

### SHORT-TERM EFFECTS OF TESTOSTERONE REPLACEMENT THERAPY ON RISK PREDICTORS FOR ARTERIOSCLEROSIS AMONG MEN WITH LATE-ONSET HYPOGONADISM: A CASE–CONTROL STUDY

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Submitted: 12 November 2019. Accepted: 03 September 2020. Published: 20 October 2020.

#### ABSTRACT

##### Background and objective

This study assessed the short-term effects of testosterone replacement therapy (TRT) on some risk predictors for arteriosclerosis among men with late-onset hypogonadism (LOH).

##### Materials and methods

A total of 25 patients with LOH who received TRT for 6 months and 21 patients without TRT were enrolled in the present study. Information regarding the following parameters were collected: Aging Males' Symptoms scale, Sexual Health Inventory for Men (SHIM), International Prostatic Symptom Score, waist circumference, and some laboratory data, including fasting blood sugar, hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol, triglycerides, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein (hs-CRP) values, and arteriosclerosis index (AI), at baseline and after 6 months. Patients in the TRT group had received intramuscular injections of testosterone enanthate (250 mg) every month for 6 months while those in the control group received no testosterone treatment during this trial.

##### Results

No significant differences were observed in any baseline patient characteristics between both groups. After 6 months, the TRT group exhibited significant improvements in SHIM scores (from 10.1 to 13.1;  $p = 0.00563$ ), hs-CRP values (from 0.157 to 0.103 mg/dL;  $p = 0.00753$ ), and the AI (from 2.10 to 1.95 mg/dL;

$p = 0.0429$ ), with a significant decrease in AMS scale (from 44.3 to 41.8;  $p = 0.0388$ ). The control group displayed no significant changes in all parameters. No patient in the TRT group had additional interventions or medications worsening their urinary symptoms.

### Conclusions

TRT for 6 months among men with LOH contributed to significant improvements in three predictive factors for arteriosclerosis. Further studies including long-term TRT are expected to demonstrate the preventive effects of testosterone for arteriosclerosis among Japanese men with LOH syndrome.

**Keywords:** *arteriosclerosis; C-reactive protein; erectile dysfunction; late-onset hypogonadism; testosterone replacement therapy*

## INTRODUCTION

Late-onset hypogonadism (LOH) has been widely recognized as a syndrome associated with various clinical conditions, including decreased muscle volume and bone mineral density, visceral obesity, metabolic syndrome, and erectile dysfunction (ED), caused by decreasing levels of testosterone in elderly men.<sup>1-3</sup> Testosterone replacement therapy (TRT) has been used worldwide for the management of these symptoms and has contributed toward maintaining quality of life among elderly men.<sup>4-6</sup>

In particular, testosterone deficiency has been considered a potential risk factor for cardiovascular disease (CVD) through arteriosclerosis caused by metabolic syndrome and various metabolic factors.<sup>7</sup> Therefore, testosterone deficiency has been significantly associated with comorbidities among elderly men, while the prevention and treatment of hypogonadism remains a clinical concern worldwide. Many previous studies have reported on the utility of TRT in improving various metabolic factors, as well as its potential for preventing the development of arteriosclerosis and CVD among hypogonadal men.

Recently, ED, high-sensitivity C-reactive protein (hs-CRP) values, and the arteriosclerosis index (AI; the low-density lipoprotein cholesterol [LDL-C]/high-density lipoprotein cholesterol [HDL-C] ratio) have been accepted as convenient clinical predictive markers for estimating arteriosclerosis

risk.<sup>8-11</sup> Accordingly, the present study assessed the short-term effects of TRT on these risk predictors for arteriosclerosis among Japanese men with LOH syndrome.

## PATIENTS AND METHODS

### *Study patients and protocol*

The biochemical diagnosis of hypogonadism was based on the Japanese criteria for free testosterone (FT) levels ( $\leq 11.8$  pg/mL).<sup>12</sup> FT levels were evaluated using blood serum samples collected between 09:00 and 11:00, and measured by a radioimmunoassay using DPC Free Testosterone kits (Mitsubishi Kagaku Iatron).

