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Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial

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Summary The aim of this study was to assess the effect of a low-dose testosterone on body composition and pulmonary function, as well as on quality of life, sexuality, and psychological symptoms in patients with chronic obstructive pulmonary disease (COPD). Twenty-nine men with moderate to severe COPD were allocated to receive either 250 mg of testosterone or placebo intra-muscularly, every fourth week, during the 26 weeks study period. Fat-free mass increased in the treatment group ($P<0.05$), and a significant difference between the treatment and the control group was seen after 26 weeks ($P<0.05$). Fat mass decreased in the treatment group ($P<0.05$), and there was a significant difference between the treatment and the control group after 12 weeks ($P<0.01$). A significantly better erectile function was reported in the treatment group at the final visit ($P<0.05$), and the overall sexual quality of life was significantly better in the treatment group after 12 weeks ($P<0.05$). No improvement in pulmonary function was found. In conclusion, administration of a low-dose testosterone to men with COPD for 26 weeks was associated with improvement of body composition, better erectile function and sexual quality of life. Furthermore, there were no clinical or biochemical side effects.

Introduction

Chronic obstructive pulmonary disease (COPD) is a devastating, debilitating disease afflicting many millions of people worldwide. There are few effective therapies for COPD. Bronchodilators and anti-inflammatory drugs are often used even if the reversible component of the airway obstruction is modest. Long-term oxygen therapy (LTOT) has been shown to improve survival and the quality of life in severely hypoxic patients.[1,2] Pulmonary rehabilitation has been part of the treatment for many years and seeks to reestablish the patients to the highest possible level of function, but cannot reverse the pulmonary abnormalities.[3]

Individuals with COPD often have progressive weight loss, and loss of lean body mass has specifically been associated with skeletal muscle dysfunction.[4,5] Reversal of weight loss has been found to improve exercise capacity and improve survival.[6,7] Abnormalities in the levels of circulating testosterone have been described,[8,9] suggesting that substitution with androgens might be a rational therapy for patients with COPD. Testosterone supplementation in men with subnormal levels of testosterone have been shown to increase fat-free mass, reduce fat-mass, improve some aspects of physical, sexual, and cognitive functions, and improve mood and quality of life,[10–12] but for

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patients with COPD the information is scarce. In a study of 217 patients, administration of nandrolon in combination with nutritional support and exercise increased fat-free mass and respiratory muscle function.[13] In another study of 23 men with stable COPD and a body mass index (BMI) below 20 kg/m^2, treatment with stanozolol in combination with respiratory rehabilitation increased BMI and lean body mass.[14] To our knowledge, no study has been conducted on the potential effect of androgen therapy on quality of life and sexuality in patients with COPD.

In this study, we investigated the effect of a physiological dose of testosterone on anthropometric measures, body composition and, pulmonary function, as well as on subjective perceptions of quality of life, sexuality, and psychological symptoms in patients with moderate to severe COPD.

Materials and methods

Patients

Included were 29 ambulatory male patients, from the pulmonary outpatients clinic, aged 54–75, with moderate to severe COPD (forced expiratory volume in 1 s—$FEV_1 < 60\%$ of predicted). When entering the study they were all in stable condition. Patients with asthma, malignancies, cardiac impairment or hepatic or endocrine disease were excluded from participation. The Tromsø Regional Ethics Committee approved the protocol, and all participants gave their written informed consent. The study was performed in accordance with the recommendations in the Helsinki Declaration.

Study design

The objective was to evaluate the effects of testosterone treatment, with subjective health scales, body composition and FEV_1 levels as primary outcome measures. Secondary outcome measures were sexual function, androgen levels, additional pulmonary function tests, and performance status. The patients were randomly allocated in a double-blind fashion to receive every fourth week either testosterone treatment (an intra muscular depot injection of testosterone enanthate 250 mg, Primoteston-Depot©, Schering, Germany), or placebo (an intra muscular injection of 0.9% saline solution). The study period was 26 weeks and each patient received a total of seven injections. For 2 days at baseline, 12 and 26 weeks the patients were admitted to the Clinical Research Unit at the University Hospital of North Norway for extensive examinations.

