# **Original Research Article**

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# Low endogenous testosterone level is associated with high-risk prostatespecific antigen level in men with prostate cancer disease

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### **ABSTRACT**

**Background:** Low serum testosterone levels is hypothesized to predict adverse outcomes in prostate cancer patients. This study was structured to investigate this hypothesis using high-risk serum prostate-specific antigen as a marker of adverse outcome of the disease.

**Methods:** This was a retrospective analysis of serum total testosterone (TT) and total prostate-specific antigen (PSA) records of prostate cancer patients in a tertiary hospital in Nigeria. Records of age, serum TT, and serum PSA test results from 1st January 2008 to 31st December 2017 were acquired from laboratory and medical records and analyzed with SPSS software version 20.

**Results:** The records of 450 men with prostate cancer were recruited for the study. The majority (56.7%) of the study cohorts were between 70 to 79 years of age. Hypogonadism was observed in 34.7% of the study cohort. The hypogonadal patients had higher PSA values compared to the eugonadal patients (p<0.001). Lower testosterone values were observed in patients with high-risk PSA levels (p<0.001). Strong significant negative correlations were observed between total PSA and endogenous testosterone within the overall study cohort (r= -0.792; p< 0.001), the hypogonadal group (r= -0.615; p < 0.001), and among the high-risk PSA group (r= -0.632; p< 0.001).

**Conclusions:** The findings of this study suggest low, rather than high, endogenous testosterone in prostate cancer disease is associated with high-risk PSA levels which implies adverse outcome in prostate cancer patients. However, further studies are warranted to confirm this association.

Keywords: Hypogonadism, PSA, Prostate-specific antigen, Prostate cancer, Testosterone

#### INTRODUCTION

Historically, high endogenous total testosterone (TT) milieu in men had generally been believed to be the core cardinal agent in the etiopathogenesis of prostate cancer disease. This notion stems from the novel report in 1941 by Huggins and Hodges who proposed that high plasma TT level was the culprit in prostate cancer risk and the various associated adverse clinicopathologic and poor prognostic features of the disease. 1.2 These adverse features of the disease attributed to high TT includes

higher Gleason scores, higher tumor burden, higher metastatic potential, higher biochemical recurrence rate following therapy and a higher serum prostate-specific antigen (PSA) levels.<sup>3-5</sup> Following that novel report of several decades ago, one of the management modalities of the disease had been hinged on the principle of reduction of TT levels or action using either medical or surgical intervention.<sup>2</sup>

Recently, this decade's long traditional norm of high TT link with prostate cancer characteristics is currently been

challenged and debated.<sup>5</sup> The challenge and debate had surfaced following the observation and report from various epidemiologic studies that low, rather than high, plasma TT level is associated with prostate cancer risk and the various adverse clinicopathologic and poor prognostic features of the disease.<sup>6-17</sup> In addition, in support of these studies is the fact that endogenous TT decreases with advancing age at the same time that prostate cancer incidence increases.<sup>6</sup>

This recent observation has provoked several authors in various studies to suggest for a review of the decade-long norm of high TT association with prostate cancer. 5-17 However, some other authors have questioned these recent assumptions of low, rather than, TT levels involvement in prostate cancer risk and these various adverse features of the disease. 5 Therefore, the relationship between endogenous TT and prostate cancer continues to be controversial and hence, merits further investigation. 5

This study was therefore designed to evaluate the relationship between TT and PSA in prostate cancer patients to examine the hypothesis that low, rather than high, endogenous TT is associated with adverse prostate cancer features using high-risk total PSA as a marker of the adverse prostate cancer feature.

The specific objectives of the present study are to determine the pattern of gonadal status (hypogonadism and eugonadism) among the study cohorts, to determine the pattern of distribution of total PSA and TT based on gonadal status among the study cohorts and to determine the relationship between total PSA and TT based on gonadal status among the study cohorts.

