Review Article
Male sexual health and dysfunction

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health Published online Jun 2, 2020
https://doi.org/10.5534/wjmh.200077

The World Journal of MEN's HEALTH

Clinical Practice Guideline Recommendation on the Use of Low Intensity Extracorporeal Shock Wave Therapy and Low Intensity Pulsed Ultrasound Shock Wave Therapy to Treat Erectile Dysfunction: The Asia-Pacific Society for Sexual Medicine Position Statement

Eric Chung[1,2,8], Joe Lee[3], Chia-Chu Liu[4], Hisanori Taniguchi[5], Hui-Liang Zhou[6], Hyun Jun Park[7]

[1]Department of Urology, Princess Alexandra Hospital, University of Queensland, Brisbane, [2]Department of Urology, Macquarie University Hospital, Sydney, Australia, [3]Department of Urology, National University Hospital, Singapore, [4]Department of Urology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, [5]Department of Urology and Andrology, Kansai Medical University, Osaka, Japan, [6]Department of Urology, First Affiliated Hospital of Fujian, Fujian, China, [7]Department of Urology and Biomedical Research Institute, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Korea, [8]AndroUrology Centre, Brisbane and Sydney, Australia

Published literature shows low intensity extracorporeal shock wave therapy (LIESWT) and low intensity pulsed ultrasound (LIPUS) therapy to improve erectile function and penile hemodynamic by inducing neovascularisation and promoting tissue regeneration. Key opinion leaders across the Asia Pacific region attended the recent biennial meeting of the Asia Pacific Society for Sexual Medicine in Australia, and presented the current evidence on LIESWT and LIPUS for erectile dysfunction (ED). The clinical findings were internally discussed, and the quality of evidence was graded based on the Oxford Centre for Evidence-Based Medicine recommendations. Existing literature supports the use of LIESWT and LIPUS in men with ED, with many clinical studies reported encouraging results with improved erectile function, good safety profile and short-term durability. However, controversial exists due to sampling heterogeneity, non-standardised treatment protocol and lack of large multi-institutional studies. There is a need to better define which subgroup of ED population is best-suited, and specific treatment protocol to optimise shock wave energy delivery. More stringent and larger multi-institutional randomised placebo-controlled trials are warranted before clinical adoption of LIESWT and LIPUS as the new standard of care for men with ED.

Keywords: Clinical outcome; Erectile dysfunction; Low intensity pulsed ultrasound; Low intensity shock wave therapy; Safety; Shock wave machine

Received: Apr 20, 2020 **Revised:** Apr 24, 2020 **Accepted:** Apr 27, 2020 **Published online** Jun 2, 2020
Correspondence to: Eric Chung https://orcid.org/0000-0003-3373-3668
AndroUrology Centre, Suite 3, 530 Boundary Street, Spring Hill, Brisbane, QLD 4000, Australia.
Tel: +61-7-3832-1168, **Fax:** +61-7-38328889, **E-mail:** ericchg@hotmail.com

INTRODUCTION

Clinical studies showed that erectile dysfunction (ED) is a common condition that has an adverse impact on various physical and psychosocial domains [1]. The contemporary medical treatment does not significantly alter the underlying pathophysiology of erectile mechanism, improve endothelial dysfunction or restore underlying physiological erectile function (EF) [2]. On the other hand, penile prosthesis implant is an irreversible treatment option and men will not be able to regain spontaneous erection again despite explant of this device [3].

Shock wave therapy has been used to treat stone disease for more than 4 decades [4] and over the years, significant scientific advances have been made to miniaturize and improve shock wave technology so that it can be applied to treat other medical conditions. Published literature on the regenerative properties of low intensity extracorporeal shockwave therapy (LIESWT) and low intensity pulsed ultrasound (LIPUS) are exciting and potentially offer many men the opportunity to regain spontaneous erection again [5]. This clinical guideline provides a brief overview of the basic technology and technical aspects on shockwave machines, as well as summary recommendations on the clinical use of LIESWT and LIPUS in ED based on published literature in ED.

MATERIALS AND METHODS

The following terms "low intensity shock wave therapy", "low intensity pulsed ultrasound", "erectile dysfunction", "shock wave machine", "neovascularization", "erectile function", "penile hemodynamic", "clinical outcome", and "safety" were used to search several databases including MEDLINE and EMBASE for inclusion in this article. Only English language articles were considered, and all studies were limited to LIESWT and ED only.

