



Larger Testicular Volume Is Independently Associated with Favorable Indices of Lung Function

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Background: Men with chronic obstructive pulmonary disease, have reduced endogenous testosterone levels, but the relationship between pulmonary function and endogenous testosterone levels, is inconsistent. Testicular volume is a known indicator of endogenous testosterone levels, male fertility, and male potency. In the present study, the authors investigated the relationship, between testicular volume and lung function.

Methods: One hundred and eighty-one South Korean men age 40–70, hospitalized for urological surgery, were retrospectively enrolled, irrespective of the presence of respiratory disease. Study subjects underwent pulmonary function testing, prior to procedures, and testicular volumes were measured by orchidometry. Testosterone levels of patients in blood samples collected between 7 AM and 11 AM, were measured by a direct chemiluminescent immunoassay.

Results: The 181 study subjects were divided into two groups, by testicular volume (≥ 35 mL vs. < 35 mL), the larger testes group, had better lung functions (forced vital capacity [FVC]: 3.87 ± 0.65 L vs. 3.66 ± 0.65 L, $p=0.037$; forced expiratory volume in 1 second [FEV₁]: 2.92 ± 0.57 L vs. 2.65 ± 0.61 L, $p=0.002$; FVC % predicted: $98.2 \pm 15.2\%$ vs. $93.8 \pm 13.1\%$, $p=0.040$; FEV₁ % predicted: $105.4 \pm 19.5\%$ vs. $95.9 \pm 21.2\%$, $p=0.002$). In addition, the proportion of patients with a FEV₁/FVC of $< 70\%$, was lower in the larger testes group. Univariate analysis conducted using linear regression models, revealed that testicular volume was correlated with FVC ($r=0.162$, $p=0.029$), FEV₁ ($r=0.218$, $p=0.003$), FEV₁/FVC ($r=0.149$, $p=0.046$), and FEV₁ % predicted ($r=0.178$, $p=0.017$), and multivariate analysis using linear regression models, revealed that testicular volume was a significant predictive factor for FEV₁ % predicted ($\beta = 0.159$, $p=0.041$).

Conclusion: Larger testicular volume was independently associated, with favorable indices of lung function. These results suggest that androgens, may contribute to better lung function.

Keywords: Respiratory Physiological Phenomena; Pulmonary Disease, Chronic Obstructive; Respiratory Function Tests; Testis; Testosterone

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Introduction

Chronic obstructive pulmonary disease (COPD) is now considered a systemic disease that affects organs beyond the lungs and airways. The disease is characterized by irreversible airflow obstruction and progressive weight loss, especially loss of lean body mass, which is associated with skeletal muscle dysfunction¹. Reduced testosterone levels and hypogonadism have been described in COPD². In adult men, this reduction is modest, but a progressive decline in testosterone production starts between the fourth and sixth decades of life^{3,4}. This decline is associated with a simultaneous increase of sex hormone-binding globulin (SHBG) levels, and thus, bioavail-

able testosterone may decline more rapidly than total testosterone⁵.

Several studies have shown that middle aged and elderly COPD patients may develop hypogonadism, and the prevalence of hypogonadism in men with COPD can range from 22% to 69%. In addition, hypogonadism has been associated with several other systemic manifestations including osteoporosis, depression, and muscle weakness^{2,6-8}. However, information regarding the relationship between pulmonary function and endogenous testosterone levels in general populations is inconsistent^{5-7,9}. Discrepancies can be mainly attributed to small sample sizes, different patient selection criteria, and circadian variations in testosterone levels. Early morning testosterone levels in young males are, on average, 50% higher than afternoon levels, and reference ranges have usually been derived using morning specimens. Furthermore, testosterone levels can fluctuate substantially on a day-to-day basis. It has been recommended that androgen status should be assessed using more than one measurement¹⁰.

Testicular volume has been shown to well represent endogenous testosterone levels, and thus, is considered as an indicator of endogenous testosterone level¹¹⁻¹⁶, fertility, and potency. Furthermore, unlike testosterone levels, testicular volumes do not fluctuate markedly, and in fact, are relatively stable. Testicular volumes have been found to vary widely between individuals in large-scale studies^{11,12,17}. Furthermore, like lung function¹⁸, testicular volume decreases with aging^{19,20}. Therefore, in the present study, we have investigated the relationship between testicular volume and pulmonary function.