#### **METHODS**

The study was conducted in the Department of Chemical Pathology and Metabolic Medicine of the University of Port Harcourt Teaching Hospital (UPTH), River State, Nigeria. The hospital is a modern tertiary hospital situated in the south-south region of the Niger Delta area of the country providing specialist medical care to the entire populace in the region. The Department of Chemical Pathology and Metabolic Medicine of the hospital is a screening and diagnostic center for various cancers using tumor markers.

It is a retrospective, descriptive, and cross-sectional analysis of total PSA and total TT records of all the prostate cancer patients who had presented to the Department of Chemical Pathology and Metabolic Medicine for serum total PSA and TT investigations as part of their pre-treatment protocols from 1st January 2008 to 31st December 2017. The study was conducted between 1st January and 23rd February 2018. Being a retrospective study, ethical approval and informed consent is not required in UPTH.

#### Inclusion criteria

 Pretreatment serum total PSA and serum TT records of men with histologically confirmed prostate cancer who had presented to the department during the study period.

#### Exclusion criteria

- Post-treatment serum total PSA and total TT.
- Pretreatment serum total PSA and serum TT records of histological confirmed prostate cancer patients who had been diagnosed with diabetes mellitus, liver disorders or thyroid disorders, including those already on treatment (medical, surgery or radiotherapy) for prostate cancer,
- Those on exogenous TT therapy, and
- Those with incomplete data.

Fasting venous whole blood specimen were collected from each patient between 8 am and 10 am daily and processed accordingly to obtain the serum samples for analysis. Laboratory analysis for total PSA and TT was done via enzyme immunoassay methods with reagents procured from Monoblind Incorporated, California, United States of America. Analytical accuracy was monitored with the use of three levels of commercial quality control sera sourced from the same manufacturer.

Data were acquired 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 diagnosis, serum total PSA in  $\mu$ g/l (normal range: 0.0-4.0), and serum TT in nmol/l (normal range: 11.0-35.0) were recruited for the study.

Prostate cancer risk was arbitrarily stratified based on serum total PSA value of  $<\!20.0\mu g/l$  as low-risk, 20.1-40  $\mu g/l$  as moderate-risk, and >40.1  $\mu g/l$  as high-risk. While using the serum TT cutoff value of 12 nmol/l suggested by Bhasin et al to define gonadal status as hypogonadism (TT<12.0 nmol/l) and eugonadism (TT>12.0 nmol/l).  $^{18}$ 

Acquired data were all entered into SPSS version 20, subsequently reviewed, coded, and analyzed accordingly. Data normality was ascertained using Shapiro-Wilk statistical test. Non-parametric distributed data were log-transformed prior to analysis. Continuous data were presented as mean  $\pm$  standard deviations and compared with independent t-test or one-way analysis of variance (one-way ANOVA) where appropriate, while categorical data were presented in numbers and percentages and compared with Chi-square test. Pearson's correlation test was used to determine relationships between continuous data. A cutoff p-value of <0.05 was designated as being statistically significant.

#### **RESULTS**

During the study period from 1st January 2008 to December 2017, 504 men with prostate cancer presented as outpatients to the Department of Chemical Pathology

and Metabolic Medicine of the University of Port Harcourt Teaching for pretreatment serum total PSA and serum total TT laboratory results. The records of the 450 (89.3%) out of the 504 records met the inclusion criteria and were recruited for the study.

Table 1: Distribution of Total PSA and TT based on different age groups of the 450 prostate cancer patients.

Parameter		Age groups (years)			
	<59	60-69	70-79	>80	p-value
n (%)	24 (5.3)	99 (22.0)	255 (56.7)	72 (16.0)	< 0.001*
PSA $\mu$ g/l (mean $\pm$ SD)	35.40±11.07	42.3±17.82	53.5±22.85	$74.2\pm28.00$	<0.001*
(Range)	(22.9-55.2)	(17.8-78.4)	18.5-110.3)	(29.4-140.3)	<0.001**
TT nmol/l (mean $\pm$ SD)	15.6±2.63	14.75±3.65	13.5±3.43	10.93±3.12	<0.001*
(Range)	(11.6-18.9)	(7.2-22.2)	(7.3-19.7)	6.8-19.8)	<0.001*

<sup>\*</sup>Statistically significant; PSA = Prostate-specific antigen; TT = Total endogenous testosterone; µg/l = Microgram per Liter; nmol/l = Nanomole per liter.

