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ORIGINAL ARTICLE

Erectile Dysfunction

Efficacy of penile low-intensity shockwave treatment for erectile dysfunction: correlation with the severity of cavernous artery disease

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We analyzed the efficacy of penile low-intensity extracorporeal shockwave treatment for erectile dysfunction (ED) combined with cavernous artery disease (CAD). ED was evaluated by the International Index of Erectile Function, subdividing patients into mild and moderate/severe forms. CAD was assessed using penile color Doppler ultrasonography. Patients (n = 111) with a positive outcome after treatment, based upon the minimal clinically important difference of the International Index of ED, were followed up for 3 months and 6 months. We found a significant mean increase in the index of erectile function, with an overall improvement in hemodynamic parameters of the cavernous artery. In particular, 93.9% of the patients with mild ED without CAD responded to treatment and 72.7% resumed normal erectile function. Only 31.2% of the patients with moderate/severe ED and CAD responded to treatment, and none resumed normal erectile function. All patients with mild ED and no CAD maintained the effects of therapy after 3 months, while no patients with moderate/severe ED and CAD maintained the benefits of treatment after 3 months. Thus, patients with mild ED and no CAD have better and longer lasting responses to such treatment, with a higher probability of resuming normal erectile function than patients with moderate/severe ED and CAD.

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Keywords: cavernous artery disease; erectile dysfunction; extracorporeal shockwave therapy; International Index of Erectile Dysfunction; penile color Doppler ultrasound

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to obtain or maintain an erection sufficient for normal sexual intercourse. ED is a common disorder in middle-aged men that profoundly affects their quality of life.[1–3] ED can result from impairment of any of the complex mechanisms that underlie penile erection. Hormonal imbalance (*e.g.*, hypogonadism), neurological disease, pelvic surgery (*e.g.*, radical prostatectomy), and atherosclerosis of the cavernous arteries can lead to ED. Vasculogenic ED is the most frequent subtype found in 70% of all cases,[4] and it can represent an early manifestation of generalized vascular disease. In addition, ED may be the first sign of cardiovascular disease (CVD) and may precede coronary and peripheral artery disease by some years.[5–7] The link between ED and CVD involves endothelial dysfunction.[8,9] In 2010, Vardi *et al.*[10] proposed the use of low-intensity extracorporeal shockwave therapy (Li-ESWT) as a new treatment option for ED, and studies have shown promising results for this therapy in patients with mild-to-severe ED.[11,12] In such patients, as has also been shown in animal models, it has been hypothesized that the improvement of the blood flow of the penis might be related to a cascade of biological responses. In particular, the release of molecules such as vascular endothelial growth factor can induce cell proliferation, recruitment, and activation of endogenous stem cells with a final antifibrotic and anti-inflammatory effect.[8,11–15] Unlike the use of a phosphodiesterase type 5 inhibitor (PDE5i), Li-ESWT therapy aims to induce tissue repair by introducing a new aspect of ED treatment that attempts to modify the underlying pathological process, providing regenerative elements and not merely alleviating the symptoms. Taking into account the regenerative properties of Li-ESWT therapy, as well as its noninvasiveness, favorable safety profile, and cost-effectiveness, it is a potentially revolutionary treatment modality but has yet to be fully validated in human clinical trials. Currently, there are still no available studies regarding the effects of Li-ESWT on patients with ED and atherosclerotic alterations to the penile cavernous arteries. Here, we aimed to evaluate the influence of atherosclerotic cavernous artery disease on the efficacy of Li-ESWT for ED.

PARTICIPANTS AND METHODS

Participants

We conducted a retrospective cohort study on 111 subjects referred for ED at the Andrology and Reproductive Medicine Unit of the University of Padua (Padova, Italy) and treated with Li-ESWT between April 2017 and May 2019. The inclusion criteria were patients with ED aged 35–65 years without previous PDE5i treatment. ED was evaluated with

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the International Index of Erectile Function (IIEF) scoring system, which includes six questions (1–5 and 15) each with scores of 0–5 based on the IIEF-15. Scores <26 are considered as diagnostic for ED.[16] Patients were divided into three groups of ED severity according to their IIEF scores: (i) mild ED with a score 17–25, (ii) moderate ED with a score 11–16, and (iii) severe ED with a score ≤10.[17]

The exclusion criteria were patients with age <35 years and >65 years, previous PDE5i treatments, testosterone treatment, end-stage renal disease or liver failure, pelvic surgery and neoplasms, or undergoing transplant surgery. Each patient underwent a complete medical history, physical examination, and blood tests for fasting plasma glucose, glycated hemoglobin (HbA1c) level, total cholesterol, triglycerides, and total testosterone (COBAS 6000, Roche Diagnostics GmbH, Basel, Switzerland). Blood collection was performed with the subject under fasting conditions between 08:00 a.m. and 10:00 a.m.

