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

Article *in* Nature Reviews Urology · July 2017
DOI: 10.1038/nrurol.2017.119

5 authors, including:

Ege Can Serefoglu
Istanbul Medipol University
183 PUBLICATIONS **1,368** CITATIONS

SEE PROFILE

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

Mikkel Fode[1], Georgios Hatzichristodoulou[2], Ege Can Serefoglu[3], Paolo Verze[4] and Maarten Albersen[5] on behalf of the Young Academic Urologists Men's Health Group

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

[1]*Department of Urology, Herlev and Gentofte Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark.*
[2]*Department of Urology and Pediatric Urology, Julius-Maximilians-University of Würzburg, Oberdürrbacher Str. 6, 97080 Würzburg, Germany.*
[3]*Department of Urology, Bagcilar Training and Research Hospital, Merkez Mahallesi, Mimar Sinan Caddesi, 6. Sokak, 34100 Bağcılar/Istanbul, Turkey.*
[4]*Urology Unit, Department of Neurosciences, Sciences of Reproduction and Odontostomatology, University Federico II of Naples, Via Pansini 5, 80131, Naples, Italy.*
[5]*Department of Urology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.*

Correspondence to M. A.
maarten.albersen@uzleuven.be

doi:10.1038/nrurol.2017.119
Published online 25 Jul 2017

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

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

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

Key points

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

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

Mechanism of action

Shockwaves and their effects on tissues

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

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

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

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

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

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

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

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

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

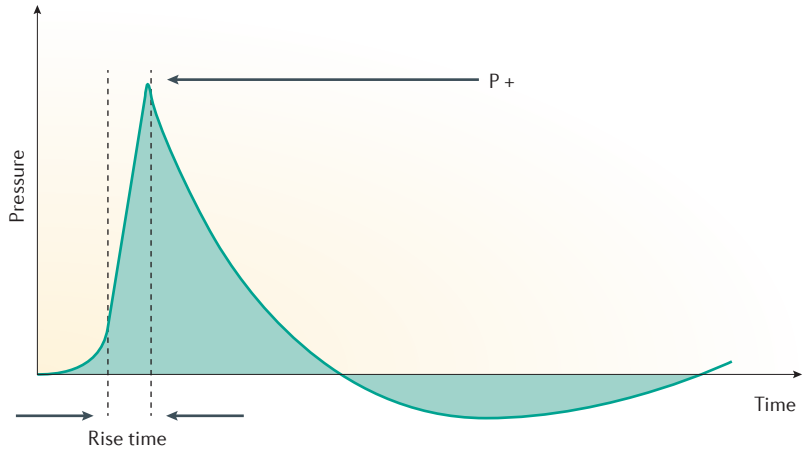

Figure 1 | **Schematic depiction of a shockwave as used in the treatment of erectile dysfunction.** A shockwave is a longitudinal acoustic wave consisting of a short pulse of about 5 µs duration that is characterized by a near instantaneous jump to a peak positive acoustic pressure, which is referred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

