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Profile of Endocrinological Derangements Affecting PSA Values in Patients with COPD

EUGENIA KARAKOU[1], CONSTANTINOS GLYNOS[2], KATERINA D. SAMARA[2], PAVLOS MSAOUEL[1], MICHAEL KOUTSILIERIS[1] and THEODOROS VASSILAKOPOULOS[2]

[1]*Department of Experimental Physiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece;*
[2]*First Department of Critical Care Medicine and Pulmonary Services, Evangelismos Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece*

Abstract. *Background/Aim: Chronic obstractive pulmonary disease (COPD) in men has been associated with testosterone deficiency, known as the late-onset hypogonadism. Prostate cancer becomes more prevalent when testosterone values decline in males. We sought to determine endocrinological derangements that may affect PSA values in male patients with COPD. Materials and Methods: A total of 69 male patients with COPD and 82 healthy volunteers were divided into subgroups according to: their age: (i) ≤60 years and (ii) >60 years; or disease severity: (i) FEV1<50% and (ii) FEV_1≥50% predicted. Results: There was a significant reduction in total and free testosterone in patients with COPD. Patients with COPD aged >60 years had significantly lower free PSA compared to the control group. Conclusion: Alterations of the male hormonal status in COPD are related with older age (>60 years) and poorer lung function (FEV_1<50% predicted). This may have implications for the use of the PSA-based screening tests in the elderly male population with COPD.*

Chronic obstructive pulmonary disease (COPD), the fourth leading cause of morbidity and mortality worldwide (1), is considered a chronic systemic inflammatory syndrome, associated with premature aging and endocrine dysfunction (2). COPD in men has been associated with testosterone deficiency, otherwise known as the late-onset hypogonadism (LOH) (3). LOH is a clinical and biochemical syndrome, characterized by reduced levels of serum total and free testosterone, concurrently with elevated sex hormone-binding globulin (SHBG) levels (4), due to disruption of the hypothalamic–pituitary–testicular axis in middle-aged and elderly men (3). Although association does not mean causation, LOH alone may worsen the systemic manifestations of COPD and impair exercise performance (5) due to peripheral muscle wasting, osteoporosis, immunological alterations, or diminished energy and vitality, which are among the clinical consequences of the hypogonadal state (6).

Prostate cancer becomes more prevalent exactly at the time in a man's life when testosterone levels decline (7). However, there is no evidence to suggest any causative relation between testosterone levels and risk for prostate cancer (7). Nevertheless, data do exist to support the notion that testosterone *vs*. prostate-specific antigen (T/PSA) ratio <1 could be an adjunct screening test validating further the PSA-weighted risk of prostate cancer in elderly men with PSA levels within the 'grey' diagnostic area (PSA ≥3-<10 ng/ml) (8). Given the high prevalence of COPD in middle-aged and older men, and the frequency of the PSA-based weighted risk for the diagnosis of prostate cancer, our study aimed to investigate the relation of PSA values with the hormonal profile of male patients with COPD.

Materials and Methods

Study subjects. A total of 69 male patients with COPD (COPD group) and 82 volunteers with normal pulmonary function tests (control group), aged 45-80 years were studied. The diagnosis of COPD was established according to GOLD Guidelines (9). Exclusion criteria included known endocrine disease, prostate cancer, alcoholism, hepatic or renal disorders, orchiectomy and current androgen and antiandrogen therapy.

Pulmonary function parameters. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1), were measured with standard spirometric techniques and the FEV_1/FVC was calculated. Male subjects were included in the COPD group when they had a post-bronchodilator FEV_1/FVC ratio of less than 0.70. COPD severity was investigated by considering post-bronchodilator FEV_1<50% predicted (9).

Correspondence to: Professor Michael Koutsilieris, Department of Experimental Physiology, Medical School, National and Kapodistrian University of Athens, 75 Micras Asias, Goudi, Athens 115 27, Greece. E-mail: mkoutsil@med.uoa.gr

Key Words: PSA, COPD, hypogonadism.

Table I. *Comparison between patients with (COPD) and Controls for the parameters of interest.*

	COPD (N=69)					Controls (N=82)						
Parameter	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	*p*-Value	*p*-Value†
Age, years	67.12	9.90	69	45	80	63.57	10.46	66	45	80	0.038	NA
Smoking p-y	79.96	45.48	70	0	200	13.32	19.49	0	0	96	0.000	0.000
T, ng/ml	2.88	1.51	2.75	0.68	7.71	4.74	1.44	4.76	2.7	9.08	0.000	0.000
FreeT, ng/dl	5.30	2.49	4.95	1.2	14.2	8.06	2.50	7.425	4.08	17	0.000	0.000
SHBG, nmol/l	37.51	15.55	35.9	13.4	80.3	46.01	19.67	41.85	16.3	111.6	0.004	0.000
DHEA-S,μg/dl	106.14	113.02	72	9	718	153.72	88.03	145	15	447	0.000	0.000
FSH, mIU/ml	9.58	9.98	6.49	1.6	65.76	7.32	6.72	4.945	1.7	40.94	0.161	0.540
LH, mIU/ml	8.76	5.47	6.63	1.69	31.83	6.74	4.23	5.43	2.39	26.06	0.012	0.050
Osteocalcin, ng/ml	12.67	7.63	11.9	2.3	38.3	14.96	4.85	14.45	6.4	29.5	0.000	0.000
PTH, pg/ml	62.79	40.27	52.6	15	213.8	49.26	17.77	47.1	18.4	105.8	0.062	0.189
Ca, mg/dl	9.40	0.59	9.4	8.1	11.3	9.69	0.42	9.65	8.7	10.7	0.000	0.001
Albumin, g/dl	4.11	0.35	4.1	3.2	4.9	4.50	0.30	4.5	3.6	5.1	0.000	0.000
PSA, ng/ml	2.17	2.36	1.19	0.17	10.1	2.12	4.16	1.375	0.13	37.4	0.818	0.602
FreePSA	0.46	0.57	0.3	0.04	3.22	0.50	0.50	0.39	0.04	3.96	0.058	0.001

