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Impact of extracorporeal shockwave therapy for erectile dysfunction and Peyronie's disease on reproductive and hormonal testicular function

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Abstract

Introduction: Extracorporeal shock wave therapy is an established treatment for erectile dysfunction and Peyronie's disease. Concerns regarding the safety of extracorporeal shock wave therapy for andrological purposes on testicular function were raised by animal studies.

Aim: To evaluate the impact of extracorporeal shock wave therapy for erectile dysfunction or Peyronie's disease on reproductive and hormonal testicular function.

Methods: We designed a prospective controlled study in which consecutive patients were enrolled. Males aged between 18 and 40 years with mild vasculogenic erectile dysfunction or acute inflammatory Peyronie's disease and normozoospermia were included. All enrolled patients were offered extracorporeal shock wave therapy, and subjects who refused extracorporeal shock wave therapy for any reason were considered as the Control group. All patients in the Intervention group were treated with DUOLITH SD1 T-TOP by a single expert urologist. Semen analysis and serum total testosterone dosage were performed before the start (T0) and 3 months after the end of extracorporeal shock wave therapy (T1) in Intervention group. The same parameters were evaluated after the extracorporeal shock wave therapy refusal (T0) and at the end of the following 3 months (T1) in Control group. Normozoospermia was

chosen as the primary outcome, serum total testosterone concentration was selected as the secondary outcome.

Results: A total of 94 patients were enrolled in the study (48 Group A, 46 Group B). At T0, all patients were normozoospermic in both groups ($p = 0.563$), and no significant difference in mean ± SD total testosterone levels was recorded between the groups (582.5 ± 107.2 vs. 634.6 ± 108.4 ng/dl; $p = 0.221$). At T1, no significant deterioration ($p > 0.05$) in semen parameters was recorded in both groups. Only a statistically significant reduction in seminal pH was found after extracorporeal shock wave therapy compared to baseline (7.9 ± 0.3 vs. 7.5 ± 0.2; $p < 0.001$) and untreated patients (7.8 ± 0.2 vs. 7.5 ± 0.2; $p < 0.001$). No significant difference in total testosterone levels was recorded in Intervention group after extracorporeal shock wave therapy compared to baseline ($p = 0.584$).

Conclusion: Extracorporeal shock wave therapy in erectile dysfunction and Peyronie's disease patients does not seem to affect reproductive and hormonal testicular function.

KEYWORDS

ESWT, semen, shock waves, testicular function, testis, testosterone

1 | INTRODUCTION

Extracorporeal shock waves therapy (ESWT) was introduced in 1980 to treat urinary tract stones.[1] In the last decades, the mechanisms of action of shock waves have been clarified, allowing the extension of the indications of ESWT and favoring their use in the context of "regenerative medicine." The energy released involves a double class of effects on the tissues treated: direct effects, not mediated by the cellular response but induced by the direct action of the energy that is released on the living structures; indirect effects, understood as cellular reactions in response to energy shock, responsible for the "translation" of the mechanical signal into a biological signal.[2,3]

In recent times, its use for the treatment of andrological diseases has become increasingly widespread, thanks to the increase in data relating to its effectiveness. Shock wave therapy can determine a significant improvement in erectile function and penile pain in selected patients with erectile dysfunction (ED)[4] and Peyronie's disease (PD),[5] respectively. Current European guidelines suggest that ESWT may be offered to individuals with mild vasculogenic ED, men with poorly responsive vasculogenic ED to phosphodiesterase 5 inhibitors (PDE5Is), subjects with ED desiring a curative option, and patients in the acute phase of PD.[6] However, standardized treatment protocols and optimal parameter settings for performing ESWT have not yet been defined.[4,5]

Although ESWT in andrology is generally well tolerated, with rare, mild, and self-limiting side effects (e.g., pain, erythema),[4,5,7] some concerns may arise from the anatomical proximity of the testes to the penis, which can theoretically be exposed to shock waves. Impairment of spermatogenesis and worsening of seminal parameters have recently been described in adult rats undergoing ESWT on the penile surface; however, there are currently no human studies available evaluating the effects of ESWT for andrological purposes on testicular function.[8]

The aim of present study was to evaluate the impact of ESWT for ED or PD on reproductive and hormonal testicular function.

