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Original Article

Efficacy of testosterone replacement therapy plus alternate-day tadalafil for patients with late-onset hypogonadism: An open-label, randomized, crossover study

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Abbreviations & Acronyms
AMS = Aging Male Symptoms scale
BMI = body mass index
BPH = benign prostatic hyperplasia
CoT = combination treatment
ED = erectile dysfunction
IPSS = International Prostate Symptom Score
IQR = interquartile range
LOH = late-onset hypogonadism
LUTS = lower urinary tract symptoms
m-IIEF-5 = modified short version of the International Index of Erectile Function
OABSS = Overactive Bladder Symptom Score
PDE5 = phosphodiesterase type 5
PSA = prostate-specific antigen
TRT = testosterone replacement therapy

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Objective: To examine the efficacy and safety of combination treatment with testosterone replacement therapy plus alternate-day tadalafil (10 mg) in patients with late-onset hypogonadism.
Methods: In this open-label, randomized, crossover study, 29 patients with late-onset hypogonadism were randomly assigned to receive testosterone replacement therapy for 12 weeks followed by combination treatment for 12 weeks (Group 1) or combination treatment for 12 weeks followed by testosterone replacement therapy (Group 2). Symptom questionnaires were administered and blood tests were performed prior to and following each treatment to assess safety and efficacy. At the end of the study, participants were asked about their treatment preferences.
Results: An adverse effect, a rheum symptom, occurred in only one participant, and 26 participants completed the study without any toxicity. Scores on the Aging Male Symptoms scale and the modified short version of the International Index of Erectile Function, and Overactive Bladder Symptom Score were significantly improved in the combination treatment phase of Group 2, whereas no significant difference between the phases were observed in Group 1. In total, 12 out of the 14 participants in Group 1 and 11 out of the 12 participants in Group 2 preferred combination treatment, which reached statistical significance ($P = 0.008$ and 0.004 for Groups 1 and 2, respectively).
Conclusions: Testosterone replacement therapy with add-on alternate-day tadalafil is a safe and satisfactory treatment for patients with late-onset hypogonadism.

Key words: combination treatment, hypogonadism, intramuscular injection, tadalafil, testosterone.

Introduction

Patients with LOH display reduced sexual desire, dysuria, ED, and urinary frequency.[1–3] The main treatment for LOH is TRT. Meanwhile, PDE5 inhibitors, such as sildenafil and tadalafil, are employed extensively for treating ED,[4,5] and daily tadalafil (5 mg) is a primary therapeutic approach for LUTS in patients with BPH in Japan.[6,7] PDE5 inhibitors cause smooth muscle cell relaxation in the prostate, urethra, bladder neck, and blood vessels,[8] and daily tadalafil therapy is reported to improve vascular endothelial function,[9] suggesting its utility as an anti-aging agent in older men.[10] In addition, previous reports have shown that daily tadalafil treatment increased serum testosterone levels,[11] and the combination of daily tadalafil and injectable testosterone undecanoate improved erectile function.[12] Thus, tadalafil can potentially increase the efficacy of TRT, thereby enhancing patient satisfaction. The aim of the present study was to investigate the efficiency and safety of CoT with alternate-day tadalafil (10 mg) and TRT in comparison with TRT alone.

Methods

The Ethics Committee of the Kyoto Prefectural University of Medicine approved this open-label, randomized, crossover study (Clinical trial number RBMR-C-1252). All the patients involved in the study provided written informed consent prior to any procedures. The inclusion criteria were as follows: diagnosis of LOH (serum free testosterone level ≤11.8 pg/mL or

total testosterone level ≤3 ng/mL) and AMS score ≥27 at the initial visit.[13] The exclusion criteria were as follows: sleep apnoea syndrome, liver dysfunction, moderate or advanced BPH (measured by transabdominal ultrasonography), breast cancer, prostate cancer, polycythemia, severe kidney dysfunction, uncontrollable abnormal cardiac rhythm, hypertension (blood pressure at rest >170/100 mmHg) or hypotension (blood pressure <90/50 mmHg), congestive heart failure, retinitis pigmentosa, use of anticoagulants or nitric acid preparations, serum PSA levels ≥4 ng/mL, or a history of cardiac infarction within 3 months, cerebral stroke within 6 months, or cardiovascular dysfunction that disturbs sexual practice. The discontinuation criteria were as follows: participants declining treatment continuation, withdrawal of agreement to participate in the study, or occurrence of unendurable adverse events. The scheduled duration of this study was set for 5 years.