p-y, Pack–years; DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone- binding globulin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Ca, serum calcium; PSA, serum prostate-specific antigen; PTH, parathyroid hormone; T, total testosterone; NA: non-applicable. †Adjusted for age effect.

Hormones. Blood samples were obtained at 07:00-10:00 a.m. for measurement of biochemical parameters. The serum levels of total testosterone [Reference Values (RV)=2.80-8.00 ng/ml], dehydroepiandrosterone sulphate (DHEA-S) (RV=50-400 μg/dl for age 36-70 years; 16-123 μg/dl for age >75 years), sex hormone-binding globulin (SHBG) (RV=14.5-48.4 nmol/l), luteinizing hormone (LH) (RV=1.7-8.6 mIU/ml), follicle stimulating hormone (FSH) (RV=1.5-12.4 mIU/ml), intact parathyroid hormone (PTH) (RV=15.0-65.0 pg/ml), osteocalcin (OC) (RV=5.0-18.0 ng/ml) were measured using electrochemiluminescence immunoassay (ECLIA; Modular Analytics E170; Roche Diagnostics, Mannheim, Germany). The serum PSA (RV=0-3 ng/ml) and free PSA (fPSA) were measured using a two-site (sandwich principle) direct chemiluminescence immunoassay (CLIA), that incorporates two highly specific monoclonal antibodies (Liaison Analyzer; Diasorin, Dietzenbach, Germany). The serum levels of free testosterone (fT) (RV>7.2 ng/dl) were calculated from testosterone, SHBG and albumin according to the Vermeulen formula (10). The serum albumin (RV=3.5-5.1 g/dl) levels were measured using colorimetric bromocresol green (BCG) assay (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany), while the serum calcium (RV=8.5-10.5 mg/dl) levels were measured using colorimetric Arsenazo III (*o*-cresolphthalein complex one) method (Cobas Integra 800; Roche Diagnostics, Mannheim, Germany).

Statistical analysis. The two groups (COPD *vs*. controls) were compared in terms of the parameters of interest using a general linear model. The two groups were compared both unadjusted and adjusted for the effect of age, which was incorporated as a covariate in the model. Independent comparisons between the two groups were made for those with age ≤60 years and for those with age >60 years using a general linear model. Thereafter, disease severity was investigated by considering three groups: COPD with FEV_1<50% predicted, COPD with FEV_1≥50% predicted and Controls. The three groups were compared using a general linear model and pair-wise comparisons were tested using post-hoc tests with Bonferroni's correction. Finally, the pair-wise association between parameters considering the group effect (COPD *vs*. Controls) was examined using a comparison of regression model. In the analysis, the parameters were ln-transformed prior to analysis. Results were considered significant when $p<0.05$. The analysis was performed using SAS r9 and Statistics v6.

Results

In our study population, men with normal respiratory function and male COPD patients were compared with respect to different parameters of interest (Table I). The two groups were significantly different in regard to the hormonal profile, smoking pack-years ($p<0.001$) and age ($p=0.038$). In the overall analysis, there was a significant reduction in total testosterone ($p<0.001$) and fT ($p<0.001$), SHBG ($p=0.004$), DHEA-S ($p<0.001$), osteocalcin ($p<0.001$), calcium ($p<0.001$) and albumin ($p<0.001$) in patients with COPD compared to those with normal lung function. In contrast, patients with COPD had increased levels of LH ($p=0.012$) compared to the control group. There was no significant difference for the FSH, PTH and the total or fPSA. Interestingly, after adjustment for age, the effect of fPSA became significant ($p=0.001$) and the effect of LH became marginally significant ($p=0.05$).

