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Original Article: Clinical Investigation

Impact of aging and comorbidity on the efficacy of low-intensity shock wave therapy for erectile dysfunction

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Abbreviations & Acronyms
ED = erectile dysfunction
EHS = erection hardness score
LI-SWT = low-intensity shock wave therapy
MPCC = mean penile circumferential change
NO = nitric oxide
PDE5i = phosphodiesterase type-5 inhibitor
SHIM = sexual health inventory for men
SRE = sleep-related erection
VEGF = vascular endothelial growth factor

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Objectives: To evaluate the efficacy of low-intensity shock wave therapy and to identify the predictive factors of its efficacy in Japanese patients with erectile dysfunction.

Methods: The present study included 57 patients with erectile dysfunction who satisfied all the following conditions: more than 6-months history of erectile dysfunction, sexual health inventory for men score of ≤12 without phosphodiesterase type-5 inhibitor, erection hardness score grade 1 or 2, mean penile circumferential change by erectometer assessing sleep related erection of <25 mm and non-neurological pathology. Patients were treated by a low-energy shock waves generator (ED1000; Medispec, Gaithersburg, MD, USA). A total of 12 shock wave treatments were applied. Sexual health inventory for men score, erection hardness score with or without phosphodiesterase type-5 inhibitor, and mean penile circumferential change were assessed at baseline, 1, 3 and 6 months after the termination of low-intensity shock wave therapy.

Results: Of 57 patients who were assigned for the low-intensity shock wave therapy trial, 56 patients were analyzed. Patients had a median age of 64 years. The sexual health inventory for men and erection hardness score (with and without phosphodiesterase type-5 inhibitor) were significantly increased ($P < 0.001$) at each time-point. The mean penile circumferential change was also increased from 13.1 to 20.2 mm after low-intensity shock wave therapy ($P < 0.001$). In the multivariate analysis, age and the number of concomitant comorbidities were statistically significant predictors for the efficacy.

Conclusions: Low-intensity shock wave therapy seems to be an effective physical therapy for erectile dysfunction. Age and comorbidities are negative predictive factors of therapeutic response.

Key words: erectile dysfunction, low-intensity shock wave therapy, low intensity shock wave treatment, predictive factor.

Introduction

PDE5i revolutionized the treatment of ED.[1,2] The drug has been well accepted internationally, and its efficacy is as high as 70–80%.[1,3] PDE5i is reported to be highly effective for achieving sufficient erection for sexual intercourse in vasculogenic ED patients, which is the most prevalent type of ED among middle-aged men, although more than 10% of patients are refractory to the treatment.[4] Diabetic ED is less responsive to PDE5i, and it depends on the severity. Of patients with two or more complications of diabetes, just 43% responded to PDE5i.[5] To date, vacuum device, intracavernous injection and prosthesis remain the second- or third-line treatment for patients with poor response, or contraindication, to PDE5i.[6] However, these treatments are relatively invasive, and discontinuation rates are high.

Extracorporeal shock wave therapy, first applied to urolithiasis of the upper urinary tract, is a common procedure in the urological field.[7] It was subsequently introduced into the orthopedic and cardiovascular disciplines to treat soft tissue musculoskeletal conditions and ischemic coronary artery disease, respectively.[8,9] The mechanism underlying the efficacy of shock wave for the ischemic heart disease is vasodilation and angiogenesis.[8] Recently, the application of LI-SWT has been introduced as a novel effective treatment for ED.[10,11] The first randomized

controlled trial showed an excellent superiority to placebo; 61% of trial group patients achieved sufficient erection for penetration.[12] Yet, we do not know the predictive factors for the efficacy of LI-SWT for ED. The goal of the present study was to assess the feasibility and efficacy of LI-SWT and the predictive factors for the treatment success of LI-SWT for Japanese patients with ED.