Symptoms of LOH were screened based on the Aging Males' Symptoms (AMS) scale ( $\geq 27$  points). Exclusion criteria were as follows: patients who had been previously administered dutasteride, finasteride, phosphodiesterase-5 (PDE-5) inhibitors, anti-androgen agents, supplements and herbal medicines, or any testosterone supplement within 6 months; those with a past or present history of chronic illnesses, such as tuberculosis, rheumatoid arthritis, other autoimmune disorders; those with a history of malignancies within 1 year; those with a history of any acute diseases requiring medical intervention within 1 year; those with acute and chronic infectious diseases within 1 year; and those

with any current active diseases that are likely to affect hs-CRP values or erectile function. In addition, patients who required additional medications or had recently changed their pharmacological therapy for dyslipidemia or diabetes mellitus during the trial period were also excluded.

Information regarding the AMS scale, Sexual Health Inventory for Men (SHIM), International Prostate Symptom Score (IPSS), waist circumference, and some laboratory data, including fasting blood sugar (FBS), hemoglobin A1c (HbA1c), LDL-C, TG, HDL-C, hs-CRP values, and AI (defined as the LDL-C/HDL-C ratio), were collected at baseline and after 6 months.

From our database of patients with LOH between 2008 and 2014, only cases with all of the aforementioned data were retrospectively extracted for the present analysis. Finally, 46 patients, who were grouped as 25 patients with LOH syndrome who had received TRT for 6 months and 21 patients without TRT for 6 months at our LOH outpatient clinic, were included in the present analysis.

Patients in the TRT group had received intramuscular injections of testosterone enanthate (250 mg; Enarmon Depot™, ASKA Pharmaceutical Co., Ltd., Tokyo, Japan) every month for 6 months, while those in the control group received no testosterone treatment during this trial.

The study was approved by our Institutional Review Board (No.2019-022) and was conducted according to the Ethical Guidelines for Medical and Health Research.

### **Statistical analysis**

Background data from each group were compared using the Mann–Whitney U test, while categorical data were compared using the chi-square test. For each group, changes in the levels of each parameter after 6 months were compared using the Wilcoxon rank-sum test. All statistical analyses were performed using SPSS™ version 22 (SPSS Inc., Chicago, IL, USA) with  $p < 0.05$  being considered statistically significant.

## **RESULTS**

Patients in the TRT and control groups had a mean age [ $\pm$ standard deviation (SD)] of  $59.1 \pm 10.3$  and  $62.6 \pm 10.4$  years and mean (SD) FT values of  $7.4 \pm 2.6$  and  $7.3 \pm 1.6$  pg/mL, respectively (Table 1). The mean SHIM scores in the TRT and control groups were 10.1 and 9.3, respectively, showing originally poor erectile function among eligible patients in both groups. No significant differences in any baseline patient characteristics were observed between both groups.

After 6 months, the TRT group exhibited significant changes in total AMS scale (from 44.3 to 41.8;  $p = 0.0388$ ), SHIM scores (from 10.1 to 13.1;  $p = 0.00563$ ), hs-CRP values (from 0.157 to 0.103 mg/dL;  $p = 0.00753$ ), and the AI (from 2.10 to 1.95 mg/dL;  $p = 0.0429$ ), whereas the control group displayed no significant changes (Table 2). Moreover, both groups showed no significant changes in IPSS, waist circumference, FBS, HbA1c, LDL-C, TG, and HDL-C after 6 months. No patients in the TRT group had additional interventions or medications for worsening of their urinary symptoms.

## **DISCUSSION**

In the present study, SHIM scores, hs-CRP values, and AI, which are considered some clinical risk predictors for arteriosclerosis, could be simultaneously improved by only 6-month TRT in men with LOH syndrome.

Our results showed that TRT was able to improve SHIM scores significantly. Accordingly, ED has been attributed to testosterone deficiency, nerve disorders, depression, some medications, and blood endothelial disorder associated with arteriosclerosis. Considering that the penile artery is one of the thinnest arteries within the entire body, ED can be considered a predictive sign of systemic vascular endothelial dysfunctions and future CVD.<sup>8,9</sup> Indeed, a meta-analysis including 91,831 subjects concluded that men with ED had a relative risk of