Assessment

A physical examination including a prostate palpation was performed. A Flowmate-spirometer (Jaeger, Germany) was used to estimate forced vital capacity (FVC) and FEV_1 1 h after inhalation of a bronchodilator. A 6-min walking distance (6-MWD) was performed with assessment of the Borg score for breathlessness after walking. Nocturnal oxygen saturation (23.00–07.00 h) was measured with an N-100 pulse oxymeter (Nellcor, CA, USA). Blood gases were analyzed using a CIBA Corning 288 Blood Gas System analyzer (Medfield, MA, USA). Men with LTOT continued their oxygen treatment during the pulmonary function tests.

Height and weight were measured in subjects wearing light clothing without shoes. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Body composition was determined by dual energy X-ray absortiometry (DEXA) (Lunar Radiation Corp; Madison, Wisconsin, USA). Blood samples including hemoglobin, hematocrit, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, prostate specific antigen (PSA), glucose, testosterone, LH, FSH, and sex hormone-binding globulin (SHBG) were collected by venipuncture in a fasting state at 08.00 h and were analyzed using standard laboratory procedures at the department of clinical chemistry. Blood samples were obtained 4 weeks after injection of study medication at the 12 week visit and after 2 weeks at the last visit. Free testosterone values were calculated from total testosterone and SHBG according to Vermeulen et al.[15]

Four questionnaires were completed: (1) the St. George's respiratory questionnaire (SGRQ);[16] (2) the Montgomery-Asberg Depression Rating Scale (MADRS);[17] (3) the International Index of Erectile Function (IIEF-5)[18] with a few additional questions on sexuality; and (4) Rapid Disability Rating Scale-2 (RDRS-2).[19] In addition the minimental state examination (MMSE)[20,21] was performed by trained nurses.

Potential adverse events were recorded every fourth week, before the injection of study medication.

Statistical analysis

SPSS (SPSS Inc. SPSS Base 10.1 for Windows User's Guide) was used for all analysis. The

non-parametric Mann–Whitney *U*-test was used to determine the differences between the groups using delta values, and non-parametric Wilcoxon Signed Ranks Test to determine the changes from baseline within the groups. No reports of treatment effects on subjective health status or sexuality were available for power calculations and estimation of sample size. Therefore, differences in treatment effects of 1 SD or more were assumed to be clinically relevant, and 30 patients would than yield a statistical power of 0.80 to detect such effects at the 0.05 significance level. Results were considered statistically significant at $P < 0.05$. Values are expressed as mean $\pm$ SD, if nothing else is noted.

Results

Patients

The clinical characteristics of the patients are shown in Table 1. There were no significant differences between the groups at baseline. Of 29 randomized patients, 27 patients completed the trial, but all completed the examinations at week 12. One patient in the control group died suddenly of a probable myocardial infarction and one patient in the treatment group discontinued the study when a lung cancer was diagnosed. There were several episodes of respiratory exacerbations, bronchitis, and pneumonia in both groups, but there were no significant differences between the groups. When justified, patients were treated with a short course of glucocorticosteroids and/or antibiotics. No other events that could be related to treatment were reported. All injections of study medication were performed by nurses, with 100% compliance.

Pulmonary function

Spirometry, 6-MWD, PaO_2 and $PaCO_2$ showed no significant changes from baseline in either group and there were no significant differences between the groups (Table 2). In the nocturnal oxygen saturation registration, no changes in the lowest oxygen saturation (SaO_2) and mean 8 h SaO_2 from baseline were seen in either group, and there were no differences between the groups. In the control group there was a statistically significant increase in time with SaO_2 below 90% (10.4 vs. 21.3%;

Table 1 Characteristics of the study population. Data are given as mean (SD).