Available literature was reviewed, and relevant studies were analysed, summarized and presented at the Micro-Energy LIESWT forum at the recent scientific meeting of the Asia Pacific Society for Sexual Medicine in 2019. The panel identified specific clinically relevant subheadings concerning LIESWT data to be provided namely (1) LIESWT/LIPUS machines; (2) mechanisms of action; (3) treatment template and patient selection; (4) clinical outcomes; and (5) safety and tolerability. Clinical findings were internally discussed, and the quality of evidence was graded based on the Oxford Centre for Evidence-Based Medicine recommendations. Any disagreements were resolved by consensus and the clinical principle was given when available data were insufficient or not suitable to draw conclusions.

TYPES OF MACHINES AND MODES OF ACTION

Shock waves are acoustic waves that are characterised by high-pressure amplitudes and the basic set up of a shock wave lithotripter machine consists a shock wave generating system, a localisation system for identifying and targeting the area of interest, and a positioning system that place the area of interest in the shock wave focus zone [6]. A coupling cushion with gel lubricant provides effective coupling for shockwaves transmission between the generator and human tissue.

The three main types of shock wave lithotripters are electrohydraulic, electromagnetic and piezoelectric machines [5]. The electrohydraulic shock wave generator consists of the electrode (spark plug) and an ellipsoidal reflector, where underwater spark gap is discharged between the tips of the electrode to cause rapid local vaporisation in the water and generate a high-amplitude pressure pulse which is reflected of the ellipsoid into a focus shock wave. Currently, there are 2 commercial electrohydraulic machines namely Omnispec ED 1000 (Medispec, Gaithersburg, MD, USA) and Urogold 100 (MTS Medical, Konstanz, Germany). In contrast, the electromagnetic shock wave is produced by a high voltage electric pulse through rapid membrane movement of the electromagnetic shock wave emitter, with an acoustic lens that focuses the electromagnetic shock wave energy. Various electromagnetic machines currently in the market includes Duolith SD1 (Storz Medical AG, Tägerwilen, Switzerland), Aries (Dornier MedTech GmbH, Wessling, Germany), Renova and MoreNova (Direx System GmbH, Wiesbaden, Germany). Lastly, the piezoelectric lithotripter requires rapid and synchronous expansion of piezoelectric crystals to create a pressure wave. These piezoelectric crystals are arranged in a spherical shape to focus the energy. The PiezoWave 2 (Richard Wolf GmbH, Knittlingen, Germany) machine has a linear double-layer technology that applies piezoelectric shockwaves to the target area.

Unlike acoustic shock waves, an ultrasound wave is a high-frequency wave and depending on the level of ultrasonic energy, therapeutic ultrasound can be classified into high-intensity and low-intensity ultrasound machines. While there are several commercial LIPUS machines marketed for the orthopedic use, to date, only one novel LIPUS device (WBL-ED; Wanbeili Medical Instrument Co., Ltd, Beijing, China) has been used for ED.

PROPOSED MECHANISMS OF ACTION ON ERECTILE FUNCTION

It is generally accepted that endothelial dysfunction plays a pivotal role in the pathogenesis of ED. It is thought that a reduced arterial inflow results in cavernous hypoxia and ensuing trophic changes within the cavernosal smooth muscle are responsible for the subsequent progression of ED [7,8].

LIESWT has been shown to induce the release of vascular endothelial growth factor (VEGF) and nitric oxide, key mediators in angiogenesis and collateral blood vessel formation [9-11]. It is postulated that LIESWT causes repetitive shear stress (microtrauma) to target tissue resulting in a cascade of biological reactions including the release of various angiogenic factors, such as endothelial nitric oxide synthase [12] and VEGF [13]. The expression of these angiogenic factors in turn triggers tissue neovascularization and vasculogenesis [14] and activates various tissue repair mechanisms such as enhanced macrophage activity [15], alteration in cellular apoptosis, synthesis of cellular proteins and activation as well as subsequent differentiation of stem/progenitor cells [16]. In animal experiments of ED models, LIESWT appears to restore underlying fibromuscular pathological changes and endothelial dysfunction within the corpus cavernosum [17,18]. It appears that there is a dose-effect relationship in LIESWT with the shock intensity ranging from 0.10–0.13 mJ/mm^2 and shock number ranging from 200–300 impulses were the optimal parameters to treat cells *in vitro* [19].

