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Low-Dose Transdermal Testosterone Therapy Improves Angina Threshold in Men With Chronic Stable Angina
A Randomized, Double-Blind, Placebo-Controlled Study

Katherine M. English, MBChB, MRCP; Richard P. Steeds, MBBS, MRCP;
T. Hugh Jones, MD, MRCP; Michael J. Diver, PhD; Kevin S. Channer, MD, FRCP

Background—Experimental studies suggest that androgens induce coronary vasodilatation. We performed this pilot project to examine the clinical effects of long-term low-dose androgens in men with angina.

Methods and Results—Forty-six men with stable angina completed a 2-week, single-blind placebo run-in, followed by double-blind randomization to 5 mg testosterone daily by transdermal patch or matching placebo for 12 weeks, in addition to their current medication. Time to 1-mm ST-segment depression on treadmill exercise testing and hormone levels were measured and quality of life was assessed by SF-36 at baseline and after 4 and 12 weeks of treatment. Active treatment resulted in a 2-fold increase in androgen levels and an increase in time to 1-mm ST-segment depression from (mean±SEM) 309±27 seconds at baseline to 343±26 seconds after 4 weeks and to 361±22 seconds after 12 weeks. This change was statistically significant compared with that seen in the placebo group (from 266±25 seconds at baseline to 284±23 seconds after 4 weeks and to 292±24 seconds after 12 weeks; $P=0.02$ between the 2 groups by ANCOVA). The magnitude of the response was greater in those with lower baseline levels of bioavailable testosterone ($r=-0.455$, $P<0.05$). There were no significant changes in prostate specific antigen, hemoglobin, lipids, or coagulation profiles during the study. There were significant improvements in pain perception ($P=0.026$) and role limitation resulting from physical problems ($P=0.024$) in the testosterone-treated group.

Conclusions—Low-dose supplemental testosterone treatment in men with chronic stable angina reduces exercise-induced myocardial ischemia. (***Circulation***. 2000;102:1906-1911.)

Key Words: testosterone ■ hormones ■ angina ■ ischemia

Worldwide, men are twice as likely to die from coronary heart disease than women, who appear to be protected by endogenous or exogenous estrogens.[1] The abuse of extremely high doses of anabolic steroids has been linked to sudden cardiac death, leading many to believe that the physiologically high levels of androgens in men have a deleterious effect on the male cardiovascular system.[2]

However, a number of recent reports contradict this theory, indicating that androgens may be beneficial to the male cardiovascular system. Not only do androgens appear to have an antiatherogenic effect in men,[3,4] but testosterone may also be an effective antianginal agent. Significant improvements in angina threshold have been demonstrated in patients given supplemental intramuscular, oral, or intravenous testosterone.[5–9] However, the doses used in these trials were supraphysiological, and there is concern about the potential carcinogenic effects of high doses of testosterone on the prostate. A contemporary study has now demonstrated that intracoro-

nary administration of physiological doses of testosterone leads to an increase in coronary blood flow in men with ischemic heart disease.[10] The clinical impact of these experimental findings has yet to be determined.

This pilot study was therefore performed to examine the effects of long-term, low-dose transdermal administration of testosterone on angina threshold in men with chronic stable angina.

Methods
Study Protocol Summary

This was a double-blind, randomized, placebo-controlled, add-on trial. Subjects entered an initial 2-week, single-blind, placebo run-in period, followed by double-blind randomization to active or placebo treatment for 12 weeks. Subjects applied two 2.5-mg self-adhesive active testosterone or placebo patches each night before retiring. The time taken to reach 1-mm ST-segment depression during the Bruce treadmill exercise test was assessed at the beginning and end of the 2-week placebo run-in period and after 4 and 12 weeks of active treatment.

