Effect of physical exercise combined with shockwave therapy on erectile dysfunction in diabetic patients

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Abstract

Introduction: The aim of the study was to evaluate whether physical exercise (PE) in addition to extracorporeal shockwave therapy (ESWT) is more effective in improving erectile function as compared to ESWT and PE alone in diabetic patients with erectile dysfunction (ED).

Material and methods: Forty-five patients with type 2 diabetes mellitus (DM) and ED were divided into three equal groups: group 1 (ESWT group) received treatment with ESWT twice weekly for 6 weeks, comprising 3000 shockwaves at an energy density of 0.25 ml/mm² and an emission frequency of 6 Hz; group 2 (PE group) received treatment with physical exercise three times per week for 12 weeks; and group 3 (combined group) was treated using physical exercise in the form of the program followed by the PE group, plus ESWT in the form of the same parameter and protocol as that of the ESWT group. Treatment outcomes were measured by International Index of Erectile Function-5 (IIEF-5) score variations recorded at 4 and 12 weeks after the end of treatment with respect to the baseline.

Results: The mean IIEF-5 scores significantly improved in all groups at the 4-week follow-up without intergroup differences. At the 12-week follow-up, the mean IIEF-5 improvement and durability were significantly higher among patients in combined groups.

Conclusions: The combined approach of ESWT and PE provides significant advantages in erectile dysfunction improvement and durability as compared to ESWT or PE alone in diabetic patients with ED.

Key words: shockwave, physical exercise, erectile dysfunction.

Introduction

Diabetic mellitus erectile dysfunction (DMED) refers to erectile dysfunction (ED) that is secondary to diabetes. It is distinguished by prolonged or frequent erection and lack of hardness or time to be satisfied [1]. This condition is a form of sexual impairment caused by diabetes [2].

ED is a common and problematic diabetes mellitus complication. The incidence, frequency, and development rate of ED relative to nondiabetic males have been found to be increased in diabetic individuals [3]. In total, 51.3% of diabetic men have self-reported symptoms of ED [4]. They are three times as likely to develop ED as nondiabetic men of similar age.
therapy with medication or invasive treatments. Therefore, in this randomized clinical trial we carried out a comparative study between the efficiencies of ESWT, PE, and a combination of both in the management of ED.

Material and methods

Subjects

Between September 2019 and October 2020, 45 T2D patients with ED were recruited from the Department of Endocrinology of Cairo University hospitals. Prior to all examinations and interventions, all patients signed written informed consent. The study protocol was approved by the faculty of the physical therapy ethical committee.

Inclusion criteria

Patients who had ED for over 6 months, were 40 to 60 years of age, had type 2 diabetes, had average ratings of over 12 on the International Index of Erectile Function (IIEF-5) five-item edition, had failed or had unsatisfactory results with oral PDE5i agents, were in a committed (married) relationship, and engaged in regular sexual activity for a minimum of 6 months before the study.

Exclusion criteria

Subjects who had any of the following conditions were excluded from enrollment: Severe ED patients (score IIEF-5 < 12), coagulopathy history or recent antiplatelet therapy history, pelvic radiation previously administered, trauma, penile anomalies, prior prostatic surgery, history of malignancy in the last 5 years, unstable spinal cord injury, psychiatric illness, cardiovascular diseases, hypertension with blood pressure > 160/100 mm Hg, smoker, alcoholic or recent anti-androgen or androgen administration. Patients were also excluded if, in the previous 7 days, ED therapy involving oral medicine, VED, ICI, or intraurethral therapy was offered. Men were invited to take part in the secondary study of sexual dysfunction at these sites.

Measurements

Research personnel were offered systematic instruction and qualification in the research procedures performed for all measurements at the baseline before randomization. All subjects were examined properly, and all medical observations and histories were documented. Body mass index (BMI) was measured as weight of the body (in kg) divided by the square height (in cm). Duration of DM, smoking history, and the use of medicines for hypertension and lipid reduction were recorded. The endocrinology department at the hospital had approved the type 2 DM diagnosis. The most
recent level of glycated hemoglobin (HbA1c) was
documented.

Sexual function

Sexual function was assessed by physical ex-
amination and history of sexual activity, using the
Arabic version of the International Index of Erec-
tile Function (IIEF-5) as a diagnostic tool [29]. In
a single session, all patients completed the IIEF-5
Arabic version without assistance. IIEF-5 is among
the most frequently used, validated, and reliable
tests for male sexual function [30]. It evaluates the
clinical severity of ED within the past 6 months.

