Original Research Article

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Endogenous testosterone to prostate-specific antigen relationship in men without prostatic diseases: a 10-year retrospective study

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ABSTRACT

Background: The relationship between endogenous testosterone and PSA in men without prostatic diseases is controversial. Hence, this study was designed to investigate this relationship among healthy Nigerian men.

Methods: A retrospective study of serum total testosterone (TT) and total PSA records of 1066 prostate disease-free men was undertaken in a Nigerian tertiary Hospital. Data on age, serum testosterone, and PSA from 1st January 2007 to December 2016 was abstracted and analysed.

Results: The mean age, serum PSA, and serum total testosterone levels among study cohorts are 58.40 ± 12.24 years, 3.0 ± 2.24 µg/l, and 15.5 ± 0.53 nmol/l respectively. There was an inverse relationship between serum PSA and testosterone levels with age. Subjects with high-risk PSA level (PSA>4.0 µg/l) had statistically significant higher PSA (p<0.001) and TT (p<0.001) values compared to the low-risk PSA level group. Subjects in the eugonadism group had higher PSA levels than those in the hypogonadism group (eugonadism $3.90\mu g/l\pm2.22$ versus hypogonadism $2.18\mu g/l\pm2.30$; p=0.012). Age correlated positively with PSA (p<0.001), but negatively with TT (p<0.001) while PSA correlated positively with TT (p<0.001).

Conclusions: The findings of this study suggest an association between endogenous TT and PSA among healthy men without prostatic diseases and augment the evidence that serum TT maybe linked to prostate diseases. Clinical decisions regarding PSA should factor the levels of endogenous TT to enhance clinical judgments.

Keywords: Age, Nigeria, PSA, Prostate-specific antigen, Testosterone

INTRODUCTION

Prostate-specific antigen (PSA) is a glycoprotein produced in the prostate tissue with the main function to liquefy the semen.^{1,2} Its serum level parallels the growth of the prostate gland and is a biomarker and screening tool for prostatic diseases inclusive prostatitis, prostatic hyperplasia, and prostate cancer.^{3,4} However, it lacks the qualities of an ideal biomarker as regards the diagnosis of diseases of the prostate especially benign and malignant tumors of the prostate gland.⁴ It is an androgen-dependent protease and its plasma level correlates with the plasma level of plasma androgens, prostate volume, and prostatic

diseases.^{5,6} Therefore, under the biological influence of androgens, PSA is a prostate tissue proliferation biomarker.

The androgen testosterone is the major androgen in men produced primary by the testicular leydig cells, and the hormone is a requisite for the normal development of male sexual characteristics including prostate gland.^{7,8} In addition, the hormone regulates, among other functions, the production and secretion of PSA from the prostate gland.^{9,10} The mechanism of testosterone-induced PSA production by testicular leydig cells is ill-defined in various reports.^{11,12} However, some authors have

postulated that the hormone is first converted to its active dihydrotestosterone form by 5-alpha aromatase enzyme, before activating specific genes through the androgen receptors (AR) with resultant production of proteins including PSA.⁶ Due to endogenous testosterone-induced proliferative effect on prostate tissue, its plasma level correlates with the plasma level of PSA.¹³

Since PSA is a product of an androgen-regulated gene, the understanding of the endogenous total testosterone (TT) to PSA relationship is relevant in the investigative protocols employed in the screening of prostate diseases. However, epidemiologic evidence regarding this relationship is inconsistent in the literature. While some authors have proposed that serum PSA increases in high testosterone milieu, others have surmised that serum PSA is not influenced by endogenous testosterone. 13-16 Moreover, a saturation theory has been proposed recently to highlight the biologic basis why endogenous testosterone does not have any effect on serum PSA beyond a certain limit.¹⁷ The inconsistencies observed in this studies could be due to the fact that most of these studies have been carried out in western populations among male Caucasians with prostate diseases, and those who are on androgen replacement therapies with exogenous testosterone. 18,19

Owing to the dearth of comprehensive data in our region regarding the association between endogenous testosterone and PSA, the primary objective of this study was to retrospectively examine the likely relationship among Nigerian men without prostate diseases.