In contrast, LIPUS has minimal thermal effects due to its low intensity and pulsed output mode, and its non-thermal effects which are normally claimed to induce therapeutic changes in tissues attract most researchers' attentions [20]. LIPUS has been demonstrated to have a range of biological effects on tissues such as promoting bone-fracture healing, accelerating soft-tissue regeneration, and inhibiting tissue inflammatory responses. Recent studies showed the biological effects of LIPUS may be associated with the upregulation of cell proliferation through activation of integrin receptors and Rho/ROCK/Src/ERK signalling pathway, and promotion of multilineage differentiation of mesenchyme stem and progenitor cell lines [20].

Summary recommendation

There is convincing basic science evidence to support the use of LIESWT in improving penile erectile hemodynamic (Level 2; Grade B). The clinical evidence on LIPUS in ED is accruing and should have similar biologic effects as LIESWT. Given the fact that ED is often multifactorial in pathogenesis, further confirmatory shock wave studies on effects of LIESWT and LIPUS across various animal models of ED should be conducted.

TREATMENT TEMPLATES AND PATIENT SELECTION

The administration of LIESWT is usually conducted in an out-patient setting and can be carried out by the clinician, nurse or patient himself. Treatment templates used are often based on existing literature and manufacturer's recommendations.

The landmark clinical trial based on Omnispec ED 1000 machine utilised a treatment template consisting of 3,000 shock waves delivered at 0.09 mJ/mm^2 to three sites along shaft penis and two at the penile crural levels [21]. The treatment protocol consisted of two treatment sessions per week for 3 weeks, with a 3-week no-treatment interval, and a second 3-week treatment period of two treatment sessions per week. The same group also published a slightly different template and treatment protocol based on 12 sessions of 1,500 pulses of 0.09 mJ/mm^2 at 120 shock waves per minute [22]. There are limited published data on MTS Urogold 100 machine and company data showed this machine can deliver an energy flux up to 0.19 mJ/mm^2.

The published study on the use of Duolith SD1 machine for ED is largely based on the LIESWT treatment template consisting of 12 sessions of twice-weekly LIESWT for 6 weeks with 3,000 shock waves given at 0.25 mJ/mm^2 (1,000 shock waves were delivered to three sites namely the distal penis, base of penis and corporal bodies at the perineum) [23,24]. A modified treatment template with LIESWT administered once weekly for four consecutive weeks where 2,000 impulses were applied at 0.25 mJ/mm^2 had been used too [25]. In another study, a different treatment template of LIESWT applied to six sites (500 shocks per site at bilateral corporal bodies) with a lower energy setting of 0.15 mJ/mm^2 was used with reasonable success rate [26]. The Aries system can provide up to 0.31 mJ/mm^2 and similar treatment template and protocol to Chung and Cartmill [23] was reported by Prieto et al [27]. A different treatment template of 1,500 shocks with energy density 0.09 mJ/mm^2 has been reported too [28]. In contrast to other radial electromagnetic machine, the Renova system provides a linear shock wave technology. The Renova machine provides an energy flux up to 0.09 mJ/mm^2 published clinical trials utilised a 4-weekly session of 3,600 shocks at 0.09 mJ/mm^2 [29,30]. The MoreNova system delivers a dual linear SW application and potentially allows for more shock wave delivery breadth. The PiezoWave 2 machine has been reported to provide up to 0.16 mJ/mm^2 energy delivery and the shock waves can be delivered at a maximum rate of 8 Hz, resulting in shorter treatment sessions than with other shock wave devices, apart from Duolith SD1 machine [5].

The participants in the majority of clinical studies have vasculogenic ED but with a varying degree of severity. The meta-analysis by Man and Li [31] showed an energy flux density of 0.09 mJ/mm^2 appeared to be superior to other protocols. The authors reported a better clinical effect with a greater number of SW and a treatment duration of fewer than 6 weeks. Zou et al [32] found that a nine-week protocol with an energy density of 0.09 mJ/mm^2 and 1,500 pluses seemed to have a better therapeutic effect than five-week protocol. Kalyvianakis et al [33] reported that retreating patients after 6 months could further improve EF without side effects, and shock wave therapy can be repeated up to a total of 18 sessions. A mixed population of both responders and non-responders to oral phosphodiesterase type-5 inhibitors (PDE5is) were studied and data from several meta-analyses showed a statistically significant EF improvement in patients with mild and severe ED and that patients who used PDE5i during treatment showed better results than those who did not [34]. Hisasue et al [35] showed that age and the number of concomitant comorbidities were statistically significant predictors for LIESWT efficacy.