TABLE 1. Baseline Characteristics of Patients in the Placebo and Active Treatment Arms

Baseline Characteristics	Active Treatment (n=22)	Placebo Treatment (n=24)
Age (mean±SEM), y	62±2	62±2
Diagnosis of CAD, n (%)		
Angiogram	14 (64)	18 (75)
Previous MI	3 (14)	2 (8)
Angina+ETT	5 (22)	4 (17)
Risk factors, n (%)		
Hypertension	4 (18)	14 (58)*
Diabetes mellitus	2 (9)	5 (21)
Family history	8 (36)	13 (54)
Current smoker	1 (4)	4 (16)
Hypercholesterolaemia at presentation	15 (68)	18 (75)
Concurrent medication, n (%)		
Aspirin	22 (100)	24 (100)
β-Blocker	18 (81)	20 (83)
Long-acting nitrate	11 (50)	11 (45)
Calcium channel blocker	11 (50)	12 (50)
Nicorandil	1 (4)	3 (12)
Statin	13 (59)	17 (70)
ACE inhibitor	3 (13)	5 (20)
Diuretics	2 (9)	9 (37)†
Baseline recordings (mean±SEM)		
Body mass index, kg/m^2	27.7±0.7	28.4±0.8
Waist-to-hip ratio	0.96±0.1	0.98±0.01
Systolic BP, mm Hg	131±4	142±4‡
Diastolic BP, mm Hg	78±2	80±2.3
Cardiac output, L/min	3.8±0.2	3.7±0.3
Pulse, bpm	61±3	63±2

CAD indicates coronary artery disease; MI, myocardial infarction; ETT, exercise treadmill testing; and BP, blood pressure.

*λ^2=7.8, P<0.01.

†λ^2=5.1, P<0.05.

‡P<0.05.

Subjects

Sixty-one men with coronary artery disease (>70% stenosis of a major coronary artery at coronary angiography, previous proven myocardial infarction, or typical symptoms of angina pectoris and a "double positive" [>1-mm downsloping ST-segment depression associated with chest pain[treadmill exercise test) were screened from April 1998 to April 1999. All patients gave written informed consent, and the study was approved by the local ethics committee. No changes were made to antianginal medication for 4 weeks before or during the trial. Patients were excluded if they had a prostate specific antigen (PSA) level above the normal range or any other contraindication to androgen therapy. They were also excluded if they had left main stem (or equivalent) stenosis, a coronary or cerebrovascular event, or other trial drugs within the preceding 3 months; severe hypertension (blood pressure >180/114 mm Hg); significant arrhythmias, or ECG abnormalities precluding ST-segment analysis.

Of 61 patients screened, 53 entered the single-blind placebo run-in phase. Of these 53, 50 patients completed the single-blind run-in phase. Twenty-five patients were randomized to each group. Three

patients were withdrawn from the active treatment arm: 1 suffered a myocardial infarction, 1 had severe skin irritation, and 1 had an elective coronary angioplasty performed earlier than expected. One patient withdrew from the placebo arm complaining of depression. All early withdrawals after placebo run-in occurred before the first assessment of double-blind treatment; therefore, these subjects were excluded from the final analysis. Twenty-two patients completed active treatment and 24 patients completed placebo treatment; they were included in the final analysis.

Trial Drug

Testosterone was given via a transdermal patch delivery system (Andropatch, Smith Kline Beecham). Identical placebo patches were manufactured by Thera-Tech Inc. Subjects applied two 2.5-mg patches at night, a dose that has previously been shown to raise levels of testosterone to within the normal range in 93% of hypogonadal men and to mimic the normal diurnal variation in hormone levels seen in vivo.[11]