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

Putative mechanisms in animal models of ED

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

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

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

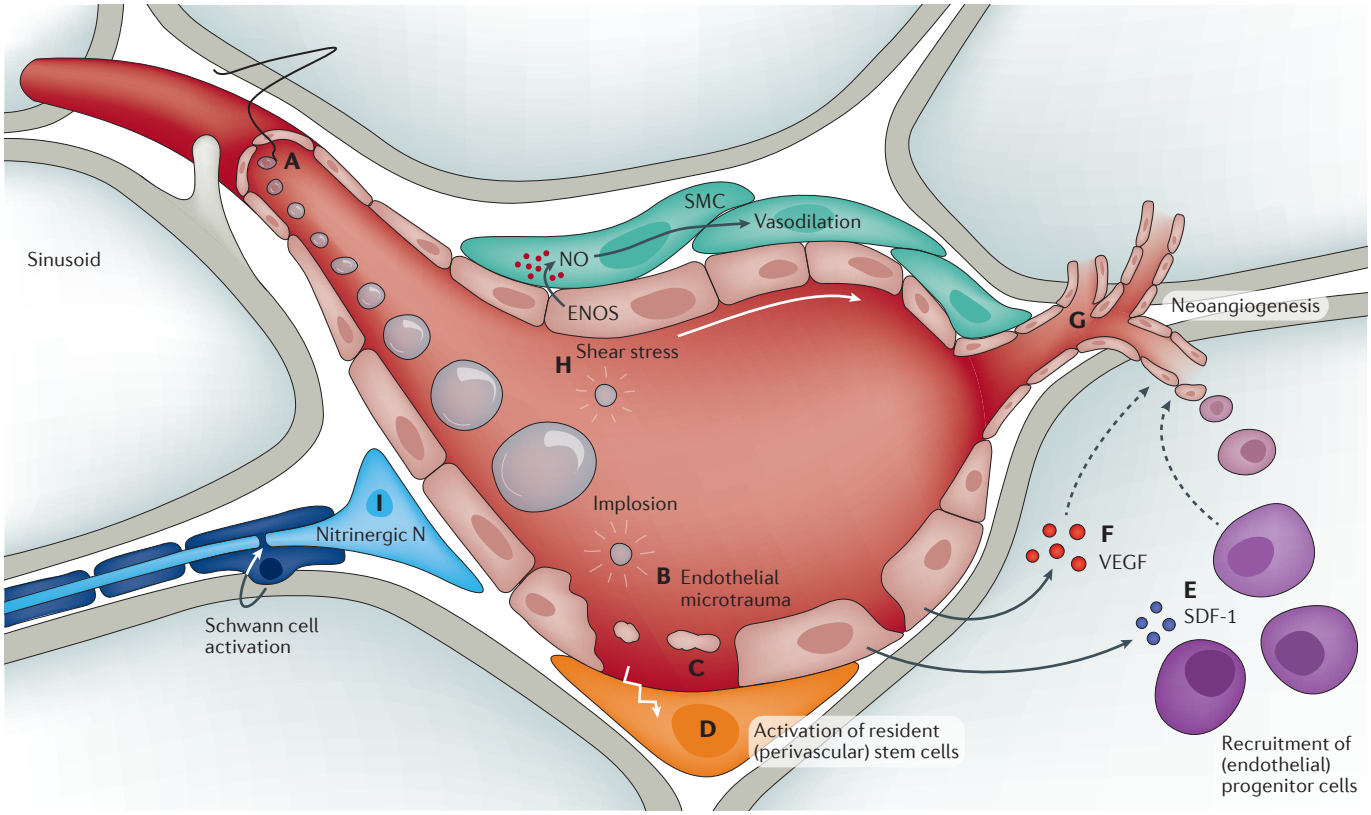

Figure 2 | **Putative mechanisms of action of shockwave therapy for ED.** Shockwaves form microbubbles (A) in the vasculature and tissue that collapse (B) and cause disruption of the endothelium (C). Endothelial disruption might activate resident stem cells (D) and result in chemokine production with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