Study design

All participants were screened by the study coordinator and all those meeting the inclusion criteria were randomly divided into two separate groups via simple randomization using a random number table.

For the present study, we chose a crossover design as follows: Group 1: TRT followed by CoT; Group 2: CoT followed by TRT.

The flow of this trial is presented in Figure 1. Briefly, the duration of the study treatment period of each patient was 24 weeks, and a two-phase treatment design was employed. In the TRT phase, participants received an intramuscular injection of 250 mg testosterone enanthate every 3 weeks over a period of 12 weeks. In the CoT phase, patients received an intramuscular injection of 250 mg testosterone enanthate every 3 weeks and alternate-day treatment with oral tadalafil (10 mg) for 12 weeks. For patients previously treated with TRT, treatment was stopped before the trial for 6 weeks as a washout period. The baseline assessment consisted of age, history of TRT, underlying diseases (e.g. diabetes, hypertension, and hyperlipidemia), BMI, smoking and drinking status. Questionnaires to assess symptoms such as the AMS, the m-IIEF-5, which included score 0 as never having sexual intercourse or stimulation, the IPSS, and the OABSS were completed at baseline as well as at the end of each intervention phase to determine the efficiency of each intervention. Biochemical tests including hemoglobin, total bilirubin, PSA, hematocrit, total testosterone, and free testosterone measurements were performed both at baseline and also after each intervention phase to assess the efficiency and safety of each intervention. The biochemical tests were examined at the time of participants' hospital visit, and the blood sampling time was not consistent. At the end of this trial, participants were asked "Which treatment did you prefer?" by the coordinating doctor, and selected their preferred treatment between TRT and CoT.

Outcomes

The primary outcome was whether CoT was superior to TRT as judged by patient preference in each group. The secondary outcomes were the efficacy and safety of CoT versus TRT.

Statistical analysis

Results from baseline measurements of Groups 1 and 2 were compared, using the chi-squared test for qualitative data. Quantitative data were tested for normality. Data with normal distribution were analyzed using Student's *t*-test, and the Mann–Whitney *U*-test was used for non-normally distributed data.

Intraindividual differences in biochemical measurements between the two phases of treatment (crossover differences) in each group were examined for normal distribution. A *t*-test was used to analyze data with normal distribution, and Wilcoxon's signed-rank test was used for data without normal distribution. Intraindividual differences in questionnaire responses between baseline and after each phase were determined using Wilcoxon's signed-rank test. In each group, the differences in treatment choice were ascertained statistically with the chi-squared goodness-of-fit test.

Results were considered statistically significant at the $P < 0.05$ level. All results are shown as median (IQR) values. Statistical tests were conducted using Statcel 4 software (OMS Publishing Ltd., Tokyo, Japan) for Microsoft Excel.

Results

Twenty-nine patients diagnosed with LOH were enrolled in this study between 13 December 2013 and 16 May 2018. Of 29 patients, 26 had been diagnosed with LOH before the study, and their median (IQR) duration of TRT was 18 (10–30.8) months. The first phase was completed by 27 patients, and the second phase was completed by 26 patients. One patient withdrew of his own volition in phase 1, one patient was lost to follow-up in phase 2, and one patient was unable to complete this study because of an adverse reaction to tadalafil (rheum symptom). In the outcome analysis, 26 participants were included (Fig. 2). Table 1 summarizes the baseline characteristics of each group. Testing of free testosterone levels could not be examined in our institution between February 2015 and February 2016. Therefore, two participants in Group 1 and four participants in Group 2 did not undergo free testosterone tests at baseline, and we excluded their free testosterone data from the analysis. BMI ($P = 0.04$), total bilirubin levels ($P = 0.004$), and free testosterone levels ($P = 0.03$) were significantly higher in Group 2 than Group 1. No significant differences were seen between the groups regarding age, history of TRT, drinking and smoking status, previous disease history (diabetes, hypertension, and hyperlipidemia), AMS score, m-IIEF-5 score, IPSS, OABSS, or creatinine, hemoglobin, PSA, hematocrit and total testosterone levels. The scores from symptom questionnaires and results from biochemical analyses in the treatment phases for each group are presented in Table 2.

