IJIR: Your Sexual Medicine Journal
https://doi.org/10.1038/s41443-018-0062-2

ARTICLE

Low-intensity shockwave therapy for erectile dysfunction in kidney transplant recipients. A prospective, randomized, double blinded, sham-controlled study with evaluation by penile Doppler ultrasonography

Kleiton G. R. Yamaçake[1] · Felipe Carneiro[2] · Jose Cury[1] · Rodolfo Lourenço[1] · Peter C. Françolin[2] · Affonso C. Piovesan[1] · Miguel Srougi[3] · Willian C. Nahas[3] · Ioannis M. Antonopoulos[1]

Received: 8 March 2018 / Revised: 15 July 2018 / Accepted: 30 July 2018

Abstract

Objectives: To study the efficacy of Low intensity Extracorporeal Shockwave Therapy (Li- ESWT) for the treatment of erectile dysfunction (ED) in kidney transplanted men.

Methods: Twenty men (mean age = 53.7 years) were selected. This was a double-blinded, prospective, randomized, sham-controlled trial. The ESWT protocol was based in a 2 treatment sessions per week for 3 weeks. The sham treatment was performed using the same device replacing the effective probe for one that emits zero energy. Baseline and follow-up assessment was performed with International Index of Erectile Function Questionnaire (IIEF) score and Erection Hardness Score (EHS) after 1, 4 and 12 months. Penile Doppler was performed before and after treatment.

Results: A total of 20 patients were recruited, 10 patients in each group. Baseline scores were similar. The mean EHS in after 1 month were 2.5 ± 0.85 (Li-EWST) and 2.4 ± 0.7 (Sham therapy), p = 0.724 . After 4 months it was 2.4 ± 0.7 and 2.6 ± 0.84, p = 0,0004 (between the moments) . The baseline IIEF score was 14.9 ± 3(Sham Theraphy) and 10.9 ± 5.1 (Li-EWST). The mean IIEF score after 1 month was 15.6 ± 6.1 (Li-EWST) and 16.6 ± 5.4 (Sham therapy). The mean IIEF score after 4 months was 17.2 ± 5.7 (Li-EWST) and 16.5 ± 5 (Sham therapy), p < 0.0001 (between the moments). IIEF score improvement was higher than 5 in 70% (ranged from 0-10) and in 10% (ranged from 1-14) in Li-ESWT and Sham groups, respectively. The mean change in IIEF score after 12 months was 4.8 in Li-ESWT group .Penile Doppler parameters were similar between groups and did not present improvements.

Conclusions: Li-ESWT is a treatment with clinical efficacy. Despite evidences suggesting neoagiogenesis, our short protocol had no impact in penile Doppler parameters.

Introduction

The prevalence of erectile dysfunction (ED) varies between 40% and 52% in men aged 40–70 years [1]. This condition has a major impact on the patient's and partner's quality of life [2].

ED in kidney transplant recipients is often multifactorial. Pharmacologic, endocrine, neurogenic, vascular, and psychogenic causes seem to play a significant role [3]. Vascular disease of the penile arteries is the most common cause of organic ED, accounting for up to 80% of cases [4, 5].

ED occurs in 50–85% of patients with end-stage renal disease in the dialysis period [6]. Although some advocate that a functioning renal allograft improves the erectile function, previous studies [6, 7] have shown that 48–56% of renal transplant recipients continue to experience ED.

The current non-surgical treatment for ED is the use of oral phosphodiesterase type 5 inhibitors (PDE5-Is) and intracavernosal injections of vasodilating agents [5]. These

✉ Kleiton G. R. Yamaçake
kleiton_med91@yahoo.com.br

[1] Division of Urology, Renal Transplantation Unit, University of São Paulo Medical School, São Paulo, Brazil

[2] Division of Radiology, University of São Paulo Medical School, São Paulo, Brazil

[3] Renal Transplantation Unit, Division of Urology, University of São Paulo Medical School, São Paulo, Brazil

Published online: 14 August 2018

have been proven to be effective and safe treatments [8]; however, they have no impact on the underlying pathophysiology of the erectile mechanism. Thus, these treatments are usually taken on demand prior to sexual activity. Recently, the effect of long-term daily use of PDE5-Is on endothelial function has induced a short-term improvement in erectile function [9–11].

In this background, extracorporeal shockwave therapy (ESWT) has emerged as a promising option for the treatment of ED. Shockwaves can induce angiogenesis according to previous studies and have been used in the treatment of chronic wounds, ischemic peripheral neuropathy, and cardiac tissue problems successfully [12, 13].

It has been shown that low-intensity energy induces nonenzymatic production of physiologic amounts of nitric oxide (NO) and activates a cascade of intracellular signaling pathways that promote the expression of angiogenic factors [14].

As a novel modality, low-intensity ESWT (Li-ESWT) aims to restore natural or spontaneous erectile function. This makes Li-ESWT unique when compared with other approaches for treating ED, all of which are designed to attenuate the symptoms [15]. To date, no studies have evaluated these alternatives in male renal transplant patients with ED.

The aim of this study is to determine the impact of the shockwave application on the erection of renal transplant patients with ED.

Materials and methods

The study protocol was reviewed and approved by the local institutional review board, and all participants provided their written informed consent. The study was registered at ClinicalTrials.gov (NCT02412345).

Study population

From 1995 to 2016, 2158 kidney transplants were performed in our single institution. Patients who met the inclusion criteria were interviewed and screened. A total of 30 men underwent an initial screening; ultimately, 20 patients were enrolled and there were no dropouts.