METHODS

Area of study

The Department of Chemical Pathology and Metabolic Medicine, University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria was the study area. The hospital is a tertiary hospital based in the south-south region of Nigeria providing specialist medical care to the population including among others the screening for cancers through the Department of Chemical Pathology

Design of study

A retrospective, descriptive, cross-sectional analysis of total prostate-specific antigen (PSA) and total testosterone (TT) laboratory test records of all the healthy men who presented for routine screening of prostate cancer in the Department of Chemical Pathology and Metabolic Medicine of the UPTH during a 10-year period spanning from 1st January 2007 to 31st December 2016.

Eligibility criteria

Inclusion criteria include all records of healthy men without the followings: a history of lower urinary tract symptoms (LUTS), abnormal digital rectal examination (DRE), established prostate disorders.

Exclusion criteria include all records with a history of the followings: LUTS, abnormal DRE, prostate disorders, on treatment for prostate disorders, and incomplete data.

Collection of specimen and analysis

Serum samples were used for all the laboratory analysis of total PSA and TT during the period under study. Fasting venous whole blood specimen was collected from each subject prior to DRE via phlebotomy between 8 am and 10 am daily and processed accordingly to obtain the serum samples. Laboratory analysis for total PSA and TT was done by enzyme immunoassay methods with reagents manufactured by Monoblind Incorporated, California, United States of America. Analytical accuracy was strictly ensured by the use of three levels of commercial quality control sera sourced from the same manufacturer.

Collection of data and classification

Data was abstracted from the laboratory records and case notes of each patient and entered into Statistical Package for Social Sciences (SPSS) version 20. Data on demographics (Age and sex), clinical variables (LUTS/DRE), serum total PSA in μ g/l (normal range: <4.0), and serum TT in nmol/l (normal range: 11.0-35.0) were recruited for the study.

Author classified serum total PSA value of <4.0 μ g/l as low-risk PSA and >4.0 μ g/l as high-risk PSA based on the historical cutoff value of 4.0 μ g/l for prostate diseases, while using the serum TT cutoff value of 12 nmol/l to define hypogonadism (TT <12.0 nmol/l) and eugonadism (TT >12.0 nmol/l).^{24,25}

Statistical analysis

Data were entered into SPSS version 20, subsequently coded, validated and analyzed. Normality of data was initially ascertained using Shapiro-Wilk test. Non-Gaussian distributed data was log-transform before analysis. Continuous data were presented as mean ±standard deviations and compared with independent t-test, while categorical data were presented in percentages. Pearson's correlation test was used to evaluate linear relationships between continuous data. A cutoff p value of <0.05 was designated as being significant.

RESULTS

From 1st January 2007 to December 2016, one thousand ninety-eight men (1098) presented as outpatients to the Department of Chemical Pathology and Metabolic Medicine of the University of Port Harcourt Teaching for routine medical checkup and screening for prostate cancer using serum total prostate-specific antigen (PSA)

and total testosterone (TT). The records of 1066 men met the inclusion criteria and were subsequently listed in the study. Using Shapiro-Wilk test, the age and serum TT data were normally distributed while that of serum total PSA was not. Subsequent data analysis was done after log-transforming serum PSA data.

Table 1: Descriptive statistics of study variables.

Variable	n	Mean±SD	Range	
Age (years)	1066	58.4±12.24	38 - 86	
PSA (µg/l)	1066	3.0 ± 2.24	0.1 - 13.3	
TT (nmol/l)	1066	15.5±0.53	3.5 - 36.2	
SD=standard	deviation;	PSA=Prostate-spe	ecific antigen;	
μg/l=microgram	n per	liter; TT=total	testosterone;	
nmol/l=nanomole per liter.				

In Table 1, the mean±standard deviation of age, PSA levels, and the testosterone levels of the 1066 cohorts were 58±12.24, 3.0±2.24, and 15.5±0.53.

Table 2: Descriptive statistics of serum PSA and serum TT based on Age groups.

Age groups (years)	n (%)	PSA μg/l ±SD	Testosterone nmol/l ± SD
<39	56 (5.3)	1.2 ± 0.26	19.3±4.90
40-49	212 (19.9)	1.9 ± 1.20	17.3 ± 4.50
50-59	334 (31.3)	2.8 ± 2.10	15.9±5.67
60-69	268 (25.1)	3.1±1.90	14.6±5.11
70-79	92 (8.6)	3.8 ± 2.51	13.8±4.40
>80	104 (9.8)	5.7 ± 2.68	11.9±4.61

SD=standard deviation; PSA=prostate-specific antigen; $\mu g/l=$ microgram per liter; TT=total testosterone; nmol/l=nanomole per liter.