When analyzing the symptom questionnaires, the AMS score ($P = 0.004$), m-IIEF-5 score ($P = 0.02$), and OABSS ($P = 0.02$) were improved significantly in the CoT phase in Group 2, whereas no differences were noted in Group 1.

Similarly, with regard to AMS subscores, somatic ($P = 0.006$) and sexual domain scores ($P = 0.03$) were

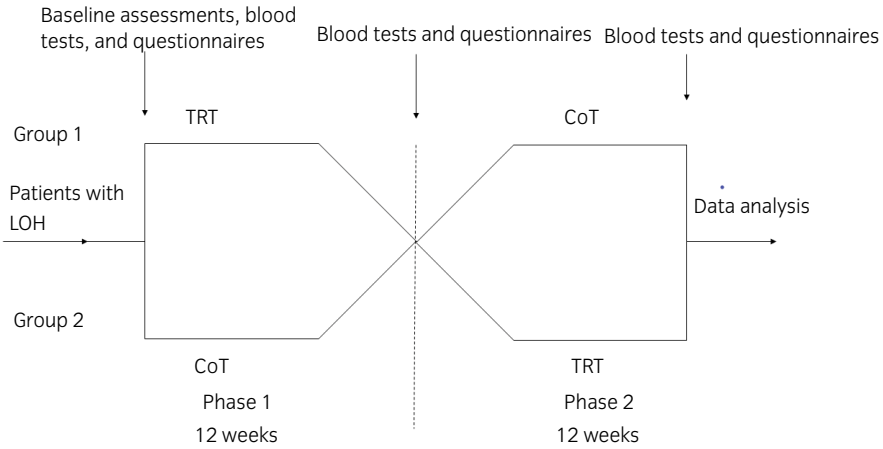

Fig. 1 The flow diagram of this trial. TRT was administered to LOH patients in Group 1, via intramuscular injection every 3 weeks for 12 weeks in phase 1. Subsequently, they received TRT with add-on alternate-day tadalafil (10 mg) as CoT in phase 2. The treatment order was reversed in Group 2. Questionnaire responses and blood samples were obtained at baseline and after each treatment phase.