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

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

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

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

Clinical data in vascular ED

Focussed Li-ESWT

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

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

Linear Li-ESWT

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

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

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

Study	Design	Rate EHS 3–4 (%)	IIEF-EF change	IIEF-5 change	Sessions×shocks	EFD (mJ/mm²)	Risk of bias (RCT only)
Vardi *et al.*[4] (2010)	• Single-arm study • *n* = 20 • Vasculogenic ED • 1–6 months follow-up period • Omnispec ED1000 (focussed)	NA	+7.4 (55%)	NA	12 × 1,500	0.09	NA
Vardi *et al.*[39] (2012)	• Monocentric RCT • *n* = 40 • Vasculogenic ED • 1-month follow-up period • Omnispec ED1000 (focussed)	77.5	+6–7 (56%)	NA	6 × 1,500	0.09	Low risk of bias
Gruenwald *et al.*[7] (2012)	• Single-arm study • *n* = 29 • PDE5I nonresponders • 1-month or 2-month follow-up period • (without and with PDE5I, respectively) • Omnispec ED1000 (focussed)	72.4	• +3.5 (without PDE5i) • +10 (with PDE5i)	NA	12 × 1,500	0.09	NA
Olsen *et al.*[40] (2014)	• Monocentric RCT • *n* = 112 • Vasculogenic ED • 5-week, 3-month, or 6-month follow-up period • Duolith SD1 (focussed)	• 57 (5-weeks) • 28 (3 months) • 19 (6 months)	NA	• (≥5 points change 43%, NS) • (≥5 points change 50%, NS) • (≥5 points change 47%, NS)	5 × 3,000	0.15	Low risk of bias; EHS not validated in Danish
Yee *et al.*[41] (2014)	• Monocentric RCT • *n* = 30 • Vasculogenic ED • 1-month follow-up period • Omnispec ED1000 (focussed)	NA	+2 (NS)	NA	12 × 1,500	0.09	Low risk of bias
Reisman *et al.*[42] (2015)	• Single-arm study • *n* = 58 • Vasculogenic ED • 6-month follow-up period • Renova (linear)	NA	+7.5	NA	4 × 3,600	0.09	NA
Srini *et al.*[45] (2015)	• Monocentric RCT • *n* = 60 • Vasculogenic ED • 12-month follow-up period • Omnispec ED1000 (focussed)	71	+8.7	NA	12 × 1,500	0.09	High risk of bias[‡]; very high drop-out rate, statistically different groups at baseline in terms of ED and comorbidity
Chung *et al.*[43] (2015)	• Single-arm study • *n* = 30 • PDE5I nonresponders • 1.5-month or 4-month follow-up period • Duolith SD1 (focussed)	60	NA	• ±2.5 (≥5 points change (60%)	12 × 3,000	0.25	NA

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

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

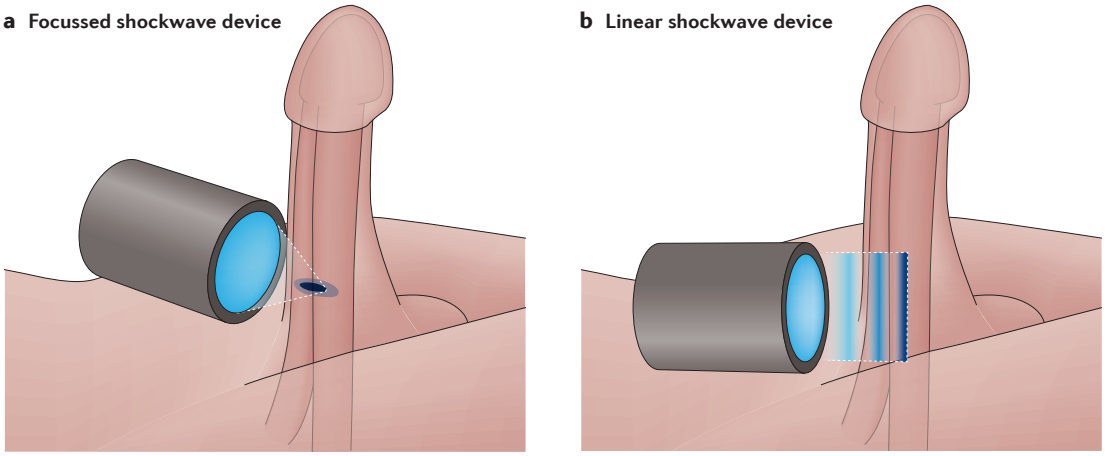

Figure 3 | **Focussed and linear shockwave therapy.** Focussed devices deliver the generated shockwaves to a focussed area at a predetermined tissue depth. Thus, the probe must be moved during the course of a treatment session in order to cover the complete corpora cavernosa including the crura. Linear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

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

Factors affecting the success of Li-ESWT

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

Postprostatectomy ED

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

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

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

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

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

IIEF-5

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

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

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

Erection hardness score (EHS)

