LOW-INTENSITY EXTRACORPOREAL SHOCKWAVE THERAPY (LI-ESWT) IN PATIENTS WITH TYPICAL DIABETES MELLITUS ERECTILE DYSFUNCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Introduction: *Erectile dysfunction and diabetes mellitus present a challenging condition to treat due to the involvement of vasculogenic, endocrinogenic, and neurogenic factors. Although PDE5I is usually the treatment of choice, not all patients are suitable or respond to it. Currently, Low-Intensity Extracorporeal Shockwave Therapy (Li-ESWT), known as a vasculogenic erectile dysfunction treatment, tends to be safe, non-invasive, and effective.* ***Objective:*** *This study aims to determine the efficacy of Li-ESWT on patients with erectile dysfunction and diabetes mellitus.****Material &Methods****: RCT data were collected from PubMed, Science Direct, and Cochrane databases. Patients with erectile dysfunction and diabetes who underwent Li-ESWT assessed through the International Index of Erectile Function (IIEF) were included. In this study, we used RevMan 5.4, Cochrane Risk of Bias 2.0, and the PRISMA checklist. Out of 603 records identified, four RCTs were identified for qualitative synthesis. Three of these studies met the criteria for inclusion in the meta-analysis.****Results:*** *All four studies reported a statistically significant increase in the Li-ESWT group compared to the control group, with the average pre-therapy IIEF score increasing from 11.68 to 17.50 after treatment ($p < 0.05$). Moreover, Li-ESWT combined with other therapy was found more superior than monotherapy. Meta-analysis showed that Li-ESWT was effective to improve erectile function in diabetic patients (SMD 1.24; 95% CI: 0.85-1.63; $p < 0.00001$; $I2 = 0\%$).****Conclusion:*** *Li-ESWT was effective for mild to moderate erectile dysfunction patients with Diabetes Mellitus.*

Keywords: *Shockwave therapy, diabetes mellitus, erectile dysfunction.*

ABSTRAK

Pendahuluan:*Disfungsi ereksi dan diabetes mellitus merupakan kondisi yang menantang untuk diobati karena melibatkan faktor vaskulogenik, endokrinonegik, dan neurogenik. Meskipun PDE5I umumnya menjadi terapi utama, tidak semua pasien cocok atau mendapatkan respon terapi. Saat ini, Gelombang Kejut Ekstrakorporeal Intensitas Rendah (Li-ESWT) dikenal sebagai terapi disfungsi ereksi vaskulogenik yang aman, non-invasif, dan efektif.* ***Tujuan:*** *Penelitian ini bertujuan untuk menentukan efektivitas Li-ESWT pada pasien disfungsi ereksi dengan diabetes mellitus.* ***Bahan & Cara:*** *Data uji coba terkontrol secara acak (RCT) dikumpulkan dari database Pubmed, Science Direct, dan Cochrane. Pasien disfungsi ereksi dengan diabetes mellitus yang menjalani Li-ESWT dinilai melalui International Index of Erectile Function (IIEF) disertakan dalam penelitian. Dalam penelitianini, kami menggunakan RevMan 5.4, Cochrane Risk of Bias 2.0, dan checklist PRISMA. Dari 603 data yang teridentifikasi, kami mendapatkan empat RCT untuk sintesis kualitatif, di mana tiga di antaranya memenuhi kriteria untuk dilakukan analisa Meta-Analisis.* ***Hasil:*** *Keempat penelitian melaporkan peningkatan yang signifikan pada kelompok Li-ESWT dibandingkan dengan kelompok kontrol dengan skor IIEF rata-rata sebelum terapi adalah 11,68, meningkat menjadi 17,50 setelah pengobatan ($p < 0,05$). Selain itu, Li-ESWT yang dikombinasikan dengan terapi lain ditemukan lebih unggul dibandingkan monoterapi. Meta-Analisis menunjukkan bahwa Li-ESWT efektif untuk meningkatkan fungsi ereksi (SMD 1.24; 95% CI :0.85-1.63; $p = <0.00001$; $I2 = 0\%$).* ***Simpulan:*** *Li-ESWT efektif untuk pasien disfungsi ereksi derajat ringan sampai sedang dengan Diabetes Mellitus.*