2 | MATERIALS AND METHODS

2.1 | Study design

We designed a prospective controlled study that included consecutive patients referred to a tertiary center (University of Naples "Federico II," Naples, Italy) from September 2018 and January 2020. The research was conducted according to the Declaration of Helsinki on ethical principles for medical research involving human subjects.[9] All patients provided written informed consent regarding study participation and publication of data.

2.2 | Patient enrollment and distribution

Males aged between 18 and 40 years with mild vasculogenic ED or acute inflammatory PD and normozoospermia were included. Mild ED was defined as International Index of Erectile Function - Erectile Function (IIEF-EF) from 22 to 25 points.[10] Vasculogenic origin of ED was assessed by careful medical history, psychosexual evaluation, and possible penile Doppler ultrasound (PDU). Acute PD was defined as

progressive worsening of penile curvature associated with pain for less than 12 months.[6] Normozoospermia was classified according to World Health Organization (WHO) 2010 criteria: total sperm number ≥39 million per ejaculate, sperm concentration ≥15 million per milliliter, progressive motility ≥32%, and normal forms ≥4%.[11]

Patients with penile infection or cancer, coagulopathy (including taking anticoagulants), hydrocele, clinically evident varicocoele, history of testicular cancer or cryptorchidism, testicular hypotrophy, anejaculation or retrograde ejaculation, hormonal abnormalities, or genetic conditions known to have an impact on semen parameters or testosterone levels were excluded. In addition, the intake of drugs with a potential effect on spermatozoa or testosterone and the onset of male accessory glands infections (MAGI) during the study period constituted additional exclusion criteria. All cases were ESWT naïve and no subject with extracorporeal shock wave lithotripsy (ESWL) history was included.

All enrolled patients were offered ESWT, and subjects who refused ESWT for any reason were considered the control group. Consequently, a non-randomized and non-blinded distribution was performed between the Intervention group and the Control group.

2.3 | ESWT protocols

All patients in the Intervention group were treated with DUOLITH SD1 T-TOP (Storz Medical AG, Tägerwilen, Switzerland) by a single expert urologist. The protocols and settings commonly adopted in our center were used as there are no standardized or optimal values. The protocol applied for ED consisted of two sessions per week for 3 weeks. Each session included 3000 shock waves addressed to two penile sites (1000 proximal + 1000 distal) and to the crura (500 right + 500 left). The protocol used for PD consisted of one session per week for 4 weeks. Each session included 3000 shock waves addressed to the major penile plaque. The energy setting was 0.10–0.25 mJ/mm^2 and 4–6 Hz in both cases.

2.4 | Outcomes evaluation

Each patient at the screening visit underwent medical history, physical examination, and any other laboratory and instrumental tests necessary to define eligibility for the study.

Normozoospermia was chosen as the primary outcome, and serum total testosterone concentration was selected as the secondary outcome.

Semen analysis and serum total testosterone dosage were performed before the start (T0) and 3 months after the end of ESWT (T1) in the Intervention group. The same parameters were evaluated after the ESWT refusal (T0) and at the end of the following 3 months (T1) in the Control group.

The semen analyses were conducted by a single experienced seminologist, according to the indications of the WHO Laboratory Manual for the Examination and Processing of Human Semen (fifth edition, 2010).[11] Semen was always collected in the laboratory by masturbation after 2–7 days of sexual abstinence, specifying the patient to collect the whole sample. On the same day as the semen collection (before 11:00 a.m.), a venous blood sample was taken for the determination of serum total testosterone levels.

2.5 | Statistics

The categorical variables were described as frequencies and percentages, whereas the quantitative variables were reported as means and standard deviations (SDs). The Kolmogorov–Smirnov test[12] was applied as normality test. The *t*-test (paired or unpaired)[13] and chi-square test[14] were used to compare the means and percentages, respectively. Statistical significance was arbitrarily set for a *p*-value <0.05. G*Power (Heinrich-Heine-Universität Düsseldorf, Germany) was used for the statistical power analysis, noting that a total sample size of 90 cases (45:45) was needed for a power of 0.80 ($\alpha = 0.05$; $\beta = 0.2$) relative to the primary outcome. The IBM Statistical Package for the Social Sciences (IBM Corp. released 2015, IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.) was used for other statistical analyses.