Inclusion criteria

- Male sex, age between 40 and 70 years, history of kidney transplant at least 6 months prior to the study, and diagnosis of ED for at least 6 months
- International Index of Erectile Function-5 (IIEF-5) score < 21 [16]
- Functioning kidney graft

Exclusion criteria

- ED due to known endocrine disease (e.g., hypogonadism and hypothyroidism)
- ED due to androgen deprivation therapy
- ED due to neurological disease (spinal cord injury, Alzheimer's disease, and Parkinson's disease)
- ED due to structural abnormality of the penis (Peyronie's disease and congenital penile curvature)
- ED due to psychogenic disorder (sudden onset, depression, and mental disorder)
- History of radical prostatectomy or other pelvic surgery
- History of pelvic irradiation
- Diabetic neuropathy
- Penile implant or artificial urethral sphincter
- Coagulopathies or anticoagulant therapy

Study design

This study was a double-blinded, single-center, prospective, randomized, and sham-controlled trial. To reach a calculation analysis power of 80% and an endpoint of 1.013 points in the IIEF-5, a minimum of 20 patients was sufficient to meet the criteria of the study. The assumed variability through previous studies was 1.4.

The patients were assigned to a group of Li-ESWT or sham treatment with an equal allocation ratio of 1:1 using a table of random numbers generated by a computer. Treatment allocation was communicated through a web-based

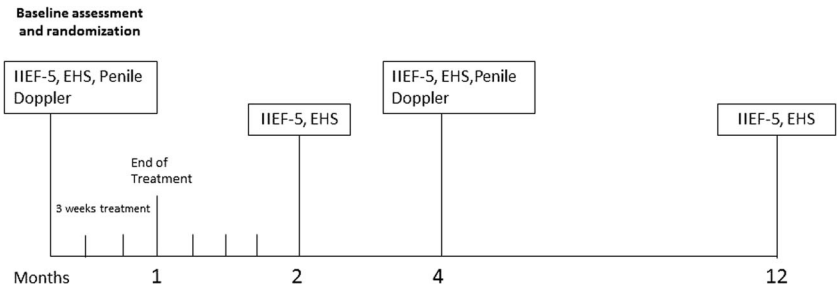

Fig. 1 Study flowchart. IIEF International Index of Erectile Function, EHS Erection Hardness Score

registration system to ensure allocation concealment. All investigators and research assistants involved in the assessment of the participants were blinded to the group assignment. The assistant who administered the treatment was the only one who was not blinded.

Study parameters

The medical and psychosexual histories of all patients were evaluated at baseline to detect comorbidities. Patients were interviewed before the treatment and answered questions regarding their medical and sexual histories.

Patients were required to discontinue PDE5-Is at least 1 month before treatment and during the entire study period. After treatment, they were re-evaluated during their clinical visit after 1, 3, and 12 months by the same investigator (Fig. 1). The 12-month analysis was applied only for the treatment group. The following parameters were studied during the initial evaluation and follow-up:

Clinical parameters

These parameters included the IIEF-5 [17]; Erection Hardness Score (EHS); [18] comorbidities such as hypertension, diabetes, and cardiovascular disease; and smoking status.

Laboratory parameters

These parameters included the levels of total testosterone, free testosterone, albumin, SHBG, FSH, LH, prolactin, urea, creatinine, total cholesterol and fractions, triglycerides T3, T4F, and TSH, and complete blood count.

Imaging tests

Penile Doppler ultrasound with pharmaco-induced erection was performed before and 4 months after treatment. The examination was conducted by the same radiologist. The diameter of the cavernous arteries was measured before and after intracavernosal injection of 20 mcg alprostadil (Caverject®, Pfizer Inc., New York, NY, USA). In addition, vascular disorders or stenotic atheromatous lesions were investigated. The peak systolic velocity (PSV; highest value regardless of the side) and end diastolic velocity (EDV; lowest value regardless of the side) of the cavernous arteries were evaluated 5, 10, and 15 min after drug injection. The diameters of the cavernous arteries (both sides) were evaluated and the resistivity index (RI) was calculated considering the highest PSV and the lowest EDV (RI = PSV-EDV/PSV).

Fig. 2 Eletropneumatic device: Swiss Dolorclast® Smart with the EVO-BLUE transductor produced by EMS (Electro Medical Systems)

Treatment

Our ESWT protocol was similar as that suggested by Vardi et al. [19], but without the break period and subsequent reapplication. The patients underwent two treatment sessions per week for 3 weeks.

The ESWT device used was the Swiss Dolorclast® Smart with the EVO-BLUE transductor (Fig. 2) produced by EMS (Electro Medical Systems, Switzerland). In this device, the shockwaves are transmitted through an eletropneumatic system.

The penis was pulled manually, and shockwaves were applied throughout the penile shaft (except the glans) and crura bilaterally by continuous movement of the applicator. The duration of each ESWT session was approximately 10 min. A total of 2000 shocks per session were applied with an energy intensity of 0.09 mJ/ mm^2. The volume of penile tissue exposed to shock waves at each site was cylindric (diameter: 18 mm, height 100 mm). No local or systemic analgesia was required during the procedure.

The sham treatment was performed using the same device. The probe was replaced by a similar device that emitted zero energy during treatment. It generated a noise and a feeling of popping at the treatment site, which was also experienced by the patients who received the shockwave treatment; this made it impossible for the patients to know which treatment group they were assigned to.

