

Low-Intensity Shock Wave Therapy and Its Application to Erectile Dysfunction

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Although phosphodiesterase type 5 inhibitors (PDE5Is) are a revolution in the treatment of erectile dysfunction (ED) and have been marketed since 1998, they cannot restore pathological changes in the penis. Low-energy shock wave therapy (LESWT) has been developed for treating ED, and clinical studies have shown that LESWT has the potential to affect PDE5I non-responders with ED with few adverse effects. Animal studies have shown that LESWT significantly improves penile hemodynamics and restores pathological changes in the penis of diabetic ED animal models. Although the mechanisms remain to be investigated, recent studies have reported that LESWT could partially restore corpus cavernosum fibromuscular pathological changes, endothelial dysfunction, and peripheral neuropathy. LESWT could be a novel modality for treating ED, and particularly PDE5I non-responders with organic ED, in the near future. However, further extensive evidence-based basic and clinical studies are needed. This review intends to summarize the scientific background underlying the effect of LESWT on ED.

Key Words: Erectile dysfunction; ESWL; Extracorporeal shockwave lithotripsy; Phosphodiesterase 5 inhibitors

BACKGROUND: ERECTILE DYSFUNCTION AND ITS TREATMENT

Erectile dysfunction (ED) is commonly encountered in the field of andrology, and is defined as an inability to maintain an erection for sexual intercourse. This pathological condition often bothers males over 40 years old. The prevalence of ED in males under 40 years old is about 1% to 10%, whereas it is 50% in the 40 to 70-year-old group [1,2]. Many pathological factors are associated with ED, including neuropathy, androgen insufficiency, dia-

betes, and dysphoria [3]. Current management for ED consists of first-line therapy with oral phosphodiesterase type 5 inhibitors (PDE5Is) and second-line therapy using intracavernosal injection (ICI) therapy with vasodilating agents. The overall clinical efficacy of these treatments may be as high as 70%, and they are reasonably safe, with rare unwanted or adverse effects. However, these therapies do not alter the underlying pathophysiology of erectile tissue, so these treatments are usually taken on demand, prior to sexual activity. Patients with severe ED who are PDE5Is and/or ICI non-responders need to be

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treated with third-line therapeutic approaches, such as implantation of a penile prosthesis due to severe pathological changes in the penis.

Many ED animal models related to diabetic ED, neurogenic ED, and endocrinological ED have been used extensively worldwide to investigate the mechanisms of ED. The fibromuscular pathological changes, endothelial dysfunction, and neuropathies in erectile tissue, which might be related to the nitric oxide-cyclic guanosine monophosphate (NO-cGMP), transforming growth factor beta 1 (TGF- β 1)/Smad, vascular endothelial growth factor (VEGF), and insulin-like growth factor signaling pathways, are possible pathological factors [4]. Zhou et al [5] investigated the fibromuscular pathological changes in the corpus cavernosum of rats with streptozotocin (STZ)-induced diabetes. They found that diabetes significantly attenuates the erectile response to cavernous nerve electrostimulation. The diabetic animals exhibited a decreased smooth muscle/collagen ratio in the corpus cavernosum and the cavernous elastic fibers were fragmented. The TGF- β 1/Smad and connective tissue growth factor signaling pathways are upregulated in diabetic rats, which might play an important role in diabetes-induced fibromuscular structural changes and deterioration of erectile function. Sánchez et al [6] focused on uncoupling of neural nitric oxide synthase (nNOS) using a metabolic syndrome-associated ED animal model: obese Zucker rats (OZR). They found that under the conditions of insulin resistance, dysfunction of the nitric system and impaired neural NO signaling were more serious in penile arteries in OZR compared to normal control lean Zucker rats. The mechanisms might include greater oxidative stress and nNOS uncoupling. An elevated level of circulating tumor necrosis factor-alpha (TNF- α) has been observed in patients with diabetic ED. Long et al [7] explored the role of TNF- α in the pathogenesis of diabetic ED using a high-fat diet/STZ-induced diabetic ED animal model and infliximab (INF), a chimeric monoclonal antibody to TNF- α . They found that increased circulating TNF- α in diabetes contributes to ED through the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent oxygen species pathway in the corpus cavernosum, which could be neutralized by INF.

