Review Article

Diagnosis of hypogonadism in patients treated with low energy shock wave therapy for erectile dysfunction: a narrative review

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Abstract: Several methods of treatment of erectile dysfunction (ED) are offered with low energy shock-wave therapy (LESWT) gaining increasing attention. Reports have documented that LESWT stimulates tissue neovascularization, proliferation and differentiation of endothelial cells, and production of nitric oxide - all can improve the condition of erectile tissue. However, the overall and sexual condition of men deteriorates with age which is linked with a constant decrease in testosterone concentration. A higher risk of sexual health disorders and reduced physical fitness correlates with a testosterone concentration of <12 nmol/L. Such patients may require testosterone replacement therapy. We conducted a target literature review to investigate whether testosterone concentration is taken into account in studies on the use of LESWT in the treatment of ED. We found that most studies did not provide any information on testosterone status. Only 8 of 25 studies examined showed values of testosterone concentrations. Only one of these analyses checked the relationship between the efficacy of LESWT and testosterone concentration. As a result, meta-analyses published to date may not show the full value of LESWT in the treatment of ED. We conclude that in the light of the significant role testosterone plays in the process of an erection and the mechanism of LESWT action, it can be recommended to examine testosterone concentration and to diagnose hypogonadism during the qualification of patients to studies on LESWT efficacy. Moreover, the effectiveness of LESWT in relation to the current testosterone concentration should also be further investigated.

Keywords: Erectile dysfunction (ED); hypogonadism; testosterone; low energy shock wave therapy (LESWT); impotence

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Introduction

An erection is a complex neurovascular process. Obtaining an erection is determined by a relatively rapid flow of blood into the corpora cavernosa, which leads to tumescence of the corpora cavernosa and activation of the veno-occlusive mechanism. The critical property allowing for such a significant increase in blood flow is rooted in the capacity for relaxation of the small cavernous arteries (helicine arteries), which enables them to delete by about 80%. This significantly surpasses the abilities of other vessels, which can only delete by about 15% (1). We present the following

article on the role of testosterone measurement diagnosing hypogonadism during low energy shock wave therapy for erectile dysfunction (ED) in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tau-20-796).

Importance of testosterone for sexual performance

Testosterone also has an impact on an erection. It increases penile rigidity and prolongs erectile response. It stimulates libido, arousal, orgasm and sexual satisfaction. The concentration of testosterone is associated with nocturnal penile tumescence, which serves as a specific exercise to maintain the fitness of erectile tissue. The lack of nocturnal penile tumescence results in an increased production of endothelin 1 (a strong vasoconstrictor), apoptosis, as well as long-term hypoxia, which leads to the loss of smooth muscles, an increase in collagen synthesis, and to fibrosis within the corpora cavernosa (2). Next, testosterone participates in the maturation of penile tissue by promoting the commitment of mesenchymal pluripotent cells into myogenic lineage and inhibiting their differentiation into adipogenic lineage (3). Moreover, testosterone stimulates perineal muscles anatomically connected to the corpora cavernosa. This helps creating and maintain a higher pressure than this in large arteries and securing proper function of the veno-occlusive mechanism.

The mechanism of action of testosterone is linked to vascular endothelium, where it regulates the production of nitric oxide through the stimulation of nitric oxide synthase (NOS) and the formation of cyclic guanosine monophosphate (cGMP). In the case of a low testosterone concentration, abnormal relaxation of smooth muscles and corpora cavernosa occurs. An opposite, catabolic role of testosterone regulates the expression and activity of phosphodiesterase-5 (PDE5) and hydrolytic enzymes engaged in the degradation of cGMP (4).

Deterioration of the overall and sexual condition of men with age was for the first time linked to testosterone by Heller and Meyers in 1944. In men, a decrease in plasma concentration is constant and amounts to about 1.4% per year (5). Unlike other endocrine diseases defined by abnormal hormone concentrations, androgen insufficiency requires specific symptoms to occur, with sexual disorders being the most important. The European Male Aging Study conducted examinations on 3,369 men aged between 40–79 years and revealed that nine symptoms are associated with the concentration of total or free testosterone. They include three main disorders of sexual health (less morning erections, less sexual thoughts, and ED); three symptoms characteristic of physical fitness [limited of physical activity (e.g., running, ability to lift heavy objects, participation in endurance sports and inability to walk more than 1 km], and difficulty kneeling, bending and skewing; and three psychological symptoms (decrease in energy, pessimism and fatigue) (6). A higher risk of sexual health disorders and reduced physical fitness correlates with a testosterone concentration of 8–13 nmol/L (2.3–3.7 ng/mL) for total testosterone, and 160–280 pmol/L (46–81 pg/mL) for free testosterone. Based on the analysis of results of men seeking sexological help, Rastrelli *et al.* determined two thresholds—below 20 nmol/L the probability of the occurrence of sexual insufficiency rises, while above 38 nmol/L, this probability is almost equal to zero (7).

