi Wang* [b], *Yung-Chin Lee* [c], *Tom F. Lue* [a,*]

[a] *Knuppe Molecular Urology Laboratory, Department of Urology, School of Medicine, University of California, San Francisco, CA, USA;* [b] *Department of Urology, The First Hospital of Jilin University, Changchun, People's Republic of China;* [c] *Department of Urology, Kaohsiung Medical University Hospital, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

Article info

Article history:
Accepted May 31, 2016

Associate Editor:
Christian Gratzke

Keywords:
Erectile dysfunction (ED)
Low-intensity extracorporeal shock wave therapy (LI-ESWT)
Meta-analysis
Clinical outcome
International Index of Erectile Function (IIEF)

Abstract

Context: As a novel therapeutic method for erectile dysfunction (ED), low-intensity extracorporeal shock wave treatment (LI-ESWT) has been applied recently in the clinical setting. We feel that a summary of the current literature and a systematic review to evaluate the therapeutic efficacy of LI-ESWT for ED would be helpful for physicians who are interested in using this modality to treat patients with ED.
Objective: A systematic review of the evidence regarding LI-ESWT for patients with ED was undertaken with a meta-analysis to identify the efficacy of the treatment modality.
Evidence acquisition: A comprehensive search of the PubMed and Embase databases to November 2015 was performed. Studies reporting on patients with ED treated with LI-ESWT were included. The International Index of Erectile Function (IIEF) and the Erection Hardness Score (EHS) were the most commonly used tools to evaluate the therapeutic efficacy of LI-ESWT.
Evidence synthesis: There were 14 studies including 833 patients from 2005 to 2015. Seven studies were randomized controlled trials (RCTs); however, in these studies, the setup parameters of LI-ESWT and the protocols of treatment were variable. The meta-analysis revealed that LI-ESWT could significantly improve IIEF (mean difference: 2.00; 95% confidence interval [CI], 0.99–3.00; $p < 0.0001$) and EHS (risk difference: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). Therapeutic efficacy could last at least 3 mo. The patients with mild-moderate ED had better therapeutic efficacy after treatment than patients with more severe ED or comorbidities. Energy flux density, number of shock waves per treatment, and duration of LI-ESWT treatment were closely related to clinical outcome, especially regarding IIEF improvement.
Conclusions: The number of studies of LI-ESWT for ED have increased dramatically in recent years. Most of these studies presented encouraging results, regardless of variation in LI-ESWT setup parameters or treatment protocols. These studies suggest that LI-ESWT could significantly improve the IIEF and EHS of ED patients. The publication of robust evidence from additional RCTs and longer-term follow-up would provide more confidence regarding use of LI-ESWT for ED patients.
Patient summary: We reviewed 14 studies of men who received low-intensity extracorporeal shock wave treatment (LI-ESWT) for erectile dysfunction (ED). There was evidence that these men experienced improvements in their ED following LI-ESWT.

* Corresponding author. Department of Urology, University of California, San Francisco, 400 Parnassus Ave., Suite A-630, San Francisco, CA 94143-0738, USA. Tel. +1 415 353 7339; Fax: +1 415 476 3803.
E-mail address: tlue@urology.ucsf.edu (T.F. Lue).

http://dx.doi.org/10.1016/j.eururo.2016.05.050
0302-2838/

1. Introduction

Phosphodiesterase type 5 inhibitors (PDE5-Is) are currently the most widely used treatments for male erectile dysfunction (ED); however, these medications merely treat ED symptoms. They do not correct the underlying penile pathophysiology, such as vascular lesions secondary to diabetes mellitus, structural lesions secondary to trauma, or neurologic injury secondary to prostatectomy, that is responsible for the ED [1]. A novel method to prevent the deterioration of erectile function due to these pathophysiologic processes is desperately needed. Based on studies generated from other clinical fields, low-intensity extracorporeal shock wave treatment (LI-ESWT) has been used to treat ED for almost 10 yr, and encouraging results have been reported.

Since the 1980s, when it was first introduced for renal lithotripsy, shock wave therapy has been rapidly adopted all over the world for different disease processes, producing either destructive effects or promoting regenerative effects. The shock wave is a kind of acoustic wave that carries energy and that, when propagating through a medium, can be targeted and focused noninvasively to affect a distant selected anatomic region. When LI-ESWT is applied to an organ, the shock waves interact with the targeted tissues and induce a cascade of biological reactions. This results in the release of growth factors, which in turn triggers neovascularization of the tissue with subsequent improvement of the blood supply [2]. LI-ESWT has been used to treat musculoskeletal disorders [3], myocardial infarction [4], nonhealing wounds [5], and ED [6].

Improvements in both International Index of Erectile Function (IIEF) and Erection Hardness Score (EHS) have been reported after using LI-ESWT for patients with ED. At the beginning of research into LI-ESWT, most studies were retrospective and included few patients. In the past 2 yr, well-designed prospective studies have been conducted and concluded that LI-ESWT is a feasible noninvasive method for improving male ED.

We performed a systematic review of the current body of literature investigating the application of LI-ESWT for ED. Our goal was to analyze the available data to determine the efficacy of LI-ESWT for ED.

2. Evidence acquisition

2.1. Search strategy

We performed a systematic search of PubMed and Embase databases for studies on LI-ESWT and ED. The search terms were *shock wave AND (erectile dysfunction OR IIEF OR EHS)*. We investigated the current studies of LI-ESWT for patients with ED, the therapeutic efficacy of LI-ESWT for patients with ED, and the relationship of therapeutic efficacy and different setup parameters and protocols.

2.2. Inclusion and exclusion criteria

All clinical studies that investigated the efficacy of LI-ESWT for ED were included regardless of study design. Both randomized controlled trials (RCTs) and cohort studies were included. No limitation was placed on PDE5-I consumption during the LI-ESWT treatment period or on the severity of ED. The follow-up data were abstracted from these studies. If more than one study was published by a medical center, only the last report was included in our review. All literature reviews, editorial comments, background, animal models, and case reports were excluded.

2.3. Data extraction and synthesis

The abstracts were independently reviewed by three authors (Z.L., G.L., T.F.L.) to determine eligibility for inclusion. The basic details of the study, setup parameters of the LI-ESWT machine, treatment protocols, assessment tools, and *p* values were abstracted manually from each of the studies (G.L., Z.L.), and the data were verified (T.F.L.).

2.4. Study outcomes

Fourteen studies were included in our review. Seven studies were RCTs and were included for meta-analysis. The patients were distributed in different areas of the world, and there were no overlaps of populations among the studies. Details are shown in Table 1 and Supplementary table.