Kata kunci: *Terapi gelombang kejut , diabetes mellitus, disfungsi ereksi.*

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INTRODUCTION

Optimal erectile function conditions including proper penile anatomy, neural integrity from the central nervous system to the peripheral level, and the presence of chemical messengers that play crucial roles in the erectile process.[1,2] Erectile Dysfunction (ED) is defined as the inability to attain and maintain a penile erection sufficient for satisfactory sexual performance.[3] The prevalence of ED is estimated to be as high as 76.5% globally and 35.6% in Indonesia[4,5] ED can be classified based on its etiology into organic, psychogenic, and mixed types. Major predictors of ED include hypertension, dyslipidemia, heart disease, and diabetes mellitus.[3]

Diabetes is a chronic disease that causes high blood sugar and, if untreated, leads to serious complications.[6] Diabetes can potentially damage the penile blood vessels and peripheral nerves, thereby disrupting blood flow into the corpus cavernosa and impairing sensory stimulation, which can cause or worsen erectile dysfunction.[7,8] It is estimated that 537 million adults worldwide suffered from diabetes, with the incidence of ED in diabetic patients being three fold higher than in those without diabetes. The number of diabetic ED patients has increased by 71% in the last decade.[9,10,11]

The main therapy for ED is usually a Phosphodiesterase 5 Inhibitor (PDE5I), but not all suitable and respond well to it.[12] The newest non-invasive alternative treatment is Low-Intensity Extracorporeal Shockwave Therapy (Li-ESWT) used for musculo skeletal disorders, wound healing, cardiovascular disorders, and erectile dysfunction.[11,13]

OBJECTIVE

In contrast to other erectile dysfunction therapies that are palliative, Li-ESWT aims to restore erectile function.11Li-ESWT is also easy to use and has minimal side effects[14]

MATERIAL &METHODS

We conducted a systematic search for studies investigating Li-ESWT for ED in diabetic patients through the databases (Science Direct, PubMed, and Cochrane) from September 2023 to January 2024, adhering to the Preferred Reporting In Systematic Reviews and Meta-Analyses (PRISMA) guideline. Keywords were (("diabetes" OR "diabetic") AND ("erection" OR "erectile" OR "erectile dysfunction") AND ("shock wave" OR "shockwave" OR "Li-ESWT" OR "ESWT")). Inclusion criteria were RCTs, human subjects suffered from diabetes, accompanied by vasculogenic and/or neurogenic erectile dysfunction (limited to peripheral neuropathy), and treated with Li-ESWT. Exclusion criteria were non-RCTs, animal studies, neurological disorders other than peripheral neuropathy (brain or spinal cord injury), penile anatomical abnormalities, history of radical prostatectomy, psychogenic ED, and non-English language studies.

Our search across three databases yielded 603 studies. After excluding duplicates (29), irrelevant titles/abstracts (346), animal studies (11), non-RCT studies (184), non-English studies (2), and studies excluded after full review (2), we identified four relevant studies (Figure 1) conducted between 2010 and 2023 in Egypt, China, Israel, USA, India, and Greece (n=253)[16,17,18,19] The data were processed qualitatively and three of them were prosessed quantitatively.

Data was extracted from four studies into quantitative studies and three of them were processed into quantitative studies by two authors (CF & JP). Data accuracy was verified by other authors. All authors read and approved the final manuscript. Data extracted from each study were ages, number of patients, Li-ESWT dosage, pre- and post-therapy IIEF scores. (see Table 1 for study characteristics)

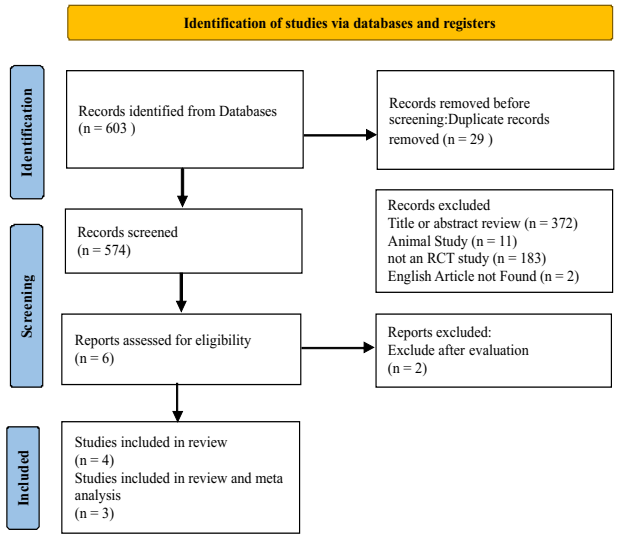

Figure 1. Prisma Flow Diagram for determining search strategies.