Those groups with COPD and those with normal lung function were divided into two subgroups according to age: group A ≤60 years and group B >60 years (Table II). In group A, differences were shown for both total testosterone ($p<0.001$) and fT ($p=0.001$), SHBG ($p=0.044$), osteocalcin ($p=0.014$) and albumin ($p=0.045$) (Table II). However, the pattern of results concerning group B was the same as in the

Table II. *Comparison between patients with (COPD) and Controls aged ≤60 years and aged >60 years.*

Age ≤60 years	COPD (N=17)					Controls (N=28)					
Parameter	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	*p*-Value
Age, years	53.24	5.63	55.00	45.00	60.00	51.00	4.90	51.00	45.00	60.00	0.176
Smoking p-y	62.82	38.41	40.00	20.00	138.00	14.02	18.07	0.00	0.00	58.50	0.000
T, ng/ml	3.11	1.82	3.38	0.84	7.04	4.73	1.56	4.46	2.80	9.08	0.000
FreeT, ng/dl	6.36	3.36	6.17	1.97	14.20	9.27	2.97	8.56	5.56	17.00	0.001
SHBG, nmol/l	28.45	10.99	29.70	13.40	50.60	35.86	13.25	31.85	16.30	66.30	0.044
DHEA-S, μg/dl	187.71	187.38	137.00	17.00	718.00	170.89	84.87	150.50	51.00	445.00	0.237
FSH, mIU/ml	5.76	4.25	3.97	1.65	17.02	4.82	4.04	3.73	1.70	23.26	0.543
LH, mIU/ml	6.32	2.95	5.89	3.07	13.92	5.69	2.65	4.81	2.63	13.03	0.448
Osteocalcin, ng/ml	12.41	8.40	10.80	2.30	35.10	15.28	4.50	14.75	8.40	29.50	0.014
PTH, pg/ml	49.17	30.08	44.40	15.00	151.30	44.85	13.32	45.30	18.40	81.60	0.977
Ca, mg/dl	9.51	0.51	9.50	8.50	10.40	9.69	0.42	9.70	8.80	10.40	0.206
Albumin, g/dl	4.36	0.33	4.30	3.70	4.90	4.54	0.25	4.55	4.00	5.00	0.045
PSA, ng/ml	2.03	2.92	0.65	0.17	9.38	1.20	0.90	1.01	0.13	4.09	0.947
FreePSA	0.22	0.23	0.16	0.04	0.92	0.30	0.21	0.27	0.04	1.04	0.095
Age >60 years	COPD (N=52)					Controls (N=54)					
Parameter	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	*p*-Value
Age, years	71.65	5.96	72.00	61.00	80.00	70.09	5.31	69.00	61.00	80.00	0.148
Smoking p-y	85.56	46.53	77.50	0.00	200.00	12.96	20.34	0.00	0.00	96.00	0.000
T, ng/ml	2.81	1.40	2.69	0.68	7.71	4.74	1.38	4.86	2.70	7.85	0.000
FreeT, ng/dl	4.96	2.06	4.94	1.20	10.70	7.43	1.96	7.01	4.08	12.70	0.000
SHBG, nmol/l	40.48	15.76	38.05	15.60	80.30	51.28	20.48	48.05	18.90	111.60	0.006
DHEA-S, μg/dl	79.48	55.44	71.00	9.00	262.00	144.81	89.10	140.5	15.00	447.00	0.000
FSH, mIU/ml	10.82	10.98	7.83	1.60	65.76	8.62	7.47	6.21	2.01	40.94	0.397
LH, mIU/ml	9.56	5.88	8.43	1.69	31.83	7.29	4.79	6.31	2.39	26.06	0.018
Osteocalcin, ng/ml	12.75	7.45	11.95	3.20	38.30	14.80	5.05	13.40	6.40	27.00	0.016
PTH, pg/ml	67.25	42.38	58.85	20.80	213.80	51.54	19.41	47.10	22.50	105.80	0.099
Ca, mg/dl	9.37	0.61	9.30	8.10	11.30	9.69	0.42	9.60	8.70	10.70	0.000
Albumin, g/dl	4.03	0.32	4.00	3.20	4.60	4.48	0.32	4.50	3.60	5.10	0.000
PSA, ng/ml	2.22	2.18	1.26	0.27	10.10	2.60	5.04	1.57	0.26	37.40	0.740
FreePSA	0.54	0.62	0.33	0.04	3.22	0.61	0.57	0.48	0.09	3.96	0.027

p-y, Pack–years; DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone- binding globulin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Ca, serum calcium; PSA, serum prostate-specific antigen; PTH, parathyroid hormone; T, total testosterone.

overall analysis without considering the age effect. Moreover, in those in group B, significant differences were shown for total testosterone ($p<0.001$) and fT ($p<0.001$), SHBG ($p=0.006$), DHEA-S ($p<0.001$), LH ($p=0.018$), osteocalcin ($p=0.016$), calcium ($p<0.001$) and albumin ($p<0.001$). COPD patients aged >60 years also exhibited significant lower fPSA levels ($p=0.027$) compared to the control group (Table II). Since the effect of fPSA, DHEA-S, LH and calcium became significant after the adjustment for age, we further investigated the relation of these parameters according to age in patients with COPD and in those with normal lung function. fPSA was positively correlated to age ($p<0.05$), with a similar trend (Figure 1A) in both groups, whereas DHEA-S was negatively correlated ($p<0.05$) (Figure 1B). LH was positively correlated to age in both groups ($p<0.05$) (Figure 1C). Finally, calcium was not significantly correlated to age in either group.

Since there was a significant reduction of fPSA in both age groups studied, we examined the relations of PSA and fPSA with other parameters of interest. PSA exhibited a significant correlation ($p<0.05$) with DHEA-S and FSH in the COPD group, and with SHBG in the control group. For these three correlations, the pattern was different ($p<0.05$) between the COPD and control group. For fPSA, the results were exactly the same as for PSA. Figure 2 depicts a scatter plot for the correlation of PSA with DHEA-S, FSH and SHBG. Figure 3 depicts a scatter plot for the correlation of fPSA with DHEA-S, FSH and SHBG.

