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ORIGINAL RESEARCH

Long-term testosterone replacement therapy reduces fatigue in men with hypogonadism

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Abstract

Background: Testosterone replacement therapy (TRT) is one of the main lines of treatment for men with hypogonadism. This study sought to evaluate the influence of TRT in men with late-onset hypogonadism (LOH), regarding fatigue, coronary artery disease (CAD), carotid intima-media thickness (CIMT) and cardiovascular risk.

Methods: This study compared men with LOH already on TRT for >1 year to newly diagnosed men with LOH who recently started TRT (controls). We included men aged >18 years with clinical manifestations of testosterone deficiency and testosterone levels of <300 ng/dL documented in two separate occasions.

Results: A total of 33 patients were included in the study group and 30 in the control group. Mean age was 49.1 years (±11.5) in those already under TRT for >1 year and 45 (±12.2) years in the control group (p=0.18). CAD was present in 14 (46.7%) patients in the control group and in 3 (9.1%) in the study group (p<0.001). TRT >1 year was not associated with lower rates of CAD in multivariable analysis. Fatigue Severity Score was significantly higher in the control group (39.2±15.0), compared to TRT >1 year (23.5±8.1; p<0.001). In a multivariable analysis adjusted for age and hypertension, TRT >1 year was associated with a 14.8-point decrease in Fatigue Severity Score (p<0.001). Overall, there were no differences between the study group and the control group regarding cardiovascular risk (p=0.31).

Conclusion: TRT for >1 year was associated with significantly lower fatigue scores. No differences were observed regarding CIMT, CAD and cardiovascular risk according to the WHO-ISH scale.

Keywords: fatigue, heart disease risk factors, hypogonadism, testosterone.

Citation

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Introduction

Testosterone is a steroidal hormone that coordinates multiple physiological functions, including carbohydrate, protein and lipid metabolism.[1] Male hypogonadism is defined by the presence of characteristic signs and symptoms, including erectile dysfunction, infertility, fatigue, and diminished libido, and low serum testosterone levels,[2] which can be due to multiple pathologies of the hypothalamic–hypophysis–testis axis.[3,4]

In middle-aged and elderly men, late-onset hypogonadism (LOH) can have a profound impact in both physical and mental health, resulting in anaemia, osteoporosis and obesity. Hypogonadism is also involved in cardiovascular health and homeostasis, being associated with both increased cardiovascular and all-cause mortality.[5,6]

Men with hypogonadism are subject to a higher risk of developing insulin resistance and diabetes, which has led the American Diabetes Association to recommend routine testosterone level assessment in patients with type 2 diabetes.[7] Although less specific, fatigue is also a concern in these patients, impairing quality of life and well-being.[8]

Testosterone replacement therapy (TRT) is one of the main lines of treatment for men with hypogonadism. It has been shown to improve sexual satisfaction, desire and erectile function[9–14] and has recently been associated with improvements in fatigue.[8,15–18] This study sought to evaluate the influence of TRT in men with LOH regarding coronary artery disease (CAD), carotid intima-media thickness (CIMT), fatigue and cardiovascular risk.

Methods

This study compared men with LOH who were already on TRT for >1 year (study group) to men newly diagnosed with LOH who recently started TRT (<1 year; control group). The outcome variables of interest were CAD, CIMT, fatigue and cardiovascular risk.

Inclusion criteria were men >18 years old with a clinical manifestation of testosterone deficiency and testosterone levels <300 ng/dL documented in two separate occasions.[11]

Manifestations of hypogonadism can be divided into sexual and non-sexual. The former includes low libido, reduced morning erections, difficulty reaching orgasms and orgasm intensity reduction. The non-sexual manifestations include fatigue, difficulty concentrating, depression, and diminished vitality and well-being. TRT was initiated and titrated according to the AUA 2018 Guidelines on the subject.[11]

Patients were excluded if they had contraindications to TRT such as active prostate cancer. Furthermore, patients were not included in the study if fatigue was attributable to other clinical conditions such as congestive heart failure. Apart from recording the abovementioned symptoms, weight, height and body mass index (BMI) were obtained.

Testosterone levels and laboratory workup

Circadian fluctuations might influence testosterone levels; therefore, all laboratory measurements were collected between 7 a.m. and 10 a.m. (circadian rhythm). Low levels were confirmed in a second analysis, and no diagnoses of testosterone deficiency were made based on low serum testosterone alone. Serum prostate-specific antigen (PSA) was also checked to exclude potential prostate cancers.