Table 1. Study characteristics.

Author (Country, Year)	Charactristic (diabetic ED patients)	Age (years)	N	DM type, duration	Sham	Li-ESWT dosage (total 12x, 15 min./session)	Areas	IIEF		FU (Mo)	P-value
								Baselines	After		
Shendy, et al (Egypt, 2020)	Li-ESWT vs PFE (Diabetic neuropathy included)	48.6 ± 5.5	42	Type 2; 9.8 ± 1.1 years	Yes	2x/week for 3 weeks, repeated after 3 weeks rest period 3000 SW, 0.09 mJ/mm2	5 points (3 along the penile shaft & 2 at crural level)	12.75 ± 3.21	17.50 ± 2.72	3	<.0001
Tao, et al (China, 2022)	LiESWT vs VED	47 ± 5.69	105	Type 2; > 6 mo	N/A	2x/week for 3 weeks and repeat after 3 weeks rest period Shock pressure 7.5KV, pulse frequency 100 x/min	Distal, body, and crura of each left and right side of penile cavernous body	13.30 ± 1.61	IIEF increased by 5 points, MCID (12 weeks) 66.7% 0f 100%	3	0.048
Spivak (Israel, USA, India, Greece; 2019)	LiESWT in PDE5I Responder vs PDE5I Non Responder	53 ± 8.9	61	N/A	Yes	2x/week for 3 weeks, repeated after 3 weeks rest period 0.09 mJ/mm2 Frequency 120 shocks/min	5 sites on the corpora	11.4 ± 4	19.4	1	<.0001
Salama, et al (Egypt, 2023)	LIESWT VS Physical Exercise	43.3 ± 4.8	45	Type 2	No (pre &post tx)	2x/week for 6 weeks, 3000 SW, 0.25 mJ/mm2	Distal penis, penile base, and perineal corporal bodies	12.13 ± 1.24	15.6 ± 1.3	3	0.001

PFE (Pelvic Floor Exercise), VED (Vacuum Erectile Device), SW (Shock Wave).

We assessed risk of bias using the Cochrane Risk of Bias 2.0 tool (RoB 2.0), which evaluates seven domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. RoB 2.0 categorizes risk as low, some concerns, or high.[15]

RESULTS

From four relevant studies, 253 subjects with diabetic ED were considered for this study. Subject ages ranged from 38 years to 64 years. Two studies (Shendy et al., Tao et al.) reported average durations of diabetes mellitus between 6 months and 11 years. All studies employed a treatment regimen of Li-ESWT for total of 12 sessions. Li-ESWT energy varied across studies from 0.09 mJ/mm^2 to 0.25 mJ/mm^2 (Shendy et al., Spivak et al., and Salama et al.) and 7.5 kV shock pressure (Tao et al.). Targeted areas on the penis received Li-ESWT spreaded across the distal area of the penis, crural region, cavernous region, and basal penis. (Table 1. Study Characteristics)

Subjects were diagnosed with Erectile Dysfunction using the 15-question IIEF questionnaire. The IIEF evaluates various aspects of sexual function, including erectile function, orgasm, desire, intercourse satisfaction, and overall satisfaction. This tool helped to establish baseline erectile function and to assess the impact of a specific treatment modality[1,2] (Table 2. Levels of severity in ED based on IIEF score). Subjects were diagnosed with diabetes using the HbA1C test. The IIEF was then used again to measure treatment effectiveness

Table 2. Levels of severity in ED based on IIEF score parameters.[1,2]

5-7	Severe ED
8-11	Moderate ED
12-16	Mild to moderate ED
17-21	Mild ED
22-25	No ED

IIEF (International Index of Erectile Function)

All four studies showed a significant relationship between Li-ESWT and improved erectile function in diabetes patients. Shendy et al. reported increased IIEF scores in Li-ESWT group with vasculogenic and neurogenic ED compared to sham group, suggesting a positive effect for patients with arterial insufficiency and diabetic peripheral neuropathy.[16] Tao et al. reported that 39.4% of Li-ESWT group achieved an IIEF increased exceeding 5 points, compared to only 14.7% in the vacuum erectile device group.[17] Spivak et al. demonstrated significant IIEF score improvements in both PDE5I responders and non-responders treated with Li-ESWT compared to the sham group.[18] Salama et al. reported that Li-ESWT significantly improved erectile function compared to physical exercise.[19] Across all four studies, the average pre-therapy IIEF

score was 11.68, increasing to 17.50 after treatment ($p < 0.05$). Three studies (Shendy et al., Tao et al., Salama et al.) also reported that combination therapy was superior to monotherapy.