We also analysed the hormonal profile of our study population, adjusted for disease severity, using three groups:

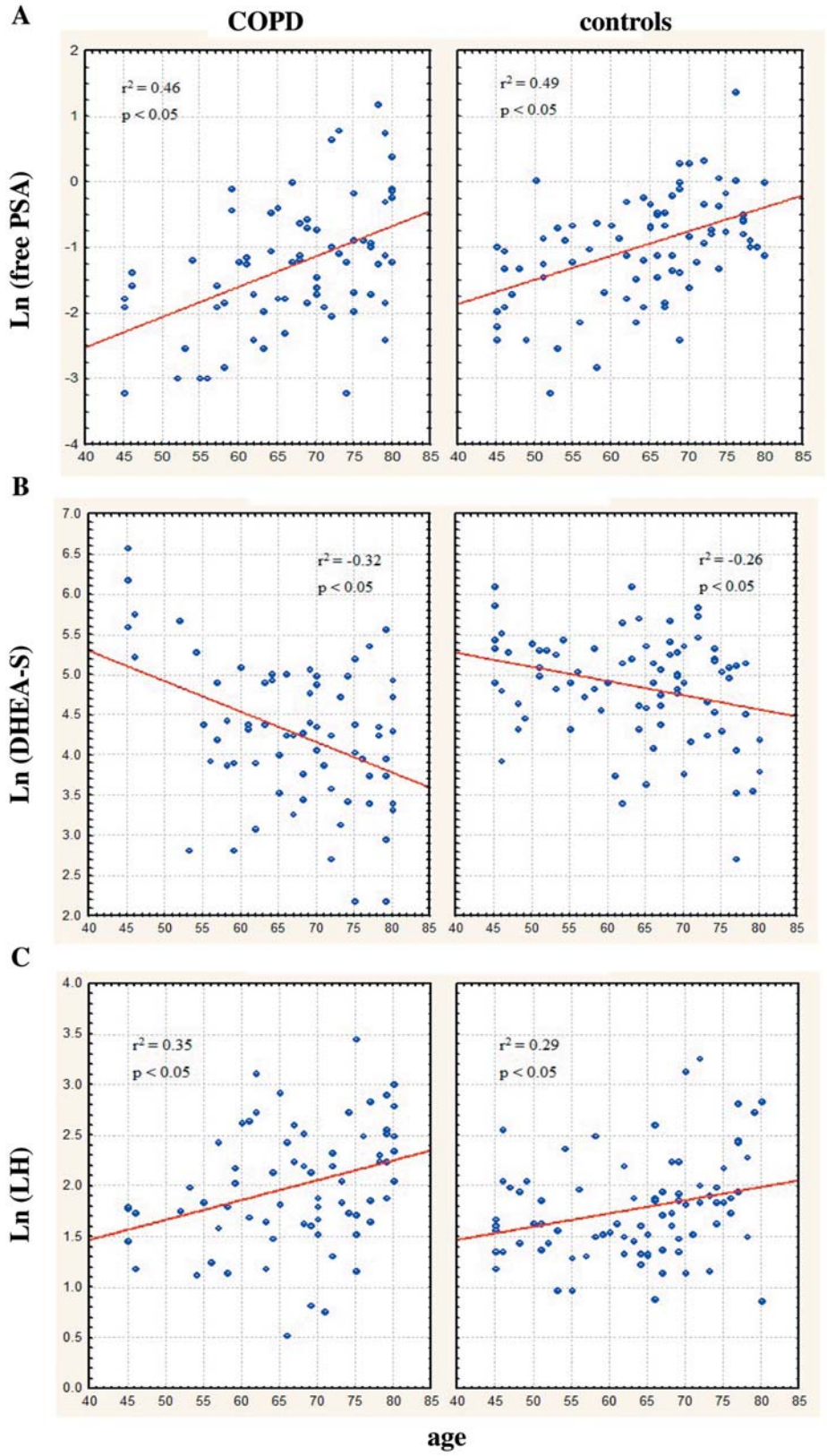

Figure 1. *Scatter plots for the correlation of free prostate-specific antigen (fPSA) (A), dehydroepiandrosterone sulphate (DHEA-S) (B) and luteinizing hormone (LH) (C) with the age in patients with COPD and in controls.*