Materials and Methods

1. Study subject selection

One hundred and eighty-one South Korean male patients (aged 40–70 years) hospitalized for urological surgery between April 2014 and March 2016 at a single tertiary academic center were retrospectively reviewed irrespective of the presence of respiratory disease. Testosterone levels of all the patients in blood samples collected between 7 AM and 11 AM were measured by a direct chemiluminescent immunoassay (Bayer ADVIA Centaur; assay range, 10–1,500 ng/dL). Regarding smoking histories, “never-smokers” were defined as those who had smoked on average <1 cigarette/day for <6 months or had never smoked. For ever-smokers, pack-years were calculated to quantify tobacco use; 1-pack-year was equivalent to smoking an average of 20 cigarettes per day for 1 year.

2. Pulmonary function tests

All study subjects underwent spirometry according to American Thoracic Society guidelines^{21,22}, before procedures.

Spirometry indices included the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and FEV₁/FVC ratio. Post-bronchodilator responses were not measured.

3. Testicular volume

Patients with conditions known to strongly influence testicular volume were excluded from the study. Testicular volumes were measured by an experienced urologist using an orchidometry.

4. Statistics

Relationships between the variables were analyzed using Pearson's linear correlation. Univariate and multivariate analyses were performed using linear regression modelling to identify independent predictors of lung factor. The Student's t test and the chi-square test were used to compare the variables of the two study groups divided by testicular volume (≥ 35 mL vs. < 35 mL).

The analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA), and p-values of < 0.05 were considered statistically significant.

5. Ethics statement

The study was approved by the Institutional Review Board of Gachon University Gil Hospital (GBIRB2016-175) and conducted in accordance with the Declaration of Helsinki. The informed consent requirement was waived due to the retrospective study design.

Results

1. Correlation study

The characteristics of the 181 study subjects are summarized in Table 1.

Univariate analysis using linear regression models showed that testicular volume was correlated with FVC ($r=0.162$, $p=0.029$), FEV₁ ($r=0.218$, $p=0.003$), FEV₁/FVC ($r=0.149$, $p=0.046$), and FEV₁ % predicted ($r=0.178$, $p=0.017$) (Table 2). Multivariate analysis using linear regression models showed that testicular volume significantly predicted FEV₁ % predicted ($\beta=0.159$, $p=0.041$) (Table 3).

2. Comparison study between the two study groups (testicular volume ≥ 35 mL vs. testicular volume < 35 mL)

The larger testes group ($n=88$) had better lung functions than the smaller testes group ($n=93$) (FVC: 3.87 ± 0.65 L vs.

Table 1. Characteristics of the study population

Characteristic	Mean±SD	Median (min-max)
Age, yr	64.4±4.6	65.0 (44.0–70.0)
Height, cm	167.7±5.8	168.0 (154.0–182.0)
Weight, kg	67.6±9.5	67.0 (49.0–97.0)
BMI, kg/m ²	24.0±2.8	23.9 (17.0–32.3)
Testosterone, ng/dL	379.8±148.3	377.0 (109.6–771.0)
Free testosterone, pg/mL	7.94±2.98	7.81 (1.28–17.87)
Testicular volume, mL	34.7±9.2	34.0 (15.0–54.0)
FVC, L	3.76±0.65	3.81 (1.75–5.63)
FEV ₁ , L	2.78±0.61	2.80 (0.82–4.36)
FEV ₁ /FVC, %	73.6±9.4	76.0 (26.0–87.0)
PredFVC, %	95.9±14.3	97.0 (45.0–128.0)
PredFEV ₁ , %	100.5±20.9	101.0 (33.0–182.0)
Smoker, n (%)	80/181 (44.2)	
Smoking, pack-years	30.2±20.5	25.0 (2.0–100.0)
FEV ₁ /FVC <70%, n (%)	41/181 (22.7)	

BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second; PredFVC: FVC % predicted; PredFEV₁: FEV₁ % predicted.