Laboratory workup for all patients included complete blood count, cholesterol, fasting glucose, HbA_{1c}, blood urea nitrogen, creatinine, ultrasensitive C reactive protein, ALT/AST, LH/FSH, SHBG, prolactin, cortisol and TSH. Adiponectin, an inflammatory biomarker linked to atherosclerosis, obesity, cardiovascular risk and cancer, was dosed using immunoenzymatic assays, with normal values being <8.95 µg/mL according to the manufacturer.[19] Haemoglobin levels of <50% were required in order to initiate TRT. All patients were treated with testosterone undecylate.

Endpoint assessment

The primary endpoint was fatigue. Fatigue was studied using a locally validated scale (Fatigue Severity Scale; FSS).[20] The FSS is composed of nine items, which are assigned to scores ranging from 1 (completely disagree) to 7 (completely agree). The total score is the sum of the nine items, and a larger score represents a higher degree of fatigue.

Secondary endpoints were (1) CIMT, assessed using ultrasound (Logic 7, GE) with >7 MHz linear probe;[21] (2) CAD, evaluated using a stratified approach wherein patients with symptoms of CAD were submitted to cardiac catheterization and patients without symptoms were submitted to a treadmill/pharmacological stress test and, if positive, underwent invasive cardiac catheterization (the absence of ischaemic changes on standard stress testing was interpreted as absence of CAD); and (3) cardiovascular risk, evaluated according to the previously validated World Health Organization – International Society of Hypertension (WHO-ISH) score,[22] which assesses the 10-year risk of a cardiovascular event (myocardial infarction or stroke), according to demographic and comorbidities data.

Statistical analyses

Continuous variables were described as mean (±standard deviation (SD)) or median (interquartile range (IQR)), as appropriate according to normality checks (Shapiro–Wilk test) and compared using Mann–Whitney *U* tests. Categorical variables were described as frequency (valid percentage) and compared using χ^2 tests.

Simple and multiple linear regression analyses were conducted to evaluate associations between variables of interest and quantitative outcomes. Simple and multiple logistic regression analyses were conducted to evaluate associations between variables of interest and binary outcomes. Analyses were performed using SAS System for Windows (Statistical Analysis System, 9.4. SAS Institute Inc, 2002–2012, Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria, 2018).

This study was approved by the ethics committee of the Pontifícia Universidade Católica de Campinas, Campinas, Brazil (reference number: 3.729.053, approved 11/27/2019).

Results

A total of 33 patients were included in the study group and 30 patients were included in the control group. Mean age was 49.1 (±11.5) years in those already under TRT for >1 year and 45 (±12.2) years in the control group (p=0.18). Men in the control group were under TRT for 4.2 (±3.5) months, whilst men in the study group were under TRT for 28.8 (±13.3) months (p<0.001). Regarding ethnicity, White men composed 71.4% of the study group and 75% of the control group. Patient characteristics are described in Table 1, and main outcomes are described in Table 2.

CIMT

The mean CIMT was 0.67 (±0.13) in the control group and 0.7 (±0.25) in the study group, demonstrating no difference (P=0.74). Therefore, no further analyses were conducted regarding this outcome.

Fatigue

FSS score was significantly higher in the control group (39.2±15.0) compared to TRT >1 year (23.5±8.1; p<0.001). In

Table 1. Patient characteristics.

