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## ORIGINAL ARTICLE

Erectile Function

# Exercise improves the effects of testosterone replacement therapy and the durability of response after cessation of treatment: a pilot randomized controlled trial

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The effects of the combination of exercise and TRT on symptoms of late-onset hypogonadism (LOH) and the durability of response after cessation of TRT were investigated. A total of fifty patients with erectile dysfunction (ED) who had a sedentary lifestyle and low serum total testosterone (T) levels were enrolled and followed for 20 weeks. Patients were randomly divided into two groups; all of them received T gel for 12 weeks and it was discontinued for 8 weeks. Patients assigned to Group II were offered a supervised exercise program for 20 weeks. Measurement of serological testing was performed and self-assessment questionnaires and Global Assessment Question (GAQ) were asked. Baseline characteristics and the initial symptom scores showed no significant difference between the two groups. Serum total T levels and the symptom scores were increased at 12 weeks in both groups, and Group II showed better results with statistical significance. There was a decrease in T levels and worsening of symptom scores at week 20 compared to week 12 in both groups, and Group II showed better results with statistical significance. On the GAQ, Group II showed higher ratio of “yes” at week 12 and the same tendency was sustained at week 20 with significant difference between two groups. The combination of exercise and TRT showed significant improvements in serum T levels and LOH symptoms compared to TRT alone. In addition, these improvements were maintained in the combination group with continuous exercise, even after cessation of TRT. *Asian Journal of Andrology* (2017) 19, 602–607; doi: 10.4103/1008-682X.184269; published online: 12 July 2016

**Keywords:** erectile dysfunction; exercise; hypogonadism; testosterone

## INTRODUCTION

It is well-known that testosterone replacement therapy (TRT) can improve many symptoms of hypogonadism in patients with late-onset hypogonadism (LOH), including effects on mood, energy level, sense of well-being, sexual function, muscle strength, erythropoiesis, bone mineral density, and cognition.<sup>1</sup> However, TRT is not a risk-free treatment because several possible adverse effects, such as polycythemia, liver dysfunction, worsening of sleep apnea, and prostate disease, have been seen in specific situations.<sup>1–3</sup> Moreover, the safety of TRT over a long period has not yet been shown conclusively. In addition, few evidence-based information is available on certain aspects of TRT, such as duration of treatment and durability of response after discontinuation of TRT. In fact, there have been few reports discussing whether symptoms of LOH return after cessation of TRT.<sup>4,5</sup> Moreover, in those studies, serum testosterone levels and symptoms of LOH were shown to be worsened after cessation of TRT. As a result of these reports, we do not know whether stopping TRT is possible or TRT must be continued life-long.

Some studies have found that the combination of TRT and exercise showed better efficacy for specific LOH symptoms than TRT alone.<sup>6,7</sup> However, in those studies, the type of exercise was mainly resistive strengthening exercise and the effects on the sexual function and the durability of response were not evaluated. Based on the results of these studies, we made our hypothesis as follows: (1) the combination of TRT and exercise is better than TRT alone for improvement of sexual functions as well as other LOH symptoms and (2) continuous combination exercise is helpful in maintaining improvement in LOH symptoms and elevated serum testosterone levels after the cessation of TRT.

Therefore, we designed and performed the present study to determine the effects of a combination of exercise and TRT on serum testosterone levels, symptoms of LOH, and the durability of response after cessation of TRT.

## MATERIALS AND METHODS

From January 2013, fifty patients with erectile dysfunction (ED) and a sedentary lifestyle (a men who do not engage in at least 1 h

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per week of moderate-intensity physical activity) with low serum total testosterone levels ( $<350$  ng dl<sup>-1</sup>) were consecutively enrolled; each patient was followed for 20 weeks. Patients received a full explanation of the content and purpose of the study before the trial and were enrolled after signing informed consent. All of the men included in the study were more than 40 years of age; each had a normal digital rectal examination (DRE) and a prostate-specific antigen (PSA) level of  $<3.0$  ng ml<sup>-1</sup>. Exclusion criteria of the study were as follows: YES to one or more questions of physical activity readiness questionnaire (PAR-Q), previous treatment for hypogonadism, the presence of congestive heart failure, unstable angina, myocardial infarction, cerebrovascular events, prostate or breast cancer, psychosis or sleep apnea, and infection with human immunodeficiency virus or any active systemic disease.