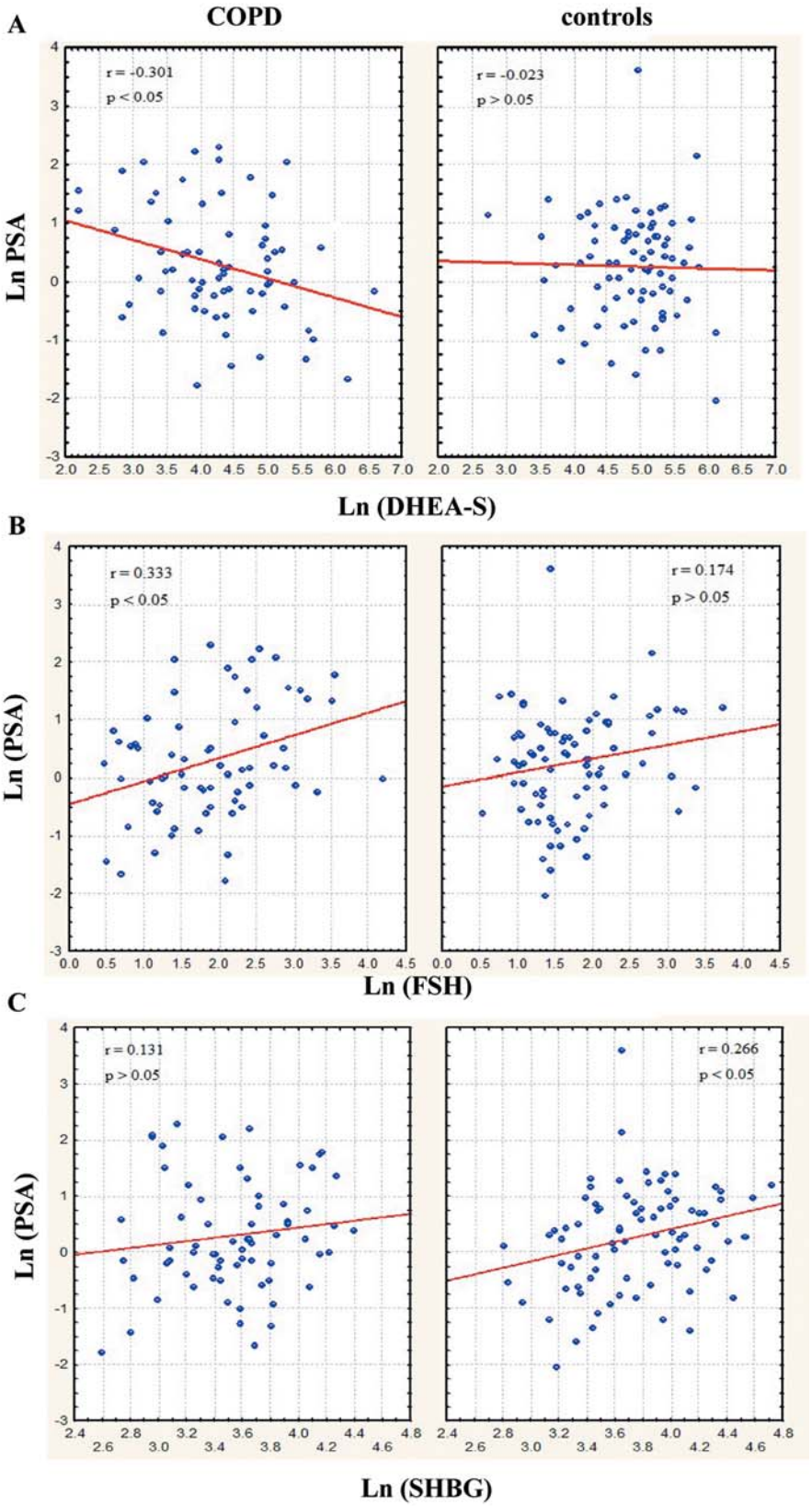

Figure 2. *Scatter plots for the correlation between total prostate-specific antigen (PSA) vs. dehydroepiandrosterone sulphate (DHEA-S) (A), follicle-stimulating hormone (FSH) (B) and sex hormone-binding globulin (SHBG) (C) in patients with COPD and in controls.*