Patient Assessment

Patients were assessed at weeks 0, 2, 6, 10, and 14 between 8 and 9:30 AM under fasting conditions. Demographic details and antianginal drug use were recorded at the beginning of the trial; body mass index and waist-to-hip ratio were calculated at the beginning and end of the trial; and pulse and blood pressure were measured at each visit (Suntech 4240 exercise blood pressure monitor). Cardiac output was measured noninvasively with suprasternal Doppler aortovelography at weeks 0, 2, 6, and 14.[12] Treadmill exercise testing was performed at weeks 0, 2, 6, and 14 according to the Bruce protocol (MAX-1 Marquette advanced exercise system, software version 002E). Patients were kept on all current medication but were asked not to use glyceryl trinitrate (GTN) for 6 hours before the test. Because most patients in this trial had severe angina pectoris, we defined our primary end point as the time to 1-mm ST-segment depression rather than time to angina or maximum exercise time. Thus, the exercise test was terminated when the criterion of ≥1-mm ST-segment depression was fulfilled. The reproducibility of the 2 baseline exercise tests was 10.4±1.8%. All treadmill tests were supervised by 1 investigator (K.M.E.) and were analyzed independently by 2 other investigators (R.P.S., K.S.C.) who were blinded to the order of the exercise tests. The Marquette 002E software package analyses the signal-averaged ECG and produces a graphical display of the level of the ST segment 80 ms after the J point versus time. These graphs were visually examined, and the time taken to reach 1-mm ST-segment depression was recorded. The mean of the 2 investigators' results was used in the final analysis. The mean interobserver difference was 2.85±0.42%.

Measurements were made of free, total, and bioavailable testosterone[3]; estradiol; luteinizing hormone; follicle-stimulating hormone; lipid profile; fibrinolytic markers; full blood count; glucose; and insulin at weeks 0, 6, and 14. Free androgen index was calculated with this formula: total testosterone divided by sex hormone binding globulin times 100. PSA was measured at the beginning and end of the trial.

Trial subjects completed angina diaries throughout the trial and completed a short form 36 (SF-36) quality-of-life questionnaire, which has been previously validated, at weeks 0, 6, and 14.[13] The SF-36 evaluates health on 8 multi-item dimensions covering functional status, well-being, and overall evaluation of health. Each domain is given a numerical score; a positive change in score indicates an improvement in health perception, whereas a negative score indicates a decline in health perception.

Statistical Analysis

We calculated the need for 45 patients to complete the trial to demonstrate with 80% power and 5% significance an improvement in exercise time of 60 seconds. Between-group changes in time to 1-mm ST-segment depression and hormone levels over time were analyzed with ANCOVA, with time point and group entered as fixed factors and baseline values entered as a covariate to adjust for slight

TABLE 2. Hormone Levels in Both Groups at Baseline and at Weeks 6 and 14

	Baseline	Week 6	Week 14	P
Total testosterone (NR=7.5–37.0 nmol/L), nmol/L				
Active	13.55±0.78	22.34±1.19	18.57±1.6	<0.0001
Placebo	12.38±0.72	11.35±0.76	12.23±0.89	
P	0.3	<0.0001*	<0.001*	
Free testosterone (NR=37.4–138.7 pmol/L), pmol/L				
Active	45.68±2.42	84.70±4.89	72.56±5.8	<0.0001
Placebo	46.36±2.54	44.86±2.76	48.69±3.29	
P	0.9	<0.0001*	<0.001*	
Bioavailable testosterone (NR >2.5 nmol/L), nmol/L				
Active	2.85±0.28	4.34±0.26	3.35±0.31	<0.001
Placebo	2.6±0.18	2.42±0.22	2.44±0.18	
P	0.5	<0.0001*	0.01*	
Free androgen index (NR=18–50 U), U				
Active	36.41±1.59	65.49±3.22	54.40±4.2	<0.0001
Placebo	39.28±2.5	37.73±2.69	39.72±2.25	
P	0.3	<0.0001*	<0.005*	
LH (NR 1.3–9.1 IU/L), IU/L				
Active	4.49±0.61	1.95±0.35	2.72±0.67	<0.0001
Placebo	5.28±0.58	5.46±0.61	5.15±0.55	
P	0.358	<0.0001*	<0.005*	
FSH (NR=1.7–12.6 IU/L), IU/L				
Active	6.43±0.91	3.22±0.59	3.29±0.74	<0.0001
Placebo	6.88±0.91	6.98±0.91	7.0±0.88	
P	0.7	0.001*	<0.005*	
Estradiol (NR <150 pmol/L), pmol/L				
Active	70.27±6.05	80.50±6.6	77.68±4.8	0.301
Placebo	67.75±4	72.13±4.2	76.46±3.8	
P	0.7	0.3	0.8	