Patients were block-randomized into two groups (Groups I and II). Testosterone replacement therapy was administered for 12 weeks in both groups using 2% testosterone gel (50 mg) applied once in the morning. In addition, a supervised 20-week physical activity program was provided for Group II only. The program was performed 3 times per week, 80 min per time and consisted of 20 min of aerobic exercise, followed by 10 min of whole body stretching and 30 min of strength exercise with the last 20 min consisting of aerobic exercise again. The intensity was adjusted to the individuals' exercise capacity as measured by seven baseline exercise tests (ergometer, sit and reach test, curl-up test, squeeze and standing high jump test, whole body reaction test, and one leg balance with eyes close test), which measured cardiopulmonary function, flexibility, muscular endurance, muscular strength, agility, and balance.<sup>8</sup> Both groups of patients were instructed to have three meals per day that had a low glycemic load, were low in saturated fats, and were rich in omega-3 fatty acids. Patients were also instructed to attempt to eat approximately 10% fewer calories per meal compared with their pretreatment diet.

Serum testosterone levels were measured by radioimmunoassay during the first visit, at week 12, and at 8 weeks after treatment cessation (week 20). Blood samples were obtained between 8 am and 11 am. Serum biochemistry for safety profiles, hemoglobin (Hb), and hematocrit (Hct) were assessed during the first visit and at week 12; glucose and lipid profiles were also checked during the first visit and at week 12. Prostate-specific antigen (PSA) was measured at baseline and at 12 and 20 weeks. The height and weight of each patient were measured and body mass index (BMI) was calculated at the first visit, at 12 weeks, and at week 20.

To determine the clinical efficacy of treatment, the International Index of Erectile Function (IIEF) questionnaire and the Aging Males' Symptoms (AMS) questionnaire, which were translated into Korean and validated for use in our population,<sup>9,10</sup> were administered to patients at baseline and at weeks 12 and 20. Sexual Encounter Profile (SEP) questions 2 ("Were you able to insert your penis into your partner's vagina?") and 3 ("Did your erection last long enough for you to have a successful intercourse?") were also administered to patients at baseline and at 12 and 20 weeks. The following Global Assessment Question (GAQ) was asked at weeks 12 and 20, "Has there been any improvement in your erectile function since the start of therapy?" Possible answers included "improved" and "not improved."

The primary efficacy outcome was total serum testosterone levels at weeks 12 and 20. The secondary efficacy outcomes were changes in IIEF and AMS scores, changes in answers to SEP questions 2 and 3, and response to the GAQ at the same visits. Means of data were calculated for each group and reported as mean  $\pm$  95% confidence interval (CI) of the standard deviation of the mean.

For statistical analysis, we used PASW Statistics for Windows, version 18.0 (SPSS, Inc., Chicago, IL, USA). Statistical analyses were conducted using the Mann-Whitney U-test, Wilcoxon signed-rank test, and Fisher's exact test.  $P < 0.05$  was considered statistically significant.

## RESULTS

There were no significant differences in baseline characteristics between two groups (Table 1). During the treatment period, two patients in Group I and four patients in Group II dropped out of the study. Two patients in Groups I and II did not continue treatment due to the expense of treatment medications, and the other two patients in Group II did not complete the exercise program due to individual schedule conflicts. No patient was withdrawn from the study for not meeting the detailed exclusion criteria or from complications related to treatment. The compliance to testosterone gel showed no significant difference between two groups.

Figure 1 shows the change in serum testosterone levels through the treatment periods. Serum testosterone levels increased significantly at 12 weeks in both groups. However, testosterone levels in Group II were significantly higher than Group I ( $P = 0.019$ ). At 20 weeks, both groups showed a significant decrease in testosterone levels compared to 12 weeks data; however, Group II showed significantly higher testosterone levels than Group I ( $P < 0.001$ ). For the change in serum testosterone levels from baseline to at 12 weeks, Group II showed a significantly wider range of increase than Group I ( $P = 0.029$ ). For the change in serum testosterone levels from 12 to 20 weeks, the change of Group II was less than Group I without statistical significance ( $P = 0.415$ ).