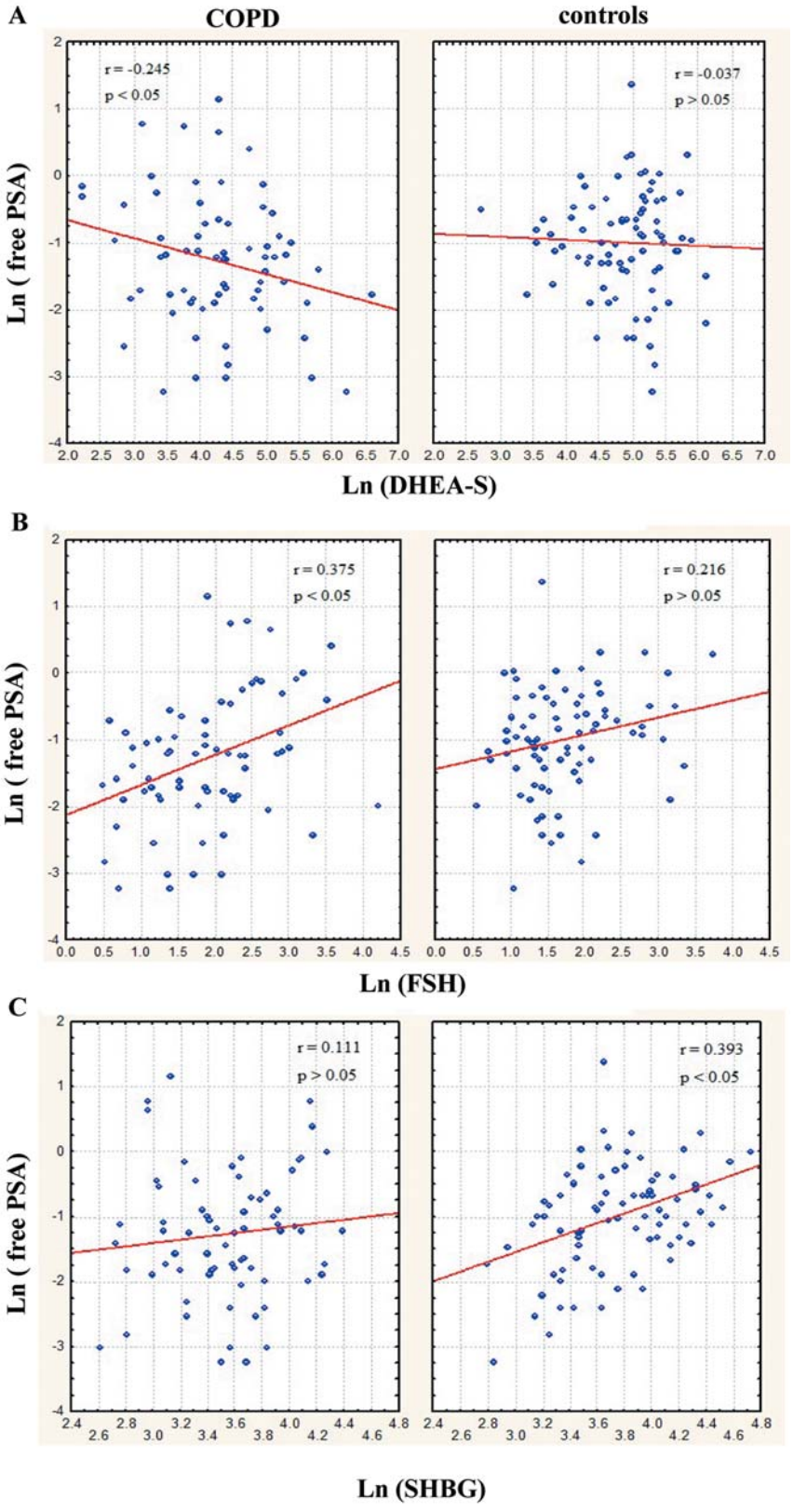

Figure 3. *Scatter plots for the correlation between free prostate-specific antigen (fPSA) vs. dehydroepiandrosterone sulphate (DHEA-S) (A), follicle-stimulating hormone (FSH) (B) and sex hormone-binding globulin (SHBG) (C) in patients with COPD and in controls.*

(i) COPD patients with FEV_1<50% predicted, (ii) COPD patients with FEV_1≥50% predicted, and (iii) those with normal lung function (controls) (Table III). According to disease severity, significant differences (p<0.05) were shown for total testosterone and fT, DHEA-S, LH, osteocalcin, PTH, calcium and albumin for both COPD subgroups compared with the control group. Differences (p<0.05) between the two COPD groups were shown only for LH and PTH. There was no significant difference for PSA, fPSA and FSH among the groups. For SHBG, only the group of COPD with FEV_1<50% predicted, significantly differed (p<0.05) from the control group.

Discussion

In the present study, we investigated the hormonal profiles of patients with COPD. The main findings of our study are: (i) there is a significant difference in the male hormonal profile of patients with COPD compared to the control group when stratified by age or disease severity; (ii) male patients with COPD aged >60 years exhibit significantly lower fPSA levels.

COPD could be considered a 'chronic systemic inflammatory syndrome' (11) that affects the hypothalamic–pituitary–testicular axis, exhibiting low gonadotropin levels (secondary hypogonadism). Herein we sought to determine the relation of endocrine derangements with age and disease severity among the groups. In the overall analysis, there was a significant decline of both total testosterone and fT along with SHBG and DHEA-S. The origin of this endocrinological derangement is still unclear in patients with COPD. In men, age-related mechanisms may be responsible for the decrease in testosterone due to decreased responsiveness of the testes to human LH, or decreased pituitary responsiveness to gonadotropin-releasing hormone (9). Thus, COPD, considered to be a disease of accelerating aging (12) can cause, by itself, hypogonadism. Remarkably in our study, both total testosterone and fT levels were reduced even in the younger group (≤60 years) of patients with COPD.

Previous studies have reported the significant decline of endogenous release of testosterone in patients with COPD with impaired pulmonary function and that continuous oxygen treatment can normalize testosterone levels (13). There is evidence that patients with COPD and hypogonadism also have significant atrophy of Leydig cells, due to hypoxic inhibition of pituitary gonadotropin secretion (14). In contrast, the levels of LH of older patients (>60 years) with COPD were significantly increased, which may be due to a feedback regulation of gonadotropin secretion. However, in the Tromsø cross-sectional study, patients with chronic bronchitis or emphysema did not have low levels of testosterone (15). The Tromsø study supported the hypothesis that it is not the COPD *per se*, but impaired pulmonary function and consequently hypoxia/hypercapnia that affects

Table III. *Comparison between levels of disease severity in patients with (COPD) and Controls.*