Statistical analysis

The χ^2-test was used to determine any relationship among the categorical variables. The between-group relationships between the baseline and post-treatment data were evaluated using the Student's *t*-test for the continuous variables. Kruskal–Wallis test was performed for the EHS (non-normal distribution). Repeated-measures ANOVA was used to assess the pre- and post-treatment changes in the IIEF-5 score and EHS. This method considers that each patient was evaluated more than once (baseline, 1 month, and 3 months). *P*-values of < 0.05 were considered statistically significant.

Table 1 Demographic and clinical data

	Overall	Sham therapy	Li-ESWT	*p*-value
Participants (*n*)	20	10	10	—
Mean age (range), years	53.7 (46–61)	52.2 (46–61)	55.1 (47–60)	0.1441
BMI (kg/m^2)	27.8 (4.6)	28.4 (5.6)	27.1 (3.4)	0.8206
Mean no. of ED risk factors	2.30 (0.86)	2.10 (0.57)	2.50 (1.08)	0.3477
Incidence of ED risk factors				
Diabetes	10 (50 %)	6 (60%)	4 (40%)	0.6563
Hypertension	20 (100%)	10 (100%)	10 (100%)	—
Dyslipidemia	7 (35%)	2 (20%)	5 (50%)	0.3498
Ischemic heart disease	4 (20%)	1 (10%)	3 (30%)	0.5820
Smoker	5 (25%)	2 (20%)	3 (30%)	1.0000
Time after kidney transplant, months	27.8 (18.3)	32.8 (23.7)	22.7 (9.2)	0.2338
Mean baseline IIEF-5 score (SD)	12.9 (4.6)	14.9 (3)	10.9 (5.1)	0.0813
Baseline IIEF-5 score				0.0956
Mild (17–21)	4 (20%)	2 (20%)	2 (20%)	—
Mild-to-moderate (12–16)	9 (45%)	7 (70%)	2 (20%)	—
Moderate (8–11)	4 (20%)	1 (10%)	3 (30%)	—
Severe (5–7)	3 (15%)	0 (0.0%)	3 (30%)	—
Baseline EHS	2 (0.86)	2 (0.67)	2 (1.05)	0.8085
Type of donor				1.0000
Deceased	13 (65%)	7 (70%)	6 (60%)	—
Living	7 (35%)	3 (30%)	4 (40%)	—
Creatinine levels (mg/dL)	1.54 (0.65)	1.35 (0.39)	1.73 (0.82)	0.2164
MDRD, clearance (mL/min/1.73 m^2)	59.3 (26.0)	65.2 (26.2)	53.3 (25.8)	0.3210
Hemoglobin levels (g/dL)	14.0 (1.8)	14.1 (1.3)	13.9 (2.3)	0.8243
Albumin levels, g/dL	4.46 (0.37)	4.37 (0.33)	4.54 (0.41)	0.3166
Total testosterone levels, mg/dL	546.2 (164.5)	562.6 (169.5)	529.7 (166.6)	0.6668

p-value (categorical variables: χ^2-test; continuous variables: Student's *t*-test)

SD standard deviation, *IIEF* international index of erectile dysfunction, *EHS* erection hardness score

Results

Demographic and clinical data

The mean patient age was 52.2 ± 4.1 years in the sham treatment group and 55.1 ± 4.4 years in the Li-ESWT group. The clinical and demographic data were similar between the groups. In particular, the mean age, body mass index, mean number of ED risk factors, time after kidney transplant, clearance levels, and testosterone levels were similar between them. The data are summarized in Table 1.

The baseline IIEF-5 score was 14.9 ± 3 (range, 11–20) in the sham treatment group and 10.9 ± 5.1 (range, 3–18) in the Li-ESWT group. Despite the lower baseline IIEF-5 score in the Li-ESWT group, it was not statistically significant ($p = 0.081$). The baseline EHS was 2 ± 0.67 in the sham treatment group and 2 ± 1.05 in the Li-ESWT group ($p = 0.80$).

IIEF-5 score and EHS

At baseline and 1 and 3 months after the last treatment, the IIEF-5 scores in the Li-ESWT group were 10.9 ± 5.1, 15.6 ± 6.1, and 17.2 ± 5.7, respectively. The IIEF-5 scores in the sham treatment group were 14.9 ± 3, 16.6 ± 5.4 and 16.5 1 ± 5, respectively. We noticed a certain difference between the behaviors over time in the two groups, with larger differences in the Li-ESWT group. The interaction was significant ($p = 0.0177$), indicating significantly different behaviors between the groups over time. The mean IIEF-5 score in the Li-ESWT group was significant among the time points ($p < 0.001$). The IIEF-5 score improved to higher than 5 points in 70% (range, 0–10) of the patients in the Li-ESWT group and in 10% (range, 1–14) of the patients in the sham treatment group 3 months after the treatment. Analysis after 12 months was performed exclusively in the Li-ESWT group; the sham treatment group has previously been informed regarding such. The mean IIEF-5 score after 12 months was 15.7 ± 6.45, showing stability of the initial improvement.

At baseline and 1 and 3 months after the last treatment, the EHSs in the Li-ESWT group were 2 ± 1.05, 2.5 ± 0.85, and 2.6 ± 0.84, respectively. The EHSs in the sham treatment group were 2 ± 0.67, 2.4 ± 0.7, and 2.4 ± 0.7, respectively. We noticed a similar behavior in both groups. In the Li-ESWT group, we noticed a slightly higher mean EHS after 3 months. The interaction was not significant ($p = 0.7244$), indicating the same behavior of the groups over time. We also observed significant differences among the time points ($p = 0.0004$). Figure 3 shows the EHS and IIEF-5 scores in both the groups. Figure 4 shows the IIEF-5 scores before and after treatment per patient in the Li-ESWT group.

