# High free testosterone index increases lung function in adult males

## Martiem Mawi* and Rully Ayu Nirmalasari**

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## ABSTRACT

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**BACKGROUND**

Increasing age and decreased testosterone concentrations in males influence muscle strength and muscle mass, particularly in skeletal muscle. There have been few studies on decreased lung function resulting from reduced mass and strength of respiratory muscles. The aim of the present study was to investigate the existence of an association between free testosterone index (FTI) and lung function in males aged between 40 and 80 years.

**METHODS**

This cross-sectional study involved 167 males aged between 40 and 80 years in Cilandak subdistrict, South Jakarta. Total serum testosterone and sex hormone-binding globulin (SHBG) concentrations were determined by electrochemiluminescence immunoassay (ECLIA) using Roche Elecsys Reagent Kit Cat 11776061 and Elecsys 2010 reagent (Cobas e601), respectively FTI was calculated using the formula free testosterone/SHBG x 100%. Forced expiratory volume in 1 second (VEP1) was assessed by means of an AS 500 spirometer.

**RESULTS**

Mean age of the subjects was $53.32 \pm 8.26$ years, mean total serum testosterone concentration was $532.59 \pm 206.92$ ng/dL, mean SHBG concentration $41.26 \pm 21.14$ nmol/L, mean FTI $48.22 \pm 14.34$ %, and mean VEP1 was $1.63 \pm 0.54$ L. There was a significant association between both SHBG and FTI on the one hand and VEP1 on the other, with Pearson correlation coefficients of -0.199 (p=0.010) and 0.271 (p=0.000), respectively. Linear multiple regression analysis indicated that FTI was the most influential variable on lung function (VEP1), higher FTI values indicating higher VEP1 (â=0.008: p=0.004).

**CONCLUSION**

In males aged 40-80 years, higher FTI values indicate better lung function as determined by means of VEP1.

**Keywords:** Testosterone, lung function, andropause, adult males

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# Indeks testosteron bebas yang tinggi meningkatkan fungsi paru pada laki-laki dewasa

## ABSTRAK

**LATAR BELAKANG**

*Peningkatan usia dan penurunan kadar hormon testosteron pada laki-laki akan mempengaruhi kekuatan dan massa otot terutama otot rangka. Penurunan fungsi paru akibat pengurangan massa dan kekuatan otot pernapasan belum banyak diketahui. Penelitian ini bertujuan untuk menentukan hubungan antara indeks testosteron dan fungsi paru pada laki-laki berusia antara 40 sampai 80 tahun.*

**METODE**

*Penelitian ini menggunakan desain potong lintang mengikut sertakan 167 laki-laki yang berusia antara 40 sampai 80 tahun di Kecamatan Cilandak Jakarta Selatan. Pemeriksaan kadar testosteron total dilakukan dengan* electrochemiluminescence immunoassay *(Eclia) dengan* Roche Elecsys Reagen Kit Cat 11776061. *Sex hormone-binding globulin (SHBG) diukur dengan metode Eclia dengan reagen elecsys 2010 (Calos e601). Indeks testosteron bebas (ITB) dihitung berdasarkan kadar testosteron bebas/SHBG x 100%. Volume ekspirasi paksa satu detik pertama (VEP1) diperiksa dengan memakai spirometer AS 500.*

**HASIL**

*Usia rata-rata subjek adalah 53,32 ± 8,26 tahun, kadar testosteron total serum rata-rata adalah 532,59 ± 206,92 ng/dL, kadar SHBG rata-rata adalah 41,26 ± 21,14 nmol/L, nilai ITB rata-rata adalah 48,22 ± 14,34 %, dan VEP1 rata-rata adalah 1,63 ± 0,54 L. Terdapat hubungan bermakna antara kadar SHBG dan ITB dengan VEP1 dengan koefisien korelasi Pearson masing-masing sebesar -0,199 (p=0,010) dan 0,271 (p=0,000). Analisis regresi ganda linier menunjukkan ITB yang paling berpengaruh terhadap fungsi paru (VEP1), semakin tinggi nilai ITB semakin tinggi VEP1 (â=0,008: p=0,004).*

**KESIMPULAN**

*Pada laki-laki yang berusia antara 40-80 tahun, peningkatan ITB akan meningkatkan fungsi paru yang diukur dengan menggunakan VEP1.*