According to the European Association of Urology (EAU), plasma testosterone concentrations <8 nmol/L are considered abnormally low and require substitution. For higher concentrations, the relationship between circulating testosterone and sexual performance is very low. According to the British Society for Sexual Medicine, men with total testosterone that is consistently lower than 8 nmol/L (free testosterone <0.18 nmol/L) usually require treatment, while those with total testosterone of <12 nmol/L (free testosterone <0.225 nmol/L) may be offered a 6-month trial of testosterone replacement therapy. According to the American Urological Association, a testosterone concentration should be checked in all men with ED in order to determine if testosterone deficiency, defined as a total testosterone level of <300 ng/dL along with hypogonadism symptoms, occurs. Additionally, men with ED and testosterone deficiency, who are considering treatment for ED with PDE5 inhibitors, should be informed that these drugs may be more effective if combined with testosterone therapy. However, many authors identify higher testosterone thresholds with libido loss and a decrease in sexual arousal (above 15 nmol/L). Rastrelli *et al.* use a threshold of 20 nmol/L, which is twice as high as that stated in official recommendations (7). Additionally, an increased concentration of luteinising hormone (LH) with a concentration of testosterone of <15 nmol/L may suggest late-onset hypogonadism (LOH). The term referring to the individual norm of testosterone concentration is returning and is defined as a typical individual value that

guarantees well-being for a particular man. Sensitivity to testosterone varies from person to person; the degree of the decrease in plasma testosterone concentration is a better predictor of LOH then the current total and bioavailable testosterone (8). A probable drop in testosterone receptor sensitivity in the central nervous system can explain both a reduction in sexual arousal of ageing men and the need to increase the dose of testosterone during the treatment of hypogonadism.

Low energy shock-wave therapy (LESWT) for ED

One of the treatments of ED that attracts great attention is LESWT. This method, despite the lack of precise recommendations due to limited data on its long-term safety and effectiveness, was included in 2013 and maintained in the newest issue of EAU guidelines. However, evidence on its efficacy in the treatment of ED is growing. ED mainly affects men over 50 years of age and is associated with vascular disorders. Many reports have documented that LESWT stimulates and activates the release of angiogenic factors that promote tissue neovascularisation, and as a result improve blood supply. Young and Dyson observed higher dynamics of formation of new blood vessels exposed to ultrasound during the early stage of healing of skin lesions in adult rats (9). The study by Nishida *et al.* on a porcine model of chronic myocardial ischemia showed a significant improvement in regional blood flow through myocardium treated with shock wave therapy for four weeks (9 spots; 200 shots per spot, 0.09 mJ/mm^2) in comparison to the control group without treatment (10). Nishida *et al.* reported that exposure to shock waves leads to a significant overexpression of the mRNA of strong angiogenesis ligands, e.g., vascular endothelial growth factor (VEGF) along with its Flt-1 receptor (VEGFR-1) and protein expression in human umbilical vein endothelial cells (HUVECs) *in vitro*, as well as the production of VEGF in the ischemic myocardium in animal models *in vivo* (10). Exposure of tissues from a healthy and ischaemic myocardium to LESWT *in vitro* promotes proliferation and differentiation of endothelial cells, an increase in the number of mature endothelial cells and those engaged in angiogenesis, as well as an increase in the number of primary cardiomyocytes and smooth muscle cells. More obvious effects were obtained for cells taken from a healthy heart than from an ischemic heart (10). Moreover, two different mechanisms promoting the production of NO during exposure to shock waves were described; enzymatic, based on the increased expression of endothelial NOS, and non-enzymatic, requiring the presence of L-arginine and hydrogen peroxide molecules.