Penile Doppler ultrasound parameters

The parameters analyzed were as follows: PSV (per side and mean value), EDV (per side and mean value), diameter of the cavernous arteries before and after injection (per side), RI, and ratio of the cavernous arteries post- and pre-injection. The mean PSV and mean EDV were similar

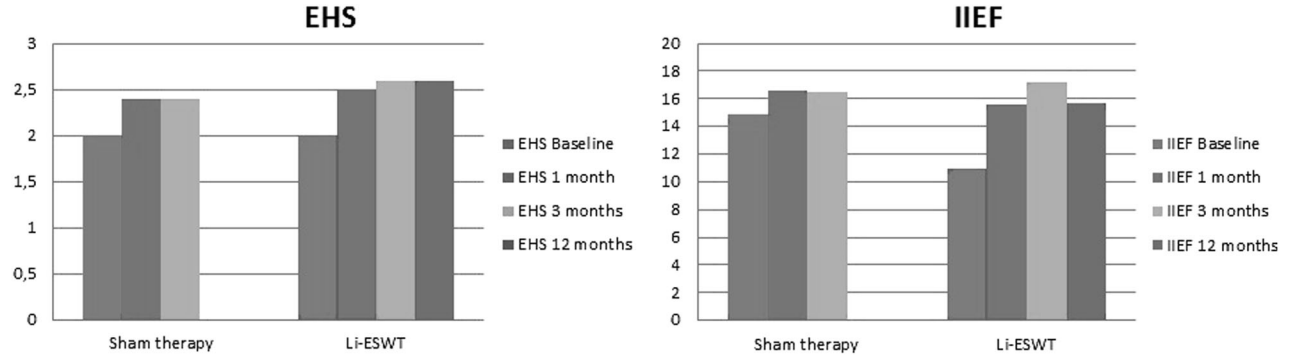

Fig. 3 Outcomes of EHS and IIEF-5 in both the groups. IIEF International Index of Erectile Function, EHS Erection Hardness Score

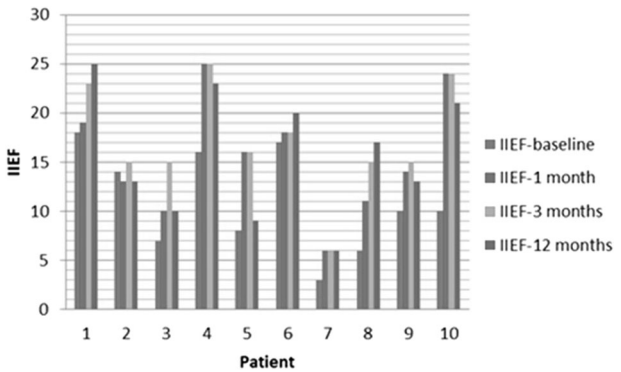

Fig. 4 IIEF-5 scores before and after treatment per patient in Li-ESWT group

between the groups. Table 2 summarizes the penile Doppler parameters between the groups before and after the treatment. Figures 5 and 6 show the box plot parameters.

Discussion

This study is the first trial to treat ED with LI-ESWT in kidney transplant recipients. The study demonstrated a significant improvement in the IIEF-5 scores after 1, 3, and 12 months. Even 12 months after treatment, the median IIEF-5 score remained significant. The main motivation in selecting renal transplant recipients was that the treatment aimed to improve the sexual performance of patients without interfering with the current or future function of the transplant. In addition, there is a concern that PDE-5-Is may affect the levels of immunosuppressive drugs and graft function after renal transplant [6]. A minimum interval of 6 months between transplantation and treatment was determined for the selection of patients with functioning renal graft for at least 6 months after transplantation; further there was a lower risk of loss of graft function during treatment.

The use of Li-ESWT for ED was first reported by Vardi et al. [19]. The acoustic waves carry energy and interact with the targeted deep tissues when targeted and focused, causing mechanical stress and microtrauma. In vitro and animal studies have shown that angiogenesis-growth factors were stimulated after Li-ESWT [20].

The underlying mechanism of action of LI-ESWT is currently under investigation. According to previous reports, the effect is primarily related to the stimulation of cell proliferation, tissue regeneration, and angiogenesis [21–23].

In the first trial reported by Vardi et al., ten of 20 patients regained good erectile function without the need for further oral therapy at 6 months [19]. Moreover, Vardi et al. performed a randomized, double-blind, sham-controlled study showing that Li-ESWT had a positive short-term clinical and physiological effect on erectile function, and ~50% of the patients regained spontaneous erection sufficient for sexual penetration [24]. In our present study, 70% of the patients showed a ≥ 5-point improvement in the IIEF-5 score. However, the EHS did not significantly improve in both groups. In the Li-ESWT group, six men had an EHS lower than 2 points and four men had an EHS of 3 points. The response rate was 50% after 3 months. Only one patient with a baseline EHS of 3 points achieved an EHS of 4 points. In the sham treatment group, eight men had EHSs of 0–2 points and two men had an EHS of 3 points. The response rate was 40% after 3 months. Three patients with a baseline EHS of 2 points achieved an EHS of 3 points. These findings may have been influenced by the small cohort and the higher prevalence of mild ED in the Li-ESWT group.