3.66±0.65 L, p=0.037; FEV₁: 2.92±0.57 L vs. 2.65±0.61 L, p=0.002; FEV₁/FVC: 75.5±7.8% vs. 71.9±10.5%, p=0.009; FVC % predicted: 98.2±15.2% vs. 93.8±13.1%, p=0.040; FEV₁ % predicted: 105.4±19.5% vs. 95.9±21.2%, p=0.002) (Table 4). Furthermore, the percentage of patients with a FEV₁/FVC of <70% was lower in the larger testes group (15.9% [14/88] vs. 29.0% [27/93], p=0.034) (Table 4).

3. Smoking

Out of the 181 study subjects, 80 (44.2%) were ever-smokers, and the mean smoking exposure of smokers was 30.2±20.5 pack-years (Table 1). Univariate analysis using linear regression models showed that testicular volume was not correlated with smoking (r=-0.094, p=0.216) (Table 2). When patients were divided into two groups according to testicular volume (testicular volume, ≥35 mL vs. <35 mL), proportions of ever-smokers and mean smoking exposure of ever-smokers were not different between the two groups (Table 4).

4. Odds ratio analysis

The odds ratio of ever-smokers in the larger versus the smaller testes group was 1.104, which was not statistically significant (95% confidence interval [CI], 0.614–1.986). However, the odds ratio of having a FEV₁/FVC ≥70% in the larger testes group versus the smaller testes group was 2.162, which was

Table 2. Relationships between PFT findings and study variables (univariate analysis using linear regression models) (n=181)

		FVC	FEV ₁	FEV ₁ /FVC	PredFVC	PredFEV ₁	TV	T
Age	r-value	-0.405	-0.391	-0.102	-0.107	-0.055	-0.085	0.038
	p-value	0.000	0.000	0.170	0.150	0.466	0.253	0.609
Height	r-value	0.478	0.353	-0.029	-0.014	-0.040	0.195	0.012
	p-value	0.000	0.000	0.696	0.849	0.592	0.008	0.867
Weight	r-value	0.286	0.252	0.056	-0.038	-0.003	0.266	-0.029
	p-value	0.000	0.001	0.458	0.611	0.968	0.000	0.703
BMI	r-value	0.070	0.102	0.086	-0.034	0.023	0.206	-0.053
	p-value	0.348	0.172	0.252	0.647	0.757	0.005	0.482
T	r-value	0.019	-0.001	-0.016	0.053	0.039	-0.024	-
	p-value	0.804	0.985	0.833	0.480	0.606	0.752	-
fT	r-value	0.094	0.091	0.030	0.058	0.052	0.027	0.624
	p-value	0.212	0.229	0.693	0.445	0.494	0.718	0.000
TV	r-value	0.162	0.218	0.149	0.126	0.178	-	-0.024
	p-value	0.029	0.003	0.046	0.090	0.017	-	0.752
Smoking	r-value	-0.108	-0.217	-0.213	-0.095	-0.200	-0.094	0.061
	p-value	0.153	0.004	0.005	0.208	0.008	0.216	0.421

PFT: pulmonary function test; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second; PredFVC: FVC % predicted; PredFEV₁: FEV₁ % predicted; TV: testicular volume; T: testosterone; r-value: Pearson correlation coefficient; BMI: body mass index; fT: free testosterone.

Table 3. Multivariate analysis using linear regression models (n=181)

		FVC	FEV ₁	FEV ₁ /FVC	PredFVC	PredFEV ₁
Age	β	-0.289	-0.294	-0.083	-0.123	-0.050
	p-value	0.000	0.000	0.285	0.121	0.523
Height	β	0.419	0.251	-0.123	0.005	-0.064
	p-value	0.000	0.002	0.185	0.961	0.491
Weight	β	-0.026	0.011	0.069	-0.099	-0.024
	p-value	0.744	0.894	0.456	0.292	0.794
Testosterone	β	0.046	0.032	0.009	0.085	0.070
	p-value	0.470	0.622	0.904	0.260	0.344
Testicular volume	β	0.036	0.109	0.127	0.110	0.159
	p-value	0.585	0.112	0.102	0.162	0.041
Smoking	β	-0.075	-0.174	-0.189	-0.085	-0.187
	p-value	0.242	0.010	0.013	0.265	0.014

FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second; PredFVC: FVC % predicted; PredFEV₁: FEV₁ % predicted.

