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Effects of chronic testosterone administration on myocardial ischemia, lipid metabolism and insulin resistance in elderly male diabetic patients with coronary artery disease

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Abstract

Background: The evidence of antiatherogenic and vasodilatatory effects of testosterone (T) suggest a possible role of the lack of this hormone in the development and pathophysiology of coronary artery disease (CAD).

Aim of the present study was to evaluate the effects of oral administration of testosterone undecanoate during a period of three months on serum lipid levels and on the occurrence of anginal attacks and daily ischemic episodes in patients with CAD.

Methods and results: Eighty seven (87) diabetic male subjects (mean age: 74±7 years) with proven CAD were randomized to a 12 week treatment with either T undecanoate (40 mg administered three daily) or placebo (P) in a double blind protocol.

Weekly episodes of angina attacks, number of ischemic episodes daily and total ischemic burden on ambulatory ECG Holter were evaluated at baseline and at the end of the study. Serum total cholesterol and triglyceride concentrations were also measured at the same time points.

Compared to P, T significantly reduced the number of anginal attacks/weeks of 34% ($p<0.05$); the silent ischemic episodes of 26% ($p<0.05$), and the total ischemic burden of 21% ($p<0.05$) on ambulatory ECG monitoring. After 12 weeks total cholesterol, plasma triglycerides and HOMA index were significantly reduced in the T group compared to P group.

Conclusions: Three months administration of T has beneficial effect on serum cholesterol and triglyceride levels in patients with CAD and reduces the number of anginal attacks, and ischemic episodes. These effect may be related to the metabolic and vasoactive properties of the hormone.

Further studies are needed in order to assess the long term relevance of these effects.

Keywords: Coronary disease; Elderly male; Diabetes; Testosterone

1. Introduction

Because of the greater risk of coronary artery disease shown by men during reproductive years with respect to women, a negative link between androgens and coronary artery disease has been postulated [1]. It had been suggested

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that this gender difference may be caused by an antiatherogenic effect of estrogens [2], but also by a proatherogenic action of androgens [3].

However recent studies demonstrated that low rather than high testosterone levels are related to CAD. English et al. showed that men with coronary artery disease (CAD) have lower levels of androgens than men with normal coronary angiograms [4] and others have reported that hypotestosteronemia in male may represent a risk factor for coronary atherosclerosis [5]. Moreover unlike data based on old studies, mainly conducted in female to male transsexuals or in subjects taking pharmacological doses of synthetic androgens, which seemed to confirm an unfavourable effect of these hormones on plasma lipid profile [6], recent results seem to suggest a beneficial effect of physiological testosterone (T) replacement on lipid profile, with lower or unchanged total cholesterol and low density lipoprotein (LDL) levels and higher or unchanged high density lipoprotein (HDL) level [7].

There is a growing evidence of anti-atherosclerotic effects and of T. Animal studies have shown that T replacement is associated with an up-regulation of the expression of arterial androgen receptor mRNA coupled with a significant reduction of neointimal plaque development. Of interest, in this study, T levels needed for plaque inhibition were within the range of physiological concentrations [8]. Other animal studies have also shown that in mice T attenuates early atherogenesis most likely through its conversion into estrogens by the enzyme aromatase expressed in the vessel wall [9]. The anti-atherosclerotic effect of T may be related, at least in part to its immuno-modulating effects like suppression of cytokine activation [10].

Furthermore, several studies have shown that acute administration of T increases coronary flow and has anti-ischemic effects in men with CAD [11–13].

Aim of the present study was to evaluate the effect of oral administration of T undecanoate on frequency of episodes of angina attacks and daily ischemia in elderly male patients with CAD. Secondary endpoints were and to assess its effects on insulin resistance and lipid profile.

2. Methods

2.1. Subjects

The study population included 141 male patients aged between 57 and 74 years (mean age 68±7 years) with chronic stable angina, proven CAD (≥70% stenosis in one of the major epicardial coronary arteries) or previous myocardial infarction; presence of transient episodes of ST segment depression on ambulatory ECG monitoring or inducible myocardial ischemia on exercise test; age >65 years, diagnosis of diabetes non insulin-dependent, no contraindications to the use of T.

Patients with recent (<3 months) unstable angina and/or acute myocardial infarction, arrhythmia (Lown IV), cardiac surgery, or any conditions that could prejudice the interpretation of the ST segment and clinical evaluation, severe hypertension (blood pressure > 180/110 mm Hg), significant arrhythmias, conduction disturbances, uncorrected hypokalemia, primary valvular or congenital heart disease, pericardial or endocardial disease, kidney or liver dysfunction, were excluded from the study. Moreover patients with prostatic hypertrophy, elevated blood levels of Prostate-specific antigen (PSA) suspected or assessed prostatic neoplasm were excluded, as well as patients presenting contraindications to androgen therapy or receiving antidepressant drugs. Patients unable to comply with the protocol or refusing the exam related to end-point and those scheduled to undergo myocardial revascularization procedures were also excluded.