Methods

The present study was a prospective, non-randomized, single-arm study. We enrolled ED patients at the outpatient clinic of Teikyo University Hospital, Tokyo, Japan. Enrolment criteria included an ED history of at least 6 months, SHIM score of ≤12 s, EHS of 1 or 2 and MPCC measured by the erectometer with at least three nights of SRE of ≤25 mm. We excluded patients with penile deformities and/or prior penile surgeries. We defined the patients' comorbidities as "comorbidities for which the patients need to take any medications." The status of all patients' comorbidity was stable and well controlled with these medications. All baseline assessments other than EHS and SHIM with PDE5i were taken after 1-month cessation of PDE5i. Technically speaking, we asked the patients to answer the questionnaires and bring them back at the next visit (usually over 1 month). The answers should be based on the status with sufficient duration over 1 month from the last PDE5i administration, especially for the SRE. We excluded the patients with neurogenic pathology, such as patients with prior radical pelvic surgeries or patients with severe diabetes that required insulin injection.

Patients were treated by a low-energy shock waves generator (ED1000, Medispec, Gaithersburg, MD, USA). LI-SWT was applied on five penile sites – three sites on the penile shaft and on both crura – with 300 shock waves (0.09 mJ/mm^2) for 3 min each (a frequency of 120 shocks/min). Treatment was delivered on only one side of the penile shaft, as shock wave depth reached both corpora. The 9-week treatment period was divided into three 3-week periods. We carried out LI-SWT twice-weekly during the first and third periods, with no treatment during the interim 3-week period, as reported by Vardi *et al.*[10]

We assessed the patients with SHIM, EHS, and MPCC at baseline, 1, 3 and 6 months after the final LI-SWT. We allowed patients on-demand use of PDE5i after LI-SWT; however, SRE was checked after 1-week cessation of PDE5i. We asked patients to complete the questionnaires (EHS and SHIM), and check the SRE without the use of PDE5i at each time-point. We did not force patients to have sexual intercourse or to take PDE5i during the study period; rather, we them instructed to have any kind of sexual activity including masturbation at any time-point with or without PDE5i. The current study was approved by the Teikyo University institutional review board (no. 10-076). All participants provided written informed consent to participate in the present study. The institutional review board also approved the consent procedures.

We used JMP 11.0 (SAS Institute, Cary, NC, USA) for statistical analyses. We used Student's *t*-test to assess the improvement of erectile function in SHIM score, EHS score and MPCC. Logistic regression analysis was carried out for the multivariate analysis on the efficacy of LI-SWT using the parameters of age, free testosterone level, body mass index, ED history, baseline MPCC and comorbidities.

Results

We assessed available post-treatment data from 56 of 57 patients. One patient was excluded, as liver cancer was found during the treatment course. Patient characteristics are shown in Table 1. Comorbidities included hypertension in 21, diabetes in 10, ischemic heart disease in five and hyperlipidemia in 13 patients.

Both subjective and objective erectile function after LI-SWT are shown in Figure 1. Subjective erectile function indicators, such as SHIM score and EHS, are shown with (n = 34) and without (n = 56) PDE5i. Each score showed significant improvement from 1 month after treatment, and it was maintained until 6 months after LI-SWT ($P < 0.05$: Student's *t*-test). Overall, 36 patients (64.2%) showed improvement in SHIM scores, and 32 patients (57.1%) achieved an EHS 3 or 4 without PDE5i within 6 months after LI-SWT. EHS 3 achievement without PDE5i at 1 month after LI-SWT in each subgroup of comorbidities was 7/21 (33.3%) in the hypertension group, 3/10 (30.0%) in the diabetes group, 2/5 (40.0%) in the ischemic heart disease group, 5/13 (38.5%) in dyslipidemia group and 21/30 (70.0%) in the group without any comorbidities. MPCC, as an objective erectile function indicator, also showed significant improvement from 1 month after treatment, maintaining it until 6 months. MPCC showed improvement in 36 patients (64%).

No adverse event was reported during or after LI-SWT. Unlike the higher intensity version used to treat urolithiasis (1.1 mJ/mm^2), the low-intensity shock wave energy (0.09 mJ/mm^2) used in the present study was not associated with any pain or side-effects.