	Control group $N = 14$	Treatment group $N = 15$
Age (years)	67.5 (5.8)	64.5 (6.5)
Range	56–75	54–74
Anthropometrics		
Weight (kg)	74.5 (13.4)	71.5 (9.4)
Height (cm)	171.8 (4.6)	173.3 (7.3)
Body mass index (kg/m^2)	25.2 (3.7)	23.8 (3.2)
Partner (yes)	11	12
Smoking		
Current (yes)	5	6
Years	42 (9)	41 (11)
Pulmonary parameters		
PaO_2 (kPa)	8.8 (1.0)	9.4 (1.0)
$PaCO_2$ (kPa)	5.7 (1.1)	5.3 (0.5)
FVC (% of predicted)	59.7 (13.2)	71.5 (18.4)
FEV_1 (% of predicted)	40.8 (10.4)	43.2 (15.5)
Treatment (n)		
LTOT	3	2
Inhaled beta$_2$-agonists	14	15
Inhaled steroids	8	9
Inhaled ipratropium bromide	7	9
Oral theofyllines	5	4
Oral prednisone	2	2

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; LTOT, long-term oxygen therapy. Normal values: PaO_2 11.0–14.0 kPa; $PaCO_2$ 4.7–6.0 kPa. There were no significant differences between the control and treatment group.

Table 2 Blood gas analyses, spirometry, 6-min walking distance, and nocturnal oxygen saturation (23.00–07.00 h) in control and treatment groups. Data are given as mean (SD).

	Control group			Treatment group		
	Baseline	Week 12	Week 26	Baseline	Week 12	Week 26
Blood gas analyses						
PaO_2 (kPa)	8.8 (1.0)	9.0 (1.0)	9.2 (1.3)	9.4 (1.0)	9.4 (1.3)	9.5 (1.4)
$PaCO_2$ (kPa)	5.7 (1.1)	5.6 (0.8)	5.8 (0.9)	5.3 (0.5)	5.3 (0.7)	5.2 (0.7)
Spirometry						
FVC (% of predicted)	59.7 (13.2)	58.3 (17.0)	64.4 (14.2)	71.5 (18.4)	71.7 (22.3)	77.3 (18.2)
FEV_1 (% of predicted)	40.8 (10.4)	40.1 (11.7)	41.2 (12.2)	43.2 (15.5)	42.4 (14.0)	43.6 (13.7)
6-min walking distance						
Distance (m)	408 (108)	398 (112)	440 (109)	423 (105)	425 (97)	447 (92)
Lowest SaO_2 (%)	86.9 (4.0)	87.8 (3.9)	87.7 (4.3)	88.9 (4.8)	87.7 (5.2)	87.6 (4.0)
Borg score	3.7 (1.5)	3.5 (1.6)	3.5 (1.3)	3.4 (1.8)	3.4 (1.1)	3.3 (1.0)
Nocturnal oxygen saturation						
Lowest SaO_2 (%)	75.9 (8.7)	82.3 (4.5)	79.5 (5.4)	81.3 (8.1)	82.3 (5.0)	80.6 (7.0)
Mean 8 h SaO_2 (%)	92.3 (1.9)	91.6 (2.4)	91.7 (3.1)	91.9 (2.9)	91.5 (2.2)	92.7 (2.6)
Time with $SaO_2 < 90$ (%)	10.4 (19.9)	20.0 (30.0)	21.3 (33.5)*	11.5 (28.5)	18.4 (31.8)	9.1 (24.4)

FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s, LTOT, long-term oxygen therapy; Borg score for breathlessness attained immediately after walking. Normal values: PaO_2 11.0–14.0 kPa; $PaCO_2$ 4.7–6.0 kPa.
*$P < 0.05$ compared with baseline.

$P < 0.05$), but there were no significant differences between the groups (Table 2).

Anthropometry and DEXA

Body weight did not change significantly during the study period and there were no differences between the groups (Fig. 1).

