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Response of erectile dysfunction to extracorporeal shock wave therapy in type 2 diabetic men

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Abstract

Introduction. Erectile dysfunction is a major complication of type 2 diabetes mellitus (T2DM). This study aimed to investigate the effect of active vs. sham low-intensity extracorporeal shock wave therapy (Li-ESWT) on erectile dysfunction in T2DM men.
Methods. Overall, 40 married T2DM men aged 40–50 years with erectile dysfunction were assigned to the study and the control group. Besides a 12-week daily administration of a 5-mg tablet of phosphodiesterase-5 inhibitor (PDE5I) tadalafil in both groups, the control group (n = 20) received sham Li-ESWT, while the study group (n = 20) received 2 active Li-ESWT (on the penile shaft with 1800 pulses and intensity of 0.09 mJ/mm^2) sessions weekly for 3 consecutive weeks; then, the procedure was repeated for another 3 consecutive weeks, with a 3-week rest between the 2 procedures. Erectile dysfunction was assessed by the 5-item version of the International Index of Erectile Function (IIEF-5). Baseline, 1-month follow-up, 3-month follow-up, and 6-month follow-up IIEF-5 scores were documented.
Results. After 1- and 3-month follow-up, there was a significant difference between the active and sham groups in favour of the active Li-ESWT group (p-value of 0.0001 and 0.01, respectively), but there was no significant difference between the groups at 6-month follow-up.
Conclusions. Li-ESWT can increase the long-term efficacy of PDE5I in T2DM men with erectile dysfunction.
Key words: low-intensity extracorporeal shock wave therapy, erectile dysfunction, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) can be described as a syndrome of multiple closely related conditions induced by a chronic state of hyperglycaemia [1] resulting from defective insulin secretion, insulin action [2], or both [3]. The chronic complications associated with DM (including neuropathy, vascular disease, nephropathy, and retinopathy) are common, and of these, erectile dysfunction (ED) deserves special attention [4].

ED is the inability to achieve or maintain a normal enough habitual erection for satisfactory sexual performance [5, 6]. ED is a highly prevalent problem in men with type 2 DM (T2DM), mainly in those with poor glycaemic control [7]. About 59.1% of T2DM men complain of ED [8]. The prevalence rate of ED is 3 times higher (35–90%) among diabetics compared with non-diabetics [9]. Affecting the quality of life of the patient and the spouse [10], ED and its correlation with cardiovascular disease require a careful and appropriate treatment [11].

Phosphodiesterase-5 inhibitor (PDE5I) medications, penile pumps, and implants [12] are the main options for ED treatment [13]. As a first-line drug for ED, PDE5I still has some limitations. In addition to non-response cases [14] and the need for continuous use, PDE5I exhibits a reduced efficacy and is not considered a fundamental treatment in patients with diabetic ED [15].

One of the non-invasive non-pharmacological treatments is the use of low-intensity extracorporeal shock wave therapy (Li-ESWT) [13], which seems to be an attractive option for the treatment of ED [12]. Li-ESWT has gained increasing interest owing to its strong angiogenic properties, especially in patients with ED [16]. It may offer considerable benefits in ED treatment, such as improved cavernous penile blood flow and increased shear stress exerted during the treatment. Shear stress induces the release of angiogenic factors, which results in revascularization, regeneration of microvasculature, and improvement of penile haemodynamics [12].

With no consensus about the effectiveness of Li-ESWT in the ED setting [17], ED in T2DM requires more attention from researchers as it can cause irreversible damage [18]. Owing to the limited number of studies assessing Li-ESWT efficacy in ED among T2DM patients, this study aimed to investigate the effect of active vs. sham Li-ESWT on ED in T2DM men.

Subjects and methods

Participants

The sample size was estimated with the G*Power software (version 3.1.9.2) (Franz Faul, Universität Kiel, Germany). In the F-test, the type I error rate was set at 5% (alpha-level of 0.05) and the effect size was 0.5 of the main outcome variable (score in the 5-item version of the International Index of Erectile Function [IIEF-5]) obtained from a pilot study conducted in 10 subjects; type II error rate was at 90% power. The proper minimum sample size for this study was 30 subjects.

A total of 40 married T2DM men aged 40–50 years were randomly selected from the Andrology Outpatient Clinic of Mit Ghamr General Hospital. The included patients com-

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plained of mild or moderate ED, scored 21–8 on IIEF-5, at least for the previous 6 months, with DM duration of ≥ 5 years, glycated haemoglobin (HbA1c) ≥ 6.5% mg/dl, and body mass index (BMI) < 30 kg/m^2.

Participants were excluded – by a physician – if they presented with hypertension, alcoholism, smoking, hyperlipidaemia, or any addiction. Also, patients with hypogonadism, family history of premature vascular disease, history of pelvic trauma and/or pelvic surgery, cancer, psychiatric disease, neuromuscular disorders, cardiovascular or pulmonary disorders, renal conditions or liver failure, thyroid gland dysfunction, prostatectomy and/or prostatic disease, spinal cord injury, or previous therapy for ED were excluded.