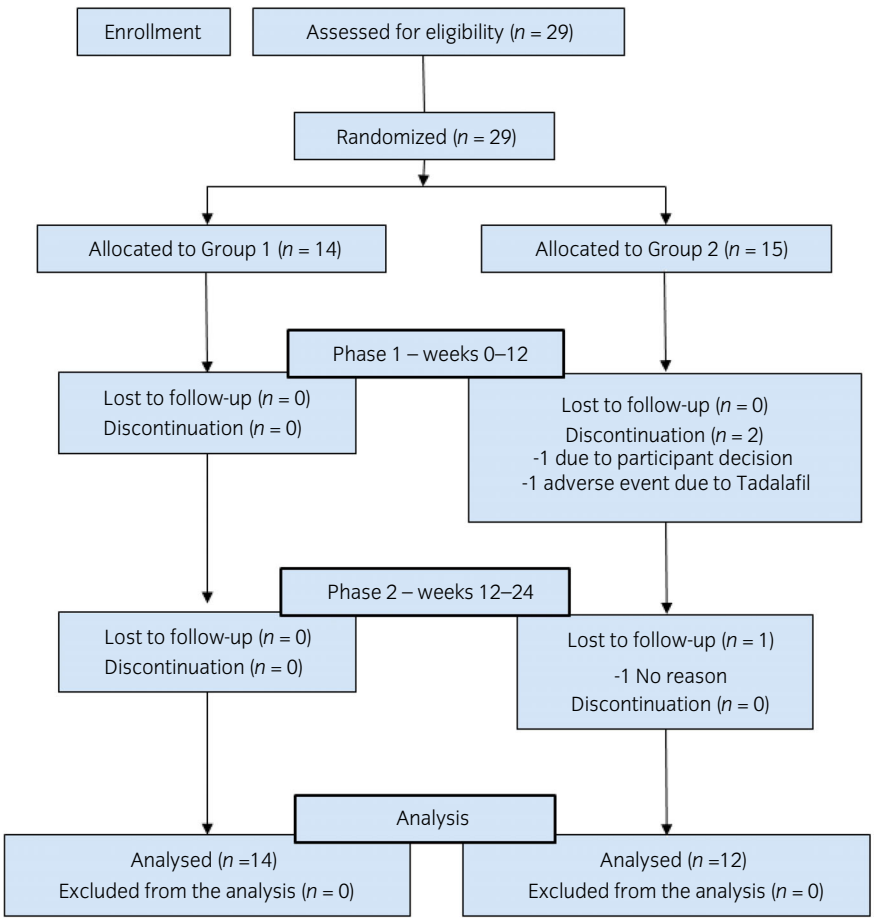

Fig. 2 The CONSORT flow diagram of this trial. Twenty-nine LOH patients were recruited. We randomized patients into two groups (Groups 1 and 2): the first phase was completed by 27 patients, and the second phase was completed by 26 patients. We included the latter in the outcome analysis.

improved significantly in the CoT phase in Group 2, but not in Group 1.

No significant differences were observed between the CoT and TRT phases with regard to IPSS or total bilirubin, creatinine, hemoglobin, hematocrit, PSA, total testosterone, and free testosterone levels in either group.

The sequential changes of symptom questionnaire scores and free or total testosterone levels of each group are shown in Figure 3. AMS scores and OABSSs were lower in the CoT phase than in the TRT phase and at baseline in Group 2. Conversely, m-IIEF-5 scores were higher in the CoT phase than in the TRT phase and at baseline in Group 2. Symptom scores between the phases and baseline were not significantly different in Group 1, and IPSS did not differ between the phases and baseline in either group.

The preferred choice of treatment in the two groups is presented in Table 3. CoT was the preferred treatment in both Groups 1 (P = 0.008) and 2 (P = 0.007).

Table 1 Baseline clinical characteristics of patients in Groups 1 and 2

Variable	Group 1 $n = 14$	Group 2 $n = 12$	P
Age, years	60.5 (54.8–67.3)	57 (53.8–61.3)	0.41
BMI, kg/m^2	22.2 (19.2–23.8)	25.4 (23.4–28.1)	0.04*
History of TRT, *n* (%)	12 (86)	11 (92)	0.64
Smoking status, *n* (%)	2 (14)	2 (17)	0.87
Drinking status, *n* (%)	6 (43)	9 (75)	0.10
Diabetes, *n* (%)	3 (21)	3 (25)	0.83
Hypertension, *n* (%)	3 (21)	4 (33)	0.50
Hyperlipidemia, *n* (%)	1 (7)	3 (25)	0.10
AMS score	47.5 (35.2–50.8)	36.5 (33.8–54.8)	0.68
Somatic domain AMS subscore	18 (15–20.8)	16 (13–20.5)	0.53
Psychological domain AMS subscore	13 (8–14.8)	10.5 (7.3–15.3)	0.62
Sexual domain AMS subscore	15.5 (11.3–18.5)	15.5 (13.8–17.5)	0.9
m-IIEF-5 score	5 (3.25–8)	10 (5–14.5)	0.14
IPSS	9.5 (7–12.5)	6.5 (4.5–12)	0.29
OABSS	3.5 (2.3–6)	2 (1–4)	0.10
Total bilirubin, mg/dL	0.62 (0.54–0.74)	1.00 (0.79–1.80)	0.004*
Creatinine, mg/dL	0.86 (0.81–1.01)	0.91 (0.85–0.97)	0.99
Hemoglobin, g/dL	15.1 (14.5–15.5)	15.8 (15.1–17.1)	0.09
Hematocrit, %	45.3 (41.6–46.3)	46.6 (44.0–50.0)	0.09
PSA, ng/mL	1.01 (0.44–1.80)	0.53 (0.38–0.92)	0.07
Total testosterone, ng/mL	3.28 (1.83–4.75)	3.69 (2.39–4.17)	0.70
Free testosterone, pg/mL	4.3 (2.35–5.73)	6.1 (4.78–10.5)	0.03*