2.5. Meta-analysis

The abstracted data were analyzed with RevMan 5.3 software (Cochrane Collaboration, London, UK). The risk of bias in the included studies was assessed by the Cochrane Collaboration's tool. The proper effect sizes and statistical analysis methods were chosen according to different data types and evaluation purposes. For continuous variables, weighted mean difference (MD) and a 95% confidence interval [CI] were used. For discontinuous variables, risk difference (RD) and a 95% CI were used. For the heterogeneity test between studies, the I^2 test was used. The data without significant heterogeneity ($p > 0.05$, $I^2 \leq 50\%$) were analyzed by the fixed-effects model. The data with heterogeneity that could not be explained were analyzed by the random-effects model. The data that could not be analyzed were described. The results of the meta-analysis are presented in forest plots. Publication bias is presented in funnel plots.

3. Evidence synthesis

A Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) flow chart of screening and selection results is shown as Figure 1.

3.1. The current studies of low-intensity extracorporeal shock wave treatment for erectile dysfunction

A total of 14 studies involving 833 patients were included in this review. All of the studies were published between 2005 and 2015. These studies were performed by different medical centers in different countries. Most of these ED patients had an organic etiology, such as a vascular lesion [7,8], a nerve injury [9], or a lesion of the cavernous body of

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

Table 1 – Current studies of low-intensity extracorporeal shock wave treatment for erectile dysfunction patients

Study	Year of publication	Country	Disease	Setup of LESW		Protocol of LESW treatment			Follow-up, mo	Evaluation tools for ED	*p* value of IIEF after LI-ESWT	Study design
				Energy density, mJ/mm^2	No. of pulses each treatment	No. of treatments each week	No. of sites of treatment	Total treatment courses, wk				
Olsen et al [19]	2015	Denmark	ED	0.15	3000	1	6	5	1, 3, 6	IIEF-5, EHS	0.67	RCT
Frey A	2015	Denmark	ED after RP	NA	3000	2	3	6	1, 12	IIEF-5	0.0049	Cohort study
Bechara et al [15]	2015	Argentina	ED	0.09	5000	1	4	4	3	IIEF-6, SEP2, SEP3, GAQ	NA	Cohort study
Chung and Cartmill [7]	2015	Australia	ED	0.25	3000	2	4	6	1, 4	IIEF-5, EDITS, overall satisfaction score	<0.05	Cohort study
Pelayo-Nieto et al [8]	2015	Mexico	ED	0.09	5000	1	4	4	1, 6	IIEF, SEP, GAQ	0.013	Cohort study
Hisasue	2015	Japan	ED	0.09	1500	2	5	9	1, 3, 6	IIEF, EHS, MPCC	<0.05	Cohort study
Srini et al [16]	2015	Indian	ED	NA	NA	NA	NA	NA	1, 3, 6, 9, 12	IIEF-EF, EHS, CGIC	0.0001	RCT
Yee et al [18]	2014	Hong Kong	ED	0.09	1500	2	5	9	1	IIEF-ED, EHS,	0.001	RCT
Palmieri et al [10]	2012	Italy	ED + PD	0.25	2000	1	NA	4	3, 6	IIEF, quality of life	<0.05	Cohort study
Vardi et al [17]	2012	Israel	ED	0.09	1500	2	5	9	1	IIEF, EHS, penile blood flow	0.0322	RCT
Zimmermann et al [14]	2009	Austria	ED + chronic pelvic pain	0.25	3000	1	NA	4	1, 3	IIEF	0.034	RCT
Chitale et al [11]	2010	UK	ED + PD	NA	3000	1	NA	6	3, 6	IIEF	0.249	RCT
Poulakis et al [12]	2006	Germany	ED + PD	0.17	2000	1	NA	5	1, 3, 6	IIEF-5	0.205	RCT
Skolarikos et al [13]	2005	Greece	ED + PD	NA	3000	NA	NA	6	3, 12	IIEF-5	0.06	Cohort study

CGIC = Clinical Global Impression of Change; ED = erectile dysfunction; EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; EHS = Erectile Hardness Score; GAQ = Global Assessment Questionnaire; IIEF = International Index of Erectile Function; LI-ESWT = low-intensity extracorporeal shock wave treatment; MPCC = maximal penile circumferential change; NA = not available; PD = Peyronie's disease; RCT = randomized controlled trial; RP = radical prostatectomy; SEP = Sexual Encounter Profile.

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis of Controlled Clinical Trials. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

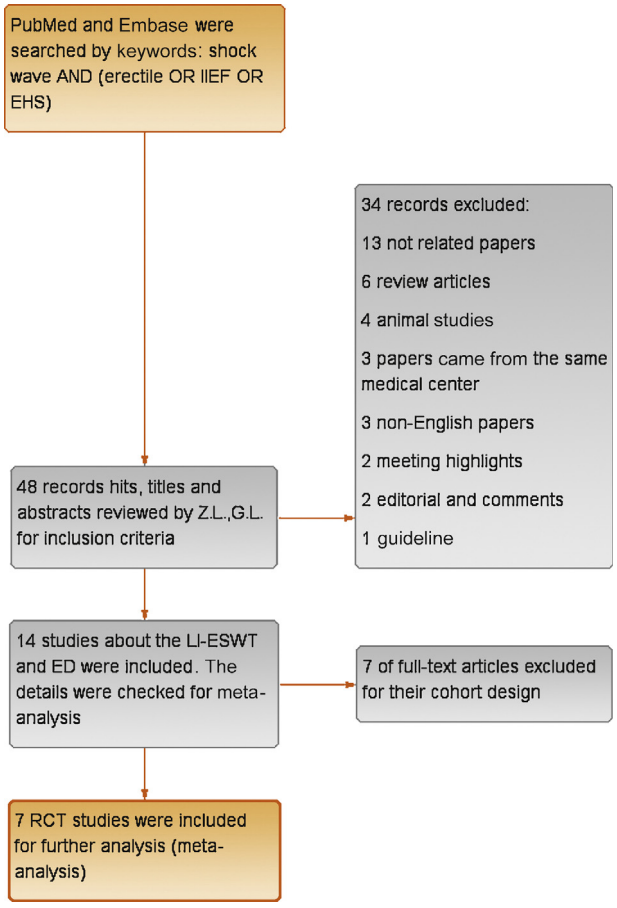

Fig. 1 – The search terms were *shock wave AND (erectile OR IIEF OR EHS)*. Forty-eight records were enrolled. After review, 14 studies about low-intensity extracorporeal shock wave treatment and erectile dysfunction were included. Seven were randomized controlled trials and were included in the meta-analysis.
ED = erectile dysfunction; EHS = Erection Hardness Score; IIEF = International Index of Erectile Function; LI-ESWT = low-intensity extracorporeal shock wave treatment; RCT = randomized controlled trial.

the penis (Peyronie's disease [PD]) [10–13]. One study focused on ED patients with chronic pelvic pain [14]. Most of the studies prohibited the usage of PDE5-Is during the treatment course. Some RCTs even set a washout period for patients who had taken PDE5-I before they started LI-ESWT. Only three studies did not limit the use of PDE5-Is during the treatment [10,11,15]. One of these studies was included for meta-analysis because of its RCT design.