The changes in symptom severity also showed similar pattern. In both groups, total IIEF scores improved significantly at 12 weeks. However, symptom scores for Group II were more improved than Group I with statistical significance ( $P = 0.028$ ). Similar to testosterone levels, symptoms worsened after cessation of TRT but Group II showed better symptom scores than Group I with statistical significance ( $P = 0.001$ ) (Figure 2). For total AMS scores, the same pattern was observed as with IIEF; Group II showed more improved symptom scores than Group I at 12 weeks ( $P = 0.045$ ) and improvement was maintained in Group II after cessation of TRT at 20 weeks ( $P = 0.007$ ) (Figure 3). In the analysis of AMS subscale

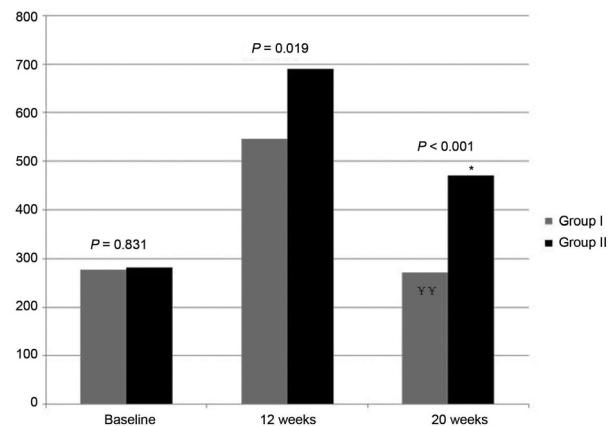
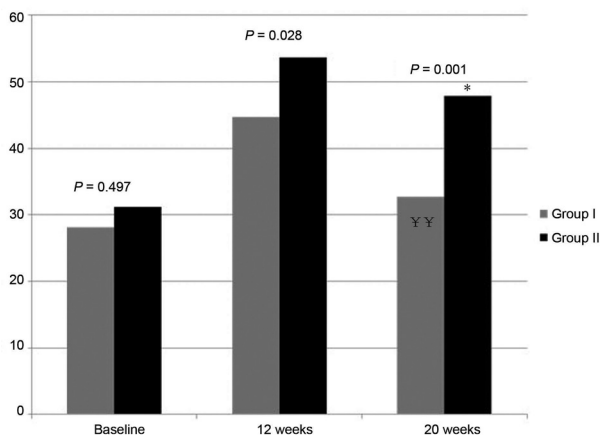


Figure 1: Changes of serum total testosterone levels and comparison between two groups ( $P$  value by independent  $t$ -test,  $P = 0.019$  at 12 weeks,  $P < 0.001$  at 20 weeks).  $^{**} P < 0.001$  by paired  $t$ -test compared to 3 months in Group I,  $^{*} P < 0.01$  by paired  $t$ -test compared to 3 months in Group II.

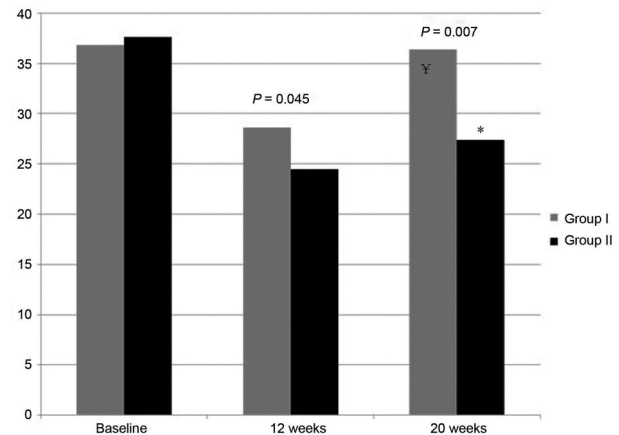
**Table 1: Comparison of baseline characteristics, serological parameters, and symptom severities before and 12 weeks after testosterone replacement therapy in both groups**

