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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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.¹⁻⁴ 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,⁵ 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.⁶⁻⁷ The link between ED and CVD involves endothelial dysfunction.⁸⁻¹⁰ In 2010, Vardi et al.⁶ 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.¹³⁻¹⁵ 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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Patients without cavernous artery disease.

The treatment protocol and evaluation methods were identical 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.

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 < 0.0001], 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 artery 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).
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% (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.

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 (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±1.16 | 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±24 | 18.2±11 | 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* |
| 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 (IU 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±2.9 | 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* |

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 |

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±4.0 | 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±9.1 | -6.2±21.1 | NS |

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 basis of both ED severity and cavernous artery disease (Table 4), we found...
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 |
|----------------------------------|--------------|-------------------------|--------------------------|
| 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)               |

Mild ED, n/total (%)

| Moderate/severe ED, n/total (%) | End of treatment | 18/35 (51.4) | 10/32 (31.2) |
|---------------------------------|------------------|-------------|-------------|
|                                 | 9/67 (13.4)      | 9/35 (25.7) | 0/32 (0)    |
|                                 | 7/67 (10.4)      | 7/35 (20.0) | 0/32 (0)    |

DISCUSSION

ED is a common disorder in middle-aged men that profoundly affects their quality of life. 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.

Studies have shown promising results of Li-ESWT for patients with ED. 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$^{-2}$. It has been shown that this Li-ESWT energy level induces cell membrane modifications and functional 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.

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 showing that Li-ESWT therapy is not effective in patients with severe ED and by Chung et al. 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. reported that patients with severe ED, with probably primary vasculogenic etiology, benefited from Li-ESWT, and the European Society of Sexual Medicine recommends limiting this therapy to subjects with vasculogenic ED.

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). 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. 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.

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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