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

Peyronie's-related ED

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

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

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

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

Quality of evidence

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

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

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

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

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

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

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

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

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

Future prospects and medical need

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

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

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

Conclusions

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

1. Hatzimouratidis, K. *et al.* Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur. Urol.* **57**, 804–814 (2010).
2. Latini, D. M. *et al.* Psychological impact of erectile dysfunction: validation of a new health related quality of life measure for patients with erectile dysfunction. *J. Urol.* **168**, 2086–2091 (2002).
3. Hanson-Divers, C., Jackson, S. E., Lue, T. F., Crawford, S. Y. & Rosen, R. C. Health outcomes variables important to patients in the treatment of erectile dysfunction. *J. Urol.* **159**, 1541–1547 (1998).
4. 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.* **58**, 243–248 (2010).
5. Gruenwald, I., Kitrey, N. D., Appel, B. & Vardi, Y. Low-intensity extracorporeal shock wave therapy in vascular disease and erectile dysfunction: theory and outcomes. *Sexual Med. Rev.* **1**, 83–90 (2013).
6. Assaly-Kaddoum, R. *et al.* Low intensity extracorporeal shock wave therapy improves erectile function in a model of type II diabetes independently of NO/cGMP pathway. *J. Urol.* **196**, 950–956 (2016).
7. Gruenwald, I., Appel, B. & Vardi, Y. Low-intensity extracorporeal shock wave therapy — a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. *J. Sex. Med.* **9**, 259–264 (2012).
8. Kitrey, N. D. *et al.* Penile low intensity shock wave treatment is able to shift PDE5i nonresponders to responders: a double-blind, sham controlled study. *J. Urol.* **195**, 1550–1555 (2016).
9. Cleveland, R. O. & McAteer, J. A. in *Smith's Textbook of Endourology* (eds Smith A. D., Preminger G., Badlani G. & Kavoussi L. R.) 527–558 (Wiley-Blackwell, 2012)
10. Bongrazio, M. *et al.* Shear stress modulates the expression of thrombospondin-1 and CD36 in endothelial cells *in vitro* and during shear stress-induced angiogenesis *in vivo*. *Int. J. Immunopathol. Pharmacol.* **19**, 35–48 (2006).
11. Belik, D. *et al.* Endothelium-derived microparticles from chronically thromboembolic pulmonary hypertensive patients facilitate endothelial angiogenesis. *J. Biomed. Sci.* **23**, 462 (2016).
12. Young, S. R. & Dyson, M. The effect of therapeutic ultrasound on angiogenesis. *Ultrasound Med. Biol.* **16**, 261–269 (1990).
13. Goertz, O. *et al.* Extracorporeal shock waves improve angiogenesis after full thickness burn. *Burns* **38**, 1010–1018 (2012).
14. Nishida, T. *et al.* Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs *in vivo*. *Circulation* **110**, 3055–3061 (2004).
15. Aicher, A. *et al.* Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. *Circulation* **114**, 2823–2830 (2006).
16. Wang, C.-J. *et al.* Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. *J. Orthop. Res.* **21**, 984–989 (2003).
17. Chen, Y.-J. *et al.* Recruitment of mesenchymal stem cells and expression of TGF-β1 and VEGF in the early stage of shock wave-promoted bone regeneration of segmental defect in rats. *J. Orthop. Res.* **22**, 526–534 (2004).
18. Kucia, M. *et al.* CXCR4-SDF-1 signalling, locomotion, chemotaxis and adhesion. *J. Mol. Histol.* **35**, 233–245 (2004).