*Keywords: Testosteron, fungsi paru, andropause, laki-laki dewasa*

## INTRODUCTION

Increased health status and longevity in Indonesia have resulted in a rapid increase in the number of older persons, which in 2010 was estimated to equal the number of under-fives at around 24 million or 9.77% of the total population. In 2020 there will be an estimated 28.8 million or 11.34% of the total population.[1]

In males, increasing age is associated with a reduction in serum androgenic hormones, particularly testosterone, with a concomitant signs of andropause, such as decreased libido, increased incidence of erectile dysfunction, and decreased muscle mass and muscle strength. The reduction in testosterone levels is caused by decreased testicular production, decreased luteinezing hormone (LH) levels[2] and decreased capacity of the brain to stimulate testosterone release.[3] The andropause has also been associated with emotional and physical changes.[4] Androgenic hormones comprise testosterone, dehydrotestosterone (DHT), dehydro-epiandrosterone (DHEA), dehydro-

epiandrosterone sulfate (DHEAS), and androstenedione.

Although DHEA levels follow the circadian rhythm, attaining peak levels in the morning hours, DHEAS levels are relatively stable throughout the day. DHEA and DHEAS are intermediate metabolites in the synthesis of other steroids, such as the male sex hormone testosterons.[5] Of the circulatory testosterone, 40% is bound to sex hormone binding globulin (SHBG) and inactive, 58% is bound to albumin and is the active form in various tissues (bioavailable testosterone), while 2% is in a free active form. Testosterone not bound to SHBG diffuses passively through the cell membrane into the target cells, where it binds androgen receptors (AR). It is the free serum testosterone and the testosterone bound to albumin that have biological functions.[2]

Symptoms of andropause appear at the age of 40-55 years. From the age of 30 years onwards there is a 10% reduction in testosterone levels for each decade, such that at the age of 50 years there will be a 30% reduction in testosterone levels, leading to the appearance of symptoms.[6] There are 10 signs of andropause, i.e. irritability, sleep disturbances, decreased libido, erectile dysfunction, decreased muscle mass, increased body weight, loss of memory, thinning of scalp hair, reduced bone density, and depression.[6]

The respiratory changes are associated with increasing age are important because they may increase the development of respiratory disorders. This is associated with increased pulmonary compliance, such as pulmonary elastic recoil, and decreased compliance of the chest wall. Both of these result in a progressive decrease in forced vital capacity (FVC), forced expiratory volume in 1 second (VEP1), and forced expiratory flow, and an increase in residual functional capacity.[7] Reduced testosterone levels with increasing age is associated with decreased muscle strength and muscle mass.[8] The Massachusetts Male Aging Study found an association between low serum testosterone concentration and mortality from

respiratory disease.[9] Patients with chronic bronchitis, which is associated high mortality risk, have low total serum testosterone concentrations.[10]

The reduced testosterone levels in older males are receiving increasing attention, particularly with regard to their effects on lung function. Therefore the aim of the present study was to determine any association existing between testosterone level and lung function in males aged between 40 and 80 years.

## METHODS

### Research design

This was a cross-sectional study to determine whether there is an association between testosterone level and lung function in males aged between 40 and 80 years. The study was conducted from July to October 2011.

### Study subjects

The subjects of the study were males aged 40 - 80 years who were residents of 5 *kelurahan* (villages) in Cilandak subdistrict, South Jakarta, comprising Cilandak Barat, Pondok Labu, Lebak Bulus, Cipete Selatan and Gandaria Selatan. Inclusion criteria in this study were: males aged 40-80 years, not suffering from pulmonary, cardiac or renal diseases and diabetes mellitus, willing to participate in the study on the basis of informed consent, capable of active communication, mobile (not requiring walking aids). The exclusion criterion was consumption of any hormonal medication in the last three years. All respondents gave signed informed consent.

### Anthropometric measurements

Height was measured to the nearest 0.1 cm using a portable microtoise, with the respondents standing without shoes. Weight was measured to the nearest 0.1 kg using Sage portable scales, in lightly clothed respondents without shoes. Body mass index (BMI) was determined by dividing weight in kg by height in square meters.

BMI was divided into 4 categories as follows: underweight ($<18.5$ kg/m$^2$), normal (18.5 - 22.9 kg/m$^2$), overweight (23.0-27.5 kg/m$^2$), and obesity ($\geq27.6$ kg/m$^2$).