DEXA showed that total body fat mass decreased compared with baseline in the treatment group, at 12 weeks (−1.85%; $P < 0.01$), and at 26 weeks (−1.5%; $P < 0.05$), and there was a significant difference between the treatment and the control group after 12 weeks (−1.85% vs. 0.09%; $P < 0.01$). Fat-free mass increased from baseline in the treatment group at 26 weeks (1.1 kg; $P < 0.05$), and a significant difference between the treatment and control group was seen after 26 weeks (1.1 vs. −0.8 kg; $P < 0.05$) (Fig. 1).

Questionnaires

The IIEF-5 score increased non-significantly in the treatment group (15.1 vs. 17.5) and decreased significantly in the control group (13.2 vs. 10.7; $P < 0.05$) from baseline. A significant difference between the groups was found after 26 weeks ($P < 0.05$) (Table 3). The overall sexual quality of life improved non-significantly in the treatment group, and at 12 weeks the sexual quality of life was significant better compared to the control group ($P < 0.05$) (Table 3).

There were no changes in the total SGRQ score or in any of the three components (symptom, activity and impact) from baseline in either group, and no differences between the groups were found. Both groups scored high on the MMSE at baseline (treatment group 28.2 ± 1.6 vs. control group 28.3 ± 1.6 of maximal 30 points), thus none of the patients were demented. There were no changes or differences during the study. None of the patients had signs of depression in the MADRS score at baseline or during the study, and there were no differences between the groups. The RDRS-2 questionnaire showed that most patients coped well with activities of daily living, and there were no differences between the groups at baseline or during the study period.

Sex hormones and clinical chemistry

The levels of sex hormones and SHBG did not differ between the groups at baseline. Total and free testosterone decreased significantly in the control group ($P < 0.05$) and total testosterone increased in the treatment group ($P < 0.05$) between baseline and the final visit. When blood samples were drawn 2 weeks after injection of study medication at the final visit, there was a difference of both total and free testosterone between the groups, however, it did not reach statistical significance (Table 4). In

the treatment group LH, FSH, and SHBG decreased significantly during the study compared to baseline ($P<0.01$), and significant differences between the groups at 12 weeks, with lower levels of FSH and SHBG ($P<0.05$), and at 26 weeks, for LH ($P<0.01$), FSH ($P<0.01$) and SHBG ($P<0.05$), were seen (Table 4).

There were no significant differences in hemoglobin, hematocrit, PSA, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides within or between groups during the study.

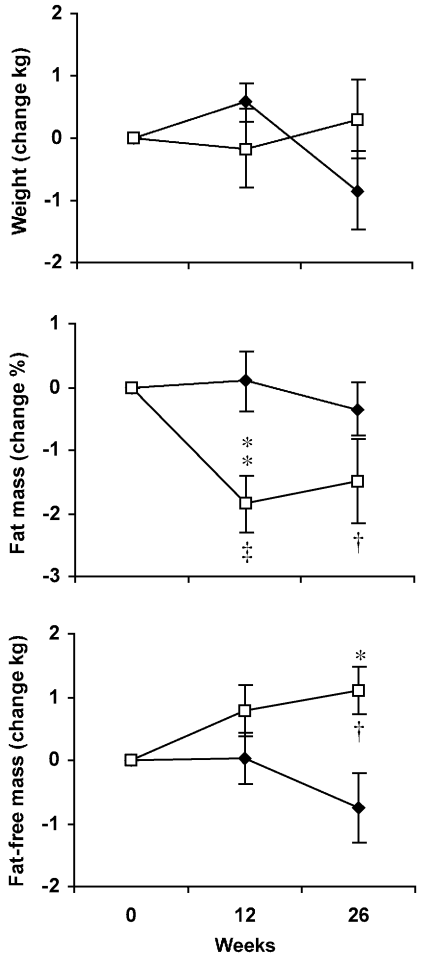

Figure 1 Changes in weight, fat mass, and fat-free mass, measured by DEXA, in men who received treatment (□) and who did not (◆). Data are given as mean ± SEM. $^{*}P<0.05$, $^{**}P<0.01$ comparing delta values with control group. $^{\dagger}P<0.05$, $^{\ddagger}P<0.01$ compared with baseline.