The IIEF score ranges between 1 and 25; a score
< 22 indicates ED. The severity of ED was evalu-
ated according to the total IIEF score; a score of
1–7 indicates severe ED, a score of 8–11 indicates
moderate ED, a score of 12–21 indicates mild ED,
and a score of 22–25 indicates no ED.

The evaluation was carried out among all pa-
tients at baseline, after 4 weeks, and after 12 weeks
of interventions.

Intervention

The patients were randomly assigned to 3 par-
allel groups: an ESWT group (to undergo ESWT
intervention), a PE group (to receive physical exer-
cise treatment), and a combined group (to receive
ESWT treatment alongside physical exercise).
A random number generator in SPSS 25 for Win-
dows (IBM Corp., Armonk, NY, USA) generated the
randomization sequence. The random allocation
sequence was implemented using sequential-
ly numerated, unmarked, sealed envelopes. The
authors of the study developed the sequence of
random allocations, engaged participants, and
assigned participants to interventions. However,
neither patients nor the clinicians were blinded to
the after-assignment procedures.

ESWT group

Patients in the ESWT group were treated
through the administration of shockwave therapy
technology (Shockmaster MP200, pneumatic-mec-
chanical radial shockwave unit, Storz Medical,
Switzerland). With no local or systemic analgesia,
ESWT was applied with ultrasound gel. All pa-
tients were treated twice per week for 6 weeks,
with 3000 shockwaves being administered to the
distal penis (1000 shockwaves), penis base (1000
shockwaves), and perineum corporal bodies (500
shockwaves to each crus). The treatment location
and the device’s probe were cleaned and disinfec-
ted before and after application to prevent in-
fection. Each patient was required to remove any
hair in the application area, 2 days before therapy
began. To reduce the risk of injury, shockwaves
were not delivered to the testes, spermatic cords,
or urethra. With both corpora reaching the depth
of the shockwaves, treatment was provided on
only one side of the penile shaft. The 3000 shocks
were administered according to the manufacturer’s
instructions at an energy density of 0.25 ml/
mm² and an emission frequency of 6 Hz per treat-
ment session, which lasted 15 min. Every patient
treated for 6 weeks with ESWT then continued to
be followed up for 12 weeks.

PE group

In the PE group, patients were treated with
physical exercise. The patients completed an
exercise regimen that included 20 min of aero-
bic exercise accompanied by 10 min of full-body
stretching, 30 min of strength exercise, and
10 min of aerobic exercise. To optimize the impact
of exercise on recovery, this training program was
administered 3 days a week. The patients spent
12 weeks carrying out this program.

Combined group

Patients in the combined group were handled
with the same guidelines and procedures as those
of the ESWT group using physical activity in the
form of the program used by the PE group plus
ESWT. To avoid exhaustion, the patients were
treated with ESWT on the days when they were
not engaging in exercises. ESWT was conducted
with exercise for 6 weeks; then ESWT was discon-
tinued and exercise resumed for 12 weeks.

Results

Sample size

The pre-study sample size calculation was per-
formed using G*POWER statistical software [F
tests- ANOVA: repeated measurements, between
variables, α = 0.05, power = 80%, and large effect
size] and revealed that N = 45 was the acceptable
sample size for this analysis.

Statistical analysis

Descriptive statistics and an ANOVA test for
comparison of the average age of the 3 groups
were performed. Data distribution was tested us-
ing the Shapiro-Wilk test. To test the homogeneity
between groups, Levene’s test for homogeneity of
variances was carried out. A mixed MANOVA was
conducted to compare the time effect (pre, post I,
and post II) and treatment effect (between groups),
as well as the relationship between therapy and
time on mean IIEF values. For subsequent multiple
comparisons, post-hoc tests were performed us-
ing the Bonferroni correction. The significance lev-
el was set to p < 0.05 for all statistical tests. IBM
SPSS version 25 for Windows (IBM Corp., Armonk, NY, USA) provided all statistical tests.

**Participant characteristics**

Table I displays the characteristics of the participants from groups A, B, and C. The age gap between the three groups ($p > 0.05$) was not significant.

**Effect of treatment on IIEF**

A mixed MANOVA showed that therapy and time correlations were significant ($F = 49.48, p = 0.001$). The main effect of time ($F = 408.48, p = 0.001$) was significant and the main effect of treatment was significant ($F = 17.85, p = 0.001$).