	FEV1 <50% predicted (N=31)					FEV1 ≥50% predicted (N=38)					Controls (N=82)					
Parameter	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	*p*-Value
Age years	68.81	7.57	69.00	53	80	65.74	11.37	68.50	45.00	80	63.57	10.46	66	45	80	0.077
Smoking p-y #*$	97.55	42.51	90.00	33	182	65.61	43.18	65.50	0.00	200	13.32	19.49	0	0	96	0.000
T*$ ng/ml	2.59	1.40	2.27	0.85	7.71	3.12	1.56	3.25	0.68	7.04	4.74	1.44	4.76	2.7	9.08	0.000
FreeT*$ ng/dl	4.75	2.04	4.35	1.97	10.70	5.76	2.75	5.35	1.20	14.20	8.06	2.50	7.425	4.08	17	0.000
SHBG* nmol/l	37.26	16.06	34.90	15.60	70.70	37.72	15.34	36.05	13.40	80.30	46.01	19.67	41.85	16.3	111.6	0.015
DHEA-S*$ µg/dl	74.74	44.61	67	17	159	131.7	142.7	77.50	9.00	718	153.7	88.03	145	15	447	0.000
FSH mIU/ml	12.30	13.29	8.10	1.60	65.76	7.35	5.33	5.81	1.65	21.82	7.32	6.72	4.945	1.7	40.94	0.056
LH#* mIU/ml	10.55	6.57	8.93	1.69	31.83	7.29	3.89	5.85	2.29	18.37	6.74	4.23	5.43	2.39	26.06	0.003
Osteocalcin*$ ng/ml	13.47	8.81	12	2.30	38.30	12.01	6.57	10.80	3.20	35.1	14.96	4.85	14.45	6.4	29.5	0.001
PTH#* pg/ml	74.65	48.29	59.70	27.75	213.8	53.12	29.59	50	15.00	159.1	49.26	17.77	47.1	18.4	105.8	0.003
Ca*$ mg/dl	9.41	0.60	9.40	8.50	11.30	9.40	0.58	9.35	8.10	11	9.69	0.42	9.65	8.7	10.7	0.002
Albumin*$ g/dl	4.11	0.34	4.10	3.20	4.60	4.12	0.37	4.10	3.50	4.90	4.50	0.30	4.5	3.6	5.1	0.000
PSA ng/ml	2.60	2.69	1.27	0.42	10.10	1.82	2.02	1.08	0.17	8.11	2.12	4.16	1.375	0.13	37.4	0.146
FreePSA	0.55	0.68	0.31	0.04	3.22	0.39	0.46	0.28	0.04	2.16	0.50	0.50	0.39	0.04	3.96	0.063

p-y, pack–years; DHEA-S, dehydroepiandrosterone sulphate; SHBG, sex hormone-binding globulin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Ca, serum calcium; PSA, serum prostate-specific antigen; PTH, parathyroid hormone; T, total testosterone; Forced Expiratory Volume in one second (FEV_1). p<0.05 for *FEV_1<50% predicted *vs.* Controls, FEV_1≥50% predicted *vs.* Controls, #FEV_1<50% predicted *vs.* FEV_1≥50% predicted.

the hormone levels (2). In our study population when adjusting for disease severity, a significant decline was shown in endogenous release of testosterone. Remarkably, the levels of LH were increased in patients with severe COPD (FEV_1<50% predicted) compared to patients with moderate airway obstruction (FEV_1≥50% predicted).

Since osteoporosis is very common in COPD (11), we evaluated the parameters involved in bone turnover and investigated possible relations with the hormonal status, age and disease severity of patients with COPD. However, previous studies have not reported any association of reduced bone mineral density with low testosterone levels in COPD (2). In the present study, we measured bone turnover-related hormones in patients with COPD and adjusted for age and disease severity. Osteocalcin levels were lower in patients with COPD compared to controls, while PTH levels were higher. PTH levels were even more elevated in patients with severe COPD, suggesting a disease-related causative component.

It has been recognized that among various parameters, age and smoking can influence total and fPSA levels (16). Several studies have reported PSA and fPSA levels to be significantly lower among current and former smokers, respectively, compared with never smokers (17-19). An inverse correlation has been reported between smoking and PSA, which achieved borderline significance (20). In addition, Gray *et al*. concluded that this inverse association was only true for fPSA but not PSA (21). To this end, current or ex-smokers have been suggested to be at low risk for prostate cancer (22). Herein, it is the first time, to our knowledge, that PSA or fPSA values have been found to be related with COPD adjusted by age and disease severity. Remarkably, COPD patients aged >60 years exhibited significant lower fPSA levels compared to the control group. However, there was no significant difference for PSA or fPSA values among the groups adjusted for COPD severity. Total PSA and fPSA levels were positively correlated with SHBG. Of note, it has been reported that male smokers have increased levels of circulating SHBG (23). To our knowledge, the underlying causes of the relation of PSA with smoking remains inconclusive and our findings on patients with COPD have not yet been reported in the literature. Since cigarette smoking alters the fPSA levels, a modification of PSA cut-off values, according to smoking status has been suggested in order to increase the accuracy of the screening results (18). Although the efficacy of PSA screening is put into question for the early detection of prostate cancer, there is sufficient evidence that in men aged 55 to 69 years, the benefits of screening could outweigh the harm (24). In our opinion, in men >60 years with COPD, a lower threshold for biopsy could be suggested when PSA levels rise substantially. To this end, the age of male patients with COPD should be considered in interpreting PSA-based screening results more accurately.