Shapiro-Wilk statistical test result revealed that age and serum TT data were normally distributed while that of serum total PSA (Z-score= +15.57; p= 0.004) was non-parametrically distributed. Subsequently, total PSA data were log-transformed prior to analysis. The mean $\pm$ standard deviation and range of study cohorts age, total PSA, and TT were  $73.7\pm6.16$  years (Range 58-88),  $53.40\pm24.67$  µg/l (Range 17.8-140.30), and  $13.4\pm3.61$  nmol/l (Range 6.8-22.2) respectively.

In Table 1, the majority (56.7%) of the study cohorts are between 70 to 79 years of age while only 5.3% of the study cohort were below 59 years of age.

In Table 2, Hypogonadism was observed in 34.7% of the study cohort. These patients with hypogonadism (TT < 12 nmol/l) had higher total PSA values compared to those with eugonadal (TT > 12nmol/l) TT level.

Table 1: Distribution of Total PSA and TT based on Gonadal Status of the 450 prostate cancer patients.

	Gona		
Parameter	Hypogonadism (TT < 12 nmol/l)	Eugonadism (TT > 12 nmol/l)	p-value
n (%)	156 (34.7)	294 (65.3)	<0.001*
PSA $\mu$ g/l (mean $\pm$ SD)	75.9±20.7	41.5±17.11	<0.001*
(Range)	(29.5-140.3)	(17.7-85.2)	<0.001**
TT nmol/l (mean $\pm$ SD)	9.43±1.55	15.67±2.28	<0.001*
(Range)	(6.8-12.0)	12.2-22.2	<0.001

<sup>\*</sup>Statistically significant; PSA= Prostate-specific antigen; TT= Total endogenous testosterone; µg/l= Microgram per Liter; nmol/l= Nanomole per Liter.

In Table 3, patients with high-risk PSA values (PSA> 40  $\mu$ g/l) had a lower TT values compared to those in the mild-risk and moderate-risk PSA groups. In Table 4,

there were varying degrees of negative correlation between total PSA and TT within the overall study group, hypogonadal group, eugonadal group, and within the different strata of PSA-based risk groups.

Table 3: Distribution of Total PSA and TT based on PSA-based Cancer Risk among the 450 prostate cancer patients.

PSA-based Risk Groups				
Parameter	Mild-risk (PSA<20 μg/l)	Moderate-risk (PSA 20-40 μg/l)	High-risk (PSA>40 μg/l)	p-value
n (%)	21 (4.7)	144 (32.0)	285 (63.3)	< 0.001
PSA μg/l (mean±SD)	18.7±0.56	29.7±5.30	67.9±19.10	<0.001
(Range)	(17.7-19.7)	(20.2-38.90)	(43.5-140.3)	<0.001
TT nmol/l (mean±SD)	18.23±2.14	$16.38 \pm 2.05$	11.7±3.02	رم مرم د 1 مرم م
(Range)	(16.2-22.2)	(11.3-19.7)	(6.8-21.3)	<0.001

<sup>\*</sup>Statistically significant; PSA= Prostate-specific antigen; TT= Total endogenous testosterone; µg/l= Microgram per Liter; nmol/l= Nanomole per Liter.

Table 4: Correlation between Total PSA and TT based on different study groups of the 450 prostate cancer patients.

