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ORIGINAL ARTICLE

Erectile Dysfunction

Is Li-ESWT effective in diabetic patients with severe erectile dysfunction?

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Noninvasive low-intensity extracorporeal shockwave treatment (Li-ESWT) has been widely used to treat erection disorders. There is no clear information regarding either the selection of patients for the treatment or the treatment protocol. In this study, we aimed to investigate the efficacy of extracorporeal shockwave therapy in diabetic patients with severe erectile dysfunction (International Index of Erectile Function-5 [IIEF-5] scores of 5 to 7). Sixty-three diabetes mellitus patients with erectile dysfunction having IIEF-5 scores of 5 to 7 and not showing a recovery of potency despite phosphodiesterase type 5 inhibitor therapy for the past 6 months were included in the study. The patients were evaluated based on their IIEF-5 scores and Erection Hardness Scale scores. The IIEF-5 score (mean ± standard deviation [s.d.]) increased from 5.29 ± 1.67 to 5.56 ± 1.85, with a difference of 0.27 ± 0.18 ($P > 0.05$). The Erection Hardness Scale scores (mean ± s.d.), on the other hand, increased from 1.46 ± 0.50 to 1.48 ± 0.50, with a difference of 0.02 ± 0 ($P > 0.05$). In conclusion, the response to phosphodiesterase type 5 inhibitors did not change after extracorporeal shockwave treatment in diabetes mellitus patients with severe erectile dysfunction (IIEF-5 scores of 5 to 7).

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INTRODUCTION

Erectile dysfunction (ED) is one of the most common diseases among men. The incidence of ED has consistently increased, and ED is associated with age, diabetes mellitus (DM), obesity, coronary artery disease, and various other comorbidities.[1,2] ED prevalence among the general population varies between 30% and 65% in men aged 40–80 years. ED prevalence in DM patients is three times higher than that in patients without diabetes mellitus.[3] In addition to ED, it has been shown that the risk of many cancers, including urological neoplasms such as bladder and kidney cancer, may increase in patients with a history of DM, although the underlying biological relationship has not been fully explained.[4]

ED is one of the most likely and common complications of DM. The combination of microangiopathy and peripheral diabetic neuropathy associated with DM impairs the erection mechanism.[2,3] Many options exist for the treatment of ED, including oral pharmacotherapy, intracavernous injection, and penile prostheses. First-line treatments for DM-related ED are phosphodiesterase 5 inhibitors (PDE5Is).[5] These medications only treat symptoms; they have no effects on ED disorders related to distal vein disorder and the pathophysiological changes that develop with DM.[6] Low-intensity extracorporeal shockwave therapy (Li-ESWT) has been used in ED therapy, and several researchers have reported significant results.[7–9] Li-ESWT has been reported as a noninvasive, safe, and efficient method in vascular ED treatment.[10] In a recent systematic review, Li-ESWT was reported to become the first-line noninvasive treatment for ED patients.[11]

Chronic hyperglycemia in DM has been reported to cause peripheral vascular damage in the corpus cavernosum.[12] Li-ESWT has been demonstrated to improve vascular expression by increasing vascular endothelial growth factor (VEGF) release in the corpus cavernosum.[13,14] The main recovery mechanism of Li-ESWT in ED is to increase the blood flow to damaged tissue by stimulating angiogenesis. Increased blood flow restores damaged tissue and improves ED.[8,15]

In studies reporting improvement via Li-ESWT in ED patients unresponsive to medical therapy related to DM, there is no clear answer to the question of which particular DM patients benefit from the treatment. Does every DM patient unresponsive to medical treatment actually benefit from Li-ESWT?

The aim of our study was to evaluate the response to PDE5Is therapy following Li-ESWT in patients with severe ED due to DM who could not achieve erection to permit satisfactory sexual performance despite PDE5Is therapy.