3 | RESULTS

A total of 94 patients were enrolled in the study. Forty-eight subjects received ESWT (Intervention group), while 46 men did not undergo any intervention (Control group). All patients of both groups at baseline (T0) were normozoospermic ($p = 0.563$), according to the inclusion criteria. Mean ± SD total testosterone levels at T0 were 582.5 ± 107.2 ng/dl in the Intervention group and 634.6 ± 108.4 ng/dl in the Control group, with no significant difference ($p = 0.221$). Baseline characteristics of patients were detailed in Table 1.

At 3 months (T1), all subjects in the Intervention group had completed the ESWT cycle, and no enrolled patients were lost to follow-up. No significant deterioration ($p > 0.05$) in semen parameters was recorded in both groups. This result was confirmed by both intragroup (Intervention group T0 vs. T1; Control group T0 vs. T1) and intergroup (Intervention group T1 vs. Control group T1) analyses (Table 2). We only found a statistically significant reduction in seminal mean ± SD pH after ESWT compared to baseline (7.9 ± 0.3 vs. 7.5 ± 0.2; $p < 0.001$) and untreated patients (7.8 ± 0.2 vs. 7.5 ± 0.2; $p < 0.001$) (Figure 1). No significant difference in serum total testosterone levels was recorded in the Intervention group after ESWT compared to baseline ($p = 0.584$) (Figure 2). Similar findings were found in the Control group and between the groups at 3 months (Table 3).

Stratifying Intervention group patients into subjects with ED and PD, no significant difference ($p > 0.05$) in semen parameters and total testosterone levels were found, neither before nor after ESWT. The significant reduction of seminal pH after ESWT was confirmed in both subgroups ($p < 0.001$).

TABLE 1 Baseline characteristics of patients

	Intervention group($n = 48$)	Control group($n = 46$)	p-Value
Age, years, mean ± SD	34.1 ± 4.6	35.0 ± 4.9	0.259
BMI, kg/m^2, mean ± SD	24.8 ± 4.8	26.1 ± 3.9	0.093
ED, *n* (%)	32 (66.7)	29 (63.0)	0.283
PD, *n* (%)	16 (33.3)	17 (37.0)	0.189
Normozoospermia,[a] *n* (%)	48 (100)	46 (100)	0.563
Serum total testosterone, ng/dl, mean ± SD	582.5 ± 107.2	634.6 ± 108.4	0.221

Note: Intervention group: extracorporeal shock waves therapy. Control group: no treatment.
Abbreviations: BMI, body mass index; ED, erectile dysfunction; PD, Peyronie's disease; SD, standard deviation.
[a]Specific semen parameters are reported in Table 2.