	Group I (n=25)			Group II (n=25)			P*	
	Baseline	12-week	P	Baseline	12-week	P	Baseline	12-week
Age (years)		57.9±7.2			60.7±7.0		0.227	
BMI (kg m <sup>-2</sup> )	26.0±3.8	26.1±3.6	0.478	25.6±2.7	25.14±2.7	0.000	0.696	0.333
Comorbidities (n) <sup>‡</sup>		12/25			10/25		0.866 <sup>‡</sup>	
Hypertension		5			6			
Diabetes mellitus		3			3			
Dyslipidemia		4			3			
BPH/LUTS		5			6			
Total testosterone (ng dl <sup>-1</sup> )	277.1±66.1	545.9±131.6	0.000	281.9±54.5	689.6±219.3	0.000	0.831	0.019
PSA (µg dl <sup>-1</sup> )	1.06±0.70	1.34±0.96	0.202	1.08±0.76	0.96±0.60	0.288	0.931	0.161
Hb (g dl <sup>-1</sup> )	14.5±1.3	15.7±1.2	0.153	15.0±1.1	15.4±1.1	0.055	0.270	0.517
Hct (%)	42.5±3.2	46.2±3.6	0.003	43.9±3.0	44.7±9.7	0.383	0.196	0.174
Glucose (mg dl <sup>-1</sup> )	131.2±47.3	134.6±47.2	0.829	124.6±47.2	121.7±58.0	0.709	0.678	0.504
Total cholesterol (ng dl <sup>-1</sup> )	176.6±43.3	183.0±44.9	0.757	198.1±40.9	180.7±28.5	0.187	0.131	0.920
Triglyceride (mg dl <sup>-1</sup> )	209.9±117.3	209.2±121.2	0.830	173.8±128.3	145.7±77.6	0.167	0.416	0.329
HDL (ng dl <sup>-1</sup> )	43.7±7.8	45.6±7.3	0.675	50.2±13.7	46.6±14.79	0.209	0.115	0.865
LDL (ng dl <sup>-1</sup> )	111.6±28.6	111.8±30.4	0.248	126.8±39.8	100.0±15.1	0.203	0.252	0.506
IIEF	28.1±14.5	44.7±13.7	0.000	31.2±13.7	53.6±10.3	0.000	0.497	0.028
AMS	36.8±7.5	28.6±4.4	0.000	37.6±13.4	24.5±7.3	0.000	0.844	0.045
SEP 2 (%)	61.1	85.0	0.088	55.6	85.0	0.074	0.684	0.344
SEP 3 (%)	28.6	60.0	0.018	33.3	85.0	0.002	0.630	0.173

\*Independent *t*-test between two groups; <sup>‡</sup>*P* value by Chi-square test between two groups; <sup>‡</sup>Some patients had multiple comorbidities. BMI: body mass index; BPH: benign prostate hyperplasia; LUTS: lower urinary tract symptoms; PSA: prostate-specific antigen; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SEP: sexual encounter profile; AMS: Aging Males' Symptoms; IIEF: International Index of Erectile Function; Hb: hemoglobin; Hct: hematocrit



**Figure 2:** Changes of total score of IIEF and comparison between two groups (*P* value by independent *t*-test, *P* = 0.028 at 12 weeks, *P* = 0.001 at 20 weeks). \**P* < 0.001 by paired *t*-test compared to 3 months in Group I, \**P* < 0.01 by paired *t*-test compared to 3 months in Group II.



**Figure 3:** Changes of total score of AMS and comparison between two groups (*P* value by independent *t*-test, *P* = 0.045 at 12 weeks, *P* = 0.007 at 20 weeks). \**P* < 0.01 by paired *t*-test compared to 3 months in Group I, \**P* < 0.01 by paired *t*-test compared to 3 months in Group II.

scores (psycho, somatic, and sexual symptoms), a similar pattern was observed; in psycho symptoms, there was no significant difference between the two groups at baseline or at 12 weeks, but the improvement was well-maintained in Group II at 20 weeks (*P* = 0.004). In somatic symptoms, there was no difference at baseline, but Group II showed a better symptom score at 12 and 20 weeks, which was not statistically significant (*P* = 0.343, *P* = 0.114). In the sexual symptom subscale, Group II showed a significantly better symptom score at 12 and 20 weeks (*P* = 0.000, *P* = 0.005), the same pattern as seen in the total AMS score.

For the ratio of “yes” responses to SEP questions 2 and 3, there were significant increases in both groups at 12 weeks compared to

baseline and there were no significant differences between the two groups at week 12 (*P* = 0.344 and *P* = 0.173 for questions 2 and 3, respectively). For the ratio of “yes” responses to SEP question 2, there was no significant difference between two groups at 20 weeks, but for SEP question 3, the results at week 20 showed a higher ratio of “yes” in Group II compared to Group I with statistical significance (*P* = 0.031).