**TABLE 1** Patients' Backgrounds in TRT and Control Groups.

Categories	TRT group (n = 25)	Control group (n = 21)	p value
Age	59.1 ± 10.3	62.6 ± 10.4	0.127
FT value (pg/mL)	7.4 ± 2.6	7.3 ± 1.6	0.253
AMS scale	44.3 ± 14.0	40.1 ± 11.5	0.169
SHIM	10.1 ± 6.8	9.3 ± 6.1	0.357
IPSS	9.6 ± 7.4	9.0 ± 7.1	0.292
Waist circumference (cm)	84.9 ± 10.4	88.0 ± 7.4	0.161
Highly-sensitive CRP (mg/dL)	0.157 ± 0.281	0.105 ± 0.072	0.172
Fasting plasma glucose (mg/dL)	140 ± 34	121 ± 45	0.194
HbA1c (%)	6.3 ± 1.0	6.1 ± 1.1	0.403
LDL-Cholesterol (mg/dL)	107 ± 23	96 ± 27	0.127
Triglyceride (mg/dL)	114 ± 47	115 ± 53	0.322
HDL-Cholesterol (mg/dL)	52.9 ± 9.7	54.8 ± 12.5	0.209
Arteriosclerosis index	2.10 ± 0.60	1.92 ± 1.03	0.239
Use of other medications			
Anti-diabetic drugs (%)	12 (48%)	11 (52%)	0.767
Lipid-lowering drugs (%)	9 (36%)	8 (38%)	0.872

TRT, testosterone replacement therapy; FT, free testosterone; AMS, aging male symptoms; SHIM, sexual health inventory for men; IPSS, International prostate symptoms score; CRP, C-reactive protein; HbA1c, hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

1.44 (95% CI, 1.27–1.63) for total CVD events and 1.25 (95% CI, 1.12–1.39) for all-cause mortality compared with those without ED.<sup>13</sup> Furthermore, patients with CVD had a significantly higher incidence of ED, which has been shown to predict the occurrence of CVD over the next 3–5 years, while the severity of ED has been closely associated with atheromatous cardiac ischemia determined through angiography.<sup>14,15</sup> In addition, a previous prospective study including 2599 participants demonstrated that ED and testosterone deficiency independently predicted mortality and that men with both conditions were at particularly high risk.<sup>16</sup> Another recent study investigating the long-term efficacy of TRT suggested that it could alleviate ED and improve various cardiometabolic risk factors for up to 12 years.<sup>17</sup> In fact, one previous longitudinal study involving 1031 hypogonadal men, among whom 373 received

TRT, showed a cumulative mortality of 21% in the untreated group and 10% in the TRT group.<sup>18</sup> However, TRT by itself has been shown to directly improve libido and erectile function.<sup>4,18,19</sup> We are unable to attain a definitive conclusion whether only an improvement in ED was directly associated with prevention of arteriosclerosis.

Therefore, the present study also evaluated hs-CRP values as alternative predictor for CVD. Accordingly, our results showed that patients receiving 6 months of TRT had significantly decreased hs-CRP values, whereas control patients had no significant changes therein. The hs-CRP test, which can measure lower levels of CRP with a sensitivity of 0.01 mg/dL, has been known to be a biomarker of systemic low-grade inflammation. Given that arteriosclerosis is currently considered to be associated with low-grade endothelial inflammation,

**TABLE 2** Changes from Baseline to 12-Month Visit in Each Parameter between TRT and Control Groups.

Categories	TRT group (n = 25)		p value	Control group (n = 21)		p value
	before	6-month visit		before	6-month visit	
AMS scale	44.3 ± 14.0	41.8 ± 6.6	0.0388	40.1 ± 11.5	38.6 ± 9.0	0.148
SHIM	10.1 ± 6.8	13.1 ± 3.5	0.00563	9.3 ± 6.1	7.5 ± 4.5	0.139
IPSS	9.6 ± 7.4	9.0 ± 7.1	0.198	9.0 ± 7.1	9.1 ± 7.1	0.441
Waist circumference (cm)	84.9 ± 10.4	86.0 ± 10.6	0.0910	88.0 ± 7.4	87.6 ± 7.1	0.464
highly-sensitive CRP (mg/dL)	0.157 ± 0.281	0.103 ± 0.200	0.00753	0.105 ± 0.072	0.104 ± 0.072	0.401
Fasting plasma glucose (mg/dL)	140 ± 34	141 ± 50	0.341	121 ± 45	128 ± 42	0.440
HbA1c (%)	6.3 ± 1.0	6.4 ± 1.5	0.0574	6.1 ± 1.1	6.0 ± 0.9	0.454
LDL-Cholesterol (mg/dL)	107 ± 23	99 ± 22	0.0849	96 ± 27	102 ± 25	0.134
Triglyceride (mg/dL)	114 ± 47	114 ± 54	0.132	115 ± 53	130 ± 60	0.0814
HDL-Cholesterol (mg/dL)	52.9 ± 9.7	52.4 ± 8.9	0.241	54.8 ± 12.5	55.0 ± 12.9	0.346
Arteriosclerosis index	2.10 ± 0.60	1.95 ± 0.53	0.0429	1.92 ± 1.03	1.97 ± 1.78	0.255