Of the 14 included studies, 7 were RCTs, and the remaining 7 were cohort studies (Table 1). According to the conventions of evidence-based medicine, RCTs provide level 1 evidence, the highest level of evidence. Consequently, the seven RCTs were included for meta-analysis.

The setup parameters of LI-ESWT were different among studies. The energy flux density (EFD) varied from 0.09 to 0.25 mJ/mm^2, and the number of shock wave pulses of each treatment was between 1500 and 5000. In most of the studies, LI-ESWT directed treatment at multiple sites on the penis during each treatment. The treatment course of most studies was not longer than 6 wk, and only three studies had a longer treatment course of 9 wk.

The IIEF was the prevailing assessment tool for ED patients, and all studies in our analysis provided the IIEF before and after LI-ESWT. This made it possible to perform further meta-analysis. Another frequently used assessment tool was the EHS, which was provided by five studies. Other tools, such as the Sexual Encounter Profile, the Global Assessment Questionnaire, maximal penile circumferential change, and the Clinical Global Impression of Change, were not used consistently throughout multiple studies and so were not used for further meta-analysis.

3.2. The quality evaluation of the studies and analysis for the risk of bias

The Cochrane Collaboration's tool was used for assessing the quality of the study and the risk of bias. The RCTs reported that the patients were assigned randomly into LI-ESWT or control groups without describing the process of randomization [16,17]. Most studies did not describe how the physicians were blinded to the study participants. When the patients in the control group received the sham treatment, the LI-ESWT output energy would need to be reduced to zero, thus it would be difficult to keep the physician blinded to this change. Only the study by Yee et al [18] reported the details of how the double blinding was

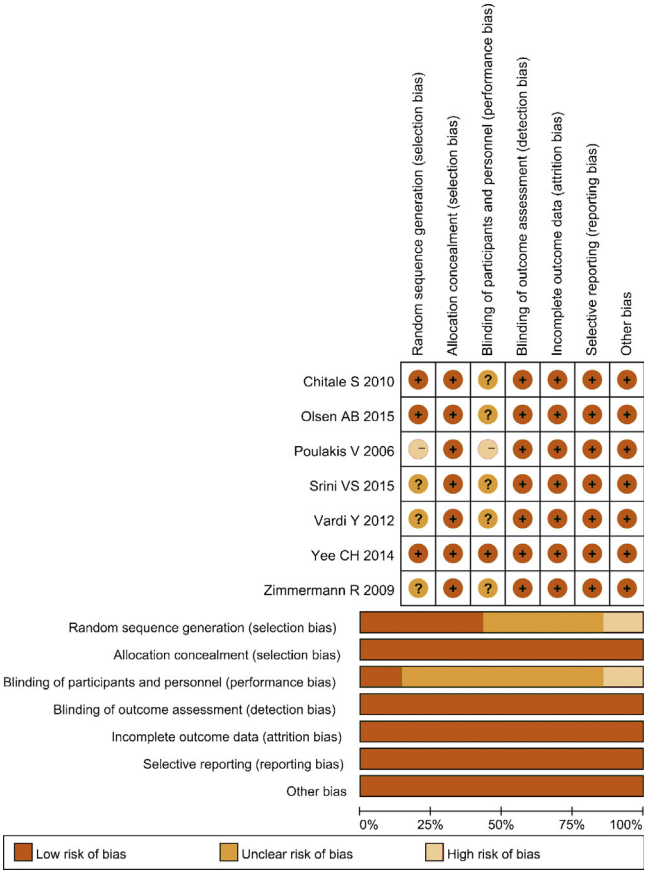

Fig. 2 – There were seven randomized controlled studies included in our meta-analysis. The quality of studies was assessed with the Cochrane Collaboration's tool. This revealed that 57.1% of the studies had an unclear risk of bias in randomization, and only 16.7% of studies had good blinding for both patients and doctors.