In contrast, LIPUS is a low intensity ultrasound (0.7–3 MHz) machine with an output in the mode of pulse wave (100 and 1,000 Hz) that delivers a much lower intensity (<3 W/cm^2) than traditional ultrasound energy, often with peak intensities of 0.5–3,000 mW/cm^2. The most common application parameters of LIPUS are intensity at 0.03 W/cm^2 (or known as 30 mW/cm^2), pulse ratio 1:4 at 1,000 Hz, and frequency at 1.5 MHz [36]. Furthermore, the applied energy density dosage of LIPUS ranges between 2 and 150 J/cm^2 [37]. A recent multicenter randomized clinical study administered a twice-weekly LIPUS treatment for 4 weeks with the treatment areas include left crus, right crus, left corpus cavernosum, and right corpus cavernosum (each session lasted for 20 minutes in total with 5 minutes per area) [38].

Summary recommendation

Published literature shows LIESWT and LIPUS should be administered in at least 3 separate locations along the penis to be effective. Current treatment templates and protocols are largely derived from earlier published studies and based on manufacturer guidelines (clinical principle). To date, there is no head-to-head comparison between focussed and linear shock wave generators, and the various LIESWT machines. Furthermore, these outcomes should be interpreted with some caution due to underlying study heterogeneities and methodological flaws with inclusion and exclusion criteria, varying treatment templates, shock wave energy flow density, the number of shockwaves per session and duration of treatment among published [5].

There is a need to define which subgroup of ED population is best suited and the LIESWT protocols including modality of shock waves energy, emission frequency and total energy delivery. The patient selection appears paramount to treatment success and patients with mild-moderate ED, younger age group, those with minimal cardiovascular comorbidities, and absence of diabetes or cavernous nerve are likely going to report high EF recovery and spontaneous erection (Level 2; Grade B). The use of adjunctive measures such as combination PDE5i may enhance LIESWT effects and EF recovery (Level 2; Grade C).

CLINICAL OUTCOMES

Published systematic review and meta-analyses showed encouraging clinical outcomes in men with ED [31,32,34,39-42]. Clavijo et al [40] who extracted data from 7 clinical trials, reported a statistically significant improvement in pooled change in International Index of Erectile Function (IIEF) score compared to sham group (6.40 points; 95% confidence interval [CI]=1.78–11.02; I^2=98.7%; p<0.001 *vs.* 1.65 points; 95% CI=0.92–2.39; I^2=64.6%; p<0.001; between-group difference, p=0.047) with significant between-group differences were found for total treatment shocks received by patients (p<0.001). Similarly, Lu et al [41] analysed 14 studies and found that LIESWT could significantly improve IIEF (mean difference [MD]=2.00; 95% CI=0.04–0.29; p=0.01) and erection hardness score (EHS) (risk difference: 0.165; 95% CI=0.04–0.29; p=0.01). Zou et al [32] reported that the effective treatment was 8.31 (95% CI=3.88–17.78) times more effective in the LI-ESWT group (n=176) than in the sham treatment group (n=101) at about 1 month after the intervention in terms of EHS, while it was 2.50 (95% CI=0.74–8.45) times more in the treatment group (n=121) than in the control group (n=89) in terms of IIEF-EF. In a more recent systematic review on published clinical trials, Dong et al [42] found that changes in the IIEF-EF score increased significantly in the treatment group (MD=3.62; 95% CI=2.99–4.25; p<0.00001). The EHS increased significantly in the treatment group in four studies (odds ratio=16.02; 95% CI=7.93–32.37; p<0.00001).

Most published studies did not extend beyond 2 years follow-up, and one study that reviewed patients at 4-year follow-up [43] showed that the observed clinical improvement is not sustained and deteriorates at 48 months after completion of LIESWT. The pooled data from meta-analyses including randomized controlled trials showed an overall positive effect in terms of IIEF-EF score improvement, although the estimates are small (ranging from about 2 to 4 points of the IIEF-EF) and the heterogeneity high [44]. Additionally, the combination of LIESWT and adjunctive therapy such as oral PDE5i appeared to be more effective than a single-agent therapy [45]. The role of LIESWT as an adjunct to other regenerative therapy such as stem cell or platelet-rich plasma injections are largely unknown at this stage [46,47].