Variable	Control group (*n*=30)	TRT >1 year (*n*=33)	Total (*n*=63)	*p* value
Age (years)	45±12.2	49.1±11.5	47.2±11.9	0.18
Height (m)	1.77±0.06	1.76±0.07	1.76±0.07	0.60
Weight (kg)	101.1±23.2	95.8±17.5	98.3±20.4	0.45
BMI (kg/m^2)	31.9±6.3	30.9±5.6	31.4±5.93	0.54
SBP (mmHg)	136.7±22.4	127.1±14.9	131.7±19.3	0.04
DBP (mmHg)	91.2±16.1	83.5±10.0	87.1±13.7	0.02
Smoker	4 (13.3%)	4 (13.3%)	8 (12.7%)	0.88
Hypertense	24 (80%)	7 (21.2%)	31 (49.2%)	<0.001
Diabetic	7 (23.3%)	3 (9.1%)	10 (15.9%)	0.53
TRT duration (months)	4.2 (±3.5)	28.8 (±13.3)	17.1 (±15.8)	<0.001
Haemoglobin (g/dL)	14.8±1.6	15.6±13	15.2±1.5	0.06
LDL (mg/dL)	111.6±29.6	97.8±40.5	104.4±36.1	0.08
Cholesterol (mg/dL)	181.7±33.5	170.5±46.9	175.9±41.1	0.20
HDL (mg/dL)	38.2±7.1	44.3±14.2	41.4±11.7	0.049
Glycemia (mg/dL)	102±16.7	100±22.2	100.9±19.7	0.23
HbA1c (%)	6.26±2.6	6.0±1.5	6.1±2.1	0.86
CRP (mg/dL)	3.8±5.8	1.7±2.8	2.7±4.6	0.003
Adiponectin (µg/mL)	5.8±2.3	5.5±4.9	5.7±3.9	0.11
TT (ng/dL)	282.5±152.9	493.9±287.1	393.2±254.5	<0.001
LH (mUI/mL)	3.5±2.7	1.5±1.7	2.5±2.4	<0.001
FSH (mUI/mL)	4.8±6.0	3.0±3.8	3.9±5.0	0.01
SHBG (nmol/L)	21.5±7.6	28.9±26.4	25.4±20.0	0.09
Prolactin (ng/mL)	9.7±4.4	8.9±4.0	9.3±4.2	0.43
Cortisol (µg/dL)	11.4±4.3	12.6±4.6	12.1±4.5	0.27
TSH (UI/mL)	2.3±1.2	2.3±1.7	2.3±1.5	0.44
Total PSA (ng/mL)	0.57±0.34	1.07±0.85	0.83±0.70	0.02

Data are presented as mean (±standard deviation) and frequency (valid percentage); *p* values refer to Mann–Whitney *U* tests (continuous) and χ^2 tests (categorical).
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; TT, total testosterone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin; TSH, thyroid-stimulating hormone; PSA, prostate-specific antigen.

the univariate linear regression, there was also an association (p<0.001), with an adjusted R^2 of 0.32. In the multivariable analysis adjusted for age and hypertension, TRT >1 year was associated with a 14.8-point decrease in the FSS (p<0.001) (Table 3).

CAD

CAD was present in 14 patients in the control group (46.7%) and 3 (9.1%) in the study group (p<0.001). In the univariate logistic regression, TRT >1 year was associated with a decrease in CAD (p=0.005), but this association was not confirmed in the multivariable analysis including age, hypertension and BMI (Table 4).

Cardiovascular risk (WHO-ISH)

WHO-ISH scores are described in Table 2. Overall, there were no differences between the study group and the control group (p=0.31). Dichotomized logistic regression analyses were also undertaken (Table 5), dividing patients with <10% and ≥10% risk. These analyses also failed to demonstrate an association between WHO-ISH <10% and TRT >1 year.

Discussion

Patients treated with TRT >1 year exhibited significantly lower fatigue severity scores. There were no differences regarding cardiovascular outcomes, namely, CIMT, CAD and

Table 2. Main outcomes – WHO-ISH cardiovascular risk, fatigue, intima-media thickness and coronary artery disease.

	Control group (*n*=30)	TRT >1 year (*n*=33)	Total (*n*=63)	*p* value
WHO-ISH				0.31
<10%	2 (6.7%)	3 (9.1%)	5 (7.9%)	
10–20%	2 (6.7%)	0	2 (3.2%)	
20–30%	26 (86.7%)	30 (90.9%)	56 (88.9%)	
Fatigue	39.2±15.0	23.5±8.1	31.0±14.2	<0.001
Carotid plaque	6 (20%)	11 (37.9%)	17 (28/8%)	0.13
CIMT	0.67±0.13	0.7±0.25	0.7±0.2	0.74
CAD	14 (46.7%)	3 (9.1%)	17 (27.0%)	<0.001

Data are presented as mean (±standard deviation) and frequency (valid percentage); *p* values refer to Mann–Whitney *U* tests (continuous) and χ^2 tests (categorical).
CAD, coronary artery disease; CIMT, carotid intima-media thickness; TRT, testosterone replacement therapy; WHO-ISH, World Health Organization – International Society of Hypertension.