In conclusion, the present study shows that male hormonal status alterations are present in COPD and are related to older age (>60 years) and poorer lung function (FEV_1<50% predicted). These results may have possible implications for the use of PSA-based screening tests in the elderly male population with COPD.

Conflicts of Interests

The Authors declare no conflicts of interest.

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References

1 Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V and Buist S: Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J *27(2)*: 397-412, 2006.

2 Laghi F, Adiguzel N and Tobin MJ: Endocrinological derangements in COPD. Eur Respir J *34(4)*: 975-996, 2009.

3 Van Vliet M, Spruit MA, Verleden G, Kasran A, Van Herck E, Pitta F, Bouillon R and Decramer M: Hypogonadism, quadriceps weakness, and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med *172(9)*: 1105-1111, 2005.

4 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS and Montori VM: Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab *95(6)*: 2536-2559, 2010.

5 Arver S and Lehtihet M: Current guidelines for the diagnosis of testosterone deficiency. Front Horm Res *37*: 5-20, 2009.

6 Petak SM, Nankin HR, Spark RF, Swerdloff RS and Rodriguez-Rigau LJ: American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients-2002 update. Endocr Pract *8(6)*: 440-456, 2002.

7 Rhoden EL and Morgentaler A: Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med *350(5)*: 482-492, 2004.

8 Karamanolakis D, Lambou T, Bogdanos J, Milathianakis C, Sourla A, Lembessis P, Halapas A, Pissimissis N, Dessypris N, Petridou ET and Koutsilieris M: Serum testosterone: A potential adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values (≥3.0 and <10.0 ng/ml). Anticancer Res *26*: 3159-66, 2006.

9 Pauwels RA, Buist AS, Calverley PM, Jenkins CR and Hurd SS: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med *163(5)*: 1256-1276, 2001.

10 Vermeulen A, Verdonck L and Kaufman JM: A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab *84(10)*: 3666-3672, 1999.
11 Nussbaumer-Ochsner Y and Rabe KF: Systemic manifestations of COPD. Chest *139(1)*: 165-173, 2011.
12 Ito K and Barnes PJ: COPD as a disease of accelerated lung aging. Chest *135(1)*: 173-180, 2009.
13 Aasebo U, Gyltnes A, Bremnes RM, Aakvaag A and Slordal L: Reversal of sexual impotence in male patients with chronic obstructive pulmonary disease and hypoxemia with long-term oxygen therapy. J Steroid Biochem Mol Biol *46(6)*: 799-803, 1993.
14 Kamischke A, Kemper DE, Castel MA, Lüthke M, Rolf C, Behre HM, Magnussen H and Nieschlag E: Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur Respir J *11(1)*: 41-45, 1998.
15 Svartberg J, Schirmer H, Medbo A, Melbye H and Aasebo U: Reduced pulmonary function is associated with lower levels of endogenous total and free testosterone. The Tromso study. Eur J Epidemiol *22(2)*: 107-112, 2007.
16 Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA and Lieber MM: Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA *270(7)*: 860-864, 1993.
17 Gelmann EP, Chia D, Pinsky PF, Andriole GL, Crawford ED, Reding D, Hayes RB, Kramer BS, Woodrum DL, Gohagan JK and Levin DL: Relationship of demographic and clinical factors to free and total prostate-specific antigen. Urology *58(4)*: 561-566, 2001.
18 Li J, Thompson T, Joseph DA and Master VA: Association between smoking status, and free, total and percent free prostate-specific antigen. J Urol *187(4)*: 1228-1233, 2012.
19 Singer EA, Palapattu GS and van Wijngaarden E: Prostate-specific antigen levels in relation to consumption of nonsteroidal anti-inflammatory drugs and acetaminophen: Results from the 2001-2002 National Health and Nutrition Examination Survey. Cancer *113(8)*: 2053-2057, 2008.
20 Kristal AR, Chi C, Tangen CM, Goodman PJ, Etzioni R and Thompson IM: Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. Cancer *106(2)*: 320-328, 2006.
21 Gray MA, Delahunt B, Fowles JR, Weinstein P, Cookes RR and Nacey JN: Demographic and clinical factors as determinants of serum levels of prostate specific antigen and its derivatives. Anticancer Res *24(3b)*: 2069-2072, 2004.
22 Watters JL, Park Y, Hollenbeck A, Schatzkin A and Albanes D: Cigarette smoking and prostate cancer in a prospective US cohort study. Cancer Epidemiol Biomarkers Prev *18(9)*: 2427-2435, 2009.
23 Field AE, Colditz GA, Willett WC, Longcope C and McKinlay JB: The relation of smoking, age, relative weight, and dietary intake to serum adrenal steroids, sex hormones, and sex hormone-binding globulin in middle-aged men. J Clin Endocrinol Metab *79(5)*: 1310-1316, 1994.
24 Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, Holmberg L, Kantoff P, Konety BR, Murad MH, Penson DF and Zietman AL: Early detection of prostate cancer: AUA Guideline. J Urol pii: S0022-5347(13)04308-5. doi: 10.1016/j.juro.2013.04.119. 2013.

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