The ideal goal for treating patients with ED should be re-

habilitating or even recovering from the pathological changes in corpus cavernosum and enabling patients to regain spontaneous sexual activity with few adverse effects. Therefore, restore pathological changes in erectile tissues to treating ED is an important scientific issues and current effort conducted studies on gene and stem cell therapies have shown the potential for restoring pathological changes in the corpus cavernosum of ED models [8-13]. However, many ethical issues et al need to be addressed. In our previous studies, we found that icariin and icaraside II, isolated from the natural drug Epimadii herba, improved erectile function in a STZ-induced diabetic ED rat model [14,15]. Both drugs are beneficial for erection-related tissue, including the nNOS positive nerves, endothelium, and smooth muscle. They could also affect the TGF- β 1/Smad signaling pathway, and so alter fibromuscular pathological changes in the corpus cavernosum, which might be a potential agent in future.

Recent several studies have reported that low-energy shock wave therapy (LESWT) has been developed for treating ED, and clinical studies have shown that LESWT has the potential to affect PDE5I non-responders with ED with few adverse effects [16].

Shock waves are a type of continuous transmitted sonic wave with a frequency of 16 to 20 MHz. Four generating principles in the field of shock waves are known, including electrohydraulic sources, an electroconductive system, electromagnetic sources, and piezoelectric sources [17]. The shock wave emitted by most equipment often has a focal zone that is several centimeters ahead of the generator. In fact, most sonic waves are gathered in the focal zone, so this is often the action spot where most of the therapeutic effects occur. The shock wave is transmitted through the water cushion and couplant into the tissue or organ with little loss and creates a focal zone. It is necessary to make sure that the target organs or target stones are in the focal zone during the shock wave treatment. The duration of each wave is often less than 10 μ s and can be divided into a compressive phase with peak acoustics of 30 to 100 MPa followed by a negative pressure tensile phase [17]. Many physical parameters can be calculated from the pressure forms, including acoustic energy and energy flux density (EFD). Acoustic energy (or effective energy) can be defined as the energy delivered to a given

cross-section, which is calculated by integrating the EFD in the given section over the area equivalent to the time integral of the pressure pulse followed by an area integral. The EFD includes the temporal pressure of the shock wave in the focal plane, which could be considered the transmitted shock wave energy at a specific location in the focal plane [17]. The pressure in the medium changes dramatically when the shock wave spreads. The energy released and the changed pressure causes mechanical and thermal effects that lead to many biological changes in various diseases. Clinical application of shock waves in the 1970s opened a new era of physical medicine. However, the mechanism underlying the effect of shock wave therapy is far from clearly understood; thus, more basic research and optimization of the therapeutic regimen are needed.

HISTORY OF HIGH- AND LOW-INTENSITY (ENERGY) SHOCK WAVE THERAPY

The first use of high intensity shock waves in medicine was by Chaussy et al [18] in Munich, Germany in 1980. This was called extracorporeal shock wave lithotripsy and was used to treat renal calculi without open surgery. This was a revolution, and this technology was subsequently used to treat gall stones, pancreatic stones, parotid gland stones, and even bone ununion and pseudoarthrosis [19-24].

In 1998, Rompe et al [25] first developed a grading system for EFD using their rabbit tendo Achillis model. They found that $EFD > 0.28 \text{ mJ/mm}^2$ would cause damage to tissue, including fibrosis, inflammation, and necrosis, and that $EFD < 0.08 \text{ mJ/mm}^2$ might be safe. This was the original source of LESWT. Although this is a rough estimate for actual use, it might play a role in guiding basic research and the clinical use of shock waves. In fact, no agreement exists on the effective EFD range for LESWT. Most researchers use $EFD < 0.1 \text{ mJ/mm}^2$ in their LESWT experi-

ments [16,26-28].