The other aspect of interest that still needs to be clarified and reach a standard protocol is the energy intensity. In a large and recent systematic review, most of the included studies used an energy density of 0.09 mJ/mm^2, following the first research by Vardi et al. [19]. In this meta-analysis, 14 clinical studies were reviewed and seven were

Table 2 Penile Doppler parameters before and after therapy

	Baseline		Post–procedure		*p*-value	
Medida	Sham therapy	Li-ESWT	Sham therapy	Li-ESWT	Interaction	Moment
PSV R, cm/s	55.5 (30.9)	48.5 (26.3)	48.6 (14.4)	50.6 (31.7)	0.4544	0.6882
PSV L, cm/s	46.0 (27.1)	59.6 (32.9)	46.8 (29.8)	55.8 (41.4)	0.7854	0.8590
Mean PSV, cm/s	50.8 (28.2)	54.1 (25.5)	47.7 (19.6)	53.2 (33.9)	0.8537	0.7440
EDV R, cm/s	−1.83 (15.63)	0.20 (8.98)	0.66 (8.25)	−1.65 (11.06)	0.3703	0.8937
EDV L, cm/s	0.70 (7.50)	−3.33 (11.59)	2.22 (7.78)	−3.60 (10.61)	0.4606	0.6050
Mean EDV, cm/s	−0.57 (11.10)	−1.57 (9.89)	1.44 (7.83)	−2.63 (9.83)	0.3547	0.7729
AD R pre, mm	0.077 (0.015)	0.071 (0.022)	0.065 (0.011)	0.068 (0.013)	0.3132	0.1008
AD L pre, mm	0.074 (0.012)	0.068 (0.020)	0.057 (0.021)	0.069 (0.020)	0.0307	—
AD R post, mm	0.108 (0.020)	0.096 (0.019)	0.106 (0.020)	0.111 (0.014)	0.1208	0.2290
AD L post, mm	0.108 (0.025)	0.099 (0.018)	0.103 (0.023)	0.112 (0.021)	0.0357	—
Ratio AD R post/AD R pre	1.43 (0.33)	1.43 (0.32)	1.68 (0.50)	1.68 (0.33)	0.9965	0.0649
Ratio AD L post/AD L pre	1.45 (0.22)	1.54 (0.37)	1.98 (0.59)	1.72 (0.50)	0.2684	0.0297
RI	1.02 (0.16)	1.02 (0.14)	0.99 (0.13)	1.06 (0.17)	0.6119	0.8564

p-value (Student's *t*-test)

PSV peak systolic velocity, *R* right, *L* left, *EDV* end diastolic velocity, *AD* artery diameter, *RI* resistivity index