19. Fuchs, S., Dohle, E., Kolbe, M. & Kirkpatrick, C. J. Outgrowth endothelial cells: sources, characteristics and potential applications in tissue engineering and regenerative medicine. *Adv. Biochem. Eng. Biotechnol.* **123**, 201–217 (2010).
20. Seemann, O., Rassweiler, J., Chvapil, M., Alken, P. & Drach, G. W. The effect of single shock waves on the vascular system of artificially perfused rabbit kidneys. *J. Stone Dis.* **5**, 172–178 (1993).
21. Gotte, G. *et al.* Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. *FEBS Lett.* **520**, 153–155 (2002).
22. Huang, J.-J. *et al.* Angiogenesis effect of therapeutic ultrasound on HUVECs through activation of the PI3K-Akt-eNOS signal pathway. *Am. J. Transl Res.* **7**, 1106–1115 (2015).
23. Ciampa, A. R. *et al.* Nitric oxide mediates anti-inflammatory action of extracorporeal shock waves. *FEBS Lett.* **579**, 6839–6845 (2005).
24. Hausner, T. *et al.* Improved rate of peripheral nerve regeneration induced by extracorporeal shock wave treatment in the rat. *Exp. Neurol.* **236**, 363–370 (2012).
25. Schuh, C., Hausner T. & Redl H. R. A therapeutic shock propels Schwann cells to proliferate in peripheral nerve injury. *Brain Circul.* **2**, 138 (2016).
26. Castela, A. &. Costa, C .Molecular mechanisms associated with diabetic endothelial–erectile dysfunction. *Nat. Rev. Urol.* **13**, 266–274 (2016).
27. Qiu, X. *et al.* Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. *J. Sex. Med.* **10**, 738–746 (2013).
28. Liu, J. *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. *IJMS* **14**, 10661–10673 (2013).
29. Lei, H. *et al.* Low-intensity pulsed ultrasound improves erectile function in streptozotocin-induced type I diabetic rats. *Urology* **86**, 1241.e11 (2015).
30. Wang, J. *et al.* Kinetics of label retaining cells in the developing rat kidneys. *PLoS ONE* **10**, e0144734 (2015).
31. Bickenbach, J. R. Identification and behavior of label-retaining cells in oral mucosa and skin. *J. Dent. Res.* **60**, 1611–1620 (1981).
32. Li, H. *et al.* Low-energy shock wave therapy ameliorates erectile dysfunction in a pelvic neurovascular injuries rat model. *J. Sex. Med.* **13**, 22–32 (2016).
33. Humphreys, B. D. Cutting to the chase: taking the pulse of label-retaining cells in kidney. *Am. J. Physiol. Renal Physiol.* **308**, F29–F30 (2015) **[ED:OK?]**
34. Lin, G. *et al.* Presence of stem/progenitor cells in the rat penis. *Stem Cells Dev.* **24**, 264–270 (2015).
35. Lin, C.-S., Xin, Z.-C., Dai, J. & Lue, T. F. Commonly used mesenchymal stem cell markers and tracking labels: limitations and challenges. *Histol. Histopathol.* **28**, 1109–1116 (2013).
36. Mulhall, J. P., Goldstein, I., Bushmakin, A. G., Cappelleri, J. C. & Hvidsten, K. Validation of the erection hardness score. *J. Sex. Med.* **4**, 1626–1634 (2007).
37. Rosen R. C., Cappelleri J. C., Smith M. D., Lipsky J. & Peña B. M. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot. Res.* **11**, 319–326 (1999).
38. Rosen, R. C. *et al.* The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* **49**, 822–830 (1997).
39. 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.* **187**, 1769–1775 (2012).
40. Olsen, A. B., 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.* **49**, 329–333 (2015).
41. Yee, C.-H., Chan, E. S., Hou, S. S.-M. & Ng, C.-F. Extracorporeal shockwave therapy in the treatment of erectile dysfunction: a prospective, randomized, double-blinded, placebo controlled study. *Int. J. Urol.* **21**, 1041–1045 (2014).
42. 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.* **27**, 108–112 (2015).
43. 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.* **115** (Suppl. 5), 46–49 (2015).
44. Pelayo-Nieto, M. *et al.* Linear shock wave therapy in the treatment of erectile dysfunction. *Actas Urol. Esp.* **39**, 456–459 (2015).
45. Srini, V. S., Reddy, R. K., Shultz, T. & Denes, B. Low intensity extracorporeal shockwave therapy for erectile dysfunction: a study in an Indian population. *Can. J. Urol.* **22**, 7614–7622 (2015).
46. Ruffo, A. *et al.* Safety and efficacy of low intensity shockwave (LISW) treatment in patients with erectile dysfunction. *Int. Braz. J. Urol.* **41**, 967–974 (2015).