NR indicates normal range; LH, luteinising hormone; and FSH, follicle-stimulating hormone. All results expressed as mean±SEM. Probability values across the groups calculated with ANCOVA; between the 2 groups, with Student's *t* test for independent variables.
*Statistically significant.

differences in baseline measurements. Between-group differences at a single time point were examined by use of 2-tailed Student's *t* test. Spearman's correlation test was performed because of the relatively small numbers in the trial. Raw SF-36 scores were not normally distributed, so within-group changes were analyzed with Friedmann's test. However, the changes in SF-36 scores were normally distributed and were compared between the 2 groups with 2-tailed Student's *t* test. Unless otherwise stated, data are expressed as mean±SEM. Statistical significance was accepted at $P<0.05$.

Results

Table 1 displays the baseline demographic characteristics of the patients in the active and placebo-treated groups. The placebo group had a higher incidence of risk factors for coronary artery disease, higher systolic blood pressure, and higher diuretic usage; otherwise, the groups were well matched. There were no significant differences between the 2 groups in any of the parameters measured on the baseline blood samples.

Table 2 shows the hormone levels at baseline and weeks 6 and 14. At baseline, the mean androgen levels were at the lower limit of the normal range in both groups. Active treatment led to significant increases in the levels of androgens, which peaked at week 6 and waned slightly by week 14. These changes were reflected in changes in the levels of gonadotrophins. No other parameters changed significantly during the treatment period in the active group. There were no significant changes in any serum measurements in the placebo group.

Mean time to 1-mm ST-segment depression was not significantly different between the 2 groups at baseline ($P=0.25$) but was significantly greater in the active group by week 14 ($P<0.05$; Table 3). Mean time to 1-mm ST-segment depression increased in both groups, but the increase in the active group was greater than that seen in the placebo group ($P=0.02$ by ANCOVA; Figure 1). The increase in mean time to 1-mm ST-segment depression in the placebo group was of a similar magnitude to that seen in previous trials using a placebo arm over the same time period.[14,15] There were no significant differences between the 2 groups in rate-pressure product at maximum exercise. The change in time to 1-mm ST-segment depression from baseline in seconds and in

TABLE 3.   Changes in Exercise Parameters in Active and Placebo Groups

	Baseline	Week 6	Week 14	P
Time to 1-mm ST-segment depression, s				
Active	309±27	343±26	361±22	0.02*
Placebo	267±25	284±23	292±24	
P	0.25	0.09	<0.05*	
Rate-pressure product at 1-mm ST-segment depression				
Active	16 870±986	16 040±1070	16 800±939	0.59
Placebo	18 990±853	17 160±835	18 100±939	
P	0.1	0.4	0.3	
Raw change in time to 1-mm ST-segment depression, s				
Active		34±17	52±17	0.02*
Placebo		18±17	25±11	
P		0.5	0.2	
Change in time to 1-mm ST-segment depression, %				
Active		26±16	37±20	0.02*
Placebo		13±9	15±6	
P		0.5	0.3	

All values are expressed as mean±SEM. Probability values between the 2 groups with time were calculated with ANCOVA; between the 2 groups at a single time point, with student's unpaired *t* tests.
*Statistically significant.

percent was also greater in the active than the placebo group at weeks 6 and 14 (both $P=0.02$ by ANCOVA).

In the active treatment group, the change in time to 1-mm ST-segment depression at week 14 was significantly negatively correlated with baseline levels of bioavailable testosterone ($r=-0.46$, $P<0.05$) but was not correlated with the peak levels of bioavailable testosterone at week 14 ($r=0.21$, $P=0.4$; Figure 2). Bioavailable testosterone was used because this is the most accurate measure of testosterone levels.[3]

Reported angina frequency, pulse rate, mean blood pressure, cardiac output, body mass index, and waist-to-hip ratio were unchanged throughout the course of the trial in both groups.

