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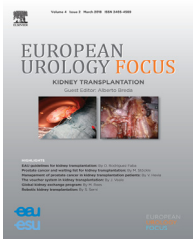

Clinical Consultation Guide

Should Low-intensity Extracorporeal Shockwave Therapy Be the First-line Erectile Dysfunction Treatment for Nonresponders to Phosphodiesterase Type 5 Inhibition?

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Low-intensity extracorporeal shockwave therapy (LI-ESWT) aims to reverse the underlying aberrant mechanisms that lead to the development of erectile dysfunction (ED) and is unlike other commonly used treatment options such as intracavernosal injection (ICI) and phosphodiesterase type 5 inhibitor (PDE-5i) agents. Therefore, there is substantial interest in this novel treatment modality. In this Clinical Consultation Guide we discuss the evidence for LI-ESWT as first-line therapy for PDE-5i nonresponders.

When considering which patients fall under the umbrella of PDE-5i nonresponders, it is important to recognize that this definition includes a heterogeneous group of men. A 72-yr-old diabetic male who has been unresponsive to PDE-5i therapy for several years is different to a 55-yr-old male who responds partially to PDE-5i therapy but is unable to have penetrative intercourse. It is therefore essential to consider baseline erectile function as well as patient expectations before treatment. Furthermore, proper counseling regarding optimizing PDE-5i therapy is important to truly consider a patient nonresponsive. Optimization of PDE-5i treatment entails applying sexual stimulation for appropriate nitric oxide release, reducing food intake (which may impair drug absorption), dose escalation as necessary, and repeated attempts. All four currently approved PDE-5i agents have demonstrated equivalent efficacy; however, given that various agents cross-react to other PDE-i drugs, this may lead to a varying side-effect profile and therefore switching agents may be warranted in cases of adverse reactions.

Classical shockwaves are characterized by high peak pressure (100 mPa or higher), a rapid pressure rise (<10 ns), a short duration (<10 ms), and a wide frequency range. Shockwaves used for biomedical purposes are generated in a fluid medium using an electrohydraulic, piezoelectric, or electromagnetic generator. The shockwaves generated are then directed to the target with or without a focusing unit. The effects of LI-ESWT seem to be tissue-dependent and disease-dependent. In animal studies, various effects of LI-ESWT were noted in different animal models of ED. In an animal model of diabetic ED with lower levels of endothelium, smooth muscle, and nNOS nerves, LI-ESWT significantly ameliorated these harmful effects from diabetes and improved nerve-stimulated intracavernous pressure [1]. In an animal model of severe injury to cavernous and pudendal nerves and internal pudendal arteries, LI-ESWT improved intracavernous pressure by enhancing angiogenesis, tissue restoration, and nerve regeneration with activation of Schwann cells and endothelial cells [2]. In an animal model of obesity-associated ED with smooth muscle atrophy, endothelial dysfunction, and lipid accumulation within the corpus cavernosum, LI-ESWT restored penile hemodynamic parameters in obese rats by restoring smooth muscle and endothelium content and reducing lipid accumulation [3]. The mechanism underlying the effect of LI-ESWT appears to be activation of resident stem/progenitor cells, which prompts cellular proliferation and accelerates penile tissue regeneration [4].

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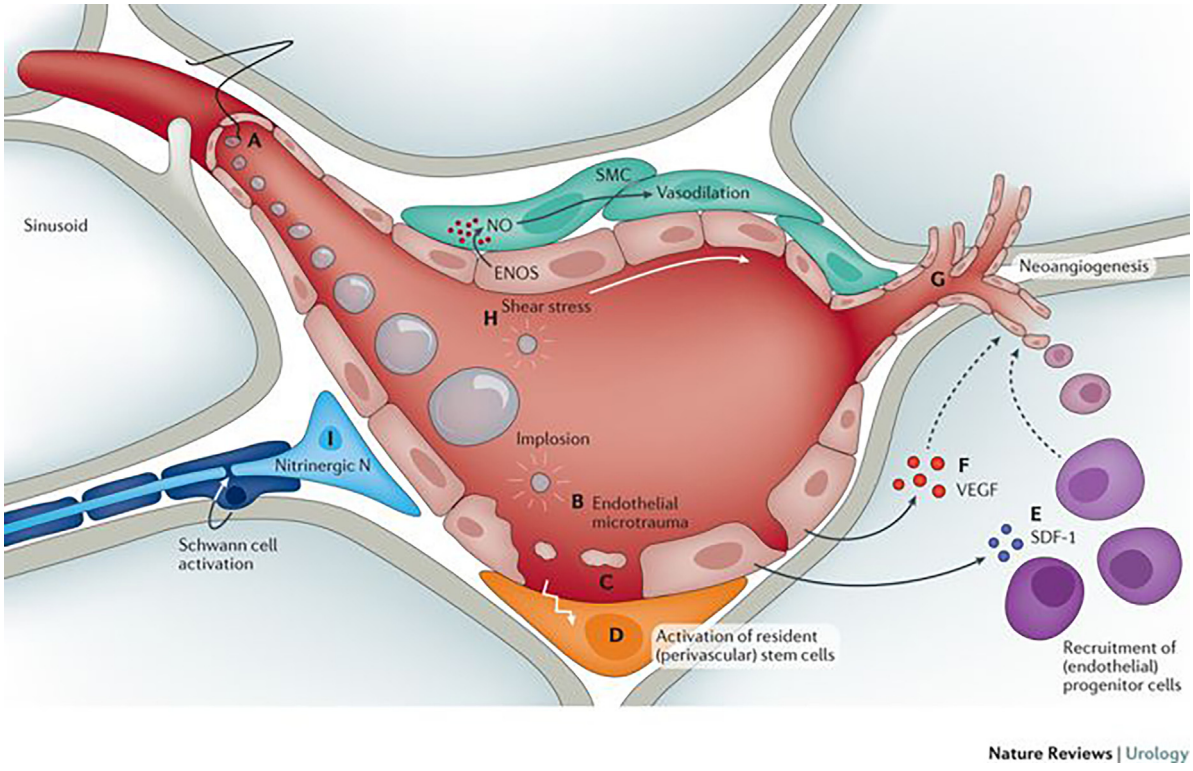

Fig. 1 – Physiological effects of low-intensity extracorporeal shockwave therapy that have been demonstrated include neoangiogenesis with upregulation of vascular endothelial growth factor, recruitment of progenitor cells, modulation of vasodilation, and nerve regeneration.