Applying the Cochrane Risk of Bias tool 2.0 (RoB 2.0) across seven domains (see Figure 2), two studies (Tao et al. and Salama et al.) showed a high risk of performance bias due to missing information on blinding. Nevertheless, the other domains had low risk of bias.

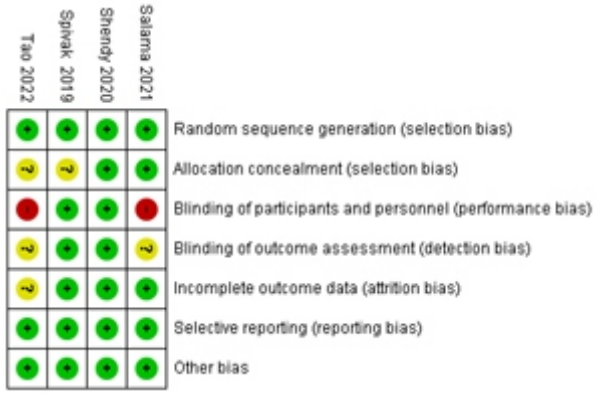

Figure 2. Risk of Bias.

We conducted a quantitative synthesis (meta-analysis) of three studies using Review Manager. A fixed-effects model revealed low heterogeneity ($Chi^2 = 0.53$, $P = 0.77$, $I^2 = 0\%$). The standardized mean difference (SMD) was 1.24 (95% CI: 0.85-1.63). These results, along with the forest plot (mean effect +1 to +2) (Figure 3) and symmetrical funnel plot (Figure 4), suggest that Li-ESWT has a significant effect on erectile function in diabetic patients with low publication bias.

DISCUSSION

Studies have shown a significant increase in the prevalence of erectile dysfunction (ED) among diabetic patients over the past decade, with estimates suggesting a rise of 71%.[10] This association is further supported by research from Lu et al., who identified a correlation between ED severity, HbA1c levels, and duration of diabetes.[20] High blood sugar is believed to contribute to ED by damaging blood vessels, nerves, and hormone regulation in the penis, ultimately leading to difficulties achieving or maintaining an erection.

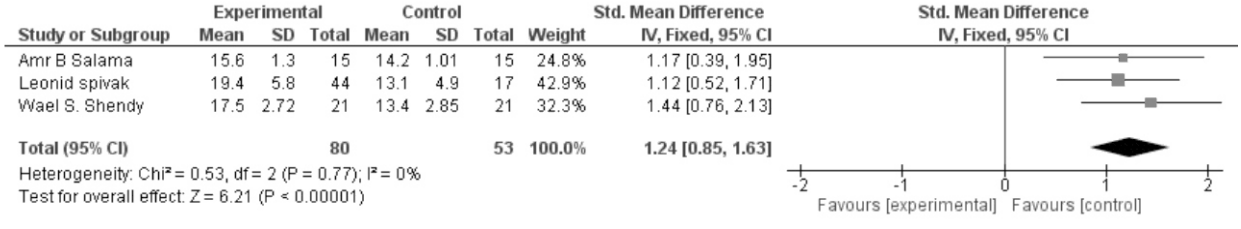

Figure 3. Meta – Analysis Results (RevMan).

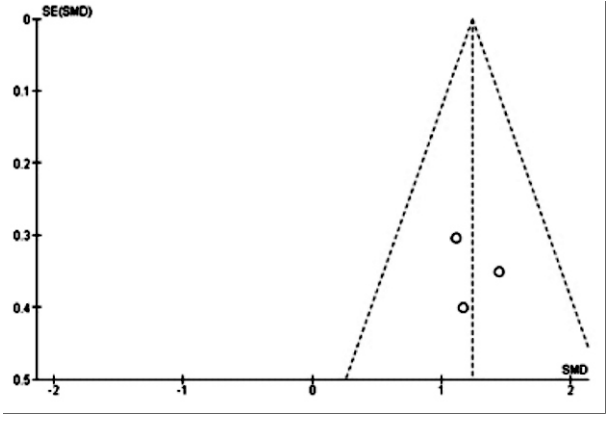

Figure 4. Funnel Plot.