47. Frey, A., Sønksen, J. & Fode, M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. *Scand. J. Urol.* **50**, 123–127 (2015).
48. Bechara, A., Casabé, A., De Bonis, W. & Ciciclia, P. G. Twelve-month efficacy and safety of low-intensity shockwave therapy for erectile dysfunction in patients who do not respond to phosphodiesterase type 5 inhibitors. *Sex. Med.* **4**, e225–e232 (2016).
49. Hisasue, S.-I. *et al.* Impact of aging and comorbidity on the efficacy of low-intensity shock wave therapy for erectile dysfunction. *Int. J. Urol.* **23**, 80–84 (2015).
50. Fojecki, G. L., Tiessen, S. & Osther, P. J. S. Effect of low-energy linear shockwave therapy on erectile dysfunction—A double-blinded, sham-controlled, randomized clinical trial. *J. Sex. Med.* **14**, 106–112 (2017).
51. Motil, I., Kubis, I. & Sramkova, T. Treatment of vasculogenic erectile dysfunction with Piezowave2 device. Application of low intensity shockwaves using novel linear shockwave tissue coverage (LSTC-ED®) technique. A prospective, multicentric, placebo-controlled study. *Adv. Sexual Med.* **6**, 15–18 (2016).
52. Lu, Z. *et al.* Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. *Eur. Urol.* **71**, 223–233 (2017).
53. Fojecki, G. L., Tiessen, S. & Osther, P. J. S. Extracorporeal shock wave therapy (ESWT) in urology: a systematic review of outcome in Peyronie's disease, erectile dysfunction and chronic pelvic pain. *World J. Urol.* **35**, 1–9 (2016).
54. Angulo, J. C. *et al.* Efficacy of low-intensity shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. *Actas Urol. Esp.* https://doi.org/10.1016/j.acuro.2016.07.005 (2016).
55. Clavijo, R. I., Kohn, T. P., Kohn, J. R. & Ramasamy, R. Effects of low-intensity extracorporeal shockwave therapy on erectile dysfunction: A systematic review and meta-analysis. *J. Sex. Med.* **14**, 27–35 (2017).
56. Fisher, W. A. *et al.* Standards for clinical trials in male and female sexual dysfunction: III. Unique aspects of clinical trials in male sexual dysfunction. *J. Sex. Med.* **14**, 3–18 (2017).
57. Masterson, T. A., Serio, A. M., Mulhall, J. P., Vickers, A. J. & Eastham, J. A. Modified technique for neurovascular bundle preservation during radical prostatectomy: association between technique and recovery of erectile function. *BJU Int.* **101**, 1217–1222 (2008).
58. Weyne, E., Castiglione, F., Van der Aa, F., Bivalacqua, T. J. & Albersen, M. Landmarks in erectile function recovery after radical prostatectomy. *Nat. Rev. Urol.* **12**, 289–297 (2015).
59. Iacono, F. *et al.* Histological alterations in cavernous tissue after radical prostatectomy. *J. Urol.* **173**, 1673–1676 (2005).
60. Miles, C. *et al.* Interventions for sexual dysfunction following treatments for cancer. *Cochrane Database Syst Rev.* https://doi.org/10.1002/14651858.CD005540.pub2 (2007).
61. Hatzimouratidis, K. *et al.* Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. *Eur. Urol.* **55**, 334–347 (2009).
62. Kilminster, S. *et al.* Predicting erectile function outcome in men after radical prostatectomy for prostate cancer. *BJU Int.* **110**, 422–426 (2011).
63. Bellorofonte, C. *et al.* [Possibility of using the piezoelectric lithotriptor in the treatment of severe cavernous fibrosis]. *Arch. Ital. Urol. Nefrol Androl* **61**, 417–422 (1989).
64. Poulakis, V. *et al.* Extracorporeal shockwave therapy for Peyronie's disease: an alternative treatment? *Asian J. Androl.* **8**, 361–366 (2006).
65. Claro, J. A. *et al.* An alternative non-invasive treatment for Peyronie's disease. *Int. Braz. J. Urol.* **30**, 199–204 (2004).
66. Strebel, R. T., Suter, S., Sautter, T. & Hauri, D. Extracorporeal shockwave therapy for Peyronie's disease does not correct penile deformity. *Int. J. Impot. Res.* **16**, 448–451 (2004).
67. Manikandan, R., Islam, W., Srinivasan, V. & Evans, C. M. Evaluation of extracorporeal shock wave therapy in Peyronie's disease. *Urology* **60**, 795–800 (2002).
68. Lebret, T. *et al.* Extracorporeal shock wave therapy in the treatment of Peyronie's disease: experience with standard lithotriptor (siemens-multiline). *Urology* **59**, 657–661 (2002).