The active treatment group showed improvements in all 8 domains of quality-of-life assessment by SF-36 at weeks 6 and 14 compared with baseline; these changes were statistically significant for role limitation resulting from physical problems

($P=0.02$) and pain perception ($P=0.03$, Table 4). Patients in the placebo group showed a reduction in quality-of-life scores in 7 of the 8 domains at week 6 and 5 of the 8 domains at week 14, but none of these changes were statistically significant. When the results between the 2 groups were compared, there was significantly greater improvement in the active group than the placebo group in social functioning ($P=0.04$), role limitation resulting from emotional problems ($P=0.03$), mental health ($P=0.04$), and general health perception ($P=0.03$) at week 6 and in role limitation resulting from physical problems ($P=0.04$) at week 14.

Safety Data
Overall, the transdermal testosterone delivery system was well tolerated. Skin irritation at the site of patch application was reported by 11 patients on active treatment and 6 on placebo. One patient, who was awaiting coronary revascular-
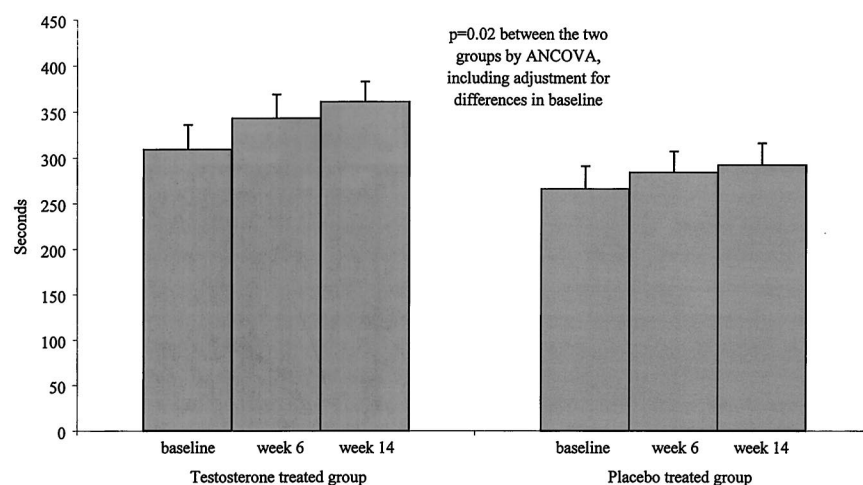

Figure 1. Time to 1-mm ST-segment depression in testosterone-treated and placebo groups at baseline and at weeks 6 and 12.
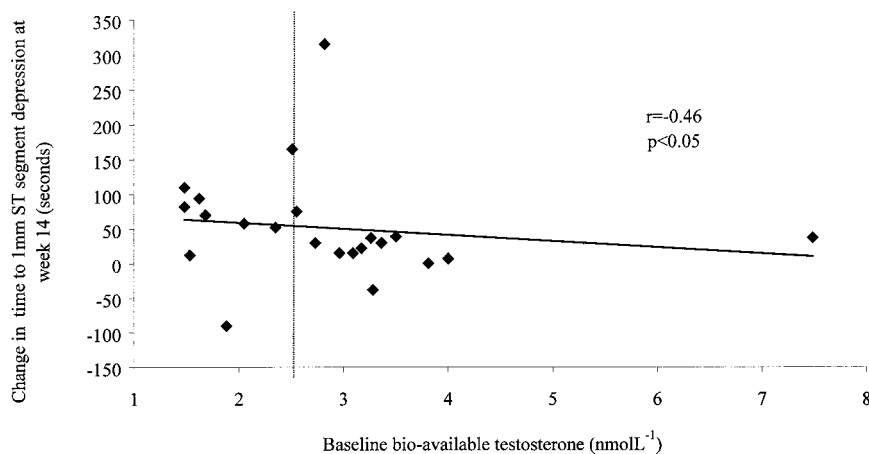
Figure 2. Correlation between baseline bioavailable testosterone and response to treatment in active treatment group. Vertical line indicates lower limit of normal range for bioavailable testosterone.

ization, suffered a myocardial infarction while on active treatment. There was no significant change in hemoglobin or PSA in either group.