There is very limited published data on LIPUS in the human clinical trial. In a multicentre, randomised controlled trial, Cui et al [38] that the response rate in the treatment group was 54/80 (67.50%), which was significantly higher than control group 8/40 (20.00%) at 12 weeks with a higher percentage of patients with positive answers to SEP-3 (successful vaginal intercourse) (73.08% *vs.* 28.95%, p<0.05).

Summary recommendation

LISWT improves EF scores and penile hemodynamic parameters in men with vasculogenic ED (Level 1; Grade B). However, the clinical long-term significance of this improvement is uncertain. Published literature suggests these positive effects of LIESWT to last up to 12 months after treatment (Level 2; Grade B).

While current evidence for the use of LIESWT and to extent LIPUS is promising, more large-scale, well-designed and long-term follow-up time studies are needed owing to the limited number and quality of the studies. At present, there is no published data on the cost-effective analysis between LIESWT and other contemporary treatment for ED. The positive benefits of concurrent adjunctive therapy such as oral PDE5i and cellular-based therapy in human remain largely unknown. Given the limitations study methodology and modest reported changes in EF scores by most of the trials, patients should be aware that the scientific evidence is controversial and that the expected improvement may not be clinically relevant. The clinical adoption of LIESWT and LIPUS as an effective treatment option should be restricted to men with mild-moderate vasculogenic ED, either responder or non-responders to PDE5is, and ideally performed in the high specialized centres with documented experience with this type of therapy (Level 2; Grade B).

SAFETY AND TOLERABILITY

No patients reported significant penile pain or required analgesia during LIESWT session. To date, treatment-related adverse events have been reported in published clinical trials as well as systematic reviews and meta-analyses [31,32,34,39-42,44]. Furthermore, there is no reported drop-out rate during LIESWT due to treatment-related adverse events. Similar safety record was reported in LIPUS treatment [38].

Summary recommendation

LISWT is a safe and well-tolerated procedure without clinically significant adverse events (Level 1; Grade A).

CONCLUSIONS

Published literature supports the clinical use of LIESWT in men with ED with improved EF, good safety records and short-term durability. Although the exact mechanisms remain to be elucidated, it is agreed upon that LIESWT stimulates the release of various angiogenic and neurotrophic factors and promotes the regeneration of cavernosal smooth muscle and endothelium. Furthermore, LIESWT has the potential to recruit endogenous mesenchymal stem cells, which has beneficial effects for the repair of damaged tissue. The patient selection appears paramount to treatment success and patients with mild-moderate ED, younger age group, those with minimal cardiovascular comorbidities, and the absence of diabetes or cavernous nerve injury are likely going to report higher EF recovery and spontaneous erection.

Currently, there is no widely adopted treatment template with existing treatment protocol often based on manufacturer's guidelines and is derived from existing literature. While current clinical studies show that the vasculogenic effects and therapeutic mechanisms among the LIESWT machines are similar, regardless of the physical differences and treatment protocols, it remains unknown if one machine is superior to another. Furthermore, other relevant factors such as the actual physiological changes in penile tissues and the long-term risk of shock waves remain largely unknown.

At this stage, more multi-institutional randomised placebo-controlled studies with dose-finding study, the comparison between various treatment protocols and shock wave machines, and the concurrent use of adjunctive measures are needed before LIESWT and LIPUS can be adopted as the standard of care in ED. Future research direction should incorporate cost-effective analysis model, mechanisms to miniaturise shock wave technology with better energy delivery for use at home, and the role of concurrent administration of similar regenerative technology to treat men with ED.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: EC, HJP. Data curation: EC, JL, CCL, HT, HLZ, HJP. Formal analysis: EC, JL, CCL, HT, HLZ, HJP. Investigation: EC, JL, CCL, HT, HLZ, HJP. Methodology: EC, JL, CCL, HT, HLZ, HJP. Project administration: EC, HJP. Resources: EC, JL, CCL, HT, HLZ, HJP. Supervision: EC, HJP. Validation: EC, JL, CCL, HT, HLZ, HJP. Writing – original draft: EC, JL, CCL, HT, HLZ, HJP. Writing – review & editing: EC, JL, CCL, HT, HLZ, HJP.