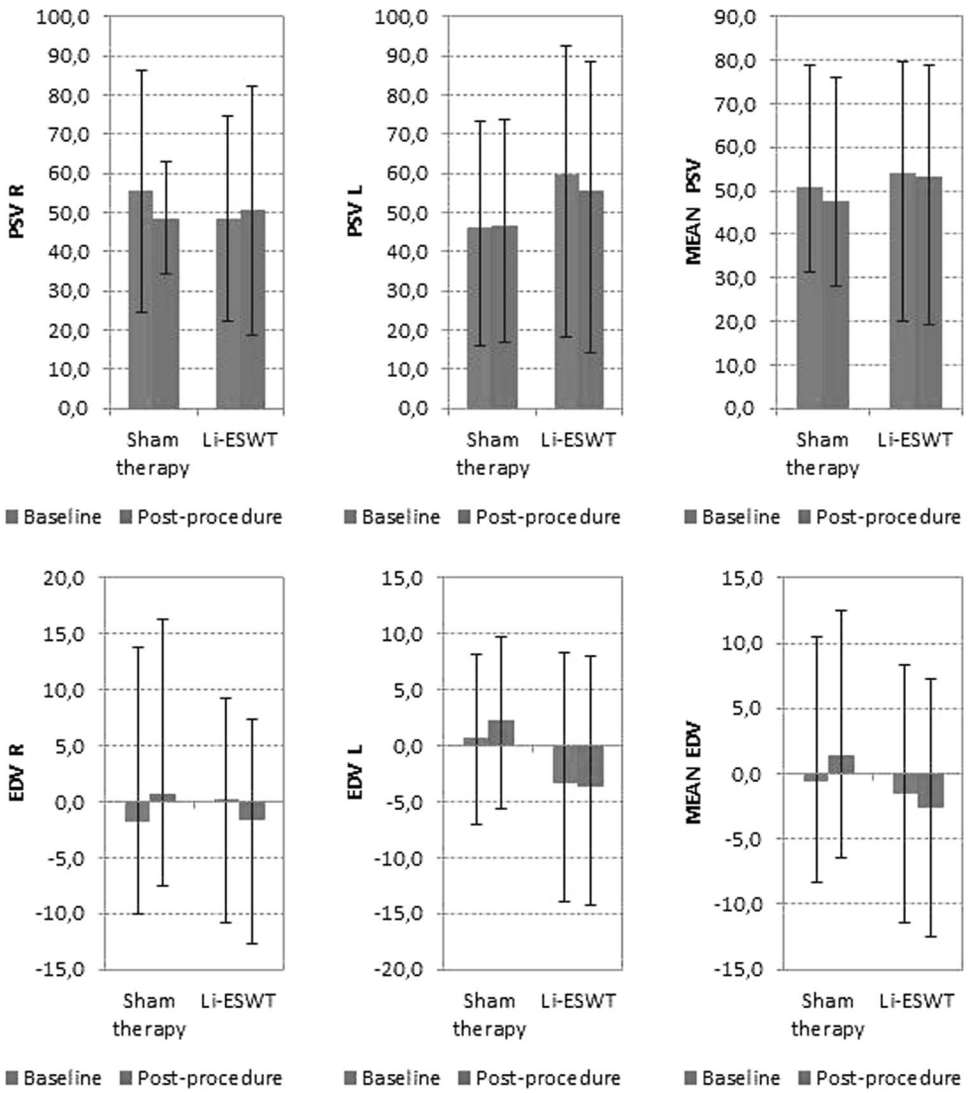

Fig. 5 Box plot of ultrasound doppler parameters of peak systolic velocity (PSV) and end diastolic velocity (EDV), per side and mean. R right, L left

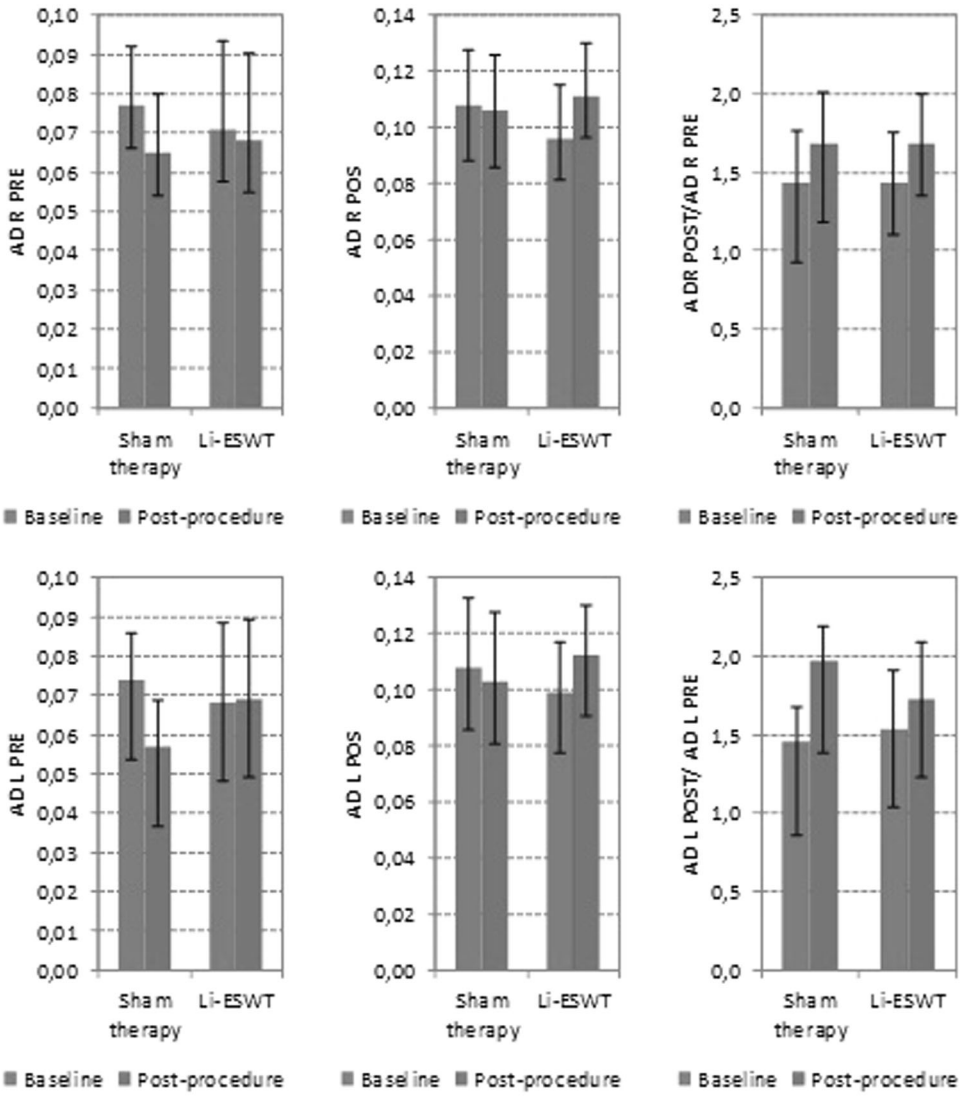

Fig. 6 Box plot of ultrasound doppler parameters of artery diameter (AD) before and after injection, per side and mean. R right, L left

randomized clinical trials comprising 169 patients in the treatment group compared with 113 patients in the control group. In this review, the energy density ranged from 0.09 to 0.25 mj/mm^2 and the number of pulses per session ranged from 1500 to 5000. The duration of the treatment was up to 6 weeks in the majority of the series and 9 weeks in the three remaining trials. The IIEF score improvement was superior in the group with the energy density of 0.09 mJ/mm^2 when compared with the group with the energy density of 0.1–0.2 mJ/mm^2 [25].

In addition, the meta-analysis showed that 3000 pulses per treatment yielded better results than 1500 or 2000 pulses per treatment; however, more frequent treatments and longer treatment courses did not improve the erectile function significantly.

In our study and other studies, the same parameter proposed by Vardi et al. was used; all disclosed encouraging results. Additional studies and longer durations of treatment are needed to establish whether the therapeutic efficacy is positively correlated with energy density. The optimal treatment protocol remains to be defined.