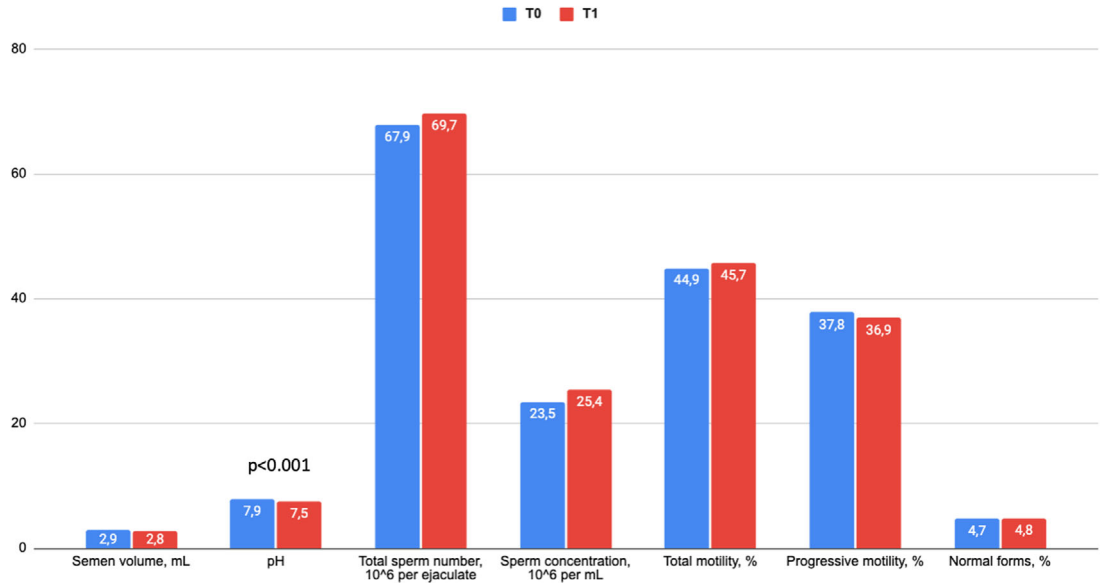

FIGURE 1 Comparison of semen parameters before and after ESWT. ESWT: extracorporeal shock waves therapy; T0: baseline; T1: 3 months of follow-up. All semen parameters (except pH) were not significantly different.

4 | DISCUSSION

ED and PD are two conditions commonly faced in andrological clinical practice and which negatively impact patients' quality of life.[15,16] Several effective treatments have been described over the years for these pathologies. Oral PDE5Is, intracavernous or topical alprostadil, vacuum devices, and penile prostheses are some therapeutic options for ED.[17–20] Non-steroidal anti-inflammatory drugs (NSAIDs), penile traction therapy (PTT), collagenases, and shortening or lengthening surgical procedures are some treatment options for PD.[21–24] In recent years, ESWT has proven to be an effective treatment in selected patients with ED and PD, to improve erectile function and relieve penile pain, respectively.[4–6]

ESWT is generally described as a safe andrological procedure characterized by mild and transient side effects.[4,5,7] However, the still limited knowledge of the biological effects of shock waves,[2,3] the description of testicular damage following ESWL,[25,26] and especially some recent pre-clinical studies showing the negative impact of low-intensity ESWT (Li-ESWT) on testicular function[8,27] have raised several concerns about the possible testicular effects of ESWT in ED or PD setting because of tissue contiguity between penis and testes.

Kalla et al. published the first article on the impact of shock waves on semen in 1988. This study reported the negative effect of high-energy shock waves delivered by a lithotripter on human semen in vitro.[28] Since then, several clinical studies have evaluated the structure and testicular function of patients undergoing ESWL for distal ureteral stones (particularly close to the male reproductive organs), producing limited and contradictory evidence.[26] A recent meta-analysis by Radfar et al. found a significant worsening in sperm concentration and motility and a significant increase in hematospermia rate after ESWL for lower ureteral calculi. However, these sperm parameters recovered 3 months after ESWL.[25] Despite this noteworthy background, it is essential to underline that energy settings, protocols, and sites of application of ESWL for distal ureteral stones and ESWT for ED and

TABLE 2 Semen parameters

	Intervention group($n = 48$)		Control group($n = 46$)		
	T0	T1	T0	T1	*p*-Values
Semen volume, ml, mean ± SD	2.9 ± 0.7	2.8 ± 0.9	3.1 ± 1.5	3.0 ± 1.4	0.062[a]
					0.663[b]
					0.910[c]
					0.322[d]
pH, mean ± SD	7.9 ± 0.3	7.5 ± 0.2	7.9 ± 0.4	7.8 ± 0.2	0.981[a]
					<0.001[b]
					0.603[c]
					<0.001[d]
Total sperm number, $\times 10^6$ per ejaculate, mean ± SD	67.9 ± 21.8	69.7 ± 29.9	70.7 ± 31.2	72.2 ± 37.4	0.201[a]
					0.426[b]
					0.540[c]
					0.209[d]
Sperm concentration, $\times 10^6$ per ml, mean ± SD	23.5 ± 7.2	25.4 ± 7.6	24.2 ± 8.3	24.8 ± 7.7	0.742[a]
					0.083[b]
					0.419[c]
					0.695[d]
Total motility, %, mean ± SD	44.9 ± 4.8	45.7 ± 5.0	46.0 ± 5.1	47.1 ± 6.1	0.059[a]
					0.347[b]
					0.755[c]
					0.064[d]
Progressive motility, %, mean ± SD	37.8 ± 5.3	36.9 ± 4.0	38.7 ± 4.6	38.1 ± 5.9	0.003[a]
					0.537[b]
					0.797[c]
					0.654[d]
Normal forms, %, mean ± SD	4.7 ± 0.5	4.8 ± 0.6	5.1 ± 1.4	5.0 ± 0.9	0.021[a]
					0.923[b]
					0.867[c]
					0.541[d]