Table 4. Characteristics of patients in two study groups

	Testicular volume		p-value
	≥35 mL (n=88)	<35 mL (n=93)	
Age, yr	64.0±5.2	64.8±3.8	0.230
Height, cm	168.5±5.7	167.0±5.7	0.079
Weight, kg	69.2±9.8	66.0±9.1	0.024
BMI, kg/m ²	24.3±2.8	23.6±2.7	0.091
Testosterone, ng/dL	382.0±152.6	377.7±145.0	0.844
Free testosterone, pg/mL	8.06±3.25	7.83±2.72	0.618
Testicular volume, mL	42.6±5.3	27.2±4.7	<0.001
FVC, L	3.87±0.65	3.66±0.65	0.037
FEV ₁ , L	2.92±0.57	2.65±0.61	0.002
FEV ₁ /FVC, %	75.5±7.8	71.9±10.5	0.009
PredFVC, %	98.2±15.2	93.8±13.1	0.040
PredFEV ₁ , %	105.4±19.5	95.9±21.2	0.002
Smoking, n (%)	40/88 (45.5)	40/93 (43.0)	0.742
Smoking, pack-years	26.0±17.2	34.2±22.8	0.086
FEV ₁ /FVC <70%, n (%)	14/88 (15.9)	27/93 (29.0)	0.034

BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1 second; PredFVC: FVC % predicted; PredFEV₁: FEV₁ % predicted.

significant (95% CI, 1.046–4.464) (Table 5).

Discussion

This is the first study undertaken to investigate whether a relation exists between testicular volume and pulmonary

function. It shows testicular volume is positively and independently associated with better lung functions. Furthermore, the proportion of patients with a FEV₁/FVC <70% was lower in the larger testes group, and multivariate analysis using linear regression models showed that testicular volume was a significant predictive factor for FEV₁ % predicted independently of smoking.

Table 5. Odds ratio analysis

		Testicular volume		OR (95% CI)	p-value
		≥35 mL	<35 mL		
FEV ₁ /FVC, %	≥70	74	66	2.162 (1.046–4.464)	0.035
	<70	14	27		
Smoking	Ever-smoker	40	40	1.104 (0.614–1.986)	0.741
	Never-smoker	48	53		
Ever-smoker, pack-years	≥30	16	22	0.545 (0.224–1.325)	0.179
	<30	24	18		

OR: odds ratio; CI: confidence interval; FEV₁: forced expiratory volume in 1 second; FVC: forced vital capacity.

A number of chronic illnesses, including COPD, can cause hypogonadism²³. The mechanism of hypogonadism in COPD is multifactorial, and depends on aging, smoking, obesity, systemic inflammation, chronic disease itself, hypoxemia, hypercapnia, and the taking of glucocorticoids²⁴. COPD can affect the hypothalamic-pituitary-testicular axis at multiple levels. In one study, approximately 75% of men with COPD had a low serum testosterone level, a low or below-normal gonadotropin level⁷. Reduced lung function and decline in lung function are associated with morbidity and mortality. However, the effects of sex hormones on lung function are not well understood. In a previous cross-sectional study conducted on 2,197 men, total and free testosterone levels were found to be positively and independently associated with FVC and FEV₁, and men with severe pulmonary obstruction had lower free testosterone levels⁹. However, another study found no relationship between free testosterone level and FEV₁, residual volume, or total lung capacity⁷. In present study, no relationship was observed between testosterone level and lung function. These discrepancies can be attributed to small sample sizes, differences in patient selection, and the inconsistent testosterone levels.