We carried out multivariate analysis to evaluate the predictive factors for LI-SWT efficacy. Logistic regression analyses showed that age and three or more comorbidities were predictive factors for EHS achievement 1 month after LI-SWT (Table 2). We then stratified the patients into four groups: (i)

Table 1 Patient characteristics

n = 56	Median (range)
Median age	64 years (27–83)
BMI	25.0 kg/m^2 (17.9–34.1)
Duration of ED	3 years (0.5–18)
SHIM	5 (1–12)
EHS	1 (1–2)
MPCC	12.8 mm (0–25)
Free testosterone	8.1 pg/mL (2.2–14.9)
Smoking history	
Never/former/current	23/14/19
Comorbidities	
None/hypertension/diabetes mellitus/ischemic heart disease/hyperlipidemia	30/21/10/5/13

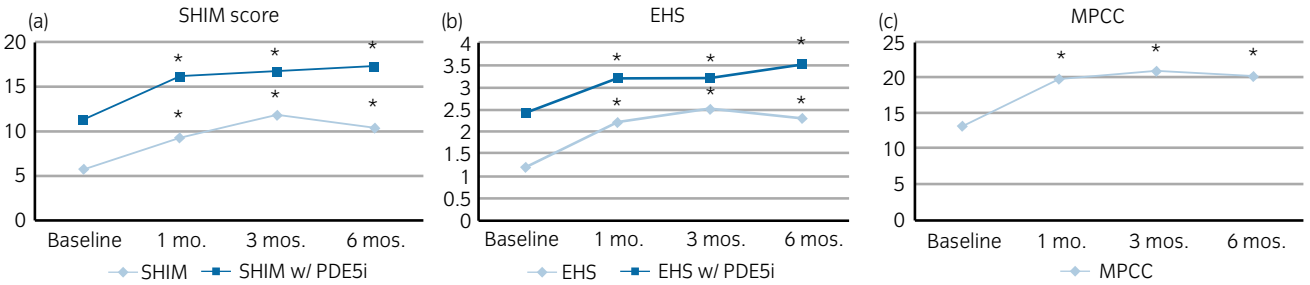

Fig. 1 Subjective and objective erectile function after LI-SWT for (a) SHIM score, (b) EHS and (c) MPCC. SHIM score and EHS are shown with (n = 34) or without (n = 56) PDE5i. *P < 0.05, compared with baseline using Student's t-test. Improvements were shown by (a) 36 patients (64.2%) in SHIM, (b) 32 patients (57.1%) in EHS and (c) 36 patients (64.2%) in MPCC.

Table 2 Logistic regression analysis for prognostic factors for EHS 3 achievement without PDE5i at 1 month after LI-SWT

	OR	95% CI		*P*-value
Age†	0.854	0.760	−0.952	0.0046
Free testosterone†	0.811	0.571	−1.152	0.2417
BMI†	1.261	0.928	−1.714	0.1389
ED history†	1.142	0.911	−1.431	0.2493
Baseline MPCC†	1.146	0.993	−1.322	0.0624
No. comorbidities (≤2 *vs* ≥3)	0.023	0.001	−0.975	0.0484

†Continuous.

patients aged <65 years with ≤2 comorbidities; (ii) patients aged <65 years with ≥3 comorbidities; (iii) patients aged ≥65 years with ≤2 comorbidities; and (iv) patients aged ≥65 years with ≥3 comorbidities (Fig. 2). Only those aged <65 years with ≤2 comorbidities showed significant improvement in each parameter (SHIM, EHS and MPCC) at 1 month and 6 months. In EHS, patients aged ≥65 years with ≤2 comorbidities showed significant improvement only at 1 month after LI-SWT.