Note: Intervention group: extracorporeal shock waves therapy. Control group: no treatment.
Abbreviations: SD, standard deviation; T0, baseline; T1, 3 months of follow-up.
[a]Intervention group (T0) vs. Control group (T0).
[b]Intervention group (T0) vs. Intervention group (T1).
[c]Control group (T0) vs. Control group (T1).
[d]Intervention group (T1) vs. Control group (T1).

PD differ substantially[4,5,26]; therefore, it was not possible to extend the conclusions of the ESWL studies to patients undergoing shock waves for andrological purposes. Currently, only a few articles are available on the impact of Li-ESWT on the testis, all being pre-clinical studies on rat models.[8,27,29,30] The first paper on the topic was published by Zang et al. in 2018. In this study, a total of 24 male Sprague Dawley rats were randomly assigned to three groups: Control group, 1.6 BAR group, and 3.2 BAR group. The two Intervention groups underwent a total of 300 shock waves on the surface of the penis at a pressure of 1.6 BAR or 3.2 BAR (corresponding to 0.09 or 0.18 mJ/mm^2) and a frequency of 2 Hz, three times per week for 3 weeks. No change in testosterone levels in both the serum and testicular tissues was recorded after Li-ESWT. Only the 3.2 BAR group exhibited a significantly lower sperm count and lower synaptonemal complex protein 3 (SYCP3) expression in testicular tissue than the control group.[8] Yu et al. in 2019 investigated the impact of Li-ESWT on testicular ischemia-reperfusion (IR) injury induced in 64 male Sprague Dawley rats randomly assigned to different groups. The authors found that Li-ESWT improved testicular IR injury in rats, likely through the activation of PI3K/AKT/NRF2 pathway, hypothesizing a potential application in the treatment of testicular torsion.[29] Xing et al. in 2020 evaluated the safe energy density and impulse number for testes in 176 male Sprague Dawley rats randomly

TABLE 3 Serum total testosterone levels

	Intervention group($n = 48$)		Control group($n = 46$)		
	T0	T1	T0	T1	*p*-Values
Serum total testosterone, ng/dl, mean ± SD	582.5 ± 107.2	593.9 ± 104.2	634.6 ± 108.4	628.2 ± 97.6	0.221[a]
					0.584[b]
					0.887[c]
					0.563[d]

Note: Intervention group: extracorporeal shock waves therapy. Control group: no treatment.
Abbreviations: SD, standard deviation; T0, baseline; T1, 3 months of follow-up.
[a]Intervention group (T0) vs. Control group (T0).
[b]Intervention group (T0) vs. Intervention group (T1).
[c]Control group (T0) vs. Control group (T1).
[d]Intervention group (T1) vs. Control group (T1).