Discussion

In this study, we have demonstrated that daily administration of small doses of supplemental testosterone to men with chronic stable angina prolongs the time to myocardial ischemia compared with the effect of placebo. The magnitude of the witnessed change resulting from active treatment over and above the effect of placebo ($\approx$22%) is in accordance with the results of 2 previous human studies that demonstrated improvements in time to myocardial ischemia of 23% and 22%, respectively, after high-dose intravenous testosterone.[8,9] Rosano et al[8] reported that the magnitude of response to testosterone was not significantly correlated with the peak hormone level, proposing that lower doses may also be effective, a suggestion that is supported by the findings of the current study.

The effect of testosterone appears to be greatest in those with lower baseline levels of androgens. The patients in this trial had relatively low baseline androgen levels, in keeping with previous findings of our own and other groups,[3,8,9] suggesting that there may be significant numbers of men with coronary artery disease who may benefit from this treatment.

TABLE 4.   Changes in Raw SF-36 Scores for Each of the Eight Domains in the Active Treatment Group

	Baseline	Week 6	Week 14	P
Physical functioning	51.9±4.8	56.8±5.1	56.5±4.9	0.580
Social functioning	72.8±6.6	81.7±6.	80.6±5.7	0.083
Role limitation–physical	34.7±8.8	42.6±11.1	57.5±8.7	0.024*
Role limitation–emotional	72.2±9.4	72.5±9.9	75.0±7.2	0.69
Mental health	77.7±2.2	81.9±3.5	80.6±3.6	0.07
Vitality	50.0±5.4	51.5±6.8	57.5±5.3	0.07
Pain	59.9±5.3	66.0±5.8	75.6±5.6	0.026*
General health perception	50.6±4	53.8±5.5	53.1±5.2	0.43

All values are mean±SEM. All probability values were calculated with the Friedmann test for nonparametric data. Positive change indicates improvement; negative change, deterioration.

*Statistically significant.

This study has not determined the mechanism behind the improvement in inducible myocardial ischemia. Experimental in vitro and in vivo studies have demonstrated that testosterone has a vasodilatory effect and that the coronary circulation is more sensitive to the vasodilatory effects of testosterone than larger vessels, such as aorta.[10,16] In this study, we witnessed no significant hemodynamic effects to suggest significant peripheral vasodilatation. Low-dose testosterone may act selectively on the coronary circulation, but this study was not designed to examine this effect.

Estrogen levels did not change in these patients, demonstrating that the beneficial effect of testosterone was not due to conversion of testosterone to estradiol by aromatase activity.

Not only does low-dose testosterone therapy appear to produce objective evidence of improvements in myocardial ischemia, but these patients showed improvements in all 8 domains measured by the SF-36. The most marked improvements in the active group were in pain perception and role limitation resulting from physical problems, suggesting that the measured effects on myocardial ischemia were affecting quality of life. However, despite the significant improvement in measured myocardial ischemia and quality-of-life scores, there were no changes seen in reported angina frequency by the patients in either group.

Currently, the incidence and consequences of absolute or relative male hypogonadism are poorly defined and probably underestimated. Age-related decreases in circulating levels of androgens may be implicated in the development of osteoporotic fractures, frailty of old age, anemia, sexual dysfunction, depression, and coronary artery disease in elderly men. Evidence already suggests that androgen replacement therapy may be beneficial in elderly men, but its use remains controversial, largely because of worries regarding cardiovascular, prostatic, and hematological adverse effects.[17] In this study, we have demonstrated that replacement of androgens to physiological levels in men with coronary artery disease improves their myocardial ischemic threshold and feeling of well-being and does not adversely affect other biochemical parameters.

This study was designed only to measure the response to treatment, not to study definitively the mechanism behind any change. Therefore, the suggestion that testosterone may act via a selective coronary vasodilatory action is speculative and requires further clarification.

Although these results and those of previous studies using intravenous and intracoronary testosterone are interesting, it must be noted that this study was planned as an initial pilot investigation and involved only small numbers of patients. The study was not powered to examine the effects of this therapy on cardiac morbidity and mortality. Large-scale clinical trials are required to confirm these results and further study the effects of androgen replacement therapy on the male cardiovascular system.

Acknowledgments

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