With respect to BMI, Group II showed a continuous decrease in BMI throughout the 20 weeks with statistical significance. However, in Group I, there was a tendency for an increase with no statistical significance.

We also investigated patient satisfaction to treatment. At 3 months and 5 months, the ratio of “yes” responses to the GAQ “Has there been

any improvement in your erectile function since the start of therapy” was investigated. The results showed a higher ratio of “yes” responses in Group II than in Group I at week 12 without statistical significance. At 20 weeks, the satisfaction rate in Group II was significantly higher than Group I after cessation of TRT ( $P = 0.043$ ).

For changes in serologic parameters during the 12 weeks of treatment, Group II showed a trend toward improving metabolic status, such as glucose and lipid profiles, but there were no changes in Group I compared to baseline status (Table 1). For Hb and Hct, both of which had increased during the first 12 weeks of testosterone administration without statistical significance, no values were observed above the upper limit of the normal range in either group (Table 1).

For PSA levels, there was no significant increase in either group at 12 weeks compared to baseline and no significant difference was observed between the two groups. After TRT, PSA levels in both groups showed nonsignificant decreases, with no significant difference between the two groups. No disorders or abnormalities were identified by follow-up DRE or based on clinical symptoms. There were two and three patients who complained of redness and itching sense at the skin of inner thigh, respectively, but these events were not serious and resolved after changing the site of gel application to the lower abdomen.

## DISCUSSION

The criteria for an optimal treatment modality might have included a shorter treatment period and a longer durability of response after completion of treatment. We are already aware of the risks associated with testosterone treatment. Still, controversies about the cardiovascular risk of treatment exist,<sup>11,12</sup> and there is concern about developing prostate cancer during testosterone replacement,<sup>2,13</sup> although the incidence of these adverse events is not significant.<sup>13</sup> In other words, we do not know the real effects of TRT on the cardiovascular system and the prostate so far. Hence, it cannot yet be clearly stated that “testosterone treatment is safe.” Therefore, it is necessary to find a way to maintain efficacy of TRT with shortened treatment periods to reduce the potential risks associated with TRT.

There have been several efforts to determine the durability of response after completion of TRT. Tsujimura *et al.*<sup>4</sup> evaluated LOH-related symptoms and endocrinologic markers at 3 months after discontinuation of TRT in patients with LOH, who had benefited from TRT. The results showed that improvements in symptoms may remain after cessation of TRT, but endocrinologic status declines to baseline level.<sup>4</sup> According to Francomano *et al.*,<sup>14</sup> withdrawal of long-acting injectable testosterone therapy provokes a return to baseline status for all cardiac and hormonal parameters within 6 months. Another study by O’Connell *et al.*<sup>5</sup> showed a similar pattern; the effects of testosterone treatment on body composition, muscle strength, and quality of life did not persist by 6 months after treatment withdrawal in intermediate-frail and frail elderly men. Based on the results of these aforementioned studies, it appears that the effects of TRT are not maintained after cessation of treatment. If so, a continuous supply of exogenous testosterone is needed to maintain constant serum testosterone levels and its positive effects. If there is a way to augment the durability of response after stopping treatment, shorter treatment periods can be used, which may then lower the risks associated with TRT. This was the reason behind our present pilot study.

Meanwhile, according to several studies, exercise has positive effects on LOH patients. In a 52-week, double-blind clinical trial, the effects of supervised exercise and diet with or without testosterone treatment on components of metabolic syndrome and newly diagnosed

type 2 diabetes in hypogonadal men were assessed by Heufelder *et al.*<sup>15</sup> Serum testosterone, glycosylated hemoglobin (A1C), fasting glucose, high-density lipoproteins (HDL), triglycerides (TG), and waist circumference were significantly improved after 52 weeks of supervised diet and exercise without testosterone treatment. Addition of testosterone significantly improved these parameters compared with supervised diet and exercise alone.<sup>15</sup>