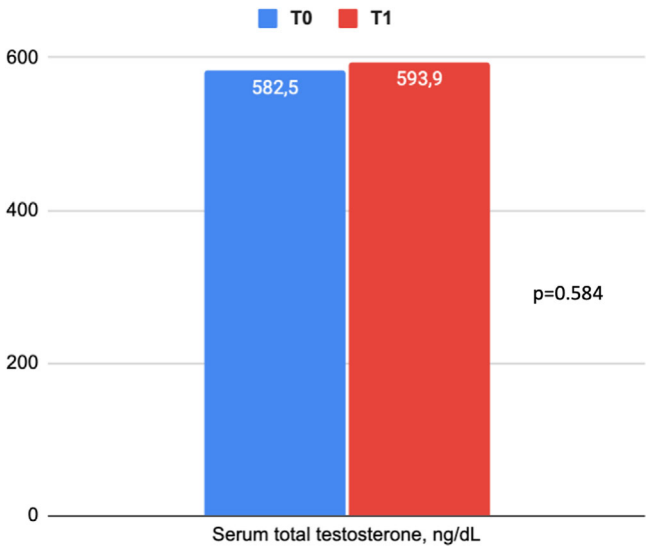

FIGURE 2 Comparison of serum total testosterone levels before and after ESWT. ESWT: extracorporeal shock waves therapy; T0: baseline; T1: 3 months of follow-up

assigned to several groups. The authors described decreased testicular weight, reduced serum testosterone, deterioration in sperm quality, histopathological changes of the testes, damage to the organelles of spermatogenic cells, and reduced antioxidant capacity of the spermatogenic epithelium. Greater energies and impulses correlated with greater testicular changes (dose-dependent effect). The energy of 0.02 mJ/mm^2 for 500 impulses was not associated with adverse effects on the testes.[27] Tian et al. in 2022 investigated the effects of Li-ESWT on 24 male Sprague Dawley androgen-deficient rats randomly assigned to different groups. The authors found that Li-ESWT can improve sperm count, motility, and serum testosterone level, enhancing tissue antioxidant capacity and antiapoptotic ability, with the most significant effect at 0.05 mJ/mm^2. Moreover, they proposed that these effects might be related to the increased vascular endothelial growth factor (VEGF) expression in Leydig cells.[30] The reported pre-clinical studies appear to be methodologically heterogeneous, providing limited and somewhat contradictory evidence. Furthermore, it should be noted that some of these articles described the application of shock waves directly to the testes via the scrotal skin,[27,29] but this modality is not part of human clinical practice. The main characteristics and findings of pre-clinical studies on Li-ESWT are summarized in Table 4.

We found that 3000 shock waves delivered on the penile surface at 0.10–.25 mJ/mm^2 and 4–6 Hz, two times per week for 3 weeks (ED) or one time per week for 4 weeks (PD), did not negatively impact either semen parameters ($p > 0.05$) or serum total testosterone levels ($p = 0.584$) of young normozoospermic male patients, after 3 months from the end of the treatment. Besides, we described a significant reduction in seminal pH after ESWT compared to baseline (7.9 vs. 7.5; $p < 0.001$). Seminal pH depends on the relative contribution of prostatic acid secretion and vesicular alkaline secretion, and it tends to increase with time after the ejaculation. Acidic ejaculate (pH < 7.2) may be associated with obstruction of seminal vesicles, while alkaline ejaculate (pH > 8.0) may be related to MAGI and consequent inflammation.[11] The decrease in pH in our cohort could be explained by the anti-inflammatory activity of the shock waves.[31–33] However, evidence on the correlation between seminal pH and other seminal parameters (e.g., number, motility) or clinical outcomes (e.g., pregnancy rate) is still limited.[34–36]

4.1 | Strengths and limitations

To the best of our knowledge, this is the first clinical study evaluating the impact on testicular function of ESWT performed in patients with ED or PD. Therefore, our article paves the way for clinical research on the effects on testicular function of ESWT used in andrology. The prospective controlled design is a significant strength of this paper.