Ethics approval

The study was approved by the local ethics committee of University of Padua, Padova, Italy (approval number 0050436), and all participants had given informed consent before their inclusion in the study.

Penile color Doppler ultrasound examination

All color Doppler ultrasound procedures were performed by the same expert operator (NC), with an ultrasound device (iU22 Philips, Eindhoven, The Netherlands) equipped with a 7–13 MHz probe (axial resolution <0.1 mm) using color-coded Doppler sonography. Penile color Doppler ultrasound (P-CDU) was performed after the intracavernous injection of 10 μg alprostadil (Pfizer Inc., New York, NY, USA). The evaluation of intracavernous blood flow was assessed at the level of penoscrotal junction in the following 20 min as described.[18] Peak systolic velocity (PSV), end diastolic velocity (EDV), resistance index (RI), and acceleration time (AccT) were measured. The cavernous artery intima-media thickness (IMT) was measured using the ultrasound device at the penoscrotal junction by selecting the best rectilinear portion at low magnification. Subsequently, the selected portion was closely analyzed at high magnification (×24), adjusting the partial and total gain in B mode to reduce the noise to the minimum level. The cavernous artery changes were divided into: (i) normal IMT (<0.3 mm); (ii) increased IMT (IMT ≥0.3 mm and ≤0.4 mm); and (iii) cavernous artery plaque (IMT >0.4 mm) according to our published data.[18] A "healthy cavernous artery" is defined as the absence of any morphological alteration (*i.e.*, neither increased IMT nor atherosclerotic plaque) in both cavernous arteries (**Figure 1**). "Cavernous artery disease" has been defined as the presence of increased IMT or plaque.[18] P-CDU pre- and post-Li-ESWT was performed with the subject in the same position.

Based on the IIEF scores and P-CDU results, we classed the patients into four groups: (1) mild ED with normal cavernous artery; (2) mild ED with cavernous artery disease; (3) moderate/severe ED with a normal cavernous artery; and (4) moderate/severe ED with cavernous artery disease.

Li-ESWT treatment

The treatment protocol and evaluation methods were identical for all patients. Li-ESWT was supplied by an electromagnetic unit with a focused shockwave source (Duolith SD1; Storz Medical AG, Tägerwilen, Switzerland). The attached probe was aimed at the penis and crura after applying commercial ultrasonography gel. During each 25-min session, 2400 pulses were delivered with an energy density of 0.12 mJ mm^{-2} and a frequency of 3 Hz. By manually stretching the penis, 300 pulses were delivered to the distal, medium, proximal shaft and crura on the right and left sides. Our protocol consisted of one treatment session per week over a period of 6 weeks. Success was determined at the end of treatment on the basis of a change in the IIEF score from baseline (before treatment), equal to or greater than the minimal clinical important difference,[19] *i.e.*, an increase of at least 7, 5, and 2 points for severe, moderate, and mild ED, respectively. All the included patients were followed up at 3 months and 6 months after the last Li-ESWT session.

Statistical analyses

To attain an adequate number in each patient group and to simplify the statistical evaluation, we grouped patients with moderate and severe ED. The number of subjects in each group was higher than the minimum to test effectiveness, with $\alpha = 0.05$ (confidence level 95%) and $\beta = 10\%$. Mean differences within subjects were compared using two-sided paired sample Student's t tests following testing for the normality of data distribution using the Shapiro–Wilk normality test. Associations between categorical variables were assessed with Pearson's correlation test. If the normality assumption was violated, the nonparametric Wilcoxon signed-rank test was applied as this is considered robust to violations of normality. Variables with statistical significance were included in a multivariate model by logistic regression to identify independent predictors. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA), and $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient information

One hundred and eleven patients were treated with our standard Li-ESWT protocol and had complete data at the end of the study. No adverse side effects were reported by patients with regard to Li-ESWT.

