# Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy

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ABSTRACT: Under the clinical impression that patients with chronic obstructive pulmonary disease (COPD) may demonstrate signs compatible with hypogonadism, we investigated whether oral glucocorticoid therapy is associated with testosterone deficiency.

Thirty six men with COPD of whom 16 were receiving oral glucocorticoid medication (mean±SEM dose 9.4±1.1 mg prednisolone) were investigated in a cross-sectional cohort study.

Patients with or without oral glucocorticoid therapy were not different in terms of age, smoking history and additional therapy. Vital capacity, forced expiratory volume in one second, airway resistance, intrathoracic gas volume and blood gases at rest were not different between the groups. However, patients receiving glucocorticoids had a shorter 6 min walking distance (mean±SEM 205±27 *versus* 288±26 m; p=0.02) compared to patients without oral steroid therapy. Serum levels of testosterone (mean±SEM 13.7±0.9) were below normal (<12 nM) in 15 of 36 patients. Serum testosterone did not correlate with any other evaluated parameter. Serum levels of free testosterone (free T) (mean±SEM 172.3±7.8 pM) were decreased in 25 of the 36 patients, including all patients receiving glucocorticoid treatment. In the 16 patients taking glucocorticoids free T was correlated (p=0.016) with the current glucocorticoid dosage (r=-0.504; p=0.007) and the body mass index (r=0.241; p=0.037). All other parameters examined revealed no significant correlations in multiple regression analysis.

Glucocorticoid treatment appears to aggravate hypogonadism and a therapeutic study using testosterone in patients with chronic obstructive pulmonary disease receiving glucocorticoid medication appears warranted.
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Many chronic and/or severe diseases and a number of drugs are known to induce hypogonadism [1]. Patients with chronic obstructive pulmonary disease (COPD) may have symptoms compatible with hypogonadism and there is evidence that these patients have significant atrophy of Leydig cells [2, 3]. This atrophy might be a consequence of hypoxic inhibition of pituitary gonadotropin secretion in patients with COPD [4].

In addition it seems likely that glucocorticoids can lower testosterone biosynthesis [5, 6] which is consistent with the decreased plasma testosterone levels found in men with Cushing's syndrome [7]. It has been shown that high-dose prednisolone or dexamethasone treatment can reduce the normal nocturnal increase in testosterone [8]. Furthermore, it has been shown that glucocorticoids can diminish the maximal serum testosterone levels after human chorionic hormone (hCG) stimulation due to a reduction of essential adrenal precursors [9]. Moreover, prolonged prednisolone treatment affects the pituitary response to gonadotropin releasing hormone (GnRH), resulting in dec-

reased luteinizing hormone (LH) secretion and low plasma testosterone [10].

Ageing leads to a decline in serum testosterone [11] and to a decreased testicular and pituitary maximal secretion after hCG and GnRH stimulation tests in men beyond the fourth decade of life [12]. Cross-sectional studies have shown an average decline in testosterone of $0.4\% \cdot yr^{-1}$ and an increase of sex hormone binding globulin (SHBG) of $1.2\% \cdot yr^{-1}$ between 39–70 yrs of age [13]. However, the physiological decrease of testosterone with normal ageing never reaches the extent seen in clinically manifested hypogonadotrophic hypogonadism.

As we had the clinical impression that patients with COPD suffer from hypogonadism more often than other patients of comparable age, we investigated whether patients with severe COPD, with or without glucocorticoid treatment, have a testosterone deficiency. The findings suggest that testosterone therapy may be a rational approach in these patients.

## Materials and methods

### Study design and patients

Thirty six patients (mean±SEM age 64.5±1.5 yrs) with stable COPD were examined in a cross-sectional cohort study. Diagnosis and treatment of COPD followed international guidelines [15]. In addition, no patients had evidence of conditions that might interfere with exercise testing. The study protocol was approved by the Ethics Committee of the State Medical Board and written informed consent was obtained from each patient.

Clinical information is given in table 1. Almost all patients were receiving a combination of inhaled and oral therapy. At the time of examination, 16 patients had been taking oral glucocorticoid treatment for a duration of 3.9±0.4 yrs. There were no significant differences between control and glucocorticoid-treated patients in the other types of drugs being used.

In addition to a medical history and routine clinical investigation of lung function, smoking, drugs and other diseases, a thorough andrological history was taken including the use of standardized diaries [16]. In addition, physical and sonographic evaluation of scrotal contents were performed.