69. Palmieri, A. *et al.* A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. *Eur. Urol.* **56**, 363–369 (2009).
70. Hatzichristodoulou, G., Meisner, C., Gschwend, J. E., Stenzl, A. & Lahme, S. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. *J. Sex. Med.* **10**, 2815–2821 (2013).
71. Chitale, S., Morsey, M., Swift, L. & Sethia, K. Limited shock wave therapy versus sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. - PubMed - NCBI. *BJU Int.* **106**, 1352–1356 (2010).
72. Mulhall, J. P., Schiff, J. & Guhring, P. An analysis of the natural history of peyronie's disease. *J. Urol.* **175**, 2115–2118 (2006).
73. Larsen, S. M. & Levine, L. A. Peyronie's disease: review of nonsurgical treatment options. *Urol. Clin. North Amer.* **38**, 195–205 (2011).
74. Gelbard, M. *et al.* Phase 2b study of the clinical efficacy and safety of collagenase *clostridium* histolyticum in patients with peyronie disease. *J. Urol.* **187**, 2268–2274 (2012).
75. Palmieri, A. *et al.* 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.* **35**, 190–195 (2011).
76. Hauck, E. W. *et al.* Extracorporeal shock wave therapy for Peyronie's disease: exploratory meta-analysis of clinical trials. *J. Urol.* **171**, 740–745 (2004).
77. Furlan, A. D., Pennick, V., Bombardier, C. & van Tulder, M. 2009 updated method guidelines for systematic reviews in the cochrane back review group. *Spine* **34**, 1929–1941 (2009).
78. Rosen, R. C., Allen, K. R., Ni, X. & Araujo, A. B. Minimal clinically important differences in the erectile function domain of the international index of erectile function scale. *Eur. Urol.* **60**, 1010–1016 (2011).
79. Albersen, M. & Lue, T. F. Sexual dysfunction: MCID provides new perspective on erectile function research. *Nat. Rev. Urol.* **8**, 591–592 (2011).
80. Fode, M. & Albersen, M. 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.* **71**, e76–e77 (2017).
81. Hatzichristou, D. G. & Kalyvianakis D. E. Erectile dysfunction shock wave therapy (EDSWT) improves hemodynamic parameters in patients with vasculogenic erectile dysfunction (ED): a triplex-based sham-controlled trial. *Eur. Urol.* **14**, e124 (2015).
82. Feldman, R. A., *et al.* The safety and efficacy of li-ESWT in 604 patients for erectile dysfunction: summary of current and evolving evidence. *Medispec.com* http://medispec.com/general/the-safety-and-efficacy-of-li-eswt-in-604-patients-for-erectile-dysfunction-summary-of-current-and-evolving-evidence/ (2015).
83. US National Library of Medicine. *ClinicalTrials.gov* https://clinicaltrials.gov/ct2/show/NCT02063061 (2016).
84. Hatzichristou, D. Low-intensity extracorporeal shock waves therapy (LI-ESWT) for the treatment of erectile dysfunction: where do we stand? *Eur. Urol.* **71**, 234–236 (2017).
85. Hamilton M. Cricket legend Sir Ian Botham bravely reveals impotence treatment after having privates zapped. *www.thesun.co.uk* https://www.thesun.co.uk/sport/1606663/sir-ian-botham-has-privates-zapped-in-bid-to-cure-impotence1606663/ (2016).
86. Cappelleri, J. C., Rosen, R. C., Smith, M. D., Mishra, A. & Osterloh, I. H. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. *Urology* **54**, 346–351 (1999).
87. 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.* **56**, 418–424 (2009).