Results are presented as median (IQR), unless otherwise indicated.
*Significantly different between Groups 1 and 2 ($P = 0.05$).

Discussion

Tadalafil, a long-acting PDE5 inhibitor, causes smooth muscle relaxation in the bladder neck, urethra, and blood vessels, and increases penile blood flow and blood flow to the prostate.[8] Via this mechanism, tadalafil improves the symptoms of ED and LUTS with BPH.[7] Ozcan *et al.*[11] showed that 3 months of daily treatment with 5 mg tadalafil increased total testosterone levels in patients with ED associated with metabolic syndrome. In addition, Shigehara *et al.*[3] showed that TRT, via its effects on the autonomic nervous system, elevates blood flow in the lower urinary tract, thereby stimulating nitric oxide synthase supplying the lower urinary tract and endothelial nitric oxide synthase supplying the blood vessels. Furthermore, physical activity combined with tadalafil therapy was reported to improve ED and metabolic variables such as BMI.[14] TRT is known to maintain bone density and muscle strength,[14] which may improve physical activity in elderly men. Thus, the combination of TRT and tadalafil can potentially exert synergistic effects. Although the efficacy of this CoT was reported previously,[15,16] this is the first study to investigate the regimen with an open-label, randomized, crossover design.

In this study, AMS scores, m-IIEF-5 scores, and OABSS in Group 2, but not in Group 1, were significantly improved in the CoT phase. According to previous research, the efficacy of tadalafil is diminished in older men.[17] Meanwhile, the drug is recommended for patients with LOH associated with metabolic syndrome.[11] Age was lower and BMI was higher in Group 2, which could explain the greater benefits of tadalafil observed in this group. Otherwise, regardless of each patient's character, it may be difficult to obtain an additional benefit from gradual add-on tadalafil after TRT. A washout period between the treatment phases may have prevented selection bias associated with the different timing of tadalafil add-on. However, the majority of participants selected the CoT due to its high effectiveness (Group 1: 12/14; Group 2: 10/12). Four participants in Group 1 and one participant in Group 2 gave specific reasons for this. Three participants perceived improvement in the sexual domain, such as in erectile strength and the quality and frequency of sexual intercourse. Two participants perceived an

Table 2 Data from the symptom questionnaires and biochemical measurements in each group and phase