### Lung function testing and blood gas analysis

Forced expiratory volume in one second, vital capacity, airway resistance, intrathoracic gas volume and residual volume were measured by whole body plethysmography (Masterlab, Jaeger, Würzburg, Germany). The transfer factor of the lung for carbon monoxide ($T$LCO) and the $T$L,CO divided by alveolar volume (Krogh factor) were determined by the single breath method. The $T$L,CO was corrected for the concentration of haemoglobin [17]. Predicted values were calculated according to European guidelines [15]. Blood gas analyses (Blood Gas Analyzer model 278; Ciba-Corning, Fernwald, Germany) were determined from the hyperaemic ear lobe to give pH and

Table 1. – Baseline characteristics of male patients with chronic obstructive pulmonary disease

| Medication | Patients receiving oral prednisolone therapy | Patients not receiving oral prednisolone therapy |
|---|---|---|
| Patients n | 16 | 20 |
| Age yrs | 65.5±2 | 63.8±2.2 |
| Weight kg | 77.8±3.3 | 86.6±4.5 |
| Height cm | 176.2±1.7 | 177.8±1.7 |
| Body mass index kg·m$^{-2}$ | 25.1±1.1 | 27.2±1.2 |
| Baseline Dyspnoea Index score | 6.1±0.5 | 6.7±0.8 |
| Systemic glucocorticoid dose mg·day$^{-1}$ | 9.4±1.1 | 0 |
| Patients receiving | | |
| Theophylline n | 14 | 12 |
| Inhaled corticoid aerosol n | 13 | 12 |
| Inhaled $\beta_2$-agonist aerosol n | 13 | 11 |
| Inhaled anticholinergic aerosol n | 9 | 6 |
| Oxygen supplementation n | 2 | 0 |
| Smoking pack-years | 58.3±8.2 | 54.6±6.4 |

Values are presented as mean±SEM. Pack-years: 1 pack-year = 20 cigarettes·day$^{-1}$ for 1 yr.

arterial partial pressures of carbon dioxide and oxygen. A clinical dyspnoea rating [18] was assessed using the German translation of the Baseline Dyspnoea Index (BDI) [19].

### Exercise testing

Exercise performance was assessed as the 6 min walking distance (6MWD) in a self-paced treadmill walking test (LE 2000; Jaeger, Würzburg, Germany) on a horizontal treadmill [20].

### Hormone measurements

Blood samples were taken at 08:00 and 11:00 h. All measurements were performed within one assay. Serum levels of LH, follicle-stimulating hormone (FSH), SHBG, and prostate specific antigen (PSA) were determined by highly specific time resolved fluoroimmunoassays (DELFIA; Pharmacia GmbH, Freiburg, Germany). The intra-assay coefficients of variation were: LH 2%, FSH 1.4%, SHBG 0.8% and PSA 2.5%. The normal ranges in our laboratory are: LH 2–10 international units (IU)·L$^{-1}$, FSH 1–7 IU·L$^{-1}$ and SHBG 11–71 nM. The upper normal limit for PSA is 4 µg·L$^{-1}$.

Testosterone was measured by radioimmunoassay (RIA), as previously described [21]. The intra-assay coefficient of variation was 5.3%. Serum levels of free testosterone (free T) were determined after ultrafiltration by RIA [22]. The detection limit for free T was 50 pM. The intra-assay coefficient of variation for free T was 8.3%. Oestradiol was measured by RIA (Sorin Biomedica, Saluggia, Italy). The intra-assay coefficient of variation for oestradiol was 5.8%. Normal values in our laboratory for testosterone are greater than 12 nM, the upper normal limit for oestradiol is 250 pM. The normal values for serum free T are greater than 200 pM [23].

### Statistical analysis

All variables were checked for normal distribution using the Kolmogorov-Smirnov one-sample test for goodness-of-fit. When necessary, analysis was performed on logarithmically transformed data. Two-sided p-values of 0.05 or less were considered significant. Covariance was evaluated by multivariate general factorial analysis of variance. After variance analysis all variables were tested by stepwise linear multiple regression analysis. Differences between different groups of patients were tested by t-test for independent samples or Pearson's Chi-squared test. All analyses were performed using the statistical software SPSS for Windows version 6.1 (SPSS, Inc., Chicago, IL, USA). In general, results are given as mean±SEM.