Animal models evaluating the physiological effect of LI-ESWT have demonstrated neoangiogenesis with upregulation of vascular endothelial growth factor, recruitment of progenitor cells, modulation of vasodilation, and nerve regeneration (Fig. 1) [5]. The first clinical study of LI-ESWT for ED was conducted by Vardi et al [6] with the hypothesis that LI-ESWT could restore blood flow to the penis and therefore improve ED. The authors treated 20 men with two treatments per week for 3 wk, which was repeated after a 3-wk period of no treatment. LI-ESWT was applied to the penile shaft and crura at five different sites, and results demonstrated an improvement in International Index of Erectile Function (IIEF) score at 1 and 6 mo. At the end of the 6-mo study period, ten men were free of PDE-5i therapy [6]. Since the initial trial by Vardi et al there has been widespread interest in the use of LI-ESWT for ED and several randomized trials have been conducted [1,7]. Unfortunately, these trials had several limitations, including small sample sizes, short follow-up, varying treatment regimens, heterogeneous populations, and different definitions of success. In addition, some trials showed an overall benefit from the treatment, while others were unable to find differences between LI-ESWT and sham treatment [8–10]. This limits the applicability of the results.

With respect to PDE-5i nonresponders, only a few trials have evaluated the effect of LI-ESWT specifically in this subpopulation [11–15]. Gruenwald et al [11] performed a prospective study among men who were poor responders to PDE-5i therapy and had a baseline erection hardness score (EHS) of $\leq$2 (inability to have penetrative intercourse). The treatment protocol was similar to the initial trial by Vardi et al [6]. Twenty-nine men completed the study and after an additional month of active PDE-5i therapy, 72.4% were able to have penetrative intercourse (EHS $\geq$3) [11]. Bechara et al [12] performed a prospective observational study among 50 men who were unresponsive to PDE-5i therapy. Treatment consisted of four sessions of LI-ESWT. During active treatment, all men remained on their regular on-demand or once daily PDE-5i therapy. They exhibited a positive response rate of 60% at the end of the study. After 12 mo, 91.7% of the responders maintained their response to treatment [12]. Likewise, Tsai et al [13] found an increased effect of PDE-5i after 12 weekly LI-ESWT sessions in 35/52 men (67.3%), while Ruffo et al [14] found positive effects after four LI-ESWT sessions among 31 PDE-5i nonresponders. In a randomized trial, Kitrey et al [15] evaluated LI-ESWT among men who had become PDE-5i nonresponders in the previous 12 mo, with 37 patients in the treatment arm and 16 in the sham group. Treatment consisted of 1500 shocks twice a week for 6 wk, with follow-up of 13 wk, similar to the study protocol used by Vardi et al [6] and Gruenwald et al [11]. Treatment success was defined as a minimal clinically important difference on the IIEF erectile function domain of at least 7 points for severe ED and 5 points for moderate ED. They found that 40.5% of men in the LI-ESWT group and 0% in the sham group responded to therapy ($p < 0.01$) after 9 wk. In the LI-ESWT group, 54.1% ($n = 20$) achieved erections hard enough for vaginal penetration (EHS 3), while no patients in the sham group did ($p < 0.0001$) [15].

In laboratory studies performed by one of the co-authors (T.L.), it was noted that the following parameters affect biologic responses: energy flux density (mJ/mm^2); number of shocks; frequency of the device (Hz); treatment frequency and interval; resident tissue stem/progenitor cell content (which is affected by age and diseases); shape and focus of the shockwaves; diameter of effective therapeutic area; and energy attenuation. Unfortunately, many articles do not provide detail for the shockwave device characteristics and parameters. This oversight may contribute to the inconsistent results reported by various authors using different devices.

Restorative therapies such as LI-ESWT are exciting given the possibility of reversing the underlying pathophysiology of ED and potentially reducing or eliminating the need for routine treatments such as ICI and PDE-5i. Although the available data hold promise, with limited adverse reactions, it should be kept in mind that positive results stem mainly from case series without control groups. The European Association of Urology guideline currently states that data are limited with respect to LI-ESWT and that clear recommendations cannot be given [16]. The American Urological Association does not recommend the use of LI-ESWT for ED outside of an investigational setting [17]. Further large randomized controlled trials with homogeneous populations and adequate follow-up are required to evaluate the efficacy and longevity of potential treatment effects. When examining the studies, LI-ESWT seems to have the best chance of success in patients with mild ED with some response to PDE-5i (our previously discussed 55-yr-old patient). Therefore, future trials will need to investigate this group specifically. Until such trials become available, we are unable to recommend LI-ESWT as a standard treatment option for men who are PDE-5i nonresponders. Patients should only be offered LI-ESWT in an investigational setting or as off-label use with a thorough understanding of the risks and benefits.

Conflicts of interest: The authors have nothing to disclose.

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