In Table 2 shows the inverse relationship between PSA and age where the increase of PSA with advancing age is associated with a steady decrease of serum testosterone.

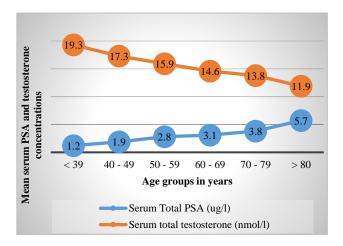


Figure 1: Relationship between mean serum concentrations of PSA, TT, and age of study subjects.

Figure 1 shows the graphical display of table 2 depicting the inverse relationship between PSA and testosterone among study cohorts.

In Table 3, we had classified the study cohorts using the traditional cutoff total PSA value of $4.0\mu g/l$ as low-risk ($<4.0\mu g/l$) or high-risk ($>4.0\mu g/l$) based on the report by Osterling²⁴ and serum total testosterone (TT) cutoff value of 12 nmol/l as hypogonadism (<12nmol/l) or eugonadism (>12nmol/l) based on the report by Bhasin et al.²⁵

Table 3: Comparison of mean values of serum PSA and serum TT based on their classified abnormalities.

Categories of Subjects with PSA and TT disorders	n (%)	Mean PSA ± SD (t-test p-value)	Mean TT ± SD (t-test p-value)
Low-risk PSA level (<4.0 µg/l)	783 (73.5)	1.89 ± 0.82	14.9±4.70
High-risk PSA level (>4.0 µg/l)	283 (26.5)	6.10±2.02 (p <0.001)*	17.1±6.50 (p <0.001)*
Hypogonadism (TT<12 nmol/l)	173 (16.2)	2.18±2.30	7.48±1.35
Eugonadism (TT>12 nmol/l)	893 (83.8)	3.90±2.22 (p=0.012)*	16.99±4.36 (p<0.001)*
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^{*}Statistically significant; SD = standard deviation; PSA=prostate-specific antigen; $\mu g/l$ =microgram per liter; TT =total testosterone; nmol/l =nanomole per liter.

73.3% of the subjects were in the low-risk PSA group compared to 26.5% in the high-risk PSA group. Subjects in the high-risk PSA group had a significant higher mean PSA (p<0.001) and TT (0.001) levels than those in the low-risk group. Hypogonadism was detected 16.2% of the study subjects based on TT levels.

These subjects with hypogonadism based had statistically significant lower mean values of both PSA (p<0.001) and TT (<0.001) compared to those with normal gonadal functions (eugonadism).

Table 4: Correlation table of Age and PSA, Age and TT, and PSA and TT among all study subjects.

Variable	Age r; p value	PSA r; p value
PSA (µg/l)	0.444; < 0.001*	
TT (nmol/l)	-0.380; <0.001*	0.426; <0.001*

*Statistically significant; r=Pearson's correlation coefficient; SD=standard deviation; PSA=prostate-specific antigen; $\mu g/l = microgram per liter;$ TT=total testosterone; nmol/l = nanomole per liter.

In Table 4 shows the significant positive correlation between age and PSA (<0.001), significant negative correlation between age and TT (<0.001), and significant positive correlation between PSA and TT (<0.001).

DISCUSSION

Since it was discovered in 1971 by Hara et al, PSA has revolutionized the screening, diagnosis, and monitoring of prostate disorders (prostatitis, benign prostate hyperplasia, and prostate cancer), however, it falls short as an ideal biomarker for these disorders. ²⁰ The molecular mechanism of PSA expression from the prostate is vague, but evidence abounds that the protein is under the influence of androgens especially testosterone. In prostate tissue. testosterone first is converted dihydrotestosterone (DHT) by the 5α-reductase enzyme before binding to nuclear androgen receptors (AR), the AR-DHT complex activates sequences of DNA response elements which act as transcription factors for the production of messenger RNA and finally proteins including PSA.^{6,9} This pathway establishes relationship between endogenous testosterone (TT) and PSA and forms the basis for the treatment of prostate tumors with anti-androgens in clinical practice.9