Various hypotheses exist for the mechanisms involved in LESWT. Yu et al [29] revealed that shockwaves enhance activation of p38 mitogen-activated protein kinase, interleukin-2 expression, and T-cell proliferation via the release of cellular adenosine triphosphate and feedback mechanisms that involve P2X7 receptor activation and FAK phosphorylation. Xu et al [30] reported that optimal intensity shock waves promote adhesion and migration of osteoblasts, and the signaling pathways activated include the integrin $\beta 1$ pathway and the extracellular signal-regulated kinase 1/2 pathway. Aicher et al [31] found that shock waves improve recruitment of circulating endothelial progenitor cells, which is beneficial for patients with chronic ischemic disease. The enhanced expression of chemoattractant factors, including stromal cell-derived factor 1 and VEGF, may explain this phenomenon. However, many reports have focused on the function or effects of shock waves, including nerve and axonal regeneration [32], reduction of oxidative stress and inflammation [33], enhancement of endothelial capillary connections [34], collagen matrix changes [35], and recruitment and differentiation of stem cells or progenitor cells [36-38].

Nishida et al [39] and Ito et al [40] reported the effectiveness of LESWT for the treatment of cardiovascular disease because it has been shown to promote angiogenesis by upregulating the expression of related molecules, including VEGF. After finding that LESWT could improve microcirculation, the focus moved gradually from shock waves to LESWT. At present, LESWT is widely used to treat ischemic necrosis of the femoral head, calcaneodynia, scapulothoracic periartthritis, radiohumeral bursitis, soft tissue inflammation, diabetic foot, and wound healing [41-45]. This technology has been used as an important component of the therapeutic schedule for most of these diseases. The classification and applications of shock waves are

Table 1. Classification and applications of shock waves

Shock wave	Characteristic	Application
High-energy	Focused mechanical destructive forces	Lithotripsy
Medium-energy	Anti-inflammation	Orthopedic disease
Low-energy	Angiogenic properties	Wound healing, soft tissue injury, peripheral neuropathy, erectile dysfunction, etc.

summarized in Table 1.

CLINICAL APPLICATION OF LOW-ENERGY SHOCK WAVE THERAPY FOR TREATING ERECTILE DYSFUNCTION

As a novel modality, LESWT aims to restore natural or spontaneous erectile ability. This makes LESWT unique when compared with other approaches for treating ED, all of which are designed to attenuate symptoms [46].

The operating steps of LESWT are as follows. The animal or patient is placed in a supine position with their penis drawn out of the prepuce. It is better to conduct the animal procedure under anesthesia and with the lower abdomen shaved. The couplant is often applied between the penis and the shock wave applicator to reduce loss of energy. More than one location should be chosen to conduct the penile treatment. The duration of each treatment and the total number of sessions are set according to the kind of equipments and experimental groups.

The first study of the efficacy of LESWT for ED was conducted by Vardi et al [16] in 2010. They evaluated the effect of LESWT on 20 males with ED who had previously responded to oral PDE5Is. They recorded the International Index of Erectile Function (IIEF) score, nocturnal penile tumescence parameters, and penile and systemic endothelial function parameters before and after 3 weeks of treatment. A significant increase in the IIEF-ED domain was recorded in all subjects, and the duration of erection, penile rigidity, and penile endothelial function improved significantly. At the 6-month follow-up, 10 of 20 subjects did not require PDE5I therapy. These results suggest a tolerable and effective approach to the treatment of ED. The potential for improving erectile function and penile rehabilitation without pharmacotherapy was exciting.

Vardi et al [47] conducted a randomized, double-blind, sham-controlled study 2 years later to investigate the clinical and physiological effects of LESWT on males with organic ED. Erectile function, penile hemodynamics, validated sexual function questionnaires, and veno-occlusive strain gauge plethysmography were assessed before and after LESWT or sham therapy. LESWT had a positive short-term clinical and physiological effect on the erectile function of males who responded to PDE5I therapy. About

50% of patients receiving LESWT developed idiopathic erection and could complete sufficient penetration without the help of a PDE5I. This trial also showed satisfactory feasibility and tolerability of LESWT. Rehabilitative characteristics were also shown, but need to be further demonstrated.