## Results

### Clinical and endocrine features

Eighty four per cent of the patients reported concurrent diseases consisting mostly of cardiac and gastro-intestinal diseases. In no case was there any evidence of long-standing hypogonadism. No severe andrological illnesses or
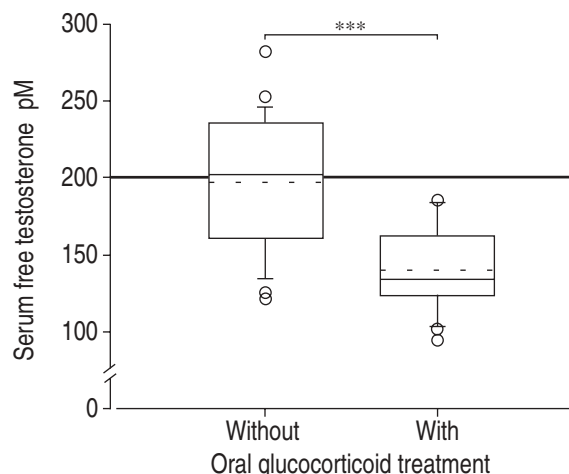
Fig. 1. – Plot of free testosterone values of 16 patients receiving oral glucocorticoid treatment compared to 20 patients not receiving oral glucocorticoid treatment. The box represents 25th and 75th percentiles respectively. Inner solid line shows the 50th percentile, inner broken line the mean. Capped bars outside reflect the 10th and 90th percentile respectively. In addition, data outside the 10th and 90th percentile are plotted as inidividual symbols. ── : lower normal limit. ***: p<0.001.

injuries were reported except for benign prostatic hyperplasia for which surgery had been performed in five patients. PSA was elevated in nine patients up to a maximum of 26.3 $\mu g \cdot L^{-1}$. Distribution of symptoms compatible with hypogonadism were similar in both groups and mainly consisted of loss of muscle strength (n=28), skin symptoms (n=18), and infrequent sex or an unsatisfactory sex life (n=16).

Serum levels of testosterone (mean±SEM 13.7±0.9 nM) were decreased in 15 patients. In the analysis of variance only BMI (r=-0.16, p=0.03) and oestradiol (r=0.09, p=0.024) levels correlated with testosterone, and these were no longer present after including SHBG in the variance analysis. Therefore, the variance analysis was continued only for biologically active free T values. Overall, serum levels of free T (172.3±7.8 pM) were below the lower normal range. In all patients taking oral glucocorticoids, decreased free T values were found (fig. 1), whereas only
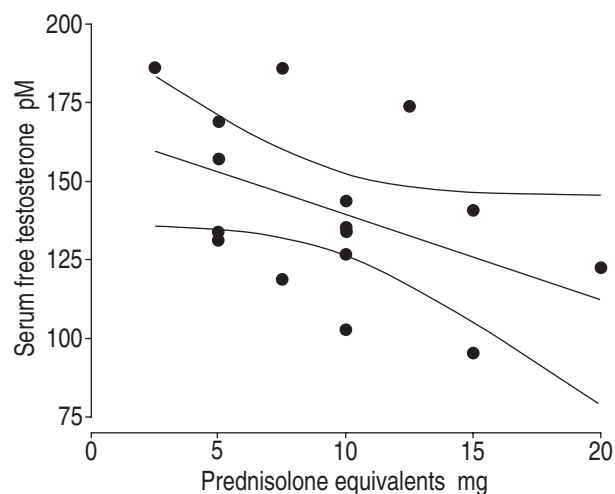
45% of the others had decreased free T levels. In patients receiving glucocorticoid medication free T was correlated (p=0.016) with the current glucocorticoid dosage (r= -0.504; p=0.007; fig. 2) and the BMI (r=0.241; p=0.037). For further details see table 2.

*Lung function testing, blood gas analysis and exercise testing*

Results of lung function testing, blood gas analysis and exercise testing are given in table 3. Walking distances were significantly decreased in patients receiving oral glucocorticoids compared to those without. All other evaluated indices of lung function, blood gas and exercise testing were not different between the two groups.

Table 2. – Hormone measurements in 16 chronic obstructive pulmonary disease patients treated with prednisolone and 20 patients not receiving prednisolone therapy

| | Patients receiving oral prednisolone therapy n=16 | Patients not receiving oral prednisolone therapy n=20 |
|---|---|---|
| Luteinizing hormone IU·L⁻¹ | 3.4±0.3 | 4.1±0.7 |
| Follicle stimulating hormone IU·L⁻¹ | 7.3±1* | 4.8±0.7 |
| Testosterone nM | 12.1±1.3 | 15.1±1.2 |
| Patients with testosterone <12 nM n | 9 | 6 |
| Sex hormones binding globulin nM | 47.6±6.2 | 61.3±5.3 |
| Free testosterone pM | 141.2±6.7* | 197.15±10 |
| Patients with free testosterone <200 pM n | 16* | 9 |
| Oestradiol pM | 60.4±3.4 | 73.5±5.3 |
| Prostate specific antigen µg·L⁻¹ | 5.06±1.7 | 2.52±0.2 |

*: difference between groups p≤0.05.