PARTICIPANTS AND METHODS

The computer and file records of 116 ED patients who presented to Department of Urology, School of Medicine of Atlas University in Istanbul (Turkey) and received Li-ESWT between January 2017 and December 2020 were reviewed retrospectively. Sixty-three ED patients with DM and International Index of Erectile Function-5 (IIEF-5) scores of 5 to 7, not showing improvement despite phosphodiesterase type 5 inhibitor therapy for the past 6 months and with no history of additional therapy other than PDE5Is, were included in our study. A total of 53 patients without DM ($n = 24$); with DM and IIEF-5 scores of 8 or higher and without sufficient data ($n = 20$); without determined vascular insufficiency via penile Doppler ultrasound ($n = 5$); with

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neurological disorders such as multiple sclerosis (n = 2); or with a history of prostatectomy/radiotherapy due to prostate cancer (n = 2) were excluded from the study.

After analyzing the patients who presented to our outpatient clinic, physical examinations were performed. In addition, vascular insufficiency was established by vascular penile Doppler ultrasound (Toshiba Medical Systems Co., Ltd., Tokyo, Japan). According to the verbal statements of the patients, the absence of erection sufficient to achieve sexual intercourse despite PDE5Is therapy for 6 months before the procedure was recorded as unresponsiveness to treatment. Furthermore, according to the verbal statements of the patients, there were no significant changes in IIEF-5 scores before and after PDE5Is treatment, which were recorded as severe ED. While all patients included had received regular PDE5Is therapy before the study, Li-ESWT (Electronica Pagani, Milan, Italy) was administered without suspending the PDE5Is therapy, and the patients received regular PDE5Is therapy for 3 months postprocedure. Since the same treatment protocol was administered to the patients for prespecified periods, the study was conducted in a single-arm fashion. Preprocedure IIEF-5 scores of the patients were evaluated by the same physician (OA), while all Li-ESWT procedures and postprocedure IIEF-5 and Erection Hardness Scale (EHS) score calculations were carried out by another physician (ME). The patients underwent Li-ESWT without local or systemic anesthesia under polyclinic conditions twice a week for 6 weeks. The treatment protocol involved two sessions. Following two sessions per week for 3 weeks, a 3-week break was given. Then, the second session of twice-a-week treatments was performed for 3 weeks. The patients received PDE5Is therapy during and for 3 months following Li-ESWT. During each session, 5000 shockwaves in total were administered into 10 foci, with an energy value of 0.15 mJ mm^{-2} and 500 shockwaves per focus (120 shockwaves per min). These 10 foci included three foci on both dorsal corpus cavernosa (proximal, medial, and distal) and two foci each on the distal and proximal segments of both crural areas.

Unless otherwise indicated, quantitative data are expressed as the mean ± standard deviation (s.d.). Categorical data are expressed as numbers (n) and percentages. Pre-Li-ESWT IIEF-5 and EHS scores were compared using the Chi-square test and Fisher's exact test, while quantitative variables were compared using Student's t-test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). This study was conducted in accordance with the guidelines of the Declaration of Helsinki, and ethical approval was obtained from Biruni University in Istanbul review board (register No. 2018/15-31).

RESULTS

Penile vascular insufficiency was established in all 63 DM patients included in our study, and 90.5% of the patients were using oral antidiabetic agents, 9.5% were using insulin, and 27.0% were using anticoagulant agents. In addition, 31.7% of the patients were smokers, 46.0% had hypercholesterolemia, 60.3% had hypertension, and 14.3% had a history of myocardial infarction (MI).

During the 3-month follow-up, the IIEF-5 score (mean ± s.d.) increased from 5.29 ± 1.67 to 5.56 ± 1.85, with a difference of 0.27 ± 0.18 ($P > 0.05$). The EHS score (mean ± s.d.), on the other hand, increased from 1.46 ± 0.50 to 1.48 ± 0.50, with a difference of 0.02 ± 0 ($P > 0.05$). Following Li-ESWT, erection sufficient to permit vaginal penetration was not observed in any patient. No statistically significant difference was found between pre- and post-Li-ESWT IIEF-5 and EHS scores (both $P > 0.05$; **Table 1**).

Twenty point six percent of patients (13/63) who showed minimal but statistically nonsignificant increases in IIEF-5 and EHS scores had no history of hypertension, hypercholesterolemia, myocardial infarction, or smoking. During Li-ESWT and the 3-month follow-up, no side effects or complications were observed, except skin ecchymosis in a few patients. Data on demographic features and laboratory findings are shown in **Table 2**.