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

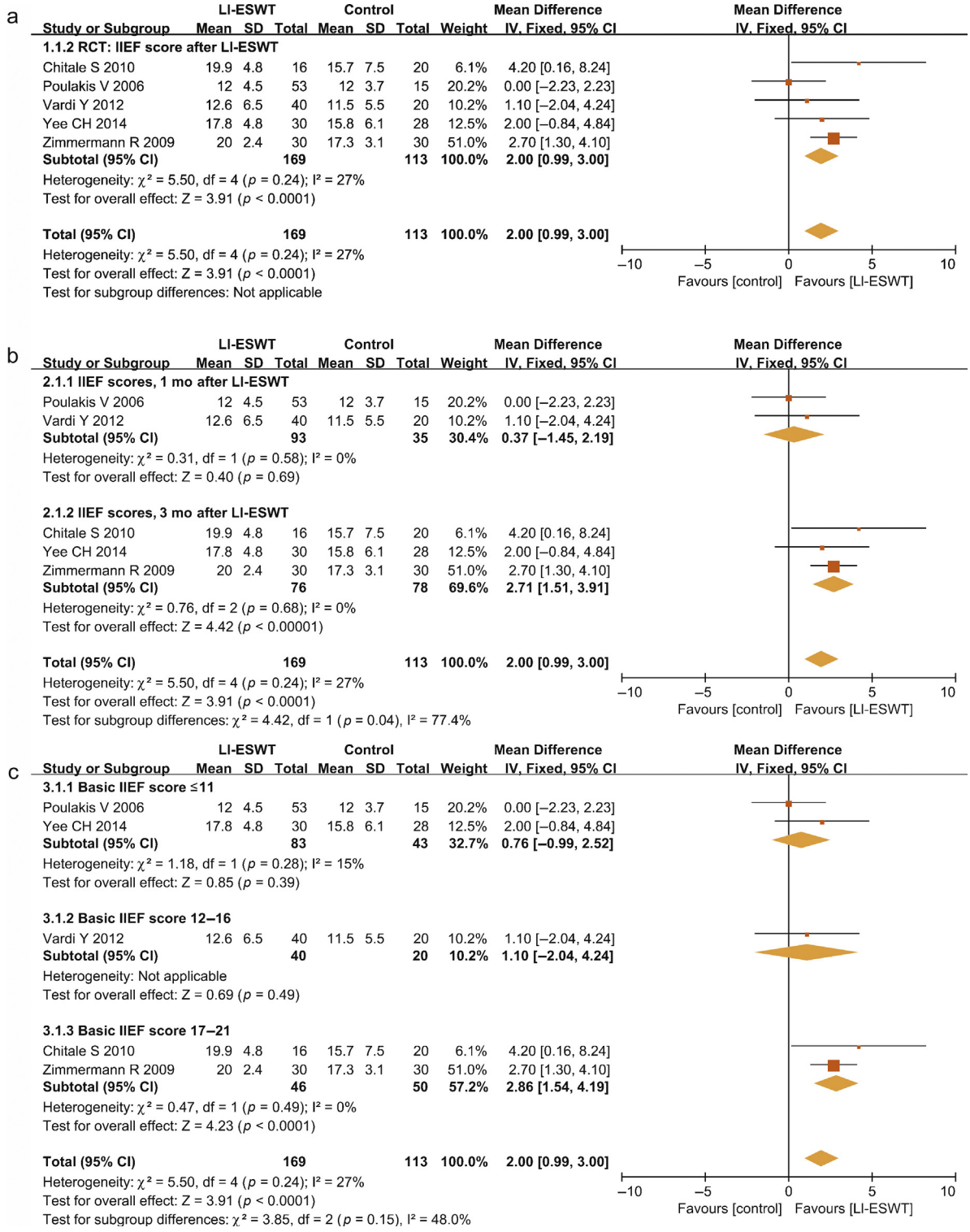

Fig. 3 – Clinical outcomes. (a) Although some studies did not prove that low-intensity extracorporeal shock wave treatment (LI-ESWT) could increase International Index of Erectile Function (IIEF), the meta-analysis results showed that LI-ESWT could improve IIEF significantly (mean difference [MD]: 2.00; 95% confidence interval [CI], 0.99–3.00; $p < 0.0001$). (b) Subgroup analysis: The studies that assessed the IIEF at 1 mo did not reveal a significant improvement (MD: 0.37; 95% CI, −1.45 to 2.19; $p = 0.69$). However, the studies assessing IIEF at 3 mo showed significant improvement (MD: 2.71; 95% CI, 1.51–3.91; $p < 0.0001$). (c) The IIEF in the group with mild erectile dysfunction (ED) increased significantly (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$), but in the severe and moderate groups, it did not ($p = 0.39$ and $p = 0.49$, respectively). (d) The studies of ED patients without any comorbidities revealed a significant increase of IIEF (MD: 2.36; 95% CI, 1.19–3.53; $p < 0.0001$) compared with the studies recruiting ED patients with Peyronie's disease. (e) The IIEF of patients in the group with LI-ESWT plus phosphodiesterase type 5 inhibitors improved more significantly (MD: 4.20; 95% CI, 0.16–8.24; $p = 0.04$).

CI = confidence interval; ED = erectile dysfunction; IIEF = International Index of Erectile Function; IV = inverse variance; LI-ESWT = low-intensity extracorporeal shock wave treatment; PD = Peyronie's disease; PDE5-I = phosphodiesterase type 5 inhibitor; RCT = randomized controlled trial; SD, standard deviation.

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

ensured. Figure 2 shows that 57.1% studies had an unclear risk of bias in randomization and that only 16.7% of studies had good blinding for both patients and doctors.

3.3. The evaluation of the therapeutic efficacy of low-intensity extracorporeal shock wave treatment for patients with erectile dysfunction

The IIEF, the prevailing assessment tool for ED patients, was available for abstraction from five RCTs. The data included mean value and standard deviation of the IIEF and the number of patients in the treatment and control groups. The studies by both Yee et al [18] and Poulakis et al [12] concluded that the IIEF did not increase significantly in the treatment group compared with the control group; the p values were 0.156 and 0.205, respectively. The remaining three RCTs reported that the IIEF increased significantly in the LI-ESWT group compared with the control group [11,14,17]; the p value was <0.05. The overall meta-analysis of the data revealed that LI-ESWT improved the IIEF significantly overall in the treatment groups (MD: 2.00; 95% CI, 0.99–3.00; $p < 0.0001$) (Fig. 3a).

Subgroup analysis was performed. Figure 3b shows that Poulakis et al [12] and Vardi et al [17] assessed IIEF at 1 mo after LI-ESWT and that the IIEF did not increase significantly (MD: 0.37; 95%CI, −1.45 to 2.19; $p = 0.69$). Three other studies, however, assessed IIEF at 3 mo after treatment and found that the IIEF increased significantly (MD: 2.71; 95% CI, 1.51–3.91; $p < 0.0001$). In Figure 3c, the studies were divided into three groups by the IIEF before LI-ESWT—≤11, 12–16, and 17–21—corresponding to severe, moderate, and mild ED, respectively. The meta-analysis showed that the IIEF of patients in the mild ED group increased significantly after LI-ESWT (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). The patients in the severe and moderate groups did not show a significant increase in IIEF ($p = 0.30$ and $p = 0.49$). In Figure 3d, the studies were divided into two groups: the ED group and the ED with PD group. The subgroup analysis showed that the patients in the ED group improved significantly in IIEF (MD: 2.36; 95% CI, 1.19–3.53; $p < 0.0001$). The patients in the ED with PD group had no significant improvement in IIEF ($p = 0.33$). Finally, the studies were divided into two groups by usage of PDE5-Is. Figure 3e shows that the IIEF increased in both groups but