Among the several factors proposed to influence the PSA to TT relationship, age seems the more pronounced, PSA increases with advancing age, while TT decreases with age as observed in this study. The increase in prostate volume with advancing age has been adduced to the increase in PSA and the influence of testosterone has been linked to this increase prostate volume with advancing age.⁵ The declining TT has been ascribed to dysfunctions along the hypothalamic-pituitary-testicular axis associated with advancing age.5,21 including the increase in sex hormone binding globulin with resultant decrease in the active bioavailable TT.15 This observations are in accord with this study where we observed an inverse relationship (Table 2 and Figure 1) between PSA and TT and supported by the positive significant correlation between age and PSA (r=0.444; p<0.001) and a negative significant correlation between age and TT (r=-0.380; p<0.001) among the study cohorts. Thus, this study therefore, affirms the fact that testosterone decreases with advancing age which is in accord with the findings from a cross-sectional study that observed a progressive decrease of TT with advancing age among healthy men.²² However, a recent study had reported a significant increment of TT with advancing age, this study had limited sample size of healthy men compared to this study that may have affected their findings. 15

The reports of epidemiologic studies on the relationship between androgens (testosterone) and PSA are inconsistent owing to the fact that most of this studies have either being carried out on subjects with already diagnosed prostate diseases or those on androgen replacement therapy for hypogonadism with exogenous testosterone. 18,19 In this retrospective study, we have included and analyzed only the data of normal men without any symptoms or signs suggestive of prostate disease and observed a positive significant relationship (r=0.426; p = p<0.001) between serum total PSA and TT. This relationship is stronger within those patients in the high-risk PSA group (PSA>4.0 µg/l) compared to subjects in the low-risk PSA group (PSA < 4.0 µg/l) The subjects in the higher-risk group had higher PSA (p<0.001) level and TT (p<0.001) level than those in the low-risk PSA group. These findings lend credence to the fact that TT concentration is the driver behind PSA increase with advancing age. However, while TT continues to decrease with age as observed in this study, PSA also continues to increase. This could be explained by the fact the as men age, so does the intra-prostatic DHT concentrations increase relative to the serum TT concentrations.²³ Therefore, DHT being the active androgens in the prostate tissues continues to exert proliferative effects in prostate tissues despite the decline in serum TT levels with advancing age.²³ In addition, the prostate volume also increases with advancing age aided by testosterone.⁵ These mentioned factors contribute to the increased PSA associated with aging despite declining endogenous serum TT.

Similar studies to ours have attempted to investigate the relationship between endogenous total testosterone (TT) to total PSA relationship among healthy men without prostate diseases. Peskoe et al had investigated the association of serum sex steroid hormones and PSA among 378 prostate disease-free healthy men of between 40 to 85 years old who had participated in the United States Health Survey from 2001–2004. In that study of Nationally representative sample, men with higher endogenous TT levels were reported to also have PSA levels even after accounting for other hormonal and non-hormonal influence. 13

Recently in 2017, Elzanaty et al had also investigated the association between TT and PSA among 119 middle-aged healthy men without prostatic diseases from the general population and reported an association between endogenous TT and PSA after an adjusted multivariate analysis. These findings by Peskoe et al and Elzanaty are in agreement with our study and augments the evidence that endogenous TT is associated with PSA. However, Mustafa et al had asked if there was actually a relationship between endogenous TT and PSA in their study and concluded that such relationship does not exist. In that study, Mustafa et al had restricted their analysis in men with PSA less than 4 ng/ml (4.0 µg/l) which may have reduced the statistical power to detect an association in that study.

CONCLUSION

The findings of this study suggest an association between endogenous TT and PSA among healthy men without prostatic diseases. This finding augments the epidemiologic evidence that serum TT is linked to benign and malignant conditions of the prostate gland. Therefore clinical decisions regarding PSA should factor the influence of endogenous TT to enhance clinical judgments.

Limitations

There were no records of sex hormone binding globulin (SHBG) and free testosterone status among study subjects. The outcome of this study may have been different if SHBG and free testosterone were taken into account. It is retrospective hospital-based study; therefore its conclusion may not reflect the status of the entire population in our region.

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