The treatment traditionally relies on palliative therapy, such as oral medications (PDE5 inhibitors), vacuum devices, and intracavernous injections.[11] While PDE5I is the primary treatment option for enhancing erectile function, a significant number (30-35%) of patients experience limited improvement, known as PDE5i non responders.[12] Li-ESWT presents a promising alternative, offering a non-invasive approach with minimal side effects. While the European Association of Urology (EAU) guidelines currently recommend Li-ESWT for vasculogenic ED only, emerging evidence suggests its potential benefits in promoting nerve regeneration as well so it might be effective topotentially improve or even restore erectile function alongside proper blood sugar management in diabetic erectile dysfunction[21,22]

Li-ESWT is a treatment developed from ESWL (Extracorporeal Shock Wave Lithotripsy) that utilizes lower-energy sound waves. Based on the intensity, ESWT is divided into high intensity (>0.60 mJ/mm^2), medium (0.28–0.60 mJ/mm^2) and low intensity ESWT (0.08–0.28 mJ/mm^2). Its focal effect can cause small damage and mechanical stress, produce biological effects, release angiogenesis and growth factors, promote angiogenesis of target tissues, and tissue regeneration. [22,23]

This study investigated the efficacy of Li-ESWT in 253 diabetic patients with mild to moderate ED from four studies (Shendy et al., Spivak et al., Tao et al., and Salama et al.). Moreover, the validated IIEF score as was used to assess changes in erectile function before and after therapy.

Shendy et al.'s study (n=42) demonstrated a positive association between Li-ESWT and ED in diabetic patients with both vasculogenic and peripheral neuropathy ED. It aligns with Fode et al.,where Li-ESWT promotes angiogenesis, modulation of vasodilation, and nerve regeneration. Li-ESWT likely achieves this by stimulating the release of growth factors (e.g., VEGF) and other signaling molecules, ultimately leading to neovascularization and improved tissue perfusion. [15,19] Li-ESWT may be ineffective to induce the necessary nerve regeneration in patients with severe nerve damage, such as those who have undergone radical cystectomy.[22]

Spivak et al.'s study (n=122, divided into PDE5I responder and non-responder groups) found a significant improvement in ED with Li-ESWT in both groups. This aligns with research by Kitrey et al. that Li-ESWT is effective for non-responder PDE5Is and able to shift them to responder PDE5I.[24, 25]

Tao et al. (n=105) and Salama et al. (n=45) compared Li-ESWT to active controls (vacuum erectile device and physical exercise, respectively). Both studies found that Li-ESWT was effective for diabetic erectile dysfunction as monotherapy, but even more effective in combination therapy aligns with Shendy et al.16Given the presumption of greater damage to the penile cavernous tissue in diabetic patients compared to non-diabetic patients, it follows that combination therapy is superior than monotherapy for treating diabetic ED might be because of different mechanism of action that work synergistically.

Apart from 1 meta-analysis study with active control (Salama et al.), the result of this meta-analysis remains significant that demonstrated a significant increase in mean IIEF score for mild to moderate ED in diabetic patients following Li-ESWT. This aligns with findings by Liu et al., suggesting Li-ESWT's effectiveness in treating mild to moderate ED.[26]

Li-ESWT causes little damage to connective tissue, skin, fat, muscle, and other tissues.[23] Kalyvianakis et al., evaluated the effectiveness and safety of Li-ESWT obtained during a 6-week treatment period and evaluated after 6 months that experienced significant changes in the IIEF score in patients with vascular erectile dysfunction without causing side effects.[27] According to Chung et al., improvements were obtained in 40% of subjects after completing Li-ESWT therapy during the evaluation 48-60 months and there was no pain or deformity of the penis after being evaluated for 5 years of long-term use of Li-ESWT.[27,28]

This study is not without limitations. First, the paucity of RCTs investigating Li-ESWT for diabetic ED. Second, a lack of standardization across Li-ESWT devices introduces potential variability. Finally, the presence of high risk of bias related to blinding. Research is needed, especially to determine optimal treatment frequency, duration, and the impact of Li-ESWT in different severity of diabetic patients with erectile dysfunction in relation to Li-ESWT, which are crucial areas for future exploration.

CONCLUSION

This systematic review and meta-analysis is the first to assess the efficacy of Li-ESWT for treating diabetic erectile dysfunction. Our findings demonstrated that Li-ESWT is effective for diabetic patients with mild and moderate erectile dysfunction. Additionally, combination therapy has a superior effect in increasing IIEF score compared to monotherapy.

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