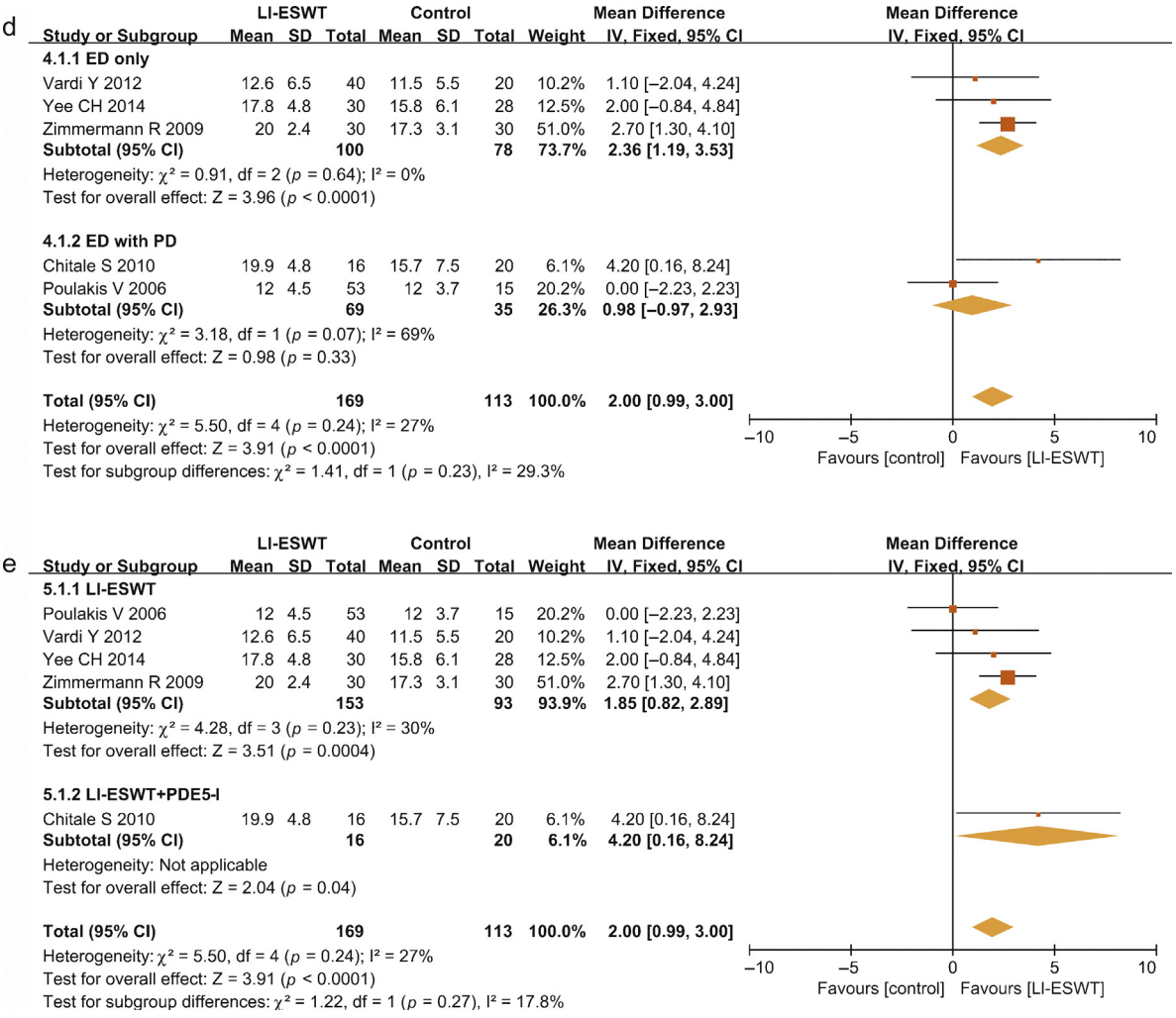

Fig. 3. (*Continued*).

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

increased more significantly in the group with LI-ESWT combined with PDE5-I use (MD: 4.20; 95% CI, 0.16–8.24; $p = 0.04$).

These results indicate that LI-ESWT increased the IIEF and improved the erectile function of ED patients. According to the results of the current studies, the patients treated by LI-ESWT developed a good therapeutic effect by 3 mo. The patients who had mild or moderate ED and the ED patients who had no comorbidities benefited more from LI-ESWT than the patients with severe ED or with comorbidities.

Different LI-ESWT setup parameters, such as EFD and number of pulses, and different treatment protocols, including treatment frequency and length of course, resulted in differences in reported efficacy. The studies were divided into three groups according to EFD. The results (Fig. 4a) showed that the studies using the highest EFD (>0.2 mJ/mm^2) reported significantly increased IIEFs (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). The improvement of IIEF in this ED and PD subgroup was partially due to the improvement of PD. After excluding this subgroup, we found that the improvement in IIEF was better in the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1–0.2 mJ/mm^2, although neither group reached statistical significance. Next, the studies were divided into two groups based on the number of shock waves delivered during each treatment. The results (Fig. 4b) showed that the studies administering more shock waves reported a significant increase in IIEF (MD: 2.86; 95% CI, 1.54–4.19' $p < 0.0001$) compared with the studies delivering fewer shock waves. To compare different durations of treatment, the studies were divided into two groups according to duration of treatment of LI-ESWT. Figure 4c shows that the studies with a treatment course of <6 wk reported a significant increase in the IIEF (MD: 2.11; 95% CI, 0.98–3.25; $p = 0.0003$).

These results suggest that different setup parameters and different treatment protocols of LI-ESWT have substantial influence on therapeutic efficacy. In summary, within the scope of this review, lower energy density, increased number of pulses, and shorter treatment courses of <6 wk resulted in better therapeutic efficacy.

The EHS data were available for abstraction from four RCTs. In the studies by Yee et al [18] and Olsen et al [19], EHS was reported at 3 mo after LI-ESWT. In the study by Yee et al, the EHS did not increase significantly. In subgroup analysis (Fig. 5), at 1 mo after LI-ESWT, the EHS increased significantly in three studies (RD: 0.47; 95% CI, 0.38–0.56; $p < 0.00001$). EHS did not improve as significantly after 3 mo as it did after 1 mo, but it still increased with statistical significance (RD: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). These results indicate that LI-ESWT improves the erectile hardness of the penis for ED patients, especially at 1 mo after treatment, and that this improvement lasts for at least 3 mo.

3.4. Discussion

LI-ESWT has been used as a novel therapy for ED patients for the past 10 yr. Clinical studies and reports focused on this topic have increased dramatically in past 5 yr, especially in 2015. This implies that LI-ESWT as a therapeutic method for patients with ED has been increasingly adopted by both physicians and patients.

The IIEF is a patient-reported assessment that is purely subjective. In this review, we found that in some studies, patients in the control group also reported improvement of the IIEF [12,17,18]; however, patients in the LI-ESWT group improved more significantly than those in the control group. The range of improvement in the IIEF was from 5.3 to 7.6 points for the LI-ESWT group in our analysis [14,18]. It is undeniable that some studies revealed improvement with statistical significance; however, this improvement may have no significant clinical value. The minimal clinically important difference (MCID) of IIEF better assesses the true clinical efficacy of LI-ESWT. We recommend that, in the future, investigators use the MCID of IIEF as a more accurate and meaningful tool for evaluating the effect of LI-ESWT in the treatment of patients with ED [20].

The clinical outcome of LI-ESWT is closely related to the energy delivered to the target unit area, or EFD. The EFD used varied from 0.09 to 0.25 mJ/mm^2 among the studies included in our analysis. Based on this review, we could not determine the best EFD for ED therapy. Studies investigating the use of LI-ESWT for various regenerative purposes have used varying energy densities. An investigation by Goertz et al showed that an energy density of 0.04 mJ/mm^2 could accelerate angiogenesis for skin burns [21]. The study by Abe et al revealed that an energy density of 0.1 mJ/mm^2 for a rat model of acute myocardial infarction suppressed ventricular remodeling and had a good anti-inflammatory effect [22]. The study by Tara et al found that an energy density of 0.11–0.21 mJ/mm^2 could encourage therapeutic angiogenesis for human ischemic tissues [23]. Ioppolo et al reported that for some musculoskeletal disorders, energy density could be increased to 0.3 mJ/mm^2 [24]. In the current review, most of the included studies used an energy density of 0.09 mJ/mm^2, which Vardi et al first reported in 2010 [17]. Most subsequent studies adopted this EFD and presented encouraging results. Additional studies and a longer duration of treatment are needed to establish whether therapeutic efficacy is positively correlated with energy density.