During the study period therapies routinely used for the treatment of CAD (e.g. acetylsalicylic acid, other antiplatelet agents, anti-anginal therapy) were continued.

2.2. Study design

After a run in period of one month to confirm the stability of the clinical status patients were enrolled in a double-blind, placebo-controlled study and were randomized to a 12 weeks double blind treatment with either T undecanoate (40 mg administered three times daily) or placebo on top of their anti-anginal therapy. A 24 hour ambulatory ECG monitoring (AEM) and fasting blood samples for serum total cholesterol, HDL-cholesterol and triglycerides were performed at baseline and at the end of the study. Patients were instructed to record in an anginal diary the number of episodes and the consumption of nitroglycerine tablets. All patients signed informed consent of the study that was approved by local ethics committee (IRCCS San Raffaele).

Randomization was computer-based and provided internally, independently from the investigating physicians. The investigating physicians were kept blind from the treatment sequences until all the database was completed and ready for statistical analysis.

2.3. Ambulatory ECG monitoring

A 24-hour 12-lead Ambulatory Electrocardiogram Monitoring (AEM) was performed using the H12-digital recorder (Mortara Instruments, Inc., Milwaukee, US, Bologna, I) at baseline and at the end of the treatment period. During each monitoring, patients were asked to adhere to their usual level of physical activity. The monitoring of period started between 08.00 and 10.00 AM and ended at the same hour of the following day.

The analysis of the 12-lead AEM was performed using the H-Scribe Holter System (Mortara Instruments, Inc., Milwaukee, US, Bologna, I). A positive response (ischemic episodes) was defined as a horizontal or downsloping ST-segment depression >1 mV (1 mm), 60 ms after J point occurring in ≥6 consecutive complexes. The ST-segment, 60 ms after J point was evaluated

after signal averaging by a computer-assisted system in all 12 leads. The leads showing the greatest ST-segment depression in the baseline 24 hour monitoring were selected for analysis. The semi-automated ECG analysis was reviewed by experienced investigators unaware of clinical data, periods of ST segment depression were labelled and printed on paper and for each analysis number of episodes, duration of each episode, total ischemic time and degree of ST segment depression were noted. Evaluation criteria consisted of number of ischemic episodes recorded on the AEMs during the 24 h. Measures included: I) number of ST depression episodes ≥ 1 mm lasting >60 s, II) number of silent episodes and III) total ischemic burden defined as the sum of the duration of ischemic episodes.

2.4. Laboratory measurements

Blood samples were collected in the morning (usually between 08:00 and 09:00) after an overnight fast. Serum total cholesterol and triglyceride concentrations were measured on fresh serum by enzymatic colour test (Olympus Diagnostica GmbH – Irish Branch – Lismeehan, O'Callaghan's Mills, Co. Clare, Ireland).

2.4.1. Insulin resistance (IR)

Glucose and insulin were measured after an overnight fasting. The blood samples were collected in 5 ml tubes immediately placed on ice and transferred to the biochemistry laboratory where samples were processed. Plasma insulin levels were measured by immunoradiometric assay using a commercially available kit (DiaSorin, Inc., Reutlinger, Germany). IR was estimated by the homeostasis model assessment (HOMA-IR) from the equation: fasting insulin × fasting glucose/22.5. HOMA was not measured in those patients treated with insulin.

2.5. Statistics

We calculated a need of 85 patients to complete the trial to demonstrated with 90% power and 5% significance a reduction in anginal episodes of 25% assuming a dropout rate of 15%.

Results were expressed as median ± standard deviation (SD). Between groups comparisons were made using the paired Student *t* test or the Mann–Whitney *U* test as appropriate, and the Chi-square tests for dichotomous variables. A 2-tailed *P* value of <.05 was considered statistically significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 12.0, Chicago, III).

3. Results

Of the 141 patients screened, 87 were found eligible for the study. Nine patients were not included because of renal failure in advanced stage (creatinine clearance <30 mg/dl); 16 patients had PSA levels >3 ng/ml; 5 had hematocrit >50%; 14 had conduction disturbances on ECG; 4 patients had inadequate ECG quality of the ECG recording and 5 because they did not perform the follow up ambulatory ECG monitoring. Patients enrolled were randomized to either T (43 patients) and or placebo (P) (44 patients).The clinical characteristics of the study patients at baseline are reported in Table 1. The two groups were well matched: there were no significant differences in incidence of risk factor for coronary artery disease, blood pressure levels, drugs intake.