The overall mean age of the patients was 53.7 (s.d.: 11.6) years, with a mean IIEF score of 12.2 (s.d.: 6.9). Detailed clinical characteristics of all patients, taken as a whole or subdivided according to ED severity and cavernous artery status, are presented in **Table 1**. The ED severity distribution showed mild ED in 39.6% (44/111) of patients and moderate/severe ED in 60.4% (67/111).

At the end of treatment, and after a further 3 months and 6 months, the IIEF score (mean±s.d.) of the patients considered as a whole was significantly improved (17.4 ± 8.1 [$P < 0.0001$], 16.7 ± 8.4 [$P < 0.0001$], and 15.9 ± 8.2 [$P < 0.001$], respectively) compared with baseline (12.2 ± 6.9). Sixty-five patients (58.6%) responded to Li-ESWT and were considered as having a successful outcome according to the aforementioned criteria; 28 patients (25.2%) had resumption of normal erectile function (IIEF ≥26). In all, 42 subjects (64.6%) who had a successful result at the end of treatment maintained their response 3 months after the end of treatment and 37 (56.9%) of them did so after 6 months.

Hemodynamic parameters

Table 2 lists the hemodynamic parameters observed at the end of treatment. All P-CDU parameters (PSV, EDV, and AccT) were significantly improved after Li-ESWT sessions. Hemodynamic variation recorded at the end of treatment in patients with normal or increased IMT is shown in **Table 3**. Patients without cavernous disease had a greater increase in PSV compared with patients with altered IMT (17.7 ± 14.0 cm s^{-1} *vs* 7.3 ± 8.4 cm s^{-1}; $P < 0.001$). No significant variations were observed in EDV and AccT values, but an inverse correlation between cavernous IMT value and IIEF score was found ($r = -0.425233$).

Table 1: General characteristics of patient groups

Clinical parameter	*All patients (n=111)*	*Mild ED with normal cavernous artery (n=33)*	*Mild ED with cavernous artery disease (n=11)*	*Moderate/severe ED with normal cavernous artery (n=35)*	*Moderate/severe ED with cavernous artery disease (n=32)*
Age (year), mean±s.d.	53.7±11.6	48±12.5	54.8±9.8*	51.5±10.7*	58.8±9.2*,#
IIEF score, mean±s.d.	12.2±6.9	21.2±2.4	18.2±1.1	8.1±2.2	9.3±3.4
Hypertension (%)	51.1	48.5	48.5	54.5	56
Dyslipidemia (%)	53.3	51.5	48.6	54.5	53.1
Smokers (%)	44.4	39.4	45.5	45.7	43.7
Diabetes (%)	14.4	11.7	18.2*	11.4	25.2*
Fasting plasma glucose (mg dl^{-1}), mean±s.d.	107±41	96.3±27	112±50*	106±40	117±45*
HbA1c (%), mean±s.d.	5.9±1.1	5.4±1.3	6.1±1.7	5.9±2.3	6.5±2.1
BMI (kg m^{-2}), mean±s.d.	28.4±4.8	28.2±4.7	28.5±5.1	28.4±4.6	29.1±4.2
Total cholesterol (mg dl^{-1}), mean±s.d.	197±41	190±36	202±43	198±39	204±40
HDL (mg dl^{-1}), mean±s.d.	50±16	51±17	50±18	49±15	52±16
Triglycerides (mg dl^{-1}), mean±s.d.	129±123	131±68	128±71	124±62	133±73
Creatinine (mmol l^{-1}), mean±s.d.	86.1±34.4	89.4±47.6	88±41.3	84.2±15.3	83.2±23.4
LH (UI l^{-1}), mean±s.d.	4.7±3.8	5.1±3.9	4.8±4.1	4.3±2.3	4.6±3.6
Testosterone (nmol l^{-1}), mean±s.d.	13.2±1.9	14.1±1.9	12.8±0.5	13.4±1.6	13.1±2.1
Penile IMT (mm), mean±s.d.	0.26±0.08	0.21±0.04	0.32±0.02*	0.23±0.04	0.35±0.05*
PSV (cm s^{-1}), mean±s.d.	40.5±14.4	43.9±14.7	41.2±16.5	41.9±16.3	37.2±15.6
EDV (cm s^{-1}), mean±s.d.	2.5±6.1	1.3±8.3	2.1±6.9	2.7±5.6	3.4±5.8*
AccT (ms), mean±s.d.	97.9±30.7	88.2±28.3	99.2±27.2	94.1±33.6	111.8±32.7*