Some studies included in our review concluded that the biological efficacy of LI-ESWT was dosage dependent [25]. It seemed that more pulses would bring better biological efficacy. With this hypothesis in mind, some studies adopted multiple treatment sites, more frequent treatments, and longer courses of treatment. Meta-analysis showed that 3000 pulses per treatment brought more improvement than 1500 or 2000 pulses per treatment; however, more frequent treatment and longer treatment course did not improve erectile function significantly. The optimal treatment protocol remains to be defined. Whether there may be a plateau stage of treatment remains uncertain and requires further investigation. In addition, based on the premise that more treatment sites would produce better results, shock waves were delivered to multiple sites, such as the dorsal surface, both sides, and both crus of the penis. It seemed that more sites treated

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

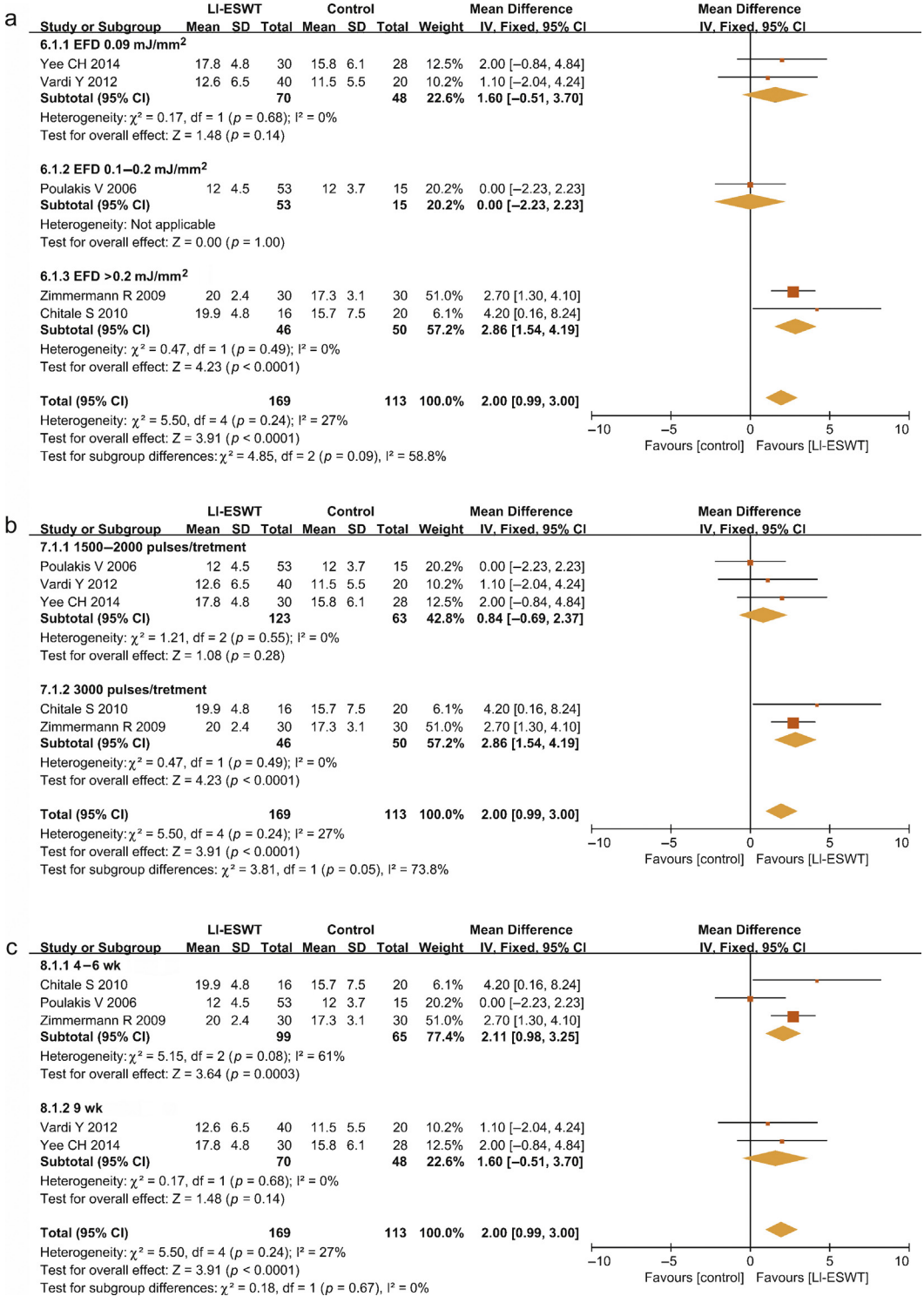

Fig. 4 – Relationship of energy dosage and treatment procedures. (a) The studies using higher energy flux density (EFD; >0.2 mJ/mm^2) resulted in significantly increased International Index of Erectile Function (IIEF; mean difference [MD]: 2.86; 95% confidence interval [CI], 1.54–4.19; $p < 0.0001$) in the erectile dysfunction (ED) and Payronie's disease groups. In ED-only groups, the improvement of IIEF was better for the group with EFD 0.09 mJ/mm^2 compared with EFD 0.1–0.2 mJ/mm^2, although it did not reach statistical significance. (b) The studies delivering more shock waves per treatment resulted in an increased IIEF (MD: 2.86; 95% CI, 1.54–4.19; $p < 0.0001$). (c) The studies with total course of treatment <6 wk revealed significant IIEF increase (MD: 2.11; 95% CI, 0.98–3.25; $p = 0.0003$) versus studies with longer courses of treatment (9 wk).
CI = confidence interval; EFD = energy flux density; IV = inverse variance; LI-ESWT = low-intensity extracorporeal shock wave treatment; SD, standard deviation.