However, our findings should be read considering several issues. The relatively small sample size and short follow-up are the main limitations. The non-randomized design is a further relevant weakness. WHO Laboratory Manual 2010[11] was used as the reference for the enrollment and semen analyses, but it could not have been otherwise because of the study period and the prospective design of the research. The internal validity of our results was limited by the failure to perform a second semen analysis in the same patient when the first was

TABLE 4 Pre-clinical studies investigating the impact of Li-ESWT on rat testes

First author	Year of publication	Country of origin	Methodological details	Main findings
Zang[8]	2018	China	24 Male Sprague Dawley rats randomly assigned to Control group, 1.6 BAR group, and 3.2 BAR group 300 Shock waves on the surface of penis at 1.6 BAR or 3.2 BAR (0.09 or 0.18 mJ/mm^2) and 2 Hz, 3 times per week for 3 weeks	No change in testosterone levels in both the serum and testicular tissue after Li-ESWT 3.2 BAR group: Significantly lower sperm count and lower expression of SYCP3 than control group
Yu[29]	2019	China	64 Male Sprague Dawley rats randomly assigned to different groups 250 Shock waves applied on the scrotal skin at 0.06 mJ/mm^2 and 2 Hz. The first treatment 30 min prior to testicular reperfusion, and then every other day for another 3 applications	Improvement of testicular IR injury by Li-ESWT Effects related to the activation of PI3K/AKT/NRF2 pathway
Xing[27]	2020	China	176 Male Sprague Dawley rats randomly assigned to several groups Shock waves with different impulse numbers (500, 1000, and 1500) and energy densities (0.02, 0.04, and 0.06 mJ/mm^2) on the scrotal skin once every 2 days for different periods (2 and 8 weeks)	Decreased testicular weight, reduced serum testosterone, worsening of sperm quality, histopathological changes of the testes, damage to the organelles of spermatogenic cells, and reduced antioxidant capacity of the spermatogenic epithelium after Li-ESWT Dose-dependent effect No adverse effects on the testes with energy density of 0.02 mJ/mm^2 and 500 impulses
Tian[30]	2022	China	24 Male Sprague Dawley androgen-deficient rats randomly assigned to different groups 300 Shock waves at 0.01, 0.05, or 0.2 mJ/mm^2 once a week for 4 weeks	Improved sperm count, motility, and serum testosterone level, as well as enhanced tissue antioxidant capacity and antiapoptotic ability after Li-ESWT Most significant effects at 0.05 mJ/mm^2 Effects related to the increased VEGF expression in Leydig cells

Abbreviations: IR, ischemia-reperfusion; Li-ESWT, low intensity-extracorporeal shock waves therapy; SYCP3, SYNAPTONEMAL COMPLEX PROtein 3; VEGF, vascular endothelial growth factor.

abnormal. The external validity of our data was limited by the chosen ESWT protocols and settings; however, there is currently no standardization. Likewise, our patient cohort was highly selected, including only young subjects with no other known conditions that could impact semen quality and testosterone production. Finally, only serum total testosterone and common semen parameters and no other hormones, sperm DNA fragmentation, or histopathological specimens were evaluated to analyze the testicular changes.

4.2 | Future perspectives

Randomized controlled trials (RCTs) with large sample size and long follow-up should be designed to verify our findings, using the WHO 2021 criteria.[37] Clinical studies to evaluate ESWT protocols and settings that are not harmful to the testes should be planned. The testicular function of men with chronic pelvic pain syndrome (CPPS) undergoing ESWT should also be investigated. Articles to assess clinical endpoints such as the pregnancy rate or the symptoms related to abnormal testosterone levels in patients treated with ESWT would be desirable.

5 | CONCLUSIONS

We found no significant changes in the reproductive and hormonal testicular function of patients treated with extracorporeal shock waves therapy for erectile dysfunction or Peyronie's disease. Therefore, it is reasonable to argue that exposing the penis to low-intensity shock waves is safe for the testes; consequently, paternally desirous and sexually active men could benefit from extracorporeal shock waves therapy without significant testicular risk. However, future randomized controlled trials with large sample size and long follow-up are needed to confirm our encouraging results.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Conceptualization: Celeste Manfredi, Giuseppe Bellastella, and Davide Arcaniolo. Study design and manuscript writing: Celeste Manfredi and Ugo Amicuzi. Data collection: Lorenzo Spirito, Paolo Cirillo, Stefano Gisone, and Marco Paoletta. Data analysis: Luigi Napolitano and Fabio Crocerossa. Scientific review: Felice Crocetto, Giuseppe Bellastella, and Davide Arcaniolo. Supervision: Ciro Imbimbo and Marco De Sio.

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