For ED, we already know about the effects of exercise on erectile function.<sup>16,17</sup> There is epidemiologic evidence that frequent vigorous exercise is associated with a 30% lower risk of ED.<sup>18</sup> Furthermore, men who are sedentary are 3 times as likely to have ED whereas moderate physical activity reduces the risk of ED by two-thirds, and in men with high physical activity, ED is reduced by over 80%.<sup>18</sup> It is known that moderate exercise increases nitric oxide (NO) production by mechanical shear forces of blood flow.<sup>19</sup> Acute exercise increases NO release for only 48 h while regular daily exercise induces 4-fold higher levels of NO lasting for about 1 week.<sup>20</sup>

Because of these findings, we selected exercise as the method to augment the effects of TRT on ED. However, it is unknown what type of exercise is best in improving symptoms and endocrinologic status in patients with LOH. The effects of resistive exercise on serum testosterone levels have been mainly investigated. It has been shown that acute vigorous resistance exercise can elevate serum testosterone levels, but there is insufficient information about the effects of long-term chronic exercise on serum testosterone.<sup>21–24</sup> Smilios *et al.*<sup>25</sup> showed that acute elevation of testosterone is not always observed after vigorous resistance exercise; it seems that the total amount of exercise over several levels is important for increasing testosterone. In addition, exercise using large muscles can result in an acute testosterone surge compared with exercise with small muscles, according to Cho *et al.*<sup>26</sup>

Most studies have tried to determine the relationship between resistive exercise and elevation of serum testosterone levels. In our present study, we did not focus on resistive exercise only. The background of our exercise program was based on unpublished data of our experience. According to our experience, cardiopulmonary function (measured by ergometer) has a significant correlation with the serum testosterone levels in LOH patients. However, six other basic exercise function tests, such as “sit and reach” (flexibility), “curl-up” (muscular endurance), “squeeze” and “standing high jump” (muscular strength), “whole body reaction test” (agility), and “one leg balance with eyes close” (balance) tests, showed no significant correlation with serum testosterone levels. With respect to erectile function and LOH symptom severity, there was a significant correlation not only with cardiopulmonary function but also with muscular endurance and strength. Therefore, the exercise program of our study consisted of 20 min of aerobic exercise, followed by 10 min of whole body stretching, 30 min of strength exercise, and 10 min of aerobic exercise.

Based on changes in BMI during treatment, we can confirm a significant decrease in BMI in Group II. Of course, long-term testosterone treatment can decrease BMI and fat according to several studies,<sup>27,28</sup> but in our present study, the treatment periods were very short; hence, the main component affecting BMI decrease might have been exercise. If the treatment periods were longer, we might be able to confirm synergistic effects of TRT and exercise, which was observed in the study by Heufelder *et al.*<sup>15</sup>

One of the mechanisms of higher serum testosterone levels at 12 weeks and maintaining serum testosterone levels after cessation of TRT in Group II is thought to be due to a decrease in adipose tissue by continuous exercise and also by a decrease in the conversion of



testosterone to estradiol by aromatase in adipose tissue,<sup>29</sup> although this theory has not been confirmed and many controversies are present. Serum estradiol level was not measured in this study, but according to a recent study by Monteagudo *et al.*,<sup>30</sup> depression, which is one of the LOH symptoms, was more severe in obese patients in whom there was a greater imbalance between serum testosterone and estradiol level. In this study, symptom improvement at week 12 was more substantial in the exercise-TRT-combination group than in the TRT-only group, and a further analysis is in need to examine whether or not it was because the exercise-treated group maintained the serum testosterone/estradiol balance better through the reduction of adipose tissue.

With respect to another mechanisms, Kumagai *et al.*<sup>31</sup> reported that the serum testosterone levels of obese men increased significantly following a 12-week course of regular aerobic exercise and dietary regulation. They explained that the aerobic exercise and dietary regulation reduced the insulin levels of obese males, leading to increased serum testosterone levels; this finding corresponded with the results of the previous study, which demonstrated that as the serum insulin level decreased, the serum testosterone level increased. In the present study, as the glucose level tended to decrease in Group II after the 3-month treatment period although the serum insulin level was not measured, we speculated that a decrease in the serum insulin level consequent to continuous aerobic exercise and dietary improvements over a 5-month period prevented a reduction in serum testosterone levels. In addition, we already know the positive effects of weight loss in obese men on erectile function; reduction in adipose tissue by continuous exercise can lower oxidative stress by decreasing free radical formation, which is associated with deactivation of NO availability.<sup>32</sup>