REFERENCES

1. Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med 2010;7:3572-88.
2. Hatzimouratidis K, Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, et al. Pharmacotherapy for erectile dysfunction: recommendations from the fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med 2016;13:465-88.
3. Chung E. Translating penile erectile hydraulics to clinical application in inflatable penile prosthesis implant. Curr Sex Health Rep 2017;9:84-9.
4. Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;2:1265-8.
5. Chung E, Wang J. A state-of-art review of low intensity extracorporeal shock wave therapy and lithotripter machines for the treatment of erectile dysfunction. Expert Rev Med Devices 2017;14:929-34.
6. Wess OJ. Shock wave technology for stone fragmentation. In: Tiselius HG, editor. Urology: shock wave therapy in practice. Heilbronn: Level 10; 2013.
7. Chung E, De Young L, Brock GB. Investigative models in erectile dysfunction: a state-of-the-art review of current animal models. J Sex Med 2011;8:3291-305.
8. Eardley I. Pathophysiology of erectile dysfunction. Br J Diabetes Vasc Dis 2002;2:272-6.
9. Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy as a new and non-invasive angiogenic strategy. Tohoku J Exp Med 2009;219:1-9.
10. Liu T, Shindel AW, Lin G, Lue TF. Cellular signaling pathways modulated by low-intensity extracorporeal shock wave therapy. Int J Impot Res 2019;31:170-6.

11. Sokolakis I, Dimitriadis F, Teo P, Hatzichristodoulou G, Hatzichristou D, Giuliano F. The basic science behind low-intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic scoping review of pre-clinical studies. J Sex Med 2019;16:168-94.
12. Ciampa AR, de Prati AC, Amelio E, Cavalieri E, Persichini T, Colasanti M, et al. Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. FEBS Lett 2005;579:6839-45.
13. Yamaya S, Ozawa H, Kanno H, Kishimoto KN, Sekiguchi A, Tateda S, et al. Low-energy extracorporeal shock wave therapy promotes vascular endothelial growth factor expression and improves locomotor recovery after spinal cord injury. J Neurosurg 2014;121:1514-25.
14. d'Agostino MC, Craig K, Tibalt E, Respizzi S. Shock wave as biological therapeutic tool: from mechanical stimulation to recovery and healing, through mechanotransduction. Int J Surg 2015;24(Pt B):147-53.
15. Sukubo NG, Tibalt E, Respizzi S, Locati M, d'Agostino MC. Effect of shock waves on macrophages: a possible role in tissue regeneration and remodeling. Int J Surg 2015;24(Pt B):124-30.
16. Suhr F, Delhasse Y, Bungartz G, Schmidt A, Pfannkuche K, Bloch W. Cell biological effects of mechanical stimulations generated by focused extracorporeal shock wave applications on cultured human bone marrow stromal cells. Stem Cell Res 2013;11:951-64.
17. Qiu X, Lin G, Xin Z, Ferretti L, Zhang H, Lue TF, 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.
18. Li H, Matheu MP, Sun F, Wang L, Sanford MT, Ning H, et al. Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. J Sex Med 2016;13:22-32.
19. Zhang X, Yan X, Wang C, Tang T, Chai Y. The dose-effect relationship in extracorporeal shock wave therapy: the optimal parameter for extracorporeal shock wave therapy. J Surg Res 2014;186:484-92.
20. Xin Z, Lin G, Lei H, Lue TF, Guo Y. Clinical applications of low-intensity pulsed ultrasound and its potential role in urology. Transl Androl Urol 2016;5:255-66.
21. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. 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;58:243-8.
22. Kitrey ND, Gruenwald I, Appel B, Shechter A, Massarwa O, Vardi Y. Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. J Urol 2016;195:1550-5.
23. 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.
24. 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.
25. 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.
26. Tsai CC, Wang CJ, Lee YC, Kuo YT, Lin HH, Li CC, et al. Low-intensity extracorporeal shockwave therapy can improve erectile function in patients who failed to respond to phosphodiesterase type 5 inhibitors. Am J Mens Health 2017;11:1781-90.
27. Prieto R, Louro Pelo N, Puigvert A, Martinez-Salamanca I. New treatments in erectile dysfunction and first clinical trial results. Paper presented at: 18th International Congress of the ISMST; 2015 Apr 15; Mendoza, Argentina. p.31.
28. Zewin T, El-Assmy A, Harraz A, Elsherbini A, Musa Z, Bayoumi A, et al. Low-intensity extracorporeal shock wave therapy for severe erectile dysfunction in poor responders to phosphodiesterase type-5 inhibitors: a short-term prospective study. Eur Urol Suppl 2016;15:e1115.
29. Ruffo A, Capece M, Prezioso D, Romeo G, Illiano E, Romis L, et al. Safety and efficacy of low intensity shockwave (LISW) treatment in patients with erectile dysfunction. Int Braz J Urol 2015;41:967-74.
30. Reisman Y, Hind A, Varaneckas A, Motil I. Initial experience with linear focused shockwave treatment for erectile dysfunction: a 6-month follow-up pilot study. Int J Impot Res 2015;27:108-12.
31. Man L, Li G. Low-intensity extracorporeal shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Urology 2018;119:97-103.
32. Zou ZJ, Tang LY, Liu ZH, Liang JY, Zhang RC, Wang YJ, et al. Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis. Int Braz J Urol 2017;43:805-21.
33. Kalyvianakis D, Memmos E, Mykoniatis I, Kapoteli P, Memmos D, Hatzichristou D. Low-intensity shockwave therapy for erectile dysfunction: a randomized clinical trial comparing 2 treatment protocols and the impact of repeating treatment. J