*P<0.05, the indicated group compared to group of mild ED with normal cavernous artery; #P<0.05, the indicated group compared to group of mild ED with cavernous artery disease and group of moderate/severe ED with normal cavernous artery. BMI: body mass index; ED: erectile dysfunction; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein cholesterol; IIEF: International Index of Erectile Function; LH: luteinizing hormone; PSV: peak systolic velocity; EDV: end diastolic velocity; AccT: acceleration time; IMT: intima-media thickness; s.d.: standard deviation

Table 2: Hemodynamic parameters at the end of treatment with respect to baseline

Hemodynamic parameter	*Baseline*	*End of treatment*	*P*
PSV (cm s^{-1}), mean±s.d.	40.5±14.4	57.9±18.6	<0.0001
EDV (cm s^{-1}), mean±s.d.	2.5±6.1	0.3±7.6	<0.008
AccT (ms), mean±s.d.	97.9±30.7	94.2±26.7	<0.0001

PSV: peak systolic velocity; EDV: end diastolic velocity; AccT: acceleration time; IMT: intima-media thickness; s.d.: standard deviation

Table 3: Hemodynamic variation at the end of treatment with respect to baseline in cavernous intima-media thickness <0.3 mm versus intima-media thickness ≥0.3 mm

Hemodynamic parameter variation	*IMT <0.3 mm*	*IMT ≥0.3 mm*	*P*
ΔPSV (cm s^{-1}), mean±s.d.	17.7±14.0	7.3±8.4	0.001
ΔEDV (cm s^{-1}), mean±s.d.	–3.1±6.2	–0.9±5.2	NS
ΔAccT (ms), mean±s.d.	–6.6±9.8	–6.3±21.5	NS

ΔPSV: change in peak systolic velocity; ΔEDV: change in end diastolic velocity; ΔAccT: change in acceleration time; IMT: intima-media thickness; NS: not significant; s.d.: standard deviation

Responders to Li-ESWT at the end of treatment and after 3 months and 6 months

Among patients with mild ED, 84.1% (37/44) responded to treatment, and 75.0% maintained this result at 3 months and 68.2% at 6 months. In the moderate/severe ED group, 41.8% (28/67) responded to treatment, while 13.4% maintained their response at 3 months and 10.4% at 6 months (**Table 4**). Patients with severe ED were prone to have a greater increase in IIEF score (7.2 ± 2.9 *vs* 4.1 ± 2.2) with respect to patients with mild ED, while patients without cavernous disease were prone to have a greater increase in IIEF score (5.8 ± 3.9 *vs* 3.8 ± 4.1; $P < 0.06$) and PSV (17.7 ± 14 cm s^{-1} *vs* 7.3 ± 8.4 cm s^{-1}; $P < 0.001$) with respect to patients with cavernous disease. Grouping patients on the base of both ED severity and cavernous artery disease (**Table 4**), we found that in the group of patients with mild ED and without cavernous artery disease, 93.9% (31/33) responded to treatment and, among them, 93.9% (31/33) maintained this result at 3 months and 87.9% (29/33) at 6 months. However, in the moderate/severe ED group with cavernous disease, only 31.2% (10/32) responded to treatment ($P < 0.001$, compared to mild ED and without cavernous artery disease) and none maintained this achievement at 3 months and 6 months. Finally, patients with mild ED and cavernous disease had results similar to patients with moderate/severe ED and no cavernous disease. In particular, about 50% of them responded to treatment and about 20% maintained this result after 3 months with a reduction to 9% at 6 months in patients with cavernous disease.

Patients with a significant improvement in IIEF scores and those with resumption of normal erectile function

Figure 2 summarizes the percentage of patients with significant improvements in IIEF and those who experienced a resumption of normal erectile function. In particular, the group of patients with mild ED and without cavernous artery disease had the higher percentage of responders to treatment (93.9%), and 72.7% (24/33) of them had resumption of normal erectile function. However, in the moderate/severe ED group with cavernous disease, only 31.2% responded to treatment ($P < 0.001$, compared to mild ED with IMT <3) and none had resumption of normal erectile function. Finally, about half of the patients in the groups of patients with mild ED and cavernous disease and patients with moderate/severe ED and no cavernous disease responded to treatment. However, the former group showed a higher percentage of patients with resumption of erectile function (18.2% *vs* 5.7%) albeit significantly lower than that observed in those with mild ED with IMT <3.