Author contributions
All authors researched data for article, made substantial contributions to discussion of content, and wrote and edited the manuscript before submission.

Competing interests statement
The authors declare no competing interests.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors biographies

Mikkel Fode received his medical degree in 2010 from the University of Aarhus and earned his PhD degree from the University of Copenhagen in 2013. He is currently a clinician and researcher at Herlev and Gentofte Hospital. His interests include sexual medicine, urological prosthesis surgery, and prostate cancer. He has published more than 60 peer-reviewed articles and book chapters on these topics. He is currently the chairman of the educational committee of the European Society for Sexual Medicine and Social Media Editor for the *Journal of Sexual Medicine*. He also serves on the board of the Danish Urological Association.

Ege Can Serefoglu is an Associate Professor of Urology in Istanbul, Turkey. After practicing as a urologist for 2 years, he worked as a postdoctorate research fellow at Tulane University Department of Urology, Division of Andrology, USA. He received the Amsterdam Young Scientist Award in 2012 and is active in the Turkish Association of Urology, European Association of Urology (EAU), European Society for Sexual Medicine (ESSM) and International Society of Sexual Medicine (ISSM). Currently, he is serving as an Associate Editor of the *Journal of Sexual Medicine*, *Sexual Medicine* and *Sexual Medicine Reviews* and is working privately in Istanbul, Turkey.

Georgios Hatzichristodoulou is an Associate Professor of Urology at the Julius-Maximilians-University of Würzburg, Germany. After a fellowship in Urology and Andrology at the St. Trudpert's Hospital in Pforzheim, Germany, he continued his academic and clinical career at the Technical University of Munich, Germany. Currently, he is Senior Physician of Urology and also leader of the Andrological Unit at the Julius-Maximilians-University of Würzburg, Germany. His main scientific and clinical interest is men's sexual health, especially Peyronie's disease and erectile dysfunction.

Paolo Verze is an Assistant Professor of Urology at the University Federico II of Naples, where he also completed his academic and clinical career. Currently, he is Staff Physician at the Urology Unit of Azienda Ospedaliera Universitaria Federico II in Naples. His main scientific and clinical interests are men's sexual health and minimally invasive urologic surgery, especially laparoscopy and robot-assisted laparoscopy. He is author of 70 original articles and review papers. He is Chairman of EAU-YAU Men's Health working party and Member of the EAU Guidelines Male Sexual Dysfunction Panel.

Maarten Albersen is currently an Assistant Professor of Urology at the University of Leuven. During and after his urology residency he has been trained in basic research by Tom Lue in San Francisco, Petter Hedlund in Milan, and Trinity Bivalacqua in Baltimore, and in clinical andrology by David Ralph in London. He has a keen clinical and scientific interest in sexual medicine, andrology, and genital oncology. He serves as the scientific chairman of the European Society for Sexual Medicine and serves on the advisory board of *Nature Reviews Urology*, and the editorial boards of the *Journal of Sexual Medicine* and *European Urology*.

Subject categories

Health sciences / Urology / Urogenital diseases / Erectile dysfunction [URI /692/4025/2768/1575]
Biological sciences / Physiology / Reproductive biology / Reproductive disorders / Sexual dysfunction [URI /631/443/494/2732/515]
Biological sciences / Developmental biology / Angiogenesis [URI /631/136/16]
Biological sciences / Neuroscience / Regeneration and repair in the nervous system [URI /631/378/1687]

ToC blurb