Variable	Group 1			Group 2		
	Phase 1	Phase 2	P	Phase 1	Phase 2	P
AMS score	41 (39.3–48.8)	45 (35.5–51.5)	0.75	32.5 (27.5–40.8)	38 (29–49.5)	0.004*
Somatic domain AMS subscore	18 (16–21.8)	19 (14.8–22.5)	0.44	13.5 (11.5–17.3)	16.5 (12.8–20.3)	0.006*
Psychological domain AMS subscore	9.5 (7.3–13.8)	10.5 (8.3–13)	0.44	7 (6–11.3)	10.5 (6–13)	0.12
Sexual domain AMS subscore	14 (12–17.8)	14 (13–15)	0.72	11 (9–12)	11.5 (10–16.5)	0.03*
m-IIEF-5 score	6.5 (5–12.3)	11 (5–19)	0.22	16 (6.5–19.3)	12.5 (4.8–15.5)	0.02*
IPSS	10 (4.5–13.8)	9.5 (7.3–12.8)	1	7 (4–11)	6 (4.75–16)	0.09
OABSS	4 (2–5)	3 (1.3–5)	0.35	1.5 (1–2.3)	2.5 (1.8–4.3)	0.02*
Total bilirubin, mg/dL	0.58 (0.53–0.68)	0.74 (0.61–0.91)	0.08	0.9 (0.77–1.39)	1.04 (0.85–1.56)	0.14
Creatinine, mg/dL	0.90 (0.81–0.98)	0.91 (0.76–1.08)	0.10	0.89 (0.83–0.98)	0.95 (0.8–0.98)	0.59
Hemoglobin, g/dL	15.6 (14.6–15.9)	15.0 (14.5–15.7)	0.05	16.1 (14.9–17.3)	16.5 (14.7–17.2)	0.11
Hematocrit, %	44 (43.0–46.8)	43.6 (42.1–45.8)	0.17	47.2 (44.0–50.3)	47.7 (43.8–50.8)	0.24
PSA, ng/mL	1.11 (0.67–1.54)	1.13 (0.54–1.84)	0.59	0.68 (0.52–0.87)	0.65 (0.57–0.76)	0.69
Total testosterone, ng/mL	3.16 (1.94–3.95)	3.66 (2.08–4.67)	0.48	2.52 (2.05–3.31)	2.47 (1.89–3.17)	0.96
Free testosterone, pg/mL	3.95 (2.43–4.43)	3.7 (3.33–5.15)	0.31	5.3 (2.95–7.78)	5.2 (2.68–6.8)	0.89

Results are presented as the median (IQR). In Group 1, patients were treated with TRT for 12 weeks (phase 1) followed by 12 weeks of treatment with TRT in combination with alternate-day tadalafil (phase 2), whereas the order of treatment was reversed in Group 2. *Significantly different between phases 1 and 2 in each group ($P < 0.05$).