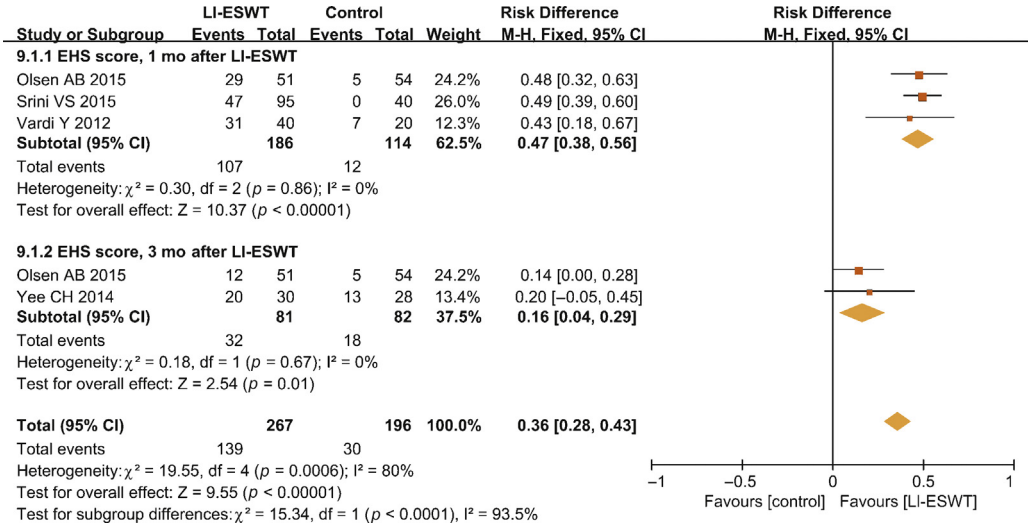

Fig. 5 – The Erection Hardness Score (EHS) increased significantly (risk difference [RD]: 0.47; 95% confidence interval [CI], 0.38–0.56; $p < 0.00001$) at 1 mo after treatment. Three months later, EHS slightly decreased but still improved with statistical significance (RD: 0.16; 95% CI, 0.04–0.29; $p = 0.01$). CI = confidence interval; EHS = Erection Hardness Score; LI-ESWT = low-intensity extracorporeal shock wave treatment; M-H = Mantel-Haenszel.

might produce better results. It is well known that shock waves can propagate 3–5 cm in human tissue [26]. It remains to be determined if it is necessary or beneficial to deliver treatment to multiple sites. This is also an area of potential future investigation.

The underlying mechanism of action of LI-ESWT is currently under investigation. According to recent reports, the effect is primarily related to the stimulation of cell proliferation, tissue regeneration, and angiogenesis [27,28]. In 2013, Qiu et al explored the therapeutic effect of LI-ESWT on a diabetic animal model and demonstrated that LI-ESWT can partially resolve diabetes mellitus–associated ED by promoting regeneration of neuronal nitric oxide synthase (nNOS)–positive nerves, endothelium, and smooth muscle in the penis [28]. Meanwhile, Liu and colleagues reported their results after treatment of a rat model of ED with LI-ESWT. The expression of some proteins, such as α-smooth muscle actin, von Willebrand factor, nNOS, and vascular endothelial growth factor, was upregulated [29]. In 2013, Siegfried and colleagues reported that LI-ESWT could stimulate the regeneration of injured nerve fibers. They believed that the potential mechanism of LI-ESWT was enhanced by neovascularization in the regenerating nerve and that VEGF and transforming growth factor β were associated with the process [30]. Very recently, it was reported that LI-ESWT improved erectile function in a rat model of pelvic neurovascular injury. Penile tissue components, especially vascular and neuronal tissue, demonstrated improved recovery after LI-ESWT therapy [27].

Several weaknesses contributed to the quality of the data provided. As shown in Table 1, five of seven studies published in 2015 were cohort studies. It is undeniable that these cohort studies have good study designs and robust data collection; each has an appropriate sample size and clear comparison. In evidence-based medicine, however, the evidence level of cohort studies is level 2, and thus they have lower power than RCTs, which provide level 1 evidence. To evaluate the efficacy of LI-ESWT more accurately, more RCTs with good study designs are needed. In addition, even in the RCTs that were included in this review, there were still some deficiencies. The details of randomization, the implementation of double blinding, the details of the treatment protocol, and the data from long-term follow-up are fundamental factors for assessing the quality of a study. As shown in Figure 2a and 2b, we found that most of the included RCTs did not describe the details of randomization or blinding, and the potential biases involved are unclear. If bias existed, it would have a great impact on the interpretation of the meta-analysis.

Most of the studies focused on the improvement of erectile function after LI-ESWT. Nevertheless, the potential impact of factors related to ED, such as age, hypertension, diabetes, hyperlipidemia, and coronary artery disease, are not discussed. Only four RCTs in our analysis provided the age data comparing the patients in the treatment and control groups [12,17–19]. No further investigation was performed to determine the influence of age on the efficacy of LI-ESWT. Three RCTs provided the profile of patient comorbidities, such as hypertension, diabetes, hyperlipidemia, and coronary artery disease, but no further information was provided about the relationship between the clinical outcome of LI-ESWT and those comorbidities [17–19]. In the future, more RCTs with stratification of age and comorbidities will help determine the influence of these factors on the efficacy of LI-ESWT for patients with ED.

With the aim of determining the efficacy of LI-ESWT alone and to avoid confusion, most of the included studies prohibited the usage of PDE5-Is during shock wave treatment. Nevertheless, because the goal of treatment is to maximize improvement of erectile function, a combination of LI-ESWT and PDE5-Is may be the best choice. Gruenwald et al found that LI-ESWT effectively converted PDE5-I nonresponders to responders [31], and our results (Fig. 3e) support the use of LI-ESWT and PDE5-Is in

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

combination. Additional clinical trials are needed to further investigate this clinical question.

4. Conclusions

In recent years, LI-ESWT as a therapy for ED has attracted extensive attention. Studies of this topic have increased sharply, and most of these studies reveal encouraging results, such as improved IIEF and EHS and an effect that lasts up to 3 mo. The setup parameters and the treatment protocols are important for the therapeutic effects of LI-ESWT for patients with ED. The mechanism of LI-ESWT is to improve or even reverse the pathologic damage of tissue that causes ED. Additional studies are needed to explore the influences of age and comorbidities on response to LI-ESWT and to define the effects of LI-ESWT in combination with PDE5-Is. From our review, it is clear that LI-ESWT may have the potential to be the first-choice noninvasive treatment for patients with ED.

Author contributions: Tom F. Lue 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: Lue, Lin.
Acquisition of data: Lin, Lu, Lee, Wang.
Analysis and interpretation of data: Lu, Lee, Lin.
Drafting of the manuscript: Lu, Lin, Reed-Maldonado.
Critical revision of the manuscript for important intellectual content: Lin, Reed-Maldonado, Lue.
Statistical analysis: Lu, Lin.
Obtaining funding: Lue, Lin.
Administrative, technical, or material support: Wang, Lu.
Supervision: Lue.
Other (specify): None.