Discussion

In this randomized, double-blind, placebo-controlled study, we found that administration of 250 mg testosterone IM every fourth week to men with moderate to severe COPD significantly increased fat-free mass, decreased fat mass, and improved erectile function and sexual quality of life.

Treatment with testosterone did not affect the result of the spirometry examination, the level of PaO_2, and the result of the 6-MWD. This is in agreement with previous studies, where androgen treatments also were combined with exercise and/or nutritional support.[13,14] However, respiratory muscle strength measured by maximal inspiratory mouth pressure (PImax) was reported to improve significantly in patients receiving androgen,[13] but PImax was not measured in our study.

Supraphysiologic doses of testosterone have been shown to increase fat-free mass and muscle size and strength in normal men,[22] and administration of low-dose testosterone to both young and old hypogonadal men decreases fat mass and increases fat-free mass.[23–25] Increasing fat-free mass was also found in the two studies of men with COPD treated with androgens, but no changes in fat mass were reported.[13,14] In agreement with these two studies we found an increase in fat-free mass, but

Table 3 Comparison of the degree of erectile dysfunction (IIEF-5) and sexual quality of life between the control and treatment groups. Data are given as mean (SD).

	Control group			Treatment group		
	Baseline $N=13$	Week 12 $N=13$	Week 26 $N=11$	Baseline $N=14$	Week 12 $N=14$	Week 26 $N=13$
IIEF-5 (0–25)*	13.2 (7.5)	12.5 (8.3)	10.7 (8.8)†	15.1 (8.7)	16.4 (7.1)	17.5 (6.3)††
Erection (0–20)	10.4 (5.5)	9.8 (6.3)	8.8 (6.5)†	12.1 (6.8)	12.9 (5.6)	13.9 (4.8)††
Satisfaction (0–5)	2.7 (2.0)	2.7 (2.2)	2.1 (2.2)†	3.1 (2.0)	3.4 (1.6)	3.5 (1.5)
Sexual quality of life (0–6)§	2.0 (1.4)	2.5 (1.2)	2.5 (1.4)	2.6 (1.7)	1.7 (1.1)††	2.2 (1.4)

*A higher score is better performance, and a score $\leqslant 7$ is classified as severe erectile dysfunction.
§A lower score represents a higher quality of life.
$^{\dagger\dagger}P<0.05$ comparing delta values with control group.
$^{\dagger}P<0.05$ compared with baseline.

Table 4 Mean (SD) levels of sex hormones, gonadotrophins, and sex hormone-binding globulin in control and treatment groups.

	Control group			Treatment group		
	Baseline	Week 12	Week 26	Baseline	Week 12	Week 26
Total testosterone (nmol/l)	20.5 (5.7)	20.7 (6.3)	16.6 (6.0)†	21.6 (5.7)	19.0 (8.0)	22.8 (13.6)†
Free testosterone (pmol/l)	356 (126)	328 (85)	275 (124)†	413 (134)	367 (174)	556 (399)
LH (IU/l)	7.4 (6.7)	8.1 (5.7)	7.9 (6.7)	5.5 (3.0)	4.5 (3.1)	1.2 (1.4)**‡
FSH (IU/l)	10.6 (10.6)	10.6 (10.0)	10.1 (11.4)	6.7 (3.1)	5.2 (3.1)*‡	1.3 (1.4)**‡
SHBG (nmol/l)	49.0 (15.0)	54.9 (20.5)	53.2 (20.6)	42.0 (10.0)	41.1 (11.1)*	32.4 (6.6)*‡

Values at 12 weeks were obtained 4 weeks after injection and at 26 weeks 2 weeks after the final injection.
*$P<0.05$.
**$P<0.01$ comparing delta values with control group.
†$P<0.05$.
‡$P<0.01$ compared with baseline.