Using logistic regression analysis, we investigated several parameters such as fasting plasma glucose, HbA1c, total cholesterol, triglycerides, total testosterone, ED severity, and baseline P-CDU (PSV, EDV, and AccT) measures to define those patients who did not have a

Table 4: Responses to low-intensity extracorporeal shockwave therapy at the end of treatment, and 3 months and 6 months later in patients with different erectile dysfunction severity and normal or cavernous artery disease

ED severity	*All patients*	*Normal cavernous artery*	*Cavernous artery disease*
Mild ED, *n*/total (%)			
End of treatment	37/44 (84.1)	31/33 (93.9)	6/11 (54.5)
3 months later	33/44 (75)	31/33 (93.9)	2/11 (18.2)
6 months later	30/44 (68.2)	29/33 (87.9)	1/11 (9.1)
Moderate/severe ED, *n*/total (%)			
End of treatment	28/67 (41.8)	18/35 (51.4)	10/32 (31.2)
3 months later	9/67 (13.4)	9/35 (25.7)	0/32 (0)
6 months later	7/67 (10.4)	7/35 (20.0)	0/32 (0)

ED: erectile dysfunction

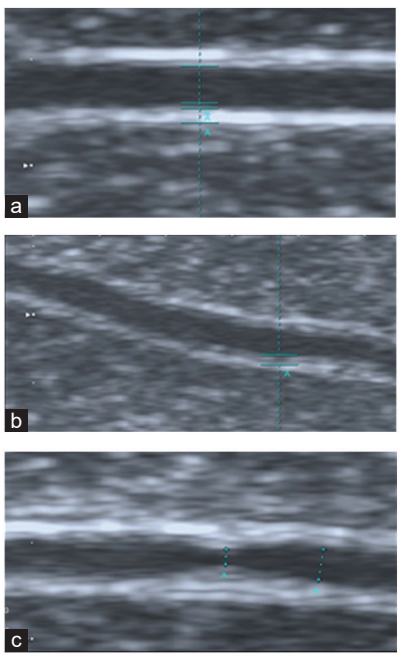

Figure 1: Ultrasound images of a "healthy cavernous artery" and of a "cavernous artery disease." (**a**) Normal cavernous artery; (**b**) intima-media thickness (IMT ≥0.3 mm); (**c**) cavernous artery plaque. IMT: penile intima-media thickness.

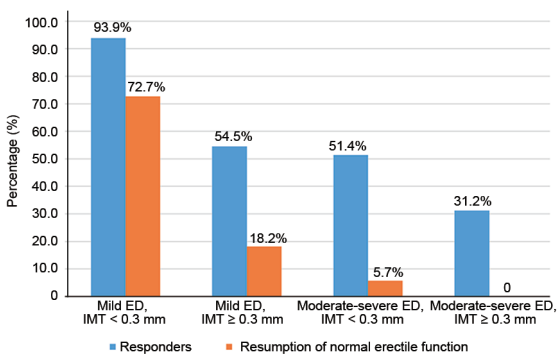

Figure 2: Percentages of patients with a significant improvement in IIEF and those who experienced a resumption of normal erectile function in the four patient groups. IIEF: International Index of Erectile Function; IMT: penile intima-media thickness; ED: erectile dysfunction.

successful response to Li-ESWT. No correlations were found between these and the response to Li-ESWT.

DISCUSSION

ED is a common disorder in middle-aged men that profoundly affects their quality of life.[3,4] There is growing evidence of pathophysiological and epidemiological associations between ED and CVD in relation to endothelial dysfunction, which frequently represents a common trait of both conditions. In fact, the vascular endothelium is not just a simple blood barrier but also an organ that synthesizes and releases substances, playing paracrine and endocrine roles in vascular tone and platelet aggregation.[12] Studies have shown promising results of Li-ESWT for patients with ED.[12,20] Li-ESWT was able to improve impaired erectile function in a variety of animal models of ED. Li-ESWT with energy levels above 0.12 mJ mm^{-2} have been shown to induce irreversible alterations to cell structure and organelles, so we decided to treat our patients with an energy limit of 0.12 mJ mm^{-2}.[12,21] It has been shown that this Li-ESWT energy level induces cell membrane modifications and funtional changes such as the stimulation of mechanosensor, induction of neangiogenesis, recruitment, improvement, and activation of endothelial progenitor cells, nerve regeneration, erectile tissue remodeling through an increase in the muscle/collagen ratio and by reducing inflammatory and cellular stress responses.[21–32] To date, there are no data regarding the effects of Li-ESWT on patients with ED with or without atherosclerotic cavernous artery disease. The results of our study, although limited to a relatively small cohort, show that patients with mild ED and without cavernous artery disease are younger and have a better and longer lasting response to treatment. At the same time, this group of subjects has also a high probability to recover normal erectile function. In contrast, patients with moderate/severe ED and cavernous artery disease are older and more likely to experience treatment failure. This observation is confirmed by the fact that patients without cavernous artery disease were prone to have a greater improvement in PSV and AccT values paralleled by better erectile function when compared with patients with cavernous artery disease.