TRT, testosterone replacement therapy; FT, free testosterone; AMS, aging male symptoms; SHIM, sexual health inventory for men; IPSS, international prostate symptoms score; CRP, C-reactive protein; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

hs-CRP values can be a predictive biomarker for the development of future CVD.<sup>10</sup> In addition, several previous reports have suggested that hs-CRP values can be a potential marker for penile vascular disorder and ED, with SHIM scores being inversely correlated with hs-CRP levels.<sup>20,21</sup> A previous study including 115 hypogonadal men demonstrated that TRT was able to decrease body weight, serum lipids, glucose, HbA1c, blood pressure, and hs-CRP values.<sup>22</sup> Traish et al. also reported that TRT continuously decreased hs-CRP values among 255 hypogonadal men.<sup>23</sup> Accordingly, the results of the aforementioned studies have been consistent with those presented herein.

Although LDL-C and HDL-C are important risk factors for CVD, the ratio between both values rather than individual levels has been more closely associated with the development of CVD.<sup>24,25</sup>

Therefore, a high LDL-C/HDL-C ratio (AI) has also been reported to have high predictive value for first cardiovascular events, with an AI of  $\leq 2.0$  currently being recommended for preventing arteriosclerosis progression in the near future.<sup>11,25,26</sup> Therefore, in addition to hs-CRP values, the present study, also evaluated the AI. Unlike the control group, the TRT group showed a significant decrease in the AI after only 6 months of TRT. Indeed, several previous studies have demonstrated that TRT in hypogonadal men was associated with reduced levels of LDL-C coupled with a beneficial increase in HDL-C.<sup>4,22,23,27</sup> Traish et al. reported that 5 years of TRT gradually and consistently reduced LDL-C while increasing and maintaining HDL-C.<sup>23</sup> These changes were particularly remarkable within the first year of TRT and, subsequently, were maintained by continuous TRT. Therefore, as the present results, even short-term

TRT can contribute to improvement in lipid profile among hypogonadal men. However, a previous study demonstrated that although TRT improved the lipid profile, including total cholesterol, LDL, and total cholesterol/HDL-C ratio, among hypogonadal men, withdrawal of TRT abolished such beneficial effects, suggesting the necessity of continuous long-term TRT.<sup>22</sup>

Certain limitations to the present study are worth noting. First, this study included only a small number of subjects and a short-term intervention. Although the present study demonstrated that 6-month TRT significantly improved some risk predictors for arteriosclerosis, which is not likely to suggest that short-term TRT could decrease the risk for arteriosclerosis for such a short term. Efficacy of continuous long-term TRT on these predictive factors should be assessed to clarify the preventive effects of TRT for arteriosclerosis. Furthermore, many participants received other medical interventions and were administered lipid-lowering or anti-diabetic medications, which could have affected some of the metabolic parameters. Moreover, information regarding patients' eating and exercise habits was lacking in the present study. In addition, all study subjects had made a diagnosis of LOH syndrome by using the FT measuring kits based on the Japanese criteria; however, the diagnostic kits cannot be made available now. Therefore, further prospective randomized studies including more participants and long-term observations are required to corroborate the results presented herein.

In conclusion, only 6-month TRT among men with LOH syndrome could improve ED and reduce hs-CRP values and the AI, which are the risk predictors for arteriosclerosis. Further studies, including long-term TRT, are expected to demonstrate the preventive effects of testosterone for arteriosclerosis among Japanese men with LOH syndrome.

#### FUNDING

No funding

#### CONFLICT OF INTEREST

The authors report no conflict of interest.

#### GRANT SUPPORT

No grant support

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