Financial disclosures: Tom F. Lue certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/ affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Tom F. Lue is a consultant for Pfizer, Eli Lilly, and Boston Scientific and chief medical officer and stock holder for AWCT, Inc.

Funding/Support and role of the sponsor: This work was supported by the US Army, Navy, Air Force, Department of Veterans Affairs and Office of Health Affairs to support the AFIRM II effort under award W81XWH-13-2-0052. The US Army Medical Research Acquisition Activity (820 Chandler Street, Fort Detrick, MD 21702-5014, USA) is the awarding and administering acquisition office. Opinions, interpretations, conclusions and recommendations are those of the authors and are not necessarily endorsed by the US Department of Defense.

Acknowledgments: We thank Dr. Chi-Fai Ng for providing us with the data details of their study. Dr. Chi-Fai Ng is from Division of Urology, Department of Surgery, Prince of Wales Hospital, the Chinese University of Hong Kong, Hong Kong, China.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.05.050.

References

[1] Hatzichristou D, d'Anzeo G, Porst H, et al. Tadalafil 5 mg once daily for the treatment of erectile dysfunction during a 6-month observational study (EDATE): impact of patient characteristics and comorbidities. BMC Urol 2015;15:111.
[2] Rassweiler JJ, Knoll T, Kohrmann KU, et al. Shock wave technology and application: an update. Eur Urol 2011;59:784–96.
[3] Hazan-Molina H, Reznick AZ, Kaufman H, Aizenbud D. Periodontal cytokines profile under orthodontic force and extracorporeal shock wave stimuli in a rat model. J Periodontal Res 2015;50:389–96.
[4] Becker M, Goetzenich A, Roehl AB, et al. Myocardial effects of local shock wave therapy in a Langendorff model. Ultrasonics 2014;54:131–6.
[5] Hayashi D, Kawakami K, Ito K, et al. Low-energy extracorporeal shock wave therapy enhances skin wound healing in diabetic mice: a critical role of endothelial nitric oxide synthase. Wound Repair Regen 2012;20:887–95.
[6] Abu-Ghanem Y, Kitrey ND, Gruenwald I, Appel B, Vardi Y. Penile low-intensity shock wave therapy: a promising novel modality for erectile dysfunction. Korean J Urol 2014;55:295–9.
[7] Chung E, Cartmill R. Evaluation of clinical efficacy, safety and patient satisfaction rate after low-intensity extracorporeal shockwave therapy for the treatment of male erectile dysfunction: an Australian first open-label single-arm prospective clinical trial. BJU Int 2015;115(Suppl 5):46–9.
[8] Pelayo-Nieto M, Linden-Castro E, Alias-Melgar A, et al. Linear shock wave therapy in the treatment of erectile dysfunction. Actas Urol Esp 2015;39:456–9.
[9] Frey A, Sonksen J, Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. Scand J Urol 2016;50:123–7.
[10] Palmieri A, Imbimbo C, Creta M, Verze P, Fusco F, Mirone V. Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial. Int J Androl 2012;35:190–5.
[11] Chitale S, Morsey M, Swift L, Sethia K. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. BJU Int 2010;106:1352–6.
[12] Poulakis V, Skriapas K, de Vries R, et al. Extracorporeal shockwave therapy for Peyronie's disease: an alternative treatment? Asian J Androl 2006;8:361–6.
[13] Skolarikos A, Alargof E, Rigas A, Deliveliotis C, Konstantinidis E. Shockwave therapy as first-line treatment for Peyronie's disease: a prospective study. J Endourol 2005;19:11–4.
[14] Zimmermann R, Cumpanas A, Miclea F, Janetschek G. Extracorporeal shock wave therapy for the treatment of chronic pelvic pain syndrome in males: a randomised, double-blind, placebo-controlled study. Eur Urol 2009;56:418–24.
[15] Bechara A, Casabe A, De Bonis W, Nazar J. Effectiveness of low-intensity extracorporeal shock wave therapy on patients with erectile dysfunction (ED) who have failed to respond to PDE5i therapy. A pilot study. Arch Esp Urol 2015;68:152–60.
[16] Srini VS, Reddy RK, Shultz T, Denes B. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. Can J Urol 2015;22:7614–22.
[17] Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol 2012;187:1769–75.
[18] Yee CH, Chan ES, Hou SS, Ng CF. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. Int J Urol 2014;21:1041–5.

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050

[19] Olsen AB, Persiani M, Boie S, Hanna M, Lund L. Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol 2015;49:329–33.
[20] Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol 2011;60:1010–6.
[21] Goertz O, Lauer H, Hirsch T, et al. Extracorporeal shock waves improve angiogenesis after full thickness burn. Burns 2012;38:1010–8.
[22] Abe Y, Ito K, Hao K, et al. Extracorporeal low-energy shock-wave therapy exerts anti-inflammatory effects in a rat model of acute myocardial infarction. Circ J 2014;78:2915–25.
[23] Tara S, Miyamoto M, Takagi G, et al. Low-energy extracorporeal shock wave therapy improves microcirculation blood flow of ischemic limbs in patients with peripheral arterial disease: pilot study. J Nippon Med Sch 2014;81:19–27.
[24] Ioppolo F, Rompe JD, Furia JP, Cacchio A. Clinical application of shock wave therapy (SWT) in musculoskeletal disorders. Eur J Phys Rehabil Med 2014;50:217–30.
[25] Kim JH, Kim JY, Choi CM, et al. The dose-related effects of extracorporeal shock wave therapy for knee osteoarthritis. Ann Rehabil Med 2015;39:616–23.
[26] Delius M, Denk R, Berding C, Liebich HG, Jordan M, Brendel W. Biological effects of shock waves: cavitation by shock waves in piglet liver. Ultrasound Med Biol 1990;16:467–72.
[27] Li H, Matheu MP, Sun F, et al. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. J Sex Med 2016;13:22–32.
[28] Qiu X, Lin G, Xin Z, et al. Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. J Sex Med 2013;10:738–46.
[29] Liu J, Zhou F, Li GY, et al. Evaluation of the effect of different doses of low energy shock wave therapy on the erectile function of streptozotocin (STZ)-induced diabetic rats. Int J Mol Sci 2013;14:10661–73.
[30] Mense S, Hoheisel U. Shock wave treatment improves nerve regeneration in the rat. Muscle Nerve 2013;47:702–10.
[31] Gruenwald I, Shenfeld O, Chen J, et al. Positive effect of counseling and dose adjustment in patients with erectile dysfunction who failed treatment with sildenafil. Eur Urol 2006;50:134–40.

Please cite this article in press as: Lu Z, et al. Low-intensity Extracorporeal Shock Wave Treatment Improves Erectile Function: A Systematic Review and Meta-analysis. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2016.05.050