These data confirm previously reported findings by Sönmez and Kara[33] showing that Li-ESWT therapy is not effective in patients with severe ED and by Chung *et al.*[34] showing that the patient selection appears paramount to treatment success and that patients with mild ED and who are younger are likely to report high erectile function recovery and spontaneous erections. In contrast, Yee *et al.*[35] reported that patients with severe ED, with probably primary vasculogenic etiology, benefitted from Li-ESWT, and the European Society of Sexual Medicine recommends limiting this therapy to subjects with vasculogenic ED.[36]

We assume that the differences in published responses to Li-ESWT treatment are probably linked to different protocols and in the severity of the atherogenic nature of ED. In fact, with the increase of atherosclerotic disease, there is a greater impairment in cavernous

endothelial function as result of a reduced activation and upregulation of endothelial nitric oxide synthase (eNOS), neural nitric oxide synthase (nNOS), and vascular endothelial growth factor receptor 2 (VEGFR2). This condition could be responsible for a reduced production of vasodilating agents such as nitric oxide (NO).[37] Thus, some studies have highlighted the positive influence of Li-ESWT on the mobilization of endothelial progenitor cells from the bone marrow and their homing to the treated vessel.[38,39] Furthermore, in a study in naturally aged rats, Li-ESWT seemed to alter the expression ratios of adrenergic receptors in the corpora cavernosa (increasing expression of alpha-2-adrenergic receptor and simultaneously decreasing expression of alpha-1-adrenergic receptor), indicating a possible decrease in sympathetic activity. This action could enhance smooth muscle relaxation through NO or similar agents, resulting in vasodilation and enabling erection.[40]

Finally, patients with mild ED and cavernous artery disease had a worse outcome after treatment and at 3 months of follow-up than those with moderate/severe ED and no artery disease as a consequence of trends in the increase in cardiovascular risk factors such as diabetes. The lack of correlation between the cardiovascular risk factors and the P-CDU parameters is probably related to concomitant drug therapies and the small number of patients. A control group would provide more insight into the direct effects of Li-ESWT, both in patients with/without atherosclerosis. It appears that Li-ESWT therapy can induce tissue repair, introducing a new form of treatment for ED aimed at modifying the underlying pathogenesis. Thus, unlike treatment using PDE5i, this treatment appears to act along with regenerative elements and not just by alleviating symptoms.

Interestingly, patients with atherosclerotic cavernous artery disease had a Li-ESWT response that was less durable than among patients without vascular alterations. Therefore, in patients with moderate/severe ED and/or cavernous disease, different Li-ESWT protocols should be investigated to identify more effective energy flux density, number of sessions of treatment, and total number of shockwaves able to improve erectile function. Furthermore, it will be interesting to perform treatment protocols with the combined use of Li-ESWT and PDE5i.

The study had some limitations such as the relatively small cohort and the lack of a placebo control group.

CONCLUSIONS

Here, we found that patients with mild ED, particularly those without cavernous artery disease, tended to be younger and have a better and longer lasting response to treatment with Li-ESWT, with a high probability of resuming normal erectile function. In contrast, patients with moderate/severe ED, especially those with cavernous artery disease, tended to be older with a high probability of treatment failure. Further studies will be needed to evaluate different Li-ESWT treatment protocols (greater number of session, frequency or intensity) associated with PDE5i in patients with moderate/severe ED and/or cavernous artery disease.

AUTHOR CONTRIBUTIONS

NC conceived, designed the study, performed the color Doppler ultrasound examinations, and wrote the manuscript. MDRP helped write the manuscript. NM performed statistical analysis. IDS and PP performed Li-ESWT treatment. AG reviewed the literature and helped write the manuscript. CF conceived and designed the study. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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