Discussion

In the current study, we set out to determine the feasibility and efficacy of LI-SWT on ED, and to assess predictive factors for such efficacy in ED patients in Japan. Vasodilation and angiogenesis of the corpus cavernosum are proposed mechanisms of LI-SWT on erectile function recovery. Shock waves induce shear stress, which induces various cytokine releases, such as NO and VEGF.[13–16] Shock wave forms NO non-enzymatically, and enhances the expression of VEGF and its receptor Flt-1.[13,15] Wang *et al.* reported that shock wave therapy produced a significantly higher number of neovessels and angiogenesis-related markers including endothelial NO synthase, VEGF and proliferating cell nuclear antigen than the control without shock wave treatment.[14]

Shock wave treatment has been applied to many clinical problems related to ischemia or low arterial perfusion. It has effectively reversed ischemia-elicited left ventricular dysfunction in miniature pigs,[17] and has activated cardiac stem cells and myocardial regeneration.[18] Recently, several randomized controlled trials showed the efficacy of shock wave treatment in coronary artery disease,[19–23] and neurogenic results have been reported to supplement these vasculogenic effects.[24] Shock wave treatment is less invasive and safer compared with conventional treatments, such as surgery, and it is easily applied to highly compromised patients with severe comorbidities.

Vardi *et al.* first reported their first land-mark pilot study of LI-SWT for relatively mild ED.[10] Their subsequent study confirmed LI-SWT efficacy for more severe ED, which was refractory to PDE5i.[11] Their third report, using a randomized controlled trial, was carried out using a sham probe without shock waves. Shock wave treatment showed a significant improvement in International Index of Erectile

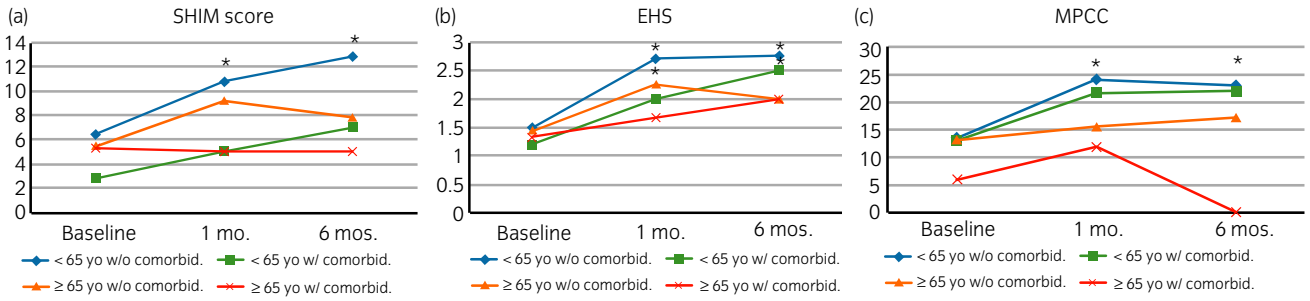

Fig. 2 Subjective and objective erectile function without PDE5i stratified with age and comorbidity status for (a) SHIM score, (b) EHS and (c) MPCC. *P < 0.05, compared with baseline using Student's t-test. SHIM score and EHS are shown with (w/; n = 34) or without (w/o; n = 56) PDE5i. Patients with two or fewer comorbidities were categorized as without comorbidities, whereas those with three or more comorbidities were categorized as with comorbidities.

Function-Erectile Function domain score compared with the sham probe. In a preclinical study, shock wave treatment improved intracavernous pressure in diabetic ED rat models.[25] LI-SWT can ameliorate diabetic ED by regenerating neuronal nitric oxide synthase-positive nerves, and increasing endothelium and smooth muscle content in the corpus cavernosum. The authors concluded that these beneficial effects appear to be mediated by recruitment of endogenous mesenchymal stem cells.[25]

The current study clearly showed that fewer comorbidities and a younger age are important positive predictors for LI-SWT efficacy. Vardi *et al.* reported the treatment outcome of LI-SWT for both mild and severe ED.[10,11] LI-SWT increased the International Index of Erectile Function-Erectile Function domain score from 13.5 to 20.9 (Δ7.4) for mild ED,[10] and from 8.8 to 12.3 (Δ3.5) for a severe ED.[11] It is apparent that ED severity influences LI-SWT treatment efficacy. Severity of ED is associated with comorbidities, such as hypertension, diabetes, hyperlipidemia and coronary artery diseases.[26] Therefore, the outcome of the present study suggests that concurrent comorbidity is a negative factor for the efficacy of LI-SWT.