At baseline 9 patients of the T group and 7 patients of the P group did not have anginal attacks in the previous week, while symptomatic patients of the two groups had similar values of anginal attacks/week ($p>0.05$). After three months of therapy, the mean number of anginal attacks/week significantly decreased in the T group respect to baseline (−34%; $p<0.05$) compared to placebo (Fig. 1). Results of ECG monitoring are summarized in Table 2. At baseline the two groups had similar number of silent episodes of myocardial ischemia. At the end of the study patients allocated to T had a significantly lower incidence of silent episodes of myocardial ischemia compared both to P group (26%; $p<0.01$).

Patients allocated to T or P had a similar total ischemic burden at baseline, ($p>0.05$). After three months of T therapy the total ischemic burden was reduced of 22% ($p<0.01$) in the T group while remaining unchanged in patients allocated to P ($p>0.05$) with a significant intergroup difference (21%, $p<0.05$).

Table 1
Baseline characteristics of patients in the testosterone and placebo group.

Baseline characteristics	Testosterone group (*N*=43)	Placebo group (*N*=44)
Age	74.5±8	75.6±11
Previous MI	13 (32)	16 (36)
Previous CABG	12 (28)	9 (20)
Risk factors, n (%)		
Hypertension	27 (63)	31 (70)
Diabetes	13 (37)	17 (39)
Dyslipidemia	28 (65)	32 (72)
Current smoker	6 (13)	5 (11)
Baselline recordings, mean±SD		
Body mass index	27.4±3	27.1±4
Fasting glycemia, mg/dl	98.3±11	94.7±14
C-reactive protein, mg/dl	4.4±1	4.8±1
Rest heart rate, bpm	74.3±7	77.6±8
Systolic blood pressure, mm Hg	125±36	121±42.
Diastolic blood pressure, mm Hg	92±13	89±11
Concomitant therapy, n (%)		
Aspirin	43 (100)	44 (100)
B-Blocker	36 (84)	39 (88)
Calcium channel blocker	23 (53)	21 (47)
ACE inhibitor	26 (60)	22 (60)
Long-acting nitrate	16 (37)	19 (43)
Statin	33 (76)	37 (84)
Diuretics	9 (21)	13 (29)

Continuous data are expressed as median±standard deviation.

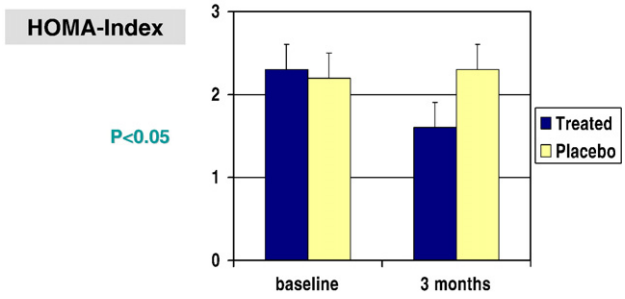

Fig. 1. Comparison of HOMA-IR changes between T and P group. After three months of testosterone administration HOMA-IR was significantly reduced in T group compared to placebo with $p<0.001$.

Comparative effects of on lipid profile are summarized in Table 3. Total cholesterol levels were reduced from −17± 6 mg/dl at the end of the third month post T supplementation and were increased of 5±0.7 mg/dl at the end of the third month post P. Triglicerydes decreased significantly in the testosterone group compared to placebo group. No significant intergroup differences were found on HDL-cholesterol levels. HOMA-IR decreased significantly in the testosterone group compared to placebo group (Fig. 1).

No significant side effect requiring discontinuation of the study medication was noted throughout the study. No patient died during the follow-up period. There was no significant change in haemoglobin or PSA in either group.

4. Discussion

The present study shows that T supplementation in patients with CAD, at the same doses used in male patients with hypogonadism, reduces the frequency of angina attacks, the number of ischemic episodes and the time of ischemia on ambulatory ECG monitoring. Moreover T has positive effects on cholesterol and triglyceride levels and reduces the insulin resistance state. Results of this chronic study are in agreement with previous studies that have suggested an anti-anginal and anti-ischemic effect of acute T administration [11–13].

The anti-ischemic effects of T seen in the present study may be related to its vasoactive properties and the effects shown on the lipid profile suggest the safety of chronic T on lipid metabolism. The metabolic effects seen in the present study are different from those obtained in normal subjects with anabolic steroids. Indeed, the abuse of anabolic steroids by athletes does not seem to lead to the same positive effects on serum lipids, in fact during administration of large doses of testosterone and anabolic steroids during a 12-week strength training period, HDL decreased and triglyceride increased [14] and significant differences in cholesterol, HDL and LDL levels were found in subjects after 18 months of therapy with anabolic hormones [15]. Besides these relevant secondary effects on lipids, therapy with anabolic steroids suppresses the hypothalamus–pituitary gland–gonad axis [16], and the reduction of testosterone levels itself might be the cause of negative effects on lipids. The same negative effects appear in healthy, nonobese, young female-to-male transsexuals which consume testosterone-ester [250 mg intramuscularly (i.m.)/2 weeks]. This treatment reduces HDL-cholesterol and the LDL-particle size, increases triglycerides and induces an android fat distribution (i.e. decrease of subcutaneous and increase of visceral fat), considered a risk factor for cardiovascular disease [17].