There have also been some studies evaluating the association between oxidative stress and testosterone levels. Sajjadian *et al.*<sup>33</sup> increased oxidative stress via buthionine sulfoximine (BSO) in an animal experiment involving mice. As a result, histological changes were induced in the testicles that reduced testosterone levels and affected semen parameters. The result of that study suggests that antioxidant activity obtained from steady exercise positively affects testicular function, possibly leading to an increase in the serum testosterone level. Furthermore, Chigurupati *et al.*<sup>34</sup> divided 6-month-old mice into two groups: one group ran a distance of 1.75 km every day whereas the other group performed no exercise until reaching an age of 20 months. At that point, testicles were examined histologically and metabolites associated with oxidative stress were quantitated, and the findings revealed that the testicular tissue in the group with steady exercise maintained a normal appearance, despite the increase in age, whereas the levels of metabolites associated with oxidative stress were significantly high in spermatogenic and Leydig cells from mice not exposed to exercise.

In addition, data from a previously reported animal experiment support the idea that regular exercise directly increases the levels of steroidogenesis-related enzymes and, thus, increases DHT in the muscles and serum. According to studies by Aizawa *et al.* and Sato *et al.*,<sup>35,36</sup> DHT concentrations increased significantly in the skeletal muscle and plasma of mice that had participated in endurance aerobic exercise on a treadmill for 25–30 min sessions, 5 times per week, when compared with mice that had not exercised.

The higher serum testosterone level and small range of serum testosterone reduction, even after the discontinuation of testosterone treatment in the exercise-treated group in the present study, could be considered due to mechanisms such as reductions in the serum insulin level, oxidative stress, and the conversion of testosterone to estradiol by

aromatase in adipose tissue, and a direct increase in the muscular and plasma DHT concentration resulting from exercise and diet regulation.

Our present study has many limitations. This was a pilot study, so the study population was small and treatment and observation periods were not long enough to assess the real effects of TRT. The absence of an exercise-only group also limits the interpretation of our results. Furthermore, the patients enrolled in both groups were relatively healthy; the results of PAR-Q were used as exclusion criteria. There were also several patients who did not complete the entire study due to the economic burden of the treatment medication. In addition, although we evaluated psycho and somatic symptoms with the AMS subscale analysis, the main focus of the study was sexual function such as erectile function, and such important evaluative elements in LOH symptoms as muscle strength and quality of life were excluded. Finally, because our analysis of symptom severity of ED and TDS relied on self-assessment questionnaires, bias in reporting is a concern. The lack of objective parameters, such a penile Doppler ultrasound, is also a limitation of this study.

However, in this study, the combination of exercise and TRT resulted in significant improvements in serum testosterone levels and LOH symptoms compared with TRT only. The differences between the two groups in serum testosterone, IIEF and AMS scores, and responses to the GAQ at 12 weeks reflect the synergistic effects of combined testosterone and exercise. Moreover, these improvements were well-maintained in the combination group with continuous exercise even after cessation of TRT. Higher serum testosterone levels, better symptom scores for both IIEF and AMS questionnaires, a higher ratio of “yes” to SEP question 3, and better responses to the GAQ at week 20 (8 weeks after stopping treatment) in Group II confirmed that exercise is a way to augment the durability of response after stopping TRT and shorten the treatment duration so as to lower the risks of treatment.

There is a need for large clinical trials including an exercise-only group, and longer treatment and longer observation periods are necessary. In addition, we need to investigate which exercise is better for improving testosterone levels and LOH symptoms.

## CONCLUSIONS

The combination of exercise and TRT showed significant improvements in serum testosterone levels and LOH symptoms compared to TRT alone. In addition, these improvements were well-maintained in the combination group with continuous exercise even after cessation of TRT. Exercise can augment the durability of response to TRT after stopping treatment, and it may be the solution to shorten the treatment duration with a lower risk from testosterone therapy. Further large-scale clinical trials including an exercise-only group with long treatment periods are necessary to support the conclusion of this present study.

## AUTHORS' CONTRIBUTIONS

DYC and MGP participated in conceiving of the study and drafted the manuscript. JKY, JKH, JGK, and MGP participated in the study design. SIC, JEJ, SJY, DHK, and MGP performed the studies and collected the data. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing interests.

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