Table 3. Association between fatigue and TRT.

	Coefficient	SE	*T* statistic	*p* value
Univariate				
TRT >1 year	–15.7	2.8	–5.5	<0.001
Adjusted R^2	0.32			
Multivariable				
TRT >1 year	–14.8	3.6	–4.1	<0.001
Age	–0.16	0.12	–1.27	0.21
Hypertension	0.05	3.5	0.01	0.99
Adjusted R^2	0.31			

Linear regressions describing the association between testosterone replacement therapy (TRT) and fatigue, quantified according to the Fatigue Severity Scale. SE, standard error.

Table 4. Association between TRT and coronary artery disease.

	Coefficient	SE	*Z* statistic	*p* value
Univariate				
TRT >1 year	–1.80	0.64	–2.8	0.005
Multivariable				
TRT >1 year	–1.11	0.83	–1.35	0.18
Age	0.04	0.034	1.07	0.29
Hypertension	2.12	0.93	2.3	0.02
BMI (kg/m^2)	0.003	0.07	0.04	0.97

Logistic regressions describing the association between testosterone replacement therapy (TRT) and coronary artery disease. BMI, body mass index; SE, standard error.

cardiovascular risk, according to the WHO-ISH scoring system.

TRT has gained increasing attention over the last decades for its benefits in multiple axes of male health. Cardiovascular benefits, such as blood pressure and lipid profile improvement and waist circumference and BMI reduction, have been hypothesized in uncontrolled studies. However, these benefits have not been demonstrated in placebo-controlled trials. The benefits in terms of sexual function, on the other hand, are self-evident, improving sexual satisfaction, desire and erectile function.[9–14]

In the present study, no differences were observed regarding cardiovascular outcomes. This study is not intended or designed to study cause–effect relations between the treatment and control groups. However, aside from the prevalence of hypertension, the samples are generally similar. The FSS on the TRT group was nearly half that of the recently initiated therapies. We believe this is indirect evidence that TRT significantly improves the well-being of the individual.

Prevalence of cardiovascular disease, either CAD or carotid disease, did not differ between groups. This was further observed by the absence of significant differences in the WHO-ISH evaluation of 10-year cardiovascular risk. Nevertheless, an unbalanced prevalence of hypertension might have influenced those results, even though this variable was accounted for in the multivariable analyses.

Table 5. Association between WHO-ISH <10% and testosterone replacement >1 year.

	Coefficient	SE	*T* statistic	*p* value
Univariate				
TRT >1 year	0.39	0.81	0.49	0.63
Multivariable				
TRT >1 year	−0.37	1.08	−0.35	0.73
Age	−0.10	0.05	−2.1	0.04
Hypertension	−2.5	1.5	−1.7	0.09
BMI (kg/m^2)	−0.2	0.1	−2.3	0.02

Logistic regressions describing the association between TRT and cardiovascular risk described by the WHO-ISH system. BMI, body mass index; SE, standard error; TRT, testosterone replacement therapy.

This study further strengthens a growing body of evidence that supports the pivotal role of TRT in individuals with LOH by adding evidence that it improves fatigue.[8,15–18] We support the American Diabetes Association's recommendation to obtain a serum testosterone in patients with type 2 diabetes as they are particularly affected by hypogonadism and benefit from TRT.[7]

Moreover, signs and symptoms of LOH are easily overlooked, which might have longstanding negative effects on male health and well-being. Primary care clinicians and cardiologists will often encounter patients reporting these unspecific complaints; therefore, considering the hypothesis of hypogonadism might significantly improve patients' quality of life.

Study limitations

This study has many limitations. It is an observational study, meaning that the TRT was already in place for the study group without a baseline analysis. The study also suffers from the limitations inherent to non-randomization. TRT might also present negative long-term effects, such as polycythaemia, which need to be carefully monitored and might warrant treatment discontinuation. Furthermore, the sample is heterogeneous and relatively small, which can limit statistical power. Nonetheless, it is a real-world assessment of patients undergoing hormonal replacement using a locally validated tool to study fatigue. This study might help build sufficient background to support a randomized trial on the subject.

Conclusion

TRT for more than 1 year was associated with significantly lower fatigue scores. No differences were observed regarding CIMT, CAD and cardiovascular risk according to the WHO-ISH scale.

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