A prospective, randomized, controlled trial by Palmieri et al [48] investigated the effects of LESWT plus tadalafil (5 mg/day) for managing patients with Peronie's disease and ED. The mean visual analog scale score, mean IIEF score, and mean quality of life score were ameliorated significantly in both the LESWT alone and ESWT plus tadalafil groups, and the combination therapy lead to better outcomes, as expected. Thus, these results suggest that LESWT should be at least a component of any strategy for treating ED.

Gruenwald et al [27] investigated LESWT as a possible treatment for patients with severe ED who responded poorly to PDE5I therapy. After treatment, the mean IIEF-ED scores increased and a significant improvement in penile hemodynamics was detected. No severe adverse events were reported during or after the trial.

Therefore, LESWT might be appropriate for a subgroup of patients with ED, particularly those with severe ED.

MECHANISTIC STUDIES OF LOW-ENERGY SHOCK WAVE THERAPY FOR ERECTILE DYSFUNCTION TREATMENT

Although clinical reports have demonstrated the therapeutic effects of LESWT on ED, the mechanism is far from clearly understood. In 2012, two groups explored the possible mechanism with diabetic animal models. Their work demonstrated the beneficial effect of LESWT on ameliorating injured tissues or cells including erection-related nerves, smooth muscle, and endothelial cells in the penis of a diabetic ED animal model. At the same time, they each found a unique effect of LESWT, including recruiting endogenous mesenchymal stem cells and down-expression of the receptor for advanced glycation end products (RAGE).

The work by Qiu et al [26] explored the effects of LESWT on the erectile function and tissue of a diabetic rat model. They used 5-ethynyl-2-deoxyuridine to track en-

ogenous mesenchymal stem cells, and the rats were grouped into normal control, diabetes mellitus (DM) control, and DM+shock wave therapy groups. Each rat in the DM+LESWT group received 300 shocks at an energy level of 0.1 mJ/mm² and frequency of 120/min. This procedure was repeated three times a week for 2 weeks. Their results showed that LESWT could partially ameliorate DM-associated ED by promoting regeneration of smooth muscle, endothelium, and nNOS-positive nerves, and LESWT appeared to be able to recruit endogenous mesenchymal stem cells, which had beneficial effects for the repair of damaged tissue.

Liu et al [28] investigated the therapeutic effect of LESWT at different doses for treating the ED of STZ-induced diabetic rats. SD rats were randomly divided into 5 groups (normal control, diabetic control, and 3 different doses of LESWT-treated diabetic groups). Different doses (100, 200, and 300 shocks each time) of LESWT treatment on penises were used to treat ED at 7.33 MPa three times a week for two weeks. The erectile function was evaluated by recording the intracavernous pressure after a 1 week washout period, and then the penises were harvested for histological study. The results showed that LESWT was able to significantly improve the erectile function of diabetic rats. The smooth muscle and endothelial content in the corpus cavernosum increased after the LESWT treatment. Up-regulation of α -SMA, vWF, nNOS, and VEGF, and down-regulation of the expression of RAGE were also observed. The therapeutic effects were related to the dose and the maximal therapeutic effect was noted in the high dosage group.

SUMMARY

LESWT has been developed for treating ED. The clinical results show that LESWT is beneficial to PDE5I non-responders with ED, with few adverse effects. Animal studies have shown that LESWT significantly improves penile hemodynamics and might restore the pathological changes in the penis of a diabetic ED animal model. Although the exact mechanisms remain to be elucidated, one possible explanation is that LESWT stimulates erection-related tissues by releasing VEGF and stromal cell-derived factor 1 and then restores the pathological changes in cavernosal

tissue, including corpus cavernosum fibromuscular changes, endothelial dysfunction, and peripheral neuropathy. However, further extensive basic and clinical studies are needed. LESWT could be a novel ED treatment modality, particularly for PDE5I non-responders with ED, in the near future.

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