Groups	N	Total PSA Versus TT Correlation coefficient (r); p-value
Based on Total Study Group	450	-0.792; <0.001*
Based on Gonadal Status		
Hypogonadism (TT<12 nmol/l)	156	-0.615; <0.001*
Eugonadism (TT>12 nmol/l)	294	-0.560; <0.001*
Based on PSA-based risk Groups		
Mild-risk (<20µg/l)	21	-0.302; 0.183
Moderate-risk (20.1-40 µg/l)	144	-0.431; <0.001*
High-risk (>40.1 μg/l)	285	-0.632; <0.001*

<sup>\*</sup>Statistically significant; PSA= Prostate-specific antigen; TT= Total endogenous testosterone; µg/l= Microgram per liter; nmol/l= Nanomole per Liter.

However, while every other correlations were statistically significant, that of the mild-risk PSA group was not. The significant negative correlations are stronger among the overall study group, hypogonadism group, and among the high-risk group.

## **DISCUSSION**

For decades following that report of Huggins and Hodges, the influence of high TT on the prostate tissue had been held sacrosanct as one of the culprit in prostate cancer risk, etiopathogenesis, and various adverse clinicopathologic and poor prognostic features of the disease. On the basis of that report by Huggins and Hodges, various interventions to reduce endogenous TT or its action on the prostate gland has been one of the main strategies in the treatment of prostate cancer. However, this assumption is currently been challenged as numerous authors have suggested that low, rather high, endogenous testosterone predicts prostate cancer risks and the various associated adverse and poor prognostic features including among others high total PSA levels. 6,17

In the present study, we have used high total PSA as a marker of poor prognostic feature since it correlates with aggressiveness, tumor burden, stage, metastasis, biochemical recurrence, and Gleason score, and observed that patients with hypogonadism had significantly higher total PSA levels than the eugonadal patients.19 In addition, those patients with the high-risk PSA level had the lowest TT level compared to patients with mild-risk and moderate-risk PSA levels. These findings suggest that low, rather than high, TT predicts higher PSA level which implies a poor prognostic feature of prostate cancer among the study cohort. In support of this finding is the observed strong negative correlation between PSA and TT among the patients with hypogonadism and highrisk PSA levels. These findings and observations in this study regarding the relationship between PSA and TT are in accord with the findings in similar studies by Alsharef et al, Garcia-Cruz et al, Schatzl et al, and Tu et al. 6,9,10,16

Alsharef et al had investigated the association between serum TT and adverse prognostic features in men with prostate cancer and observed that low serum TT was associated with higher PSA, higher grade, locally advanced and metastatic prostate cancer. However, Alsharef et al had used the serum free testosterone in their study in contrast to the total serum TT employed in this study. Garcia-Cruze et al concluded in their study that prostate cancer patients with low TT have poor prognostic factors and tumor burden before treatment.

Schatzl et al reported in their study that prostate cancer patients with low TT had higher Gleason score compared to those with normal TT. Recently, Tu et al had investigated whether low TT at prostate cancer diagnosis was associated with aggressive prostate cancer and poor outcomes and observed that low TT was associated with aggressive prostate cancer and prostate cancer-specific survival.

of TT-induced mechanism low adverse clinicopathologic and poor prognostic features in prostate cancer disease is poorly understood. However, Tu et al posit that the low TT milieu in men might activate some oncogenic pathways that select for specific molecular features that are indicative of adverse or poor prognostic outcome. 16 While Loeb et al posit that the high or normal TT levels keep the prostate cells and early prostate cancer cells in a differentiated state and that the loss of this TT function secondary to low serum TT may lead to the development of less-differentiated cancer with adverse and poor prognostic features.<sup>20</sup>

# CONCLUSION

The findings of this study suggest low, rather than high, endogenous testosterone predicts higher PSA in prostate cancer patients. Therefore, low serum testosterone could serve as a biomarker to complement PSA in predicting prostate cancer.

However, further studies are warranted to confirm this association. It is a retrospective hospital-based study conducted in a single center, therefore its conclusion may not reflect the status of the entire population in the region.

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