Targeted literature review

We conducted a targeted literature review of studies which exclusively examined the efficacy of LESWT in various group of patients or compared LESWT to sham protocol in the treatment of ED. We used combinations of the following key words: erectile dysfunction and low energy shock wave treatment. No specific timeframe, geographical scope or language restrictions were applied. The search in PubMed and Embase via Ovid was run on in January 2020. Our review showed that the majority of studies on the efficacy of this method did not provide any information on the current testosterone concentration, or only excluded patients with hormonal deprivation of hormonal disorders. However, all those patients suffered from a key symptom of hypogonadism, which is ED. Only 8 of 25 studies examined and showed values of testosterone concentrations (*Table 1*). Interestingly, testosterone levels were more often provided for cohorts treated with PDE5i likely due to the recommendation to check testosterone status when pharmacotherapy is not effective. Therefore, the question arises of which symptoms of hormonal disorders were used as exclusion criteria from these trials. A significant percentage of patients included in these studies was burdened with cardiovascular disease (CVD) or CDV risk factors that intensify a physiological drop in the testosterone concentration in men (41). Only one of these analyses checked the relationship between the efficacy of LESWT and testosterone concentration; however, the study group was small (n=20) and heterogeneous. As a result, meta-analyses published to date may not show the full value of LESWT in the treatment of ED.

Taking into account the testosterone mechanism of action, the evidence of its benefit in patients with ED who are not-responders to PDE5 inhibitors, and the vascular mode of action of LESWT, we recommend including systematic, standardized diagnostics of hypogonadism and performing analysis on testosterone concentration and LESWT efficacy into further studies on this method in the treatment of ED.

Conclusions

In the light of the significant role testosterone plays in the process of an erection and the mechanism of LESWT

Table 1 Characteristics of the studies on LESWT in patients with erectile dysfunction androgen status characteristics in the study population

Study	Study type	Patients in total [sham] group, device	Age median [range]; mean (SD)	Follow-up after the end of LESWT	Evaluation tools for ED	PDE5i treatment status	Testosterone status	Included in meta-analyses
Vardi 2010 (11)	Cohort study	20, ED1000	56.1 (10.7)	1, 3, 6 months	IIEF, EDITS, SEAR, QEQ, RS, NPT, FMD	PDE5i responders. Discontinued PDE5i therapy until the first 1-mo follow-up examination	No data	
Vardi 2012 (12)	RCT	40 [20], ED1000	LESWT 58 [27–72], Sham 57 [35–77]	1, 3 months	IIEF, EHS, FMD	PDE5i responders. Discontinued PDE5i during the entire study period	Patients on hormonal therapy and those with hormonal abnormalities were excluded	Angulo, 2017 (13), Clavijo 2017 (14), Man 2018 (15), Sokolakis, 2019 (16), Zou 2017 (17)
Gruenwald 2012 (18)	Cohort study	29, ED1000	61.3 [41–79]	1, 2 months	IIEF, QEQ, EHS, FMD	Poor responders to PDE5i. Discontinued PDE5-I therapy until the first 1-mo follow-up examination and then active PDE5i medication was started	Patients on hormonal therapy were excluded	Angulo, 2017 (13)
Olsen 2014 (19)	RCT	49 [51], Duolith® SD1	LESWT 59 [41–80], Sham 60 [37–79]	5, 12, 24 weeks	IIEF, EHS	PDE5i responders. Discontinued PDE5i during the entire study period	No data	Angulo 2017 (13), Lu 2017 (20), Sokolakis 2019 (16), Zou 2017 (17)
Reisman 2014 (21)	Cohort study	58, Renova®	56.75 (9.91)	1, 3, 6 months	IIEF, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	PDE5i responders and non-responders. No PDE5i 3 weeks prior to treatment, during shockwave treatment, and until the first follow-up, 1 month post treatments	Patients with hormonal pathology were excluded	Angulo, 2017 (13)
Yee 2014 (22)	RCT	30 [28], ED1000	LESWT 58.9 (7.6), Sham 63.3 (6.4)	1 month	IIEF, EHS	Discontinued PDE5i during the entire study period	Patients with endocrine disease (e.g., hypogonadism) and on androgen deprivation therapy were excluded	Angulo 2017 (13), Clavijo 2017 (14), Lu 2017 (20), Man 2018 (15), Sokolakis 2019 (16)

Table 1 (*continued*)