In an autopsy study, the total volume of Leydig cells in the testes of men with a history of chronic bronchitis and emphysema of at least 15 years' duration, and with morphological evidence of the cardiopulmonary effects of hypoxia, was significantly less than the volume in matched controls²⁵. Other chronic conditions, such as, diabetes, stroke, and cancer, have also been associated with late-onset hypogonadism in men, and thus, it appears that a diminished testosterone level is common response to chronic disease²⁶. However, our finding of a linear association between testicular volume and pulmonary function may suggest a potential link between gonadal and pulmonary functions.

The literature is somewhat inconsistent regarding the relationship between smoking and testosterone levels. Most cross-sectional studies indicate that smoking increases total testosterone and that smoking cessation reduces testosterone levels in men. As SHBG levels are elevated in smoking men, it has been suggested that this reported increase in testosterone

levels is a consequence of increased SHBG levels^{27,28}. However, Kirbas et al.²⁸ studied the association between hypogonadism, smoking, and obstructive sleep apnea and found no relationship between current smoking and testosterone levels. In the present study, univariate analysis using linear regression models showed that both testicular volume and testosterone levels were not correlated with smoking.

The human testis has been evaluated in term of its endocrine function, daily sperm output in ejaculates, general appearance of seminiferous tubules, differential cell counts in the testis, and daily sperm production²⁹. Although many reports regarding Prader's orchimeter-derived testicular volume are available, no uniform reference values are available, due to differences in the nature of the populations studied (geographic area, nutritional status, ethnicity, and environmental factors)^{11,13,30}. The normal range of one testicular volume has been reported to be 14–30 mL^{12,13,31,32}, but human testicular volumes are markedly dependent on ethnicity^{30,33,34}. For example, testicular volumes have been reported to greater in Caucasian than in Oriental populations³⁴. As compared with the results of Auger and Eustache³⁵, our study population had smaller total testicular volumes (34.7±9.2 mL vs. 55.7±18.7 mL) (Table 1), and thus, it is not appropriate to compare our Korean data with Caucasian data directly. However, testicular volumes in this study were similar to those found in large-scale studies of healthy young Korean men^{11,17}, which means testicular volumes in our study population were within normal limits, as we excluded patients with conditions known to influence testicular volume.

Like lung function¹⁸, clinically assessed testicular volume varies with age³⁶. In a large cohort of males aged 0–28 years, maximum testicular volume was attained at 17–18 and 21–22 years among non-gypsies and gypsies, respectively³⁷. Findings of testicular volume declines with aging are not universal, as some have reported a decrease^{19,20} and others no change³⁸. It has also been reported age, malnutrition and illness exert independent effects on testicular volume³⁹, and that age is associated with a reduction in testicular volume only in the eighth decade of life^{39,40}. However, recent studies suggest that

mild testicular volume decline often occurs earlier from the 50 or 60s^{41,42}. Reduced testicular volume is associated with hormonal abnormalities, including low testosterone and increased luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels^{12,42}. In aged men, testicular volume, testicular parenchymal weight, and daily sperm production are significantly reduced²⁹. In addition, plasma LH, FSH, and estradiol concentrations are elevated whereas plasma testosterone, free testosterone, and the ability of the testis to secrete testosterone following stimulation are diminished. However, testosterone levels can fluctuate substantially day-to-day and sometimes within days. Therefore, testicular volume, which is relatively stable, represents androgen status better than a single measurement of testosterone level.

Several studies have reported a positive relationship exists between testicular volume and body weight^{11,17}. In the present study, height, weight, and body mass index exhibited significant association with testicular volumes by univariate analysis (Table 2). However, body weight was not found to independently predict FEV₁ % predicted by multivariate analysis. In fact, only smoking and testicular volume were found to independently predict FEV₁ % predicted (Table 3).

We enrolled the relatively small number of subjects from a specific setting. Furthermore, our results cannot be applied to other populations, given the limited demographics of the study population. Another limitation is that we used pre-bronchodilator spirometric values to evaluate lung function, and thus, we cannot rule out the possibility of transient airflow obstruction in some patients.

Summarizing, although the present study was not conducted using a large-scale, longitudinal design, it shows larger testicular volume was independently associated with favorable indices of lung function, and suggests that androgens may contribute to better lung function.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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