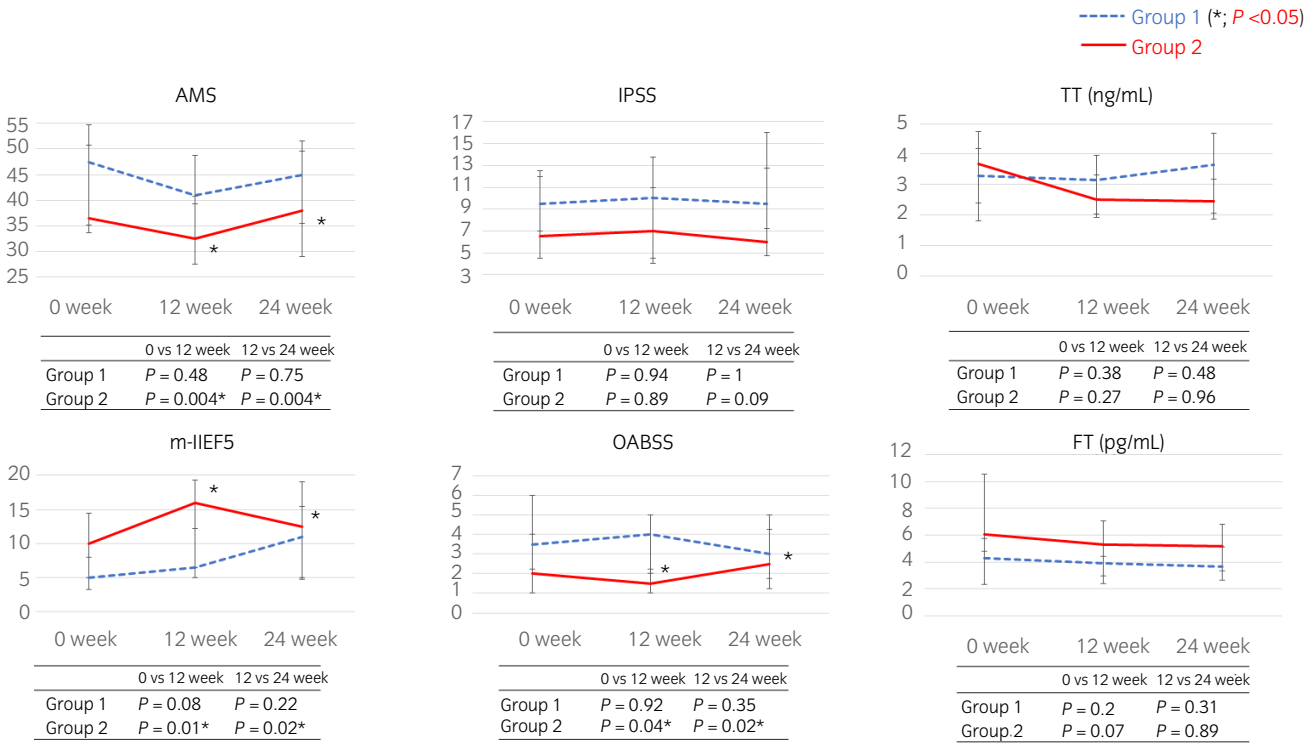

Fig. 3 The sequential changes of symptom questionnaire scores and total testosterone or free testosterone level in each group. The questionnaires included the AMS, m-IIEF-5, IPSS, and OABSS. Data are presented as median (IQR).

Table 3 Preferred treatment in Groups 1 and 2 at the end of the trial

	TRT only, *n*	TRT plus tadalafil, *n*	A *vs* B *P*-value
Group 1	2	12	0.008*
Group 2	1	11	0.007*

*Significantly different ($P < 0.05$).

improvement in the somatic domain; one was able to increase exercise duration and one felt a surge of energy. This was attributable to add-on tadalafil providing additional benefit when used in combination with TRT.

The general daily dosage of tadalafil for treating LUTS or ED is 5 mg,[7] but an on-demand dose of 10 or 20 mg can also be used for ED.[18] The most frequent dose-related adverse effects are reported to be headache (10 or 2 mg on demand)[5] and myalgia (daily 5-mg dose).[7] In contrast, Choi *et al.*[19] reported the efficacy of 5 mg alternate-day tadalafil in men with ED and LUTS. Compared with 5 mg once-daily tadalafil, IIEF score was lower at week 4 in that study. Dosage-dependent efficacy was reported previously in on-demand tadalafil for ED.[5] Although an alternate-day regimen of 10 mg tadalafil was uncommon, toxicity occurred in only one participant, a rheum symptom, and most patients considered the treatment effective in this study. Therefore, we concluded that this dosage is valid and safe.

Recently, ED was described as an initial symptom of vascular endothelial dysfunction,[20] and this symptom was improved by tadalafil. Thus, early tadalafil administration would be expected to improve arterial sclerosis and lower the risk of cardiovascular events.[9]

In addition, previous reports indicated that long-term TRT diminished the risk of metabolic syndrome,[21] and normalization of testosterone levels is accompanied by decreased risk of mortality from myocardial infarction and stroke.[22] As a result, long-term treatment with TRT and tadalafil may reduce the risk of myocardial infarction and stroke, highlighting the potential of this regimen as an anti-aging treatment.

The present study has several limitations, such as the small number of participants, the method of alternate-day administration of tadalafil, the potential placebo effect of add-on tadalafil, and the absence of a washout period between each treatment phase. Additionally, the format of the last question did not include an option to select 'neither TRT nor CoT', the questioner was not a third person, and tadalafil was supplied free of charge by its supplier, which may have affected patients' treatment choice. However, the efficacy of alternate-day tadalafil was previously reported,[19] and the majority of participants in the present study preferred CoT; thus, we consider that TRT with add-on tadalafil is effective for treating LOH.

In conclusion, TRT plus add-on tadalafil is safe and improves treatment satisfaction in patients with LOH.

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Conflict of interest

None declared.

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