Table 3. – Lung function, blood gas and exercise testing parameters in patients with chronic obstructive pulmonary disease

| Evaluated parameter | Patients receiving prednisolone therapy n=16 | Patients not receiving prednisolone therapy n=20 |
|---|---|---|
| VC % pred | 73.3±4.4 | 68.2±3.5 |
| FEV1 % pred | 33.4±4.7 | 39.8±3.6 |
| IGV % pred | 205±19.2 | 160.4±10.6 |
| $R_{aw}$ kPa·L⁻¹·s⁻¹ | 0.43±0.05 | 0.39±0.05 |
| $T_{L,CO}$ % pred | 77.5±6.8 | 83.7±5.6 |
| $P_{a,O_2}$ at rest kPa | 9.12±0.44 | 9.12±0.24 |
| $P_{a,CO_2}$ at rest kPa | 4.88±0.21 | 5.01±0.16 |
| 6MWD | 205.1±26.7* | 287.5±25.5 |

Values are presented as mean±SEM. VC: vital capacity; FEV1: forced expiratory volume in one second; IGV: intrathoracic gas volume; $R_{aw}$: airway resistance; $T_{L,CO}$: transfer factor for carbon monoxide; $P_{a,O_2}$: arterial partial pressure of oxygen; $P_{a,CO_2}$: arterial partial pressure; 6MWD: 6 min walking distance; % pred: percentage of predicted value. *: difference between groups p≤0.05.



Fig. 2. – Daily oral glucocorticoid dose expressed as prednisolone equivalent *versus* serum free testosterone in 16 patients treated with prednisolone. The regression line and the 95% confidence limits are shown. r=-0.504; p=0.007.

## Discussion

We investigated patients with severe COPD with or without glucocorticoid treatment. The groups were not different in terms of clinical features, smoking habits and most of the lung function indices measured at rest (table 1). However, walking distances were shorter in patients with oral glucocorticoids compared to those without. Shorter walking distance may be compatible with the hypothesis stating that oral glucocorticoids contribute to respiratory muscle weakness in COPD patients [24].

Similarly, the muscle weakness observed in patients treated with glucocorticoid might have been a consequence of the significantly reduced (fig. 1) free T values that we and others [25] found in comparison to COPD patients without glucocorticoid therapy. Free T values were significantly correlated with the current glucocorticoid do-sage (fig. 2). Possible reasons for the observed hypogona-dism may be glucocorticoid-induced suppression of the adrenals [9], a direct inhibitory effect *via* testicular glucocorticoid receptors [5] or decreased testosterone biosynthesis *via* reduced content of LH receptors in Leydig cells [6].

Another possible reason for the hypogonadism might be hypoxic inhibition of LH secretion [4, 26] due to the COPD together with an exaggerated effect of the general mild decrease in testosterone during ageing [11, 13]. Although single time point LH analysis may be misleading because of its pulsatility, only five of the present patients showed subnormal serum LH as a possible result of inhibition of pituitary LH secretion resulting in secondary hypogonadism with subnormal testosterone values (range 8.4–10.3 nM). On the other hand, elevation of LH, which would be expected with low testosterone levels, was not seen in either group, and no correlation was found between gonadotrophins and lung function. Although we cannot exclude partial inhibition of pituitary LH secretion, we agree with others [1, 25, 27] that COPD alone is not likely to be the primary cause of the observed hypogonadism. An effect of ageing on testosterone levels was not observed in this study; this otherwise minor effect is probably outweighed by additional medication and illnesses which are known to decrease testosterone values [13, 14]. However, nine out of 20 patients with COPD not receiving glucocorticoid medication also had decreased free T levels. The aetiology is likely to be multifactorial, but, as all patients receiving glucocorticoid treatment had decreased free T levels, it is clear that the glucocorticoid medication appears to aggravate hypogonadism. Therefore, in this study other possible contributory factors such as COPD, ageing, other intercurrent illnesses and medication appeared to be less important than glucocorticoid treatment and were not consistent within the patient group without oral glucocorticoids.

It has previously been demonstrated that testosterone antagonizes the deleterious effects of cortisone on diaphragmatic endurance in rats [28] and has a clear anabolic effect on muscle size and strength in normal human males [29]. In addition, in patients with chronic obstructive pulmonary disease, anabolic steroids have been shown to increase respiratory muscle mass and strength [30]. Other studies have shown that testosterone reverses the deleterious effects of glucocorticoid drugs on bone density and soft tissues in asthmatic males [31]. To clarify whet- her testosterone/might have a beneficial influence on lung function in patients with chronic obstructive pulmonary disease receiving oral glucocorticoid treatment, a controlled clinical trial appears warranted.

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