**Within-group comparison**

At post I and post II, there was a significant increase in IIEF compared to pretreatment in the three groups ($p < 0.001$). In group A, there was a significant decrease in IIEF at post II compared to post I ($p < 0.01$). In group B, there was a significant increase in IIEF at post II compared to post I ($p < 0.001$). In group C, there was a significant increase in IIEF at post II compared to post I ($p < 0.001$).

**Between-group comparison**

There was no significant difference between the pretreatment groups in IIEF ($p > 0.05$). Comparison between post I groups showed a significantly higher value in group A IIEF versus group B ($p = 0.007$) and a significantly higher value in group C IIEF versus group B ($p = 0.001$). However, the difference between groups A and C ($p = 0.29$) was not significant. In the post II group C, IIEF was significantly higher compared to groups A and B ($p = 0.001$) while in group B, IIEF was significantly higher compared to group A ($p = 0.001$) (Table II).

**Discussion**

In modern society, ED is a common disorder in males and directly impacts the consistency of a couple’s sex life. In diabetic patients, the etiology of ED is multifactorial [31]. The mechanisms suggested include neuropathy, vasculopathy, resistance to insulin, visceral adiposity, and hypogonadism. Microvascular dysfunctions are accountable for peripheral circulatory ischemic damage [31]. In addition, both somatic and autonomic neuropathies may lead to DM-induced ED due to the loss of sensory impulses from the penis to the reflexogenic erectile center and the markedly reduced parasympathetic activity essential for relaxation of the corpus cavernous smooth muscle [31]. Men with DM appear to have more serious ED and all of the PDE5Is in this clinical scenario are less successful. PDE5i agents are somewhat recognized as ED first-line therapy [32].

These drugs, however, are not beneficial in all patients, especially those with diabetes-induced ED. Medical treatment addresses only the symptom of ED and does not improve the underlying pathophysiology of the disease mechanism. Penile rehabilitation philosophy is built on the concept that such therapy would ultimately recover the erectile system and enable men to recover spontaneous erection. To our knowledge, this is the first research into the effectiveness of the conjunction of ESWT and physical activity in T2DM and ED patients [13].

Our findings show that the combined strategy offers advantages over ESWT or PE alone in terms of mean IIEF-5 score improvement and outcome durability. The key finding of this study is that treatment of ED in T2DM patients with either ESWT, PE, or both led to significant changes in the IIEF-5 score at 4 and 12 weeks after completion of therapy (as compared to the baseline). In addition, PE and ESWT had comparable efficiencies.

**Table I. Basic characteristics of participants**

| Parameter | Group A | Group B | Group C | $p$-value |
|-----------|---------|---------|---------|-----------|
| Age, mean ± SD [years] | 43.33 ±4.89 | 42.06 ±3.8 | 42.73 ±5.68 | 0.77 |

SD – standard deviation, $p$-value – level of significance.

**Table II. Mean IIEF at pretreatment, post I, and post II of groups A, B, and C**

| Parameter | Group A | Group B | Group C | $p$-value |
|-----------|---------|---------|---------|-----------|
| Mean ± SD | A vs. B | A vs. C | B vs. C |
| Pretreatment | 12.13 ±1.24 | 12.53 ±1.3 | 12.26 ±1.03 | 1 | 1 | 1 |
| Post I | 15.6 ±1.3 | 14.2 ±1.01 | 16.33 ±1.23 | 0.007 | 0.29 | 0.001 |
| Post II | 13.66 ±1.17 | 15.4 ±1.18 | 18.2 ±0.86 | 0.001 | 0.001 | 0.001 |
| $p$ = 0.001 | $p$ = 0.001 | $p$ = 0.001 |

SD – standard deviation, $p$-value – level of significance.
The percentages of progress in the ESWT group were 28% and 12.6%, while the percentages in the PE group were 13% and 22.9%, and the percentages in the ESWT and PE combined group were 33.1% and 48.4% after 4 and 12 weeks, respectively. This showed that in the ESWT and combined groups, the percentage change after 4 weeks was higher than that in the PE alone group, meaning the response to ESWT is faster than the response to PE. There was a decline in the improvement of the ESWT group after 12 weeks, but there was an increase in the PE group and the combined group after 4 weeks as opposed to the measurement. This means that ESWT’s durability alone is less than the durability of the PE and ESWT combinations. No pain or side effects connect the shockwave energy and exercise treatment used in the present research.