Aging is also related to ED severity, and might be responsible for cytokine release through LI-SWT. Indeed, the angiogenic and neurogenic response to VEGF stimulation is attenuated in the aged mouse brain as a result of reduced VEGF receptor activity.[27] This suggests that younger age is also an enhancing factor for the clinical response of LI-SWT through angiogenic cytokines inducing vasodilation and angiogenesis. Thus, efficacy is deteriorated in elderly patients.

The outcome analysis for ED should always be carried out excluding the contamination of psychogenic factors and the placebo effect. Rigiscan is the gold standard to assess SRE; however, we previously confirmed the significant correlation between the erectometer and Rigiscan. Therefore, the erectometer enables us to assess objective erectile function easily and quantitatively.[28] In the current study, MPCC (reflecting SRE) was significantly improved, and it was also affected by age and concurrent comorbidities. Testosterone level largely influences SRE;[29] however, there was no significant change in free testosterone level after LI-SWT (data not shown). Indeed, MPCC using the erectometer added the reliable consequence of LI-SWT efficacy to this study.

The most prominent limitations of the present study were the lack of a placebo controlled arm and the relatively low number of participants, although the efficacy was confirmed in a previous placebo controlled study.[12] Furthermore, we did not carry out a hemodynamic assessment of the corpus cavernosum using, for example, the flow mediated dilation, which was carried out by Vardi *et al.*[10] In the current study, we excluded patients with prior pelvic surgeries or severe diabetes that can induce neurogenic ED. In future, we should investigate the efficacy of LI-SWT on neurogenic ED rather than vasculogenic ED. The present study successfully showed the effectiveness, even in the small number of patients; however it will still be necessary to confirm the results in large number of ED patients in the future. A future study should also confirm the effect of age and comorbidities on LI-SWT efficacy in a large-scale randomized controlled trial with validated hemodynamic assessment.

We reported the initial outcome of LI-SWT for ED in Japan and the predictors for its generalized efficacy on ED. LI-SWT is safe and effective treatment for ED, and could be carried out in the office for outpatients without any adverse events. The future indication of LI-SWT for ED patients might include first-line therapy and salvage therapy for PDE5i refractory patients. The present study showed that LI-SWT could treat approximately 60% of moderately mild ED patients as the first-line treatment. Gruenwald *et al.* showed the possibility of salvage treatment for more severe ED patients. LI-SWT will enhance the efficacy of PDE5i for those who hardly respond to PDE5i alone.[11] As the first-line treatment, younger age and less comorbidity were predictive factors for LI-SWT efficacy, and ED patients aged 65 years or younger with two or fewer comorbidities were found to be good candidates for LI-SWT.

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Conflict of interest

None declared.