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Study	Study type	Patients in total [sham] group, device	Age median [range]; mean (SD)	Follow-up after the end of LESWT	Evaluation tools for ED	PDE5i treatment status	Testosterone status	Included in meta-analyses
Chung 2015 (23)	Cohort study	30,	48 [42–68]	6 weeks, 4 months	IIEF, EDITS	PDE5i poor and non-responders. No data on the use of PDE5i during the study	Patients on androgen-deprivation therapy and presenting hormonal abnormalities were excluded	Angulo 2017 (13), Lu 2017 (20)
Hisasue 2015 (24)	Cohort study	56, ED1000	64 [27–83]	1, 3, 6 months	IIEF, EHS, MPCC	On-demand use of PDE5i after LI-SWT was allowed. SRE was checked after 1-week cessation of PDE5i	Free testosterone was 8.1 pg/mL (2.2–14.9)	Angulo 2017 (13), Lu 2017 (20)
Pelayo-Nieto 2015 (25)	Cohort study	15, Renova®	59.6 [45–70]	1, 6 months	IIEF, EHS, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	No data	No data	Angulo 2017 (13), Lu 2017 (20)
Srini 2015 (26)	RCT	95 [40], ED1000	No data	1, 3, 6, 9, 12 months	IIEF, EHS, CGIC, NPT, Penile Doppler	PDE5i responders. Discontinued PDE5i during the entire study period after 4-week washout period	Patients on hormonal therapy and those with hormonal abnormalities were excluded	Angulo 2017 (13), Clavijo 2017 (14), Lu 2017 (20), Man 2018 (15), Sokolakis 2017 (16), Zou 2017 (17)
Bechara 2016 (27)	Cohort study	40, Renova®	Responders 65 [50–82], Non-responders 64.4 [48–82]	1, 3, 6, 9, 12 months	IIEF, EHS, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	PDE5i non-responders. Patients remained on their regular high on-demand or once-daily PDE5i	Patients with untreated hypogonadism were excluded	Angulo 2017 (13), Lu 2017 (20)
Kitrey 2016 (28)	RCT	37 [18], ED1000	LESWT 60 [28–78], Sham 64 [29–81]	1 month	IIEF, EHS, FMD, CGIC	PDE5i non-responders. EF and penile hemodynamics were evaluated on maximal doses PDE5i	Patients with hormonal abnormalities were excluded	Clavijo 2017 (14), Man 2018 (15), Sokolakis 2019 (16), Zou 2017 (17)
Ruffo 2016 (29)	Cohort study	31, Renova®	59.93 (12.16)	1, 3 months	IIEF, SEP-Q2, SEP-Q3, GAQ-Q1, GAQ-Q2	Discontinued PDE5i during the entire study period after 3-week washout period	Patients on anti-androgens were excluded	

Table 1 (*continued*)

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Study	Study type	Patients in total [sham] group, device	Age median [range]; mean (SD)	Follow-up after the end of LESWT	Evaluation tools for ED	PDE5i treatment status	Testosterone status	Included in meta-analyses
Fojecki 2017	RCT	126 [63], FBL10	LESWT 65.4 (7.9), Sham 63.3 (9.5)	9, 19 weeks	IIEF, EHS, SQoL-M, EDITS	Mixed group of responders, non-responders and PDE5i naïve patients. No data on the use of PDE5i during the study	Patients on antiandrogens and with the total testosterone level <8 nmol/dL were excluded. Total testosterone was 14.4 (4.7) in the LESWT group and 13.5 (4.1) in the sham group	Clavijo 2017 (14), Man 2018 (15), Sokolakis 2019 (16)
Ayala 2017 (30)	Retrospective	710, Duolith® SD1	58 [24–83]		EHS	No data	No data	
Tsai 2017 (31)	Prospective cohort study	52, Duolith® SD1	60.1 (11.5)	1 and 3 months	IIEF-5, EHS	PDE5i non-responders. Patients were considered non-responders after being evaluated on maximal doses of PDE5i. During the study, all patients remained on their regular high on-demand or once-daily PDE5i dosing schedules	Patients were enrolled after their hypogonadism was corrected. Testosterone was 501.4±183.6 ng/dL. In 9 patients it was <350 ng/dL	Sokolakis, 2019 (16)
de Oliveira 2018 (32)	Cohort study	25, PiezoWave2	61 [27–73]	3 weeks, 3 months	IIEF, PSV, EDV	PDE5i allowed during the study.	No data.	
Yamaçake 2018 (33)	RCT	10 [10]	LESWT 55.1 [47–60], Sham 52.2 [46–61]	1, 3, 12 months	IIEF-5, EHS, Penile Doppler ultrasound	Discontinued PDE5i during the entire study period after 4-week washout period	Patients with endocrine disease (e.g., hypogonadism) and on androgen deprivation therapy were excluded. The overall testosterone level was 546.2±164.5 mg/dL	Sokolakis, 2019 (16)
Eryilmaz 2019 (34)	Cohort study	40 [20], Duolith® SD1	Unfocused LESWT 45.6, Focused LESWT 44.3	3 months	IIEF, EHS	PDE5i non-responders. No data on the use of PDE5i during the study	The mean testosterone level was 12.85. None of the patients had hypogonadism	