Intervention

The ED patients were divided into the active Li-ESWT (study) and the sham Li-ESWT (control) group, 20 individuals in each group. Besides a 12-week daily administration of a 5-mg tablet of PDE5I medication (tadalafil, prescribed by an andrology physician) in both groups, the study group received Li-ESWT (Chattanooga Intelect RPW) in accordance with the protocol by Vardi et al. [19] – twice weekly for 3 consecutive weeks; then, the procedure was repeated for another 3 successive weeks, with a 3-week rest period between the 2 procedures. The treatment was applied in a private physiotherapy centre in Mit Ghamr city for 15 minutes per session at an energy level of 0.09 mJ/mm^2 and a frequency of 120 shocks/minute (1800 pulses per session). Apart from the left and right crura of the penis, shock waves were delivered to the distal, middle, and proximal penile shaft after placing an ultrasound gel used as a coupling agent on the treated area. The men in the sham Li-ESWT group received shock waves of the same parameters but with a sham application.

Outcome measures

IIEF-5 was used to assess the improvement of ED. Baseline IIEF-5 scores were collected before the study for all participants. Then, ED was assessed again for follow-up at 1, 3, and 6 months after the end of the treatment.

Statistical analysis

The data were subjected to the Shapiro-Wilk test to verify normality of distribution. The variables (age, weight, height, BMI, diabetes duration, HbA1c, and IIEF-5 score) were normally distributed, so they were all treated with parametric tests. ANOVA was used to determine the differences between groups concerning age, weight, height, BMI, diabetes duration, and HbA1c, but mixed multilevel analysis of variance (MANOVA) served to establish the effect of treatment and time as for the IIEF-5 score (SPSS version 23, IBM Corp., New York, USA). The level of significance was set at 0.05.

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved by the Ethical Committee for Scientific Research of Faculty of Physical Therapy, Cairo University (approval No.: P.T.REC/012/002577).

Informed consent

Informed consent has been obtained from all individuals included in this study.

Results

Demographic data

The characteristics of the subjects are demonstrated in Table 1. ANOVA found no significant difference between the 2 groups with regard to age, weight, height, BMI, diabetes duration, or HbA1c ($p > 0.05$).

Table 1. Both-group demographic data

Characteristics	Active Li-ESWT	Sham Li-ESWT	*p*	Significance
Age (years)	47.85 ± 1.59	46.20 ± 3.08	0.05	NS
Weight (kg)	82.6 ± 4.48	81.9 ± 2.88	0.56	NS
Height (cm)	176.4 ± 6.3	178 ± 4.78	0.37	NS
BMI (kg/m^2)	26.58 ± 1.66	25.9 ± 1.63	0.19	NS
Diabetes duration (years)	9.65 ± 0.98	9.4 ± 1.31	0.501	NS
HbA1c (mg/dl)	7.25 ± 0.5	7 ± 0.7	0.205	NS

Data are expressed as mean ± standard deviation.
Li-ESWT – low-intensity extracorporeal shock wave therapy, BMI – body mass index, HbA1c – glycated haemoglobin, NS – not significant (significance at $p < 0.05$)

Effect of treatment on IIEF-5 score

In general, there was a significant effect of both treatment and time on the IIEF-5 score ($p < 0.05$), as shown in Table 2.

Table 2. Mixed ANOVA for the effect of treatment on IIEF-5

MANOVA	*F*	*p*
Effect of treatment (group)	7.4	0.01
Effect of time	71.1	0.000
Effect of interaction	19.63	0.000

IIEF-5 – 5-item version of the International Index of Erectile Function, *F* – MANOVA test

Within- and between-group analysis

The pre-treatment mean value of IIEF-5 in the active Li-ESWT group was 15.6 ± 0.99, while after 1-month follow-up the score equalled 19.3 ± 1.4. The mean difference was 3.7, and the percent of change was 24%. The mean value of IIEF-5 at 3-month follow-up and 6-month follow-up was 18.85 ± 1.56 and 18.35 ± 1.3, respectively, with a percentage change of 21% and 15.6%. There was a significant increase of IIEF-5 score at 1-month follow-up, 3-month follow-up, and 6-month follow-up compared with the baseline IIEF-5 level ($p = 0.0001$).

The pre-treatment mean value of IIEF-5 in the sham Li-ESWT group was 16 ± 0.79, while after 1-month follow-up the score equalled 17.25 ± 1.01. The mean difference was 1.25, and the percent of change was 8%. The mean value of IIEF-5 at 3-month follow-up and 6-month follow-up was 17.75 ± 0.9 and 17.85 ± 0.8, respectively, with a percentage change of 11% and 11.5%. There was a significant increase of IIEF-5 score at 1-month follow-up, 3-month follow-up, and 6-month follow-up compared with the baseline IIEF-5 level ($p = 0.0001$).

To determine the difference between the 2 groups in the mean pre-treatment, 1-month follow-up, 3-month follow-up,

and 6-month follow-up IIEF-5 scores, multiple pairwise comparisons were performed. For the pre-treatment value, there was no significant difference between the groups ($p = 0.16$). After 1-month follow-up and 3-month follow-up, there was a significant difference between the active and sham Li-ESWT groups (p-value of 0.0001 and 0.01, respectively) in favour of the active Li-ESWT group. Finally, no significant difference was observed between the groups at 6-month follow-up ($p = 0.15$).