DISCUSSION

As shown in epidemiological studies, the risk factors for ED include cardiovascular diseases, diabetes, obesity, smoking, and a sedentary lifestyle.[16,17] Several studies have demonstrated that hypogonadism might have an effect on ED. In men, functional hypogonadism is characterized by serum testosterone levels <12.1 nmol l^{-1} (<350 ng dl^{-1}), sexual dysfunction (difficulty reaching orgasm, decreased libido, ED, and decreased physiological erections and ejaculate), impaired spermatogenesis, and changes in cholesterol levels; functional hypogonadism can lead to many problems, such as irritability, depressed mood, difficulty concentrating, anemia, osteoporosis, and hot flashes.[18–20] The testosterone level (mean ± s.d.) of our patients was 464.48 ± 125.36 ng dl^{-1}. None of our patients had hypogonadism.

According to several studies, sexual function disorder is encountered 30.0% more often in obese men than that in normal-weight men. The body mass index (BMI; mean ± s.d.) of our patients was 24.87 ± 4.09 kg m^{-2}. This mean value indicated that most of our patients were overweight. There is a significant relationship between DM duration and ED.[21,22] In Brazil, Rhoden *et al.*[23] found that those

Table 1: Pre- and post-Li-ESWT IIEF-5 score/EHS score analysis

Score	*Mean±s.d.*	*P*
Pre-Li-ESWT IIEF-5 score	5.29±1.67	0.61
Post-Li-ESWT IIEF-5 score	5.56±1.85	
Pre-Li-ESWT EHS score	1.46±0.50	0.79
Post-Li-ESWT EHS score	1.48±0.50	

Li-ESWT: low-intensity extracorporeal shockwave therapy; IIEF-5: International Index of Erectile Function-5; EHS: Erection Hardness Scale; s.d.: standard deviation

Table 2: Patient demographic and laboratory characteristics

Characteristic	*Patients (total=63)*
Age (year), mean±s.d.	57.11±5.06
BMI (kg m^{-2}), mean±s.d.	24.87±4.09
ED duration (year), mean±s.d.	2.10±0.46
DM duration (year), mean±s.d.	8.46±2.65
HbA1c (%), mean±s.d.	7.24±1.06
Total testosterone (ng dl^{-1}), mean±s.d.	464.48±125.36
Patients, n (%)	
DM	63 (100.0)
Oral antidiabetic agent use	57 (90.5)
Insulin use	6 (9.5)
Anticoagulant agent use	17 (27.0)
Vascular insufficiency established by penile doppler ultrasonography	63 (100.0)
PDE5Is treatment	63 (100.0)
Smoking history	20 (31.7)
Hypercholesterolemia	29 (46.0)
Hypertension	38 (63.8)
MI history	9 (14.3)

s.d.: standard deviation; BMI: body mass index; ED: erectile dysfunction; DM: diabetes mellitus; HbA1c: hemoglobin A1c; PDE5Is: phosphodiesterase 5 inhibitors; MI: myocardial infarction

with diabetes for more than 10 years presented with ED more often than those with diabetes for less than 5 years. The DM duration of the patients (mean ± s.d.) in our study was 8.46 ± 2.65 years, and the ED duration (mean ± s.d.) was 2.10 ± 0.46 years.