Most of the previous studies have focused on improving erectile function following Li-ESWT. However, the potential impact of ED-related risk factors such as age, hypertension, diabetes, dyslipidemia, and coronary disease has not been discussed. In a meta-analysis of seven randomized clinical studies [25], only four studies mentioned data regarding age and comorbidities, however, none correlated the influence of risk factors on the treatment outcomes. Additional clinical studies with age stratification and comorbidity assessment will help determine the influence of these risk factors on the efficacy of Li-ESWT in patients with ED.

In addition, with the aim of and focus on determining the effect of Li-ESWT alone and avoiding confounding factors, most studies banned the use of PDI-5 during treatment.

However, as the goal is to optimize erectile function to the maximum, perhaps the combined use of Li-ESWT and PDI-5 is a better option. Gruenwald et al., demonstrated that Li-ESWT converted non-responders of PDI-5 to responders [26]. Further testing is needed to investigate these findings better.

Regarding the type of device, the majority of the studies used the Omnispec ED1000 (Medispec, Yehud, Israel). Meanwhile, the recent study by Olsen and colleagues used the Duolith SD1 T-Top [27]. They included 105 patients and randomized them to either LI-ESWT or sham therapy. Five weeks after the final treatment, no difference in the IIEF-EF score changes was observed between the groups. However, based on the EHS questionnaire findings, significantly more patients in the LI-ESWT group had improved their scores to 3 or 4 (erections hard enough for penetration) ($p < 0.0001$) [27]. The Omnispec ED1000 and the Duolith SD1 T-Top use the same technique to generate shockwaves. However, our study is the first to use de Swiss Dolorclasth EVO BLUE for Li-ESWT in ED, in which the shockwaves are transmitted through an electropneumatic system; this generation source utilizes kinetic energy stored in a compressed air compressor and electric power. This is different from other sources of energy such as electrohydraulic energy, in which shockwaves are generated by high-voltage discharging to a spark plug in an underwater source, and electromagnetic energy, in which shockwave generation is based on the physical principle of electromagnetic induction, as used, for example, in loudspeakers, which use an electromagnetic coil and a metal membrane opposite to it. A low-pressure acoustic pulse is generated by acceleration of the membrane away from the coil owing to electromagnetic forces.

Besides the clinical assessment findings and questionnaire scores used by all the studies, our study also reported penile hemodynamic parameters, providing an objective measurement. The 4-month period after treatment was determined by the fact that neoangiogenesis peaks from 3 to 4 months after the application of shockwaves [20]. However, it was not possible to demonstrate any significant improvement in the main parameters, such as blood flow and arterial diameter. We believe that the findings were mainly influenced by the small cohort and variability of the measurements, although they were analyzed by the same radiologist. We also believe that vascular growth occurs at the peripheral of the cavernous tissue and at the microvasculature. Owing to the reduced caliber of the cavernous artery, changes in the microcirculation may not necessarily reflect the alterations detected by penile Doppler ultrasound. Conversely, a recent report has shown that Li-ESWT exerts a genuine effect on the erectile mechanism by improving penile blood flow [24]. In addition, Kalyvianakis et al. revealed a mean PSV increase of 4.5 and 0.6 cm/s in the Li-ESWT and sham groups, respectively ($p < 0.001$) and found that patients with no improvement in the IIEF-5 score had no improvement in the PSV as well [28].

We acknowledge some limitations in our present study, which include the lack of a fully blinded 12-month follow-up. When an interim analysis was performed after 3 to 4 months, the men in the sham treatment group were promised that if there was an effect in the Li-ESWT group, they would also be offered active treatment. Consequently, the analysis at 12 months was not fully blinded.

We believe that further basic research is crucial to explore the various pathophysiological mechanisms of Li-ESWT on the erectile tissues, including long-term efficacy, safety, and histological modifications. The current results appear promising, although several important factors regarding Li-ESWT, such as modalities of shockwave energy, treatment templates and protocols, patient characteristics, actual physiological changes in the penile tissues, and longer-term success and safety have yet to be fully elucidated.

Conclusion

This study presents a novel technology that appears to be effective for treating ED among kidney transplant recipients.

We believe that ESWT for ED is an intriguing therapy option and may soon serve as a minimally invasive procedure to help patients achieve erection in addition to oral pharmacotherapy. Our treatment protocol was effective; it is the first study in this area conducted among kidney transplant recipients.

Additional studies including large multicenter, longer-term, randomized, and sham-controlled studies are required before Li-ESWT can be adopted as a standard therapy and a treatment that can “cure” ED.

Author's contribution KGRY: manuscript writing and data collection; FC: data management; JC**:** project management and data analysis; RL: data collection and treatment application; PCF: data collection; ACP: manuscript revision; MS: project management and data analysis; WCN: project management; and IMA: manuscript editing and project design.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the