Discussion

Besides the limited effectiveness of the existing treatments, there is a possibility that ED will grow within 10 years after the initial DM diagnosis [20]. Some promising new modalities of care have recently become popular as alternative treatments for DM-related ED. In several different animal studies, one of those, Li-ESWT, has been reported to boost local penile blood supply [9]. The present study aimed to investigate the response of ED in T2DM men to active vs. sham Li-ESWT (applied twice weekly for 3 successive weeks and then, after a 3-week rest, again twice weekly for 3 successive weeks) in addition to the administration of tadalafil 5 mg once daily for 12 weeks.

The results of the active Li-ESWT group at 1-month and 3-month follow-up showed a more improved IIEF-5 score than in the sham Li-ESWT group. Despite the higher percentage of IIEF-5 improvement in the active Li-ESWT group than in the sham one, there was no significant difference between the groups at 6-month follow-up.

However, a well-defined rationale remains missing for the pathophysiological mechanism of ESWT effect on ED and penis [9]. The suggested mechanism of action is the upregulation of growth factors and recruitment of progenitor [21] and mesenchymal stem cells [22], which in turn induce tissue regeneration, neo-angiogenesis, and enhanced endothelial function [21].

Li-ESWT resembles shear stress and causes changes in membrane permeabilization, which contributes to the activation of signalling cascades, leading to angiogenesis, inhibition of inflammatory responses, regulation of nitric oxide release, and targeting of the endothelial progenitor cells and stem cells to the treated area. Recently, it has been suggested that Li-ESWT in a rodent model of DM-induced ED can affect penial neural tissue with an elevation of neuronal nitric oxide. However, it is well known that there is a reduction in the content of penile functional cells such as endothelial and smooth muscle cells; it has also been shown that the content of these functional cells becomes elevated even after Li-ESWT in diabetic patients with ED [20].

Human studies have revealed a statistically significant improvement in flow-mediated dilation in patients treated with Li-ESWT, indicating that animal studies in terms of penile haemodynamics and endothelial function may well correlate with human studies [23].

A study examined the impact of Li-ESWT on 29 men with ED who failed to respond to PDE5I, 21 of whom had DM. It was found that the 21 diabetics responded to Li-ESWT owing to the significant improvement of cavernosal blood flow and penile endothelial function [24].

Another study reported effectiveness and safety of 20-minute Li-ESWT sessions in the treatment of 20 ED patients. The sessions were characterized by an energy density of 0.09 mJ/mm^2 and repeated twice weekly for 3 weeks; then, after a 3-week rest, the procedure was repeated with 300 shocks per treatment point (1500 per session) and a frequency of 120 per minute. Besides, 10 men did not use PDE5I after 6 months of follow-up; an improvement in the IIEF score was reported at 1 month and persevered for 6 months. The period of a 3-week no-ESWT treatment after the 6th session of ESWT is required to augment the highest response of expression of ESWT-induced neovascularization [19]. Also, in a study that included 57 ED patients, a significant improvement in the erection domain of IIEF was observed at 1, 3, and 6 months after the last Li-ESWT session ($p < 0.001$) [25].

In 81.03% of ED patients, Li-ESWT was successful among 58 PDE5I respondents or non-respondents. A substantial improvement was observed in the erectile function domain, with a 6-month post-treatment mean difference of 7.5 ± 4.7 (the baseline IIEF-5 score was 14.8 ± 4.8). As a result, the administration of PDE5I was stopped in 4 patients because spontaneous erections were restored [26].

Again, 7 weeks after the last session, 12 sessions of ESWT (twice weekly with a 3-week rest period after the 6th treatment session) produced a significant improvement in erectile function domain score of IIEF in the active ESWT group (16.6 ± 3.0 at baseline vs. 21.7 ± 8.2, $p < 0.001$) as compared with the sham group (16.7 ± 3.2 at baseline vs. 14.5 ± 5.4). The patients received energy densities of 20, 15, and 12 mJ/mm^2 applied with the same sequence to the root of the penis, to the shaft, and a few millimetres proximally to the glans, respectively, with a frequency of 5 Hz and 3000 shock waves divided equally to the 3 treatment areas of the penis [27].

The combined approach involving 2400 shock wave low-intensity pulses and 5 mg of tadalafil (once daily) resulted in a significant improvement of IIEF-5 score, maintained even for 6 months after the intervention, compared with tadalafil alone in T2DM men with ED [28].

Limitations

The lack of 1-year follow-up and involvement of different age classes is the main limitation of this trial, which must be addressed in future studies.

Conclusions

The program of a 12-week administration of 5 mg tadalafil once daily with 12 sessions of Li-ESWT (twice weekly with a 3-week rest period after the 6th session) performed at the start of the program can increase the long-term efficacy of PDE5I after the end of the intervention in T2DM patients with ED.

Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

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