References

1 Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. *N. Eng. J. Med.* 1998; **338**: 1397–404.
2 Yasuda M, Ide H, Furuya K *et al.* Salivary 8-OHdG: a useful biomarker for predicting severe ED and hypogonadism. *J. Sex. Med.* 2008; **5**: 1482–91.
3 Carson CC, Burnett AL, Levine LA, Nehra A. The efficacy of sildenafil citrate (Viagra) in clinical populations: an update. *Urology* 2002; **60**: 12–27.
4 Kobayashi K, Hisasue S, Kato R *et al.* Outcome analysis of sildenafil citrate for erectile dysfunction of Japanese patients. *Int. J. Impot. Res.* 2006; **18**: 302–5.
5 Carson CC 3rd. Sildenafil: a 4-year update in the treatment of 20 million erectile dysfunction patients. *Curr. Urol. Rep.* 2003; **4**: 488–96.
6 Smith IA, McLeod N, Rashid P. Erectile dysfunction – when tablets don't work. *Aust. Fam. Physician* 2010; **39**: 301–5.
7 Chaussy C, Schmiedt E, Jocham D, Brendel W, Forssmann B, Walther V. First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. *J. Urol.* 1982; **127**: 417–20.
8 Furia JP, Rompe JD, Cacchio A, Maffulli N. Shock wave therapy as a treatment of nonunions, avascular necrosis, and delayed healing of stress fractures. *Foot Ankle Clin.* 2010; **15**: 651–62.
9 Ito K, Fukumoto Y, Shimokawa H. Extracorporeal shock wave therapy for ischemic cardiovascular disorders. *Am. J. Cardiovasc. Drugs* 2011; **11**: 295–302.
10 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.
11 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.
12 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.
13 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.
14 Wang CJ, Wang FS, Yang KD *et al.* Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. *J. Orthop. Res.* 2003; **21**: 984–9.
15 Nurzynska D, Di Meglio F, Castaldo C *et al.* Shock waves activate in vitro cultured progenitors and precursors of cardiac cell lineages from the human heart. *Ultrasound Med. Biol.* 2008; **34**: 334–42.
16 Holfeld J, Zimpfer D, Albrecht-Schgoer K *et al.* Epicardial shock-wave therapy improves ventricular function in a porcine model of ischaemic heart disease. *J. Tissue Eng. Regen. Med.* 2014; doi: 10.1002/term.1890.
17 Fu M, Sun CK, Lin YC *et al.* Extracorporeal shock wave therapy reverses ischemia-related left ventricular dysfunction and remodeling: molecular-cellular and functional assessment. *PLoS ONE* 2011; **6**: e24342.
18 Di Meglio F, Nurzynska D, Castaldo C *et al.* Cardiac shock wave therapy: assessment of safety and new insights into mechanisms of tissue regeneration. *J. Cell Mol. Med.* 2012; **16**: 936–42.
19 Leibowitz D, Weiss AT, Rott D, Durst R, Lotan C. The efficacy of cardiac shock wave therapy in the treatment of refractory angina: a pilot prospective, randomized, double-blind trial. *Int. J. Cardiol.* 2013; **167**: 3033–4.
20 Schmid JP, Capoferri M, Wahl A, Eshtehardi P, Hess OM. Cardiac shock wave therapy for chronic refractory angina pectoris. A prospective placebo-controlled randomized trial. *Cardiovasc. Ther.* 2013; **31**: e1–6.
21 Wang Y, Guo T, Ma TK *et al.* A modified regimen of extracorporeal cardiac shock wave therapy for treatment of coronary artery disease. *Cardiovasc. Ultrasound* 2012; **10**: 35.
22 Assmus B, Walter DH, Seeger FH *et al.* Effect of shock wave-facilitated intracoronary cell therapy on LVEF in patients with chronic heart failure: the CELLWAVE randomized clinical trial. *JAMA* 2013; **309**: 1622–31.
23 Yang P, Guo T, Wang W *et al.* Randomized and double-blind controlled clinical trial of extracorporeal cardiac shock wave therapy for coronary heart disease. *Heart Vessels* 2013; **28**: 284–91.
24 Mense S, Hoheisel U. Shock wave treatment improves nerve regeneration in the rat. *Muscle Nerve* 2013; **47**: 702–10.
25 Qiu X, Lin G, Xin Z *et al.* Effects of low-energy shockwave therapy on the erectile function and tissue of a diabetic rat model. *J. Sex. Med.* 2013; **10**: 738–46.
26 Lee RK, Chughtai B, Te AE, Kaplan SA. Sexual function in men with metabolic syndrome. *Urol. Clin. North Am.* 2012; **39**: 53–62.
27 Gao P, Shen F, Gabriel RA *et al.* Attenuation of brain response to vascular endothelial growth factor-mediated angiogenesis and neurogenesis in aged mice. *Stroke* 2009; **40**: 3596–600.
28 Suzuki K, Sato Y, Horita H *et al.* The correlation between penile tumescence measured by the erectometer and penile rigidity by the RigiScan. *Int. J. Urol.* 2001; **8**: 594–8.
29 Corona G, Rastrelli G, Balercia G *et al.* Perceived reduced sleep-related erections in subjects with erectile dysfunction: psychobiological correlates. *J. Sex. Med.* 2011; **8**: 1780–8.