institutional and/or national research committee, and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts male aging study. J Urol. 1994;151:54–61.
2. Althof SE. Quality of life and erectile dysfunction. Urology. 2002;59:803–10.
3. El-Assmy A, El-Bahnasawy MS, Dawood A, AboBieh E, Ali-El Dein B, El-Dein AB, et al. Vasculogenic erectile dysfunction in renal transplant recipients--assessment of potential risk factors. Scand J Urol Nephrol. 2004;38:511–6.
4. Jensen J, Lendorf A, Stimpel H, Frost J, Ibsen H, Rosenkilde P. The prevalence and etiology of impotence in 101 male hypertensive outpatients. Am J Hypertens. 1999;12:271–5.
5. Shamloul R, Ghanem H. Erectile dysfunction. Lancet. 2013;381:153–65.
6. Malavaud B, Rostaing L, Rischmann P, Sarramon JP, Durand D. High prevalence of erectile dysfunction after renal transplantation. Transplantation. 2000;69:2121–4.
7. Toorians AW, Janssen E, Laan E, Gooren LJ, Giltay EJ, Oe PL, et al. Chronic renal failure and sexual functioning: clinical status versus objectively assessed sexual response. Nephrol, Dial, Transplant: Off Publ Eur Dial Transplant Assoc - Eur Ren Assoc. 1997;12:2654–63.
8. Eardley I, Donatucci C, Corbin J, El-Meliegy A, Hatzimouratidis K, McVary K, et al. Pharmacotherapy for erectile dysfunction. J Sex Med. 2010;7(1 Pt 2):524–40.
9. Aversa A, Bruzziches R, Vitale C, Marazzi G, Francomano D, Barbaro G, et al. Chronic sildenafil in men with diabetes and erectile dysfunction. Expert Opin Drug Metab Toxicol. 2007;3:451–64.
10. Porst H, Rajfer J, Casabe A, Feldman R, Ralph D, Vieiralves LF, et al. Long-term safety and efficacy of tadalafil 5 mg dosed once daily in men with erectile dysfunction. J Sex Med. 2008;5:2160–9.
11. Vardi Y, Appel B, Ofer Y, Greunwald I, Dayan L, Jacob G. Effect of chronic sildenafil treatment on penile endothelial function: a randomized, double-blind, placebo controlled study. J Urol. 2009;182:2850–5.
12. Aicher A, Heeschen C, Sasaki K, Urbich C, Zeiher AM, Dimmeler S. Low-energy shock wave for enhancing recruitment of endothelial progenitor cells: a new modality to increase efficacy of cell therapy in chronic hind limb ischemia. Circulation. 2006;114:2823–30.
13. Young Academic Urologists Men's Health Group. Fode M, Hatzichristodoulou G, Serefoglu EC, Verze P, Albersen M. Low-intensity shockwave therapy for erectile dysfunction: is the evidence strong enough. Nat Rev Urol. 2017;14:593–606.
14. Gotte G, Amelio E, Russo S, Marlinghaus E, Musci G, Suzuki H. Short-time non-enzymatic nitric oxide synthesis from L-arginine and hydrogen peroxide induced by shock waves treatment. FEBS Lett. 2002;520:153–5.
15. Eardley I. Can an erectogenic pharmacotherapy regimen after radical prostatectomy improve postoperative erectile function? Nat Clin Pract Urol. 2006;3:72–73.
16. Gonzales AI, Sties SW, Wittkopf PG, Mara LS, Ulbrich AZ, Cardoso FL, et al. Validation of the International Index of Erectile Function (IIFE) for use in Brazil. Arq Bras Cardiol. 2013;101:176–82.
17. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the international index of erectile function. Urology. 1999;54:346–51.
18. Mulhall JP, Goldstein I, Bushmakin AG, Cappelleri JC, Hvidsten K. Validation of the erection hardness score. J Sex Med. 2007;4:1626–34.
19. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol. 2010;58:243–8.
20. Wang CJ, Wang FS, Yang KD, Weng LH, Hsu CC, Huang CS, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res: Off Publ Orthop Res Soc. 2003;21:984–9.
21. Kovanecz I, Nolazco G, Ferrini MG, Toblli JE, Heydarkhan S, Vernet D, et al. Early onset of fibrosis within the arterial media in a rat model of type 2 diabetes mellitus with erectile dysfunction. BJU Int. 2009;103:1396–404.
22. Petschnik AE, Fell B, Kruse C, Danner S. The role of alpha-smooth muscle actin in myogenic differentiation of human glandular stem cells and their potential for smooth muscle cell replacement therapies. Expert Opin Biol Ther. 2010;10:853–61.
23. Liu J, Zhou F, Li GY, Wang L, Li HX, Bai GY, et al. Evaluation of the effect of different doses of low energy shock wave therapy on the erectile function of streptozotocin (STZ)-induced diabetic rats. Int J Mol Sci. 2013;14:10661–73.
24. Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. J Urol. 2012;187:1769–75.
25. Lu Z, Lin G, Reed-Maldonado A, Wang C, Lee YC, Lue TF. Low-intensity extracorporeal shock wave treatment improves erectile function: a systematic review and meta-analysis. Eur Urol. 2017;71:223–33.
26. Gruenwald I, Appel B, Vardi Y. Low-intensity extracorporeal shock wave therapy--a novel effective treatment for erectile dysfunction in severe ED patients who respond poorly to PDE5 inhibitor therapy. J Sex Med. 2012;9:259–64.
27. Olsen AB, Persiani M, Boie S, Hanna M, Lund L. Can low-intensity extracorporeal shockwave therapy improve erectile dysfunction? A prospective, randomized, double-blind, placebo-controlled study. Scand J Urol. 2015;49:329–33.
28. Kalyvianakis D, Memmos E, Mykoniatis I, Kapoteli P, Memmos D, Hatzichristou D. Low-intensity shockwave therapy for erectile dysfunction: a randomized clinical trial comparing 2 treatment protocols and the impact of repeating treatment. J Sex Med. 2018;15:334–45.