we also found a reduction of fat mass. Most of our patients had a normal BMI and were not selected because of being malnourished[14] or depleted.[13] In patients with a BMI $<20\,kg/cm^2$ a further reduction of an already low percentage of body fat would not be expected.[14] As treatment with testosterone did not increase weight in our patients, treatment in our study was mainly associated with an improvement in body composition. The increase in fat-free mass although significant was modest, but the patients in our study continued their ordinary life while participating in the study and no nutritional or exercise interventions were made. It is likely that a standardized exercise program and/or nutritional intervention in combination with testosterone administration would have increased the fat-free mass even more. In addition we used a low, physiological testosterone dose and we did not adjust the dose on an individual basis. In a clinical setting the interval of the dose is usually changed to more frequent injections, based on the patients' physiological changes and well being.

This is the first study on androgen treatment reporting better erectile function and sexual quality of life in men with COPD, and, as androgen administration did not improve the St. George's respiratory questionnaire, we believe this to be a specific treatment effect. Sexual problems, specifically erectile dysfunction are common in men with COPD. Declining sexual activity is considered a result of diverse causes. Low levels of testosterone have been demonstrated in hypoxic COPD patients[8,9] and the changes have been correlated with the degree of hypoxemia.[26] It has also been suggested that hypoxemia suppresses the hypothalamic–pituitary–testicular axis,[27] and we have previously reported that normalization of testosterone levels and reversal of sexual impotence may be achieved in hypogonadal men with respiratory failure and hypoxia who receive LTOT for 1 month.[9] Androgen is necessary but not essential for normal libido and to our knowledge its exact role in erectile function remains unclear. Testosterone replacement has been shown to improve quality of erection and level of libido in patients with erectile dysfunction.[28] But in a recent study testosterone levels were not correlated to erectile dysfunction or the degree of erectile dysfunction.[29] In the present study the level of erectile function differed among the participants—from severe erectile dysfunction to normal erectile function—and all but one man had a total and free testosterone in the normal range at the time of inclusion. Although men with moderate to severe COPD compared with healthy men have lower testosterone levels, they may still have levels within the normal range. Thus, the low level of biochemical hypogonadism in our study is not surprising. COPD is a progressive disease and during the study period testosterone levels decreased significantly in the control group, while increasing significantly in the treatment group, as expected. Even though the testosterone levels did not differ significantly between the groups at the final visit, it is likely that the improvement in erectile function and sexual quality of life was caused by increased testosterone levels.

The treatment was very well tolerated and besides respiratory exacerbations no events were reported that might be related to treatment. In regards to other safety assessments, there was no change in prostate size and PSA levels. Testosterone has a stimulatory effect on erytropoieses, and some studies have reported an increase of the hematocrit over 51% in elderly patients,[30,31] but available data suggest that the frequency of this

side effect is related to supraphysiological levels.[32] In the present study there was no increase in hematocrit. COPD patients have an increasing incidence of sleep disturbances and nocturnal desaturation; Matsumoto et al.[33] suggested that in some hypogonadal men, testosterone replacement may negatively affect ventilatory drives and induce or worsen obstructive sleep apnea. However, testosterone treatment was not associated with an increase in nocturnal desaturation in our study. Another concern has been the risk of a decrease in HDL-cholesterol possibly increasing the risk of ischemic heart disease. However, in agreement with other studies, administration of testosterone did not affect the HDL-cholesterol.[34]

In conclusion, administration of a low-dose testosterone to men with moderate to severe COPD was associated with improvement of body composition, with increased fat-free mass and reduced fat mass. Testosterone treatment was also associated with better erectile function and sexual quality of life. Furthermore, there were no clinical or biochemical side effects. Considering that for many patients with COPD even small improvements in well being can be of great value, treatment with testosterone is intriguing, not least in its effect on sexuality. However, further studies exploring this line of treatment are warranted, especially studies with testosterone doses adjusted on an individual basis.

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