## Laboratory assays

A fasting blood sample was drawn from the median cubital vein of each subject, with the subject in the supine position, between 8.00 A.M. and 10.00 A.M. The sample was collected in a plain tube, left to clot for 30-45 minutes, and subsequently centrifuged at 3000 rpm for 15 minutes to separate the serum. Measurement of total testosterone and SHBG was by electrochemiluminescence immunoassay (ECLIA), respectively using an Elecsys 2010/ Cobas e601 and Roche Elecsys Reagent Kit Cat. 11776061 (R1: Anti-testosterone-ad-biotin, R2: Testosterone-Ruthenium) and Roche Elycsys Reagen Kit Cat. 03052001 (R1: Anti-SHBG-ad-biotin, R2: anti SHBG-Ruthenium). The intra-assay coefficients of variation of testosterone and SHBG were 5.9% and 5.8%, respectively. The free testosterone index (FTI) was calculated according to the formula total serum testosterone/ SHBG) x 100. Fasting blood glucose was measured by spectrophotometry using an Advia 1800 instrument and Bayer Advia 180074024 glucose reagent (R1: ATP, NAD, sodium azide; R2: Hexokinase, G6PD). Detection limit: 0.6mg/ dL, linearity: 0-700 mg/dL. Conversion factor: mg/dL x 0.05555 mmol/L.

## Measurement of lung function

In this study the VEP1 was used as an indicator of lung function. Data on height, weight, age and gender of the subjects were entered in the minicomputer of the AS 500 spirometer. The standing subjects faced the instrument and took one inspiration and then performed a single forced expiration into the mouth piece attached to the spirometer. The examination was performed three times, after which the mean of the three values was calculated.

## Research ethics

The present study obtained ethical clearance from the Research Ethics Commission of the Faculty of Medicine, Trisakti University.

## Data analysis

All variables were checked for normal distribution using the Kolmogorov-Smirnov one-sample test for goodness-of-fit. The Pearson correlation test was used to determine a relationship between VEP1 and age, BMI, fasting blood glucose, total serum testosterone, SHBG, and FTI as covariates. Covariates with a significant association with VEP1 were entered into a linear multiple regression model to determine the covariates with the greatest influence on lung function. Two-sided p-values of less then 0.05 were considered significant. Data processing was by means of SPSS for Windows version 17.

## RESULTS

Of the 167 subjects participating in this study the mean age was $53.32 \pm 8.26$ years. There were 72 (43.1%) subjects with senior high school education, 124 (74.3%) were unemployed, mean BMI was $24.23 \pm 4.01$ kg/ m$^2$ and VEP1 was $1.63 \pm 0.54$ L. Mean fasting blood glucose was $108.58 \pm 42.96$ mg/dL, total testosterone $532.38 \pm 206.92$ nmol/L, SHBG $41.04 \pm 21.12$ nmol/L, and FTI $48.13 \pm 14.28$ % (Table 1).

The results of the Pearson correlation analysis between VEP1 and hormone concentration and other covariates showed that SHGB and FTI were significantly correlated with VEP1, the Pearson correlation coefficients being -0.199 (p=0.010) and 0.271 (p=0.000), respectively (Table 2). Both significant variables were entered into a linear multiple regression model with VEP1 as the dependent variable.

The results of the linear multiple regression showed that FTI was of greatest influence on

Table 1. Characteristics of participating subjects (n=167)

| Characteristic | Mean ± SD |
|---|---|
| Age (years) | 53.2 ± 8.26 |
| BMI (kg/m²) | 24.33 ± 4.01 |
| Education * | |
| No education | 6 (3.6%) |
| Primary school | 48 (28.7%) |
| Junior high school | 28 (16.8%) |
| Senior high school | 72 (43.1%) |
| Academy/University | 13 (7.8%) |
| Employment * | |
| Unemployed | 43 (25.7%) |
| Employed | 124 (74.3%) |
| Fasting blood glucose (mg/dL) | 108.58 ± 42.96 |
| VEP1 (L) | 1.63 ± 0.54 |
| Total serum testosterone (ng/dL) | 532.38 ± 206.92 |
| SHBG (nmol/L) | 41.04 ± 21.12 |
| FTI (%) | 48.13 ± 14.28 |

*Frequency (percentage); BMI=body mass index; SHBG=sex hormone binding globulin; VEP1=forced expiratory volume in 1 second; FTI=free testosterone index