ESWT has been widely used to treat various disorders, including urolithiasis [33], chronic damage to the motor system, and Peyronie’s disease [34]. A shockwave is a form of high-energy mechanical acoustic wave that yields a pressure impulse as it spreads through a medium. The waves can be non-invasively modified, allowing for the delivery of a controllable amount of energy at the desired location. The concentrated waves interact with selected deep tissues, inducing several biological changes, including weakening fibrous adhesions, stimulating capillary formation, and promoting hyperplasia of the vascular endothelial cells [14]. Several controlled clinical trials in recent years have shown ESWT’s beneficial effects in patients with physical ED [14–18].

The underlying mechanisms of ESWT’s positive impact still hard to be fully explained, although some animal studies have elucidated that. ESWT has been shown to considerably boost the erectile capacity of diabetic rats and to contribute to the growth of smooth muscle and endothelial cells [35], and, thus, to elicit a time- and treatment-dependent reduction in the ratio of intracavernosal pressure to mean arterial pressure, likely due to apoptosis and collagenisation of smooth corporal muscle [36].

Research using molecular biology techniques has shown that ESWT upregulated the α-smooth muscle actin, von Willebrand factor, neuronal NO synthase, and vascular endothelial growth factor expression and downregulated the receptor’s expression for advanced glycation end products in the corpus cavernosum [37]. We believe that ESWT enhances erectile function through a variety of measures, which include eliminating fibrosis and apoptosis, improving microcirculatory blood flow in local tissue, and releasing tissue factors such as endothelium-derived relaxing factor and various growth factors.

ESWT’s proposed mechanisms of action in ED patients may reflect the reasoning behind the consistency of the findings reported in patients undertaking the combined approach. Admittedly, energy from ESWT’s acoustic waves has been proposed to stimulate cellular and molecular pathways, increasing the production of local growth factors and enhancing endothelial activity, angiogenesis, and nerve fiber regeneration. ESWT therefore has the ability to recover normal erections and treat the disease [38].

Penile erection is a physiologic mechanism involving increased arterial inflow and venous outflow limits [19]. Endothelial inflammation which interferes with the production of nitric oxide (NO) is a key element of vascular diseases, particularly ED [39]. Neuronal and endothelial NO mediate the vascular portion of sexual excitement by engorgement of the corpora cavernosa tissue and subsequent penile erection. It is well understood that the erectile flow of blood is controlled by the smooth muscle cells of penile arterial vessels being constricted or relaxed [40]. Physical exercise (PE) may eventually lower ED, and PE has been established as the lifestyle factor most strongly associated with erectile function, in addition to being the most significant vascular health promoter. Therefore, moderate- and vigorous-intensity PA is correlated with healthy erectile function and lower ED risk [19–22]. PE induces endothelial function and NO development and has been consistently demonstrated to enhance erectile function. PE also increases erectile function by inducing a rise in serum total testosterone in males. Hence, there is good evidence that regular PE considerably increases erectile function [27].

First, while both ESWT or PE alone and the combined model involving ESWT and PE produced statistically significant changes in the mean IIEF-5 ratings, the degree of difference reported in patients receiving the latter modality of care was significantly higher in patients receiving the combined approach of ESWT and PE in the 4- and 12-week follow-ups. Durability following treatment with ED remains largely under-investigated. In addition, we verified PE’s durability alone or the combined approach, even up to the 12-week follow-up.

Interestingly, a deterioration was noticeable in patients receiving ESWT alone at the 12-week follow-up, while efficacy remained stable in patients receiving PE or the combination treatment. Based on the findings of this research, patients with diabetic ED should be advised on the possible benefits offered by a combination approach involving ESWT and PE in terms of enhancing the clinical effectiveness of IIEF-5 and its durability.

In our present research, we recognize the various limitations, such as the lack of a placebo (control) arm, objective penile hemodynamic measurements, the limited number of participants, and the
short-term follow-up. We believe that even more basic research is needed to explore the different pathophysiological mechanisms of combining ESWT with PE in relation to erectile tissue including long-term effectiveness, safety, and histological changes.

Although current findings appear promising, several main factors related to ESWT and PE, such as shockwave energy, physical activity, shockwave treatment models and protocols, patient characteristics, actual physiological changes in penile tissue, and long-term effectiveness and protection, have yet to be completely investigated.

In conclusion, both ESWT and PE significantly improve the management of ED in diabetic patients, though the combined approach of ESWT and PE provides significant advantages in erectile dysfunction improvement and durability as compared to ESWT or PE alone in diabetic patients with ED.

Conflict of interest
The authors declare no conflict of interest.

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