Table 1 (*continued*)

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Study	Study type	Patients in total [sham] group, device	Age median [range]; mean (SD)	Follow-up after the end of LESWT	Evaluation tools for ED	PDE5i treatment status	Testosterone status	Included in meta-analyses
Kim 2019 (35)	RCT	96 [43], MT 2000H	LESWT 63.2 (5.4), Sham 65.1 (7.9)	4, 7 weeks	IIEF, EHS, SEP-Q2, SEP-Q3;	Discontinued PDE5i during the entire study period after 4-week washout period	No data	
Sramkowa 2019 (36)	RCT	60 [30], PiezoWave2	54 [40–70]	4, 12 weeks	IIEF, SEP-Q2, SEP-Q3, EHS, GAQ	All patients were at least partial responders to PDE5i. Discontinued PDE5i during the entire study period after 4-week washout period	Testosterone concentration was measured. Patients with hypogonadism were not excluded. Testosterone concentration in the treated group was 18.1 (5.8) nmol/L and in the sham group was 18.8 (5.7) nmol/L	
Vita 2019 (37)	Prospective cohort study	20, ED1000	58.5 (10.3)	6 weeks or 6+6 weeks in non-responders, 3 months	IIEF-5, EHS, CGIC-I,	PDE5i poor or non-responders. Patients were allowed to maintain their pre-study therapy during the trial	Patients with hypogonadism were excluded. Total testosterone was 15.9 (6.2) nmol/L. Testosterone levels correlated positively with the CGIC-I at multistep linear regression (ß=0.617, P=0.01). Serum testosterone correlated positively with ESH at the bivariate analysis only in non-diabetic patients (r=0.804, P=0.009)	
Costa 2019 (38)	Prospective cohort study	18, Duolith® SD1	61.1 (7.2)	1 and 3 months	IIEF-5, GAQ-Q1	PDE5i poor or non-responders. Discontinued PDE5i during the entire study period after 4-week washout period	Patients with endocrinologic disorder (hypogonadism, hypothyroidism) were excluded	

Table 1 (*continued*)

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Study	Study type	Patients in total [sham] group, device	Age median [range]; mean (SD)	Follow-up after the end of LESWT	Evaluation tools for ED	PDE5i treatment status	Testosterone status	Included in meta-analyses
Musa 2019 (39)	Prospective cohort study	55, Dornier Aries	51 (11.56)	3, 6, 12, 18 months	IIEF-EF, EHS	PDE5i non-responders. Discontinued PDE5i after 1 month washout period, but were allowed after 3 months LESWT treatment for LESWT non-responders	Patients were considered PDE5i non-responders after correction of testosterone levels. Values not given. Hypogonadism was documented but not reported	
Verze 2019 (40)	Matched-pair comparison	78 [78], ED1000	56.0 (9.6), tadalafil 5 mg + LESWT, 58.2 (3.2), tadalafil 5 mg alone	4, 12, 24 weeks	IIEF-5	Patients with diabetes and ED received tadalafil 5 mg once daily bedtime for 12 weeks and LESWT	Patients with hypogonadism were excluded	

CGIC-I, Clinical Global Impression of Change-Improvement Component; ED, erectile dysfunction; EDITS, Erectile Dysfunction Inventory of Treatment Satisfaction; EDV, end-diastolic velocity; EHS, Erectile Hardness Score; FMD, flow-mediated dilatation; GAQ, Global Assessment Question; IIEF, International Index of Erectile Function; NPT, nocturnal penile tumescence; PSV, peak systolic velocity; PDE5i, phosphodiesterase 5 inhibitor; QEQ, Quality of Erection Questionnaire; RS, rigidity score; RCT, randomised controlled trial; SEAR, Self-Esteem and Relationship Questionnaire; SEP, Sexual Encounter Profile; SQoL-M, Sexual Quality of Life Men questionnaire.

action, it can be recommended to examine testosterone concentration and to diagnose hypogonadism during the qualification of patients to studies on LESWT efficacy. Moreover, the effectiveness of LESWT in relation to the current testosterone concentration should also be further investigated. Testosterone check and excluding hypogonadism is important before enrollment to studies on LESWT efficacy.

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Footnote

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