Table 2. Relationship between hormone concentration and other covariates and lung function

| Hormone and covariates | VEP1 |
|---|---|
| Age | - 0.147 |
| BMI | 0.045 |
| Fasting blood glucose (mg/dL) | - 0.049 |
| Total testosterone (ng/dL) | - 0.037 |
| SHBG (nmol/L) | - 0.199* |
| FTI (%) | 0.271* |

*$p < 0.05$; BMI=body mass index; SHBG=Sex hormone binding globulin; FTI=free testosterone index; VEP1=forced expiratory volume in 1 second

lung function (VEP1), with higher FTI values indicating high VEP1 ($\beta$=0.008; p=0.004) (Table 3).

## DISCUSSION

The results of this study showed that FTI was of greatest influence on lung function in males aged 40–80 years. Our findings were consistent with those of a study conducted on 2197 male subjects aged 29 years and older, where free testosterone level and FTI were significantly associated with lung function, measured from forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1).[11]

Our study determined only FTI and not serum free testosterone concentrations. FTI is capable of describing androgen status of an individual, because FTI reasonably approximates bioavailable testosterone with the use of equilibrium dialysis and has been shown to be suitable for clinical use.[12]

The present study determined the physiologic serum levels of total testosterone and SHBG, and calculated the FTI. The lack of association between total testosterone and lung function may be explained by the fact that there is no sufficiently significant variation in physiologic testosterone levels across different age groups for clearly differentiating between individual lung functions. In addition, serum testosterone levels might only play a minor role in lung functions of healthy males. It is debatable whether it is only older males with low testosterone levels who can experience

Table 3. Linear multiple regression with VEP1 as dependent variable

| Independent variable | VEP1 | | |
|---|---|---|---|
| | β | Beta | p |
| SHBG | -0.005 | -0.197 | 0.342 |
| FTI | 0.008 | 0.225 | 0.004 |

$\beta$=regression coefficient; Beta=standardized beta coefficient; SHBG=sex hormone binding globulin; FTI=free testosterone index; VEP1=forced expiratory volume in 1 second

improved lung function. In the Massachusetts Male Aging Study an association was found between low total serum testosterone levels and respiratory disease mortality,[11] observable only with calculated free testosterone, and not with total testosterone. Patients with chronic bronchitis and associated high mortality risk, have been shown to have lower serum testosterone levels.[10] Furthermore, lower serum testosterone levels have been associated with an increased morbidity not only in people suffering from respiratory diseases but have been shown to predict an increased mortality in both middle-aged and old men owing to cardiovascular disease and metabolic syndrome.[13,14]

Increasing age in males is associated with decreasing capacity for testosterone synthesis, caused by decreased hypophyseal production of luteinizing hormone (LH), which is necesary for stimulating Leydig cells to produce testosterone. In addition, older males have higher concentrations of SHBG, which binds to testosterone and decreases the availability of circulatory free testosterone to various tissues, such as the muscles. Advanced age also cause a flattening of the daily testosterone concentration curve, in contrast to younger males, where testosterone production has a morning peak. However, the decrease in testosterone levels in men occurs at a slower rate in comparison with the decrease in estrogen levels in postmenopausal women.[2]

Testosterone serves to regulate various physiological processes in the body, comprising muscle protein metabolism, various sexual aspects, cognitive functions, secondary sexual characteristics, erythropoiesis, plasma lipids, and bone metabolism.[15,16] The reduction in testosterone levels affect the functioning of various organs and tissues, such as the mass of the respiratory muscles.

This study demonstrated that FTI was of great influence on lung function (VEP1). Several investigators report that in patients with chronic obstructive pulmonary disease (COPD) there is a reduction in testosterone due to

hypoxia, leading to a decrease in muscle mass and muscle strength.[17,18] Administration of testosterone to COPD patients may result in an increase in the mass and strength of the skeletal muscles, particulary the respiratory muscles, resulting in improved lung function.[19,20]

One limitation of the present study is that it did not measure free serum testosterone concentrations, but only calculated FTI, even though FTI has been used by several investigators and has yielded reliable results in studies of cross-sectional design.[11,21] Another limitation of this study is its cross-sectional community-based design, which limits the interpretation of the results and the conclusions that can be drawn as to direction of causality.

## CONCLUSION

In males aged 40-80 years, raised FTI increases lung function as determined by means of VEP1.

## ACKNOWLEDGEMENTS

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