Our results are in agreement with previous studies that have demonstrated a beneficial effect of acute administration of T on exercise-induced myocardial ischemia in men with CAD [11,12] and with other studies that have shown a positive effect of low-dose transdermal administration of T on angina threshold in men with chronic stable angina [13] suggesting that the effect seen acutely with pharmacological doses are sustained in chronic with physiological replacement. The beneficial effect of T supplementation on daily episodes of myocardial ischemia may also suggest that the acute vasoactive effects of the hormone are sustained long term. Whether the effects of T upon myocardial ischemia are mediated by its tissue conversion in estrogens or whether the effects are due to a direct effect of the hormone upon K channels is still a matter of speculation. Several physiological actions of T in men are estrogen receptors (ERs) mediated after conversion of T to estradiol (E_2) by site specific aromatases in target tissues particularly interesting for our study is the documented presence of aromatase in endothelial cells [18,19] and vascular smooth muscle [20]. Anyway, unlike women E_2 supplementation in male have controversial effects on vascular reactivity. Although some potential benefits on vascular reactivity in men have been

Table 2
Parameters of myocardial ischemia on ambulatory ECG monitoring at baseline and follow up in patients allocated to testosterone or placebo.

	Testosterone		Placebo	
	Baseline	3 months	Baseline	3 months
Episodes/patient	2.1±0.4	1.5±0.2*	2.2±0.2	2.3±0.3
Silent	1.68±0.3	1.23±0.2*	1.88±0.4	1.67±0.3
Symptomatic	0.8±0.2	0.5±0.1	0.7±0.1	0.6±0.2
Duration (s)	234±31	216±28	245±42	223±32
Burden (s/24 h)	472±52	378±44*	498±61	476±50

*$P<0.05$.

Table 3
Lipid profile and glucose blood levels in the testosterone and placebo groups at baseline and three months.

	Testosterone		Placebo	
	Baseline	3 months	Baseline	3 months
Total cholesterol, mg/dl	256±32	239±25*	240±29	245±27
HDL-cholesterol, mg/dl	28±6	31±11	29±7	30±7
Triglycerides, mg/dl	231±54	199±37*	226±40	223±39
Fasting glucose mg/dl	107.8±37	109±38	111±32	109±40

*$P<0.05$.

described after oestrogen administration [21], it do not seem to have a clinical role: in the study of Davis et al. [22] parenteral oestrogen therapy did not increase total exercise time or time to the onset of electrocardiographic changes of ischaemia in men with chronic stable coronary artery disease.

The clinical application of androgen replacement therapy remain controversial because of the potential prostatic and haematological adverse effects, however no data confirming an increase in voiding symptoms, prostate examination abnormalities or postvoid residual urine volumes during T treatment have been reported [23–25]. Moreover Sreekumaran Nair et al. [26] did not report any major adverse effect in 87 elderly men after two years of T administration. Only one study reported a 12% increase in prostate size [24]. The prostate specific antigen (PSA) was unmodified in most studies [13,24] and increased slightly within the normal range in others [25–28].

A recent review [29] supports efforts to exploit the wider therapeutic benefits of T in men should not be deterred or hampered by concerns regarding increased CAD risks. In androgen deficiency, the T replacement therapy is not contraindicated in male patients with known CAD. In elderly men androgen replacement, besides many benefits on various organs and apparatus, may also improve CAD and quality of life. The lack of long-term morbidity and mortality data prevents the use of androgens in primary and secondary prevention of CAD, especially when other established medical treatment modalities of proven benefit exist.

We have shown that T replacement therapy improves insulin resistance in elderly CAD patients. Our study confirm other recent reports that demonstrated improvement in glycaemic control fasting blood glucose and HbA1c with T treatment in similar patients [30,31].

This study have several limitations. Effects of T administration on quality-of-life were not assessed. Potential benefit on quality-of-life of elderly subjects have been recently reported in elderly healthy [32] men and in men with CAD [13]. According to our results testosterone administration in male patients with CAD seems to be effective and safe. However the follow up period is to shorten to exclude side effects related to a long-term testosterone administration; moreover further studies are needed in order to assess the long term relevance of clinical benefits observed.

5. Conclusion

Chronic T administration improves myocardial ischemia, lipid profile and insulin resistance in male patients with CAD. These effects probably mediated by both its vasoactive and metabolic actions. Further studies are needed to assess the effect of T replacement on stronger cardiovascular end points before suggesting androgens in the therapeutic approach of cardiovascular disease in males.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [33].

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