Sex Med 2018;15:334-45.

34. Sokolakis I, Hatzichristodoulou G. Clinical studies on low intensity extracorporeal shockwave therapy for erectile dysfunction: a systematic review and meta-analysis of randomised controlled trials. Int J Impot Res 2019;31:177-94.
35. Hisasue S, China T, Horiuchi A, Kimura M, Saito K, Isotani S, et al. Impact of aging and comorbidity on the efficacy of low-intensity shock wave therapy for erectile dysfunction. Int J Urol 2016;23:80-4.
36. Warden SJ. A new direction for ultrasound therapy in sports medicine. Sports Med 2003;33:95-107.
37. Ahmadi F, McLoughlin IV, Chauhan S, ter-Haar G. Bio-effects and safety of low-intensity, low-frequency ultrasonic exposure. Prog Biophys Mol Biol 2012;108:119-38.
38. Cui W, Li H, Guan R, Li M, Yang B, Xu Z, et al. Efficacy and safety of novel low-intensity pulsed ultrasound (LIPUS) in treating mild to moderate erectile dysfunction: a multicenter, randomized, double-blind, sham-controlled clinical study. Transl Androl Urol 2019;8:307-19.
39. Angulo JC, Arance I, de Las Heras MM, Meilán E, Esquinas C, Andrés EM. Efficacy of low-intensity shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Actas Urol Esp 2017;41:479-90.
40. Clavijo RI, Kohn TP, Kohn JR, Ramasamy R. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: a systematic review and meta-analysis. J Sex Med 2017;14:27-35.
41. Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol 2017;71:223-33.
42. Dong L, Chang D, Zhang X, Li J, Yang F, Tan K, et al. Effect of low-intensity extracorporeal shock wave on the treatment of erectile dysfunction: a systematic review and meta-analysis. Am J Mens Health 2019;13:1557988319846749.
43. Chung E, Scott S, Ng B. An intermediate term clinical outcomes of low intensity shock wave therapy in men with erectile dysfunction: a minimum 48 months follow up of prospective open-label single arm study. BJU Int 2019;123(Suppl 3):4-20.
44. Capogrosso P, Frey A, Jensen CFS, Rastrelli G, Russo GI, Torremade J, et al. Low-intensity shock wave therapy in sexual medicine-clinical recommendations from the European Society of Sexual Medicine (ESSM). J Sex Med 2019;16:1490-1505.
45. Verze P, Capece M, Creta M, La Rocca R, Persico F, Spirito L, et al. Efficacy and safety of low-intensity shockwave therapy plus tadalafil 5 mg once daily in men with type 2 diabetes mellitus and erectile dysfunction: a matched-pair comparison study. Asian J Androl 2019. doi: 10.4103/aja.aja_121_19 [Epub].
46. Shan HT, Zhang HB, Chen WT, Chen FZ, Wang T, Luo JT, et al. Combination of low-energy shock-wave therapy and bone marrow mesenchymal stem cell transplantation to improve the erectile function of diabetic rats. Asian J Androl 2017;19:26-33.
47. Zhu GQ, Jeon SH, Bae WJ, Choi SW, Jeong HC, Kim KS, et al. Efficient promotion of autophagy and angiogenesis using mesenchymal stem cell therapy enhanced by the low-energy shock waves in the treatment of erectile dysfunction. Stem Cells Int 2018;2018:1302672.