Animal studies have shown that Li-ESWT might be effective in chronic ischemic diseases, as it increases the number of endothelial precursor cells in circulation in parallel with an increase in vascular endothelial growth factor (VEGF) and chemoattractant factor production.[24,25] Cavernous endothelial cell dysfunction is one of the most important pathological changes in vasculogenic ED. Penile Doppler ultrasonography (USG) is a reliable method in the evaluation of cavernous vasculogenic insufficiency.[26] Experimental models and clinical studies have shown that hyperhomocysteinemia and folic acid depletion increase atherosclerosis and impair cavernous perfusion. Giovannone *et al.*[27] confirmed this relationship with penile Doppler USG. Cavernous vascular insufficiency of the patients included in this study was revealed by penile Doppler USG. In a study by Gruenwald *et al.*,[25] the Li-ESWT response of 29 patients who were low responders to PDE5Is therapy and had severe vasculogenic ED and multiple cardiovascular risk factors, cardiovascular disease, and diabetes mellitus was evaluated. In their study, patients who were nonresponsive to PDE5Is were reported to achieve erection sufficient to permit vaginal penetration through the use of Li-ESWT. At the end of a 3-month follow-up, a 76.0% improvement in the IIEF-erectile function domain (IIEF-ED) score and an increase in response to PDE5Is inhibitors in 72.0% of the patients were observed. In this study by Gruenwald *et al.*,[25] the number of DM patients was 21 (72.4%), and their level of ED was not classified according to IIEF-5 scores. In a recent study conducted by Shendy *et al.*,[28] a significant increase in the IIEF-EF scores of patients with vasculogenic and neurogenic ED due to DM in the 3rd month post-Li-ESWT was reported.

In our study, on the other hand, the responses to Li-ESWT of 63 DM patients who were unresponsive to PDE5Is therapy and had severe vasculogenic ED diagnosed under penile Doppler USG, had cardiovascular disease, and had severe IIEF-5 scores of 5 to 7 were evaluated. In our study, despite PDE5Is therapy for 6 months before Li-ESWT and for 3 months during and after the procedure, none of our patients achieved an erection sufficient to permit vaginal penetration. In a recent study conducted by Eryilmaz *et al.*[29] 53.7% of the Li-ESWT group of 20 patients who were unresponsive to PDE5Is therapy had DM. In their study, significant changes in IIEF-5 scores and EHS scores were observed; however, due to the lack of IIEF-5 score classification of DM patients, the efficiency of this treatment in patients with severe ED has not been established clearly.

Vardi *et al.*[30] in 2012 revealed that the success rate of Li-ESWT is low in patients with severe ED and DM. In our study, although there was a minimal increase in the IIEF-5 and EHS scores of DM patients with severe ED, no significant efficacy of Li-ESWT was demonstrated. Huang *et al.*[31] reported that following Li-ESWT, 22 patients (58.0%) responded to PDE5Is treatment among 38 patients with ED who had not previously responded to PDE5Is treatment. In their study, the total number of patients with comorbidities (DM, hypertension, and hyperlipidemia) was 10 patients. In our study, on the other hand, the response to PDE5Is treatment was not significant, and 100.0% (63) of our patients had DM, with 63.8% (38/63) having hypertension and 46.0% (29/63) having hyperlipidemia. Fojecki *et al.*[32] in a randomized double-blind study in 2017 divided 126 ED patients into two groups and administered active Li-ESWT and sham Li-ESWT; they reported that Li-ESWT had no effect on ED, with no significant difference observed between the two groups.

In an animal model study by Qiu *et al.*[33] in which the effect of Li-ESWT on erectile function in rats with DM was investigated, erectile function was higher in the group receiving Li-ESWT than that in the group not receiving Li-ESWT; histologically, more neurogenic nitric oxide synthase (nNOS) was found in nerve, endothelial and smooth muscle cells in the group receiving Li-ESWT. The patients included in this study were not evaluated in terms of peripheral neuropathy due to DM, which can be considered one of the limitations of our study.

CONCLUSION

There is no established gold-standard method for the nonsurgical treatment of ED. More studies are required to determine the actual efficiency of Li-ESWT, which has been reported as a novel and promising nonsurgical method. Our study showed that Li-ESWT administration did not increase the response to PDE5Is treatment in DM patients with severe ED who could not achieve an erection despite PDE5Is treatment and whose IIEF-5 scores ranged from 5 to 7. Although Li-ESWT is a safe and painless treatment, more studies are needed to determine its efficacy.

AUTHOR CONTRIBUTIONS

Both authors conceived the study, collected the clinical data, participated in data analysis, and wrote the original draft. Both authors read and approved the final manuscript.

COMPETING INTERESTS

Both authors declare no competing interests.

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