

Is there a Clinically Useful Relationship between Testosterone and Prostate Specific Antigen in Patients with Lower Urinary Tract Symptoms?

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Abstract

Introduction: Relationship between Testosterone and Prostate Specific Antigen (PSA) in patients with Lower urinary Tract Symptoms (LUTS) is ambiguous. The present study aims to establish the relationship of these variables in patients with LUTS, with a larger study cohort.

Methods: A retrospective study was done over a period of 4 years at a tertiary care center. Free and total PSA were correlated with age, prostate volume and Testosterone using appropriate statistical tests in 1156 patients. Patients were stratified into two groups based on PSA level of 4 ng/ml and correlation was studied separately.

Results: A weak negative correlation was present between free PSA and Testosterone levels (-0.182, $p < 0.001$) and total PSA and Testosterone levels (-0.223, $p < 0.001$) and between prostate volume and serum Testosterone (-0.45, $p < 0.001$). Volume correlated positively with free and total PSA. When groups were independently analysed no significant correlation was found between Testosterone and PSA in patients with PSA > 4 ng/ml but a weak negative correlation was found between free PSA and Testosterone (-0.156, $p < 0.001$).

Conclusion: In patients with LUTS, Testosterone and PSA levels are poorly interrelated especially when PSA is more than 4 mg/ml. There is a need to explore whether this weak association between PSA, prostate volume and total Testosterone is of any clinical utility.

Keywords: Testosterone; PSA; LUTS parameters; Spermatogenesis; Sperm maturation; Testicular function

Introduction

Many studies have previously tried to establish correlation between Testosterone and PSA in different subsets of population with varying results. Our present understanding of this correlation is based on studies with small sample size and results have been more or less contradictory to each other. The sample population for such studies has been normal healthy adult men, hypo gonadal men or patients with prostate cancer. It is still unclear whether there is a correlation between these parameters and if it can be put to any clinical use. The association between Testosterone and PSA is of utmost importance to the urologist, especially in patients who present with symptoms of prostatic enlargement often referred to as LUTS. These patients can be the ideal population to study the correlation, but studies based on this population are limited. The present study employs a much larger cohort of clinically relevant population of patients with LUTS to assess the correlation between Testosterone and PSA.

Materials and Methods

A retrospective study was conducted at our institute with the aim of studying the correlation between PSA and Testosterone in men with prostatic enlargement. Records of adult men between 45-85 years of age presenting to the outpatient department with LUTS, from January 2009 to December 2013 were reviewed. After approval by the ethics committee, demographic data, findings on clinical examination, ultrasonographic examination indicating the volume of prostate gland, urine routine and culture, and biochemical parameters like total Testosterone, free and total PSA were recorded after informed consent wherever possible. All included patients had undergone investigations from a single laboratory. All patients with PSA > 4 ng/ml were offered Trans rectal prostate biopsy. Patients taking 5 alpha reductase inhibitors, having active urinary tract infection as indicated by urine culture and microscopy or tenderness on digital rectal examination were excluded

from the final analysis. Only patients for whom all the above mentioned parameters were available were included in the study. After exclusion of conditions like infections, prostatitis, and prostate cancer that may lead to elevations in PSA, 1156 patients were included in the final analysis. PSA was measured using chemiluminescent micro-particle immunoassay and Testosterone was measured using the chemiluminescent immunoassay method. The normal range of Testosterone was taken as 5.6-19 nmol/L. The samples were taken in the morning between 9AM to 11 AM and at least 48 hours following the digital rectal examination as a rule.

The data was recorded on a spreadsheet and analyzed using SPSS version 22. Correlation was studied between prostate volume, age, free and total PSA and serum Testosterone. Normality of data was checked using the Kolmogorov Smirnov normality test. Patients were subsequently divided into two groups based on PSA levels less than or greater than 4. The correlation of Testosterone to free and total PSA was performed in both the groups using appropriate statistical tests. Variables in the two groups were compared using the independent sample t test. Logistic regression analysis was performed and P-values < 0.05 were considered to be statistically significant.

Results

A total of 6974 patients were registered with our outpatient

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department for LUTS. Of these a large number of patients did not have all the required investigations to be part of the study. After exclusion of causes that could lead to falsely elevated PSA only 1156 patients were finally included. The mean age of our patients was 58.79 ± 12.73 years and the mean total Testosterone was 8.17 ± 3.99 nmol/ml. The mean total PSA in our study population was 3.07 ± 22.25 ng/ml and the mean free PSA was 0.41 ± 1.43 pg/ml. Based on the Kolmogorov Smirnov normality test, the PSA and Testosterone distribution in the sample population was found to be non-parametric and spearman's rho coefficient was used to derive correlation between the tests. A weak negative but statistically significant correlation was found to exist between serum total Testosterone and free PSA levels ($-0.182, p < 0.001$) (Figure 1). Also, a weak negative but statistically significant correlation was found between PSA and serum Testosterone levels ($-0.223, p < 0.001$) (Figure 2). A statistically significant positive correlation was found between free and total Testosterone ($0.202, p < 0.001$). Total PSA levels showed a weak and statistically insignificant positive correlation with age, while serum Testosterone showed a weak but significant negative correlation with age ($-0.112, p = 0.082$).

When the patient population was divided into two groups based on a PSA level less than 4 ng/ml and more than 4 ng/ml, 869 patients were found to have PSA less than 4 ng/ml while 287 patients had PSA above the cut off. While there was no statistically significant difference in the mean age of patients in the two groups, a significant difference was appreciable in mean Testosterone (-1.67486), total PSA levels ($9.988, p < 0.001$) and free PSA levels ($0.840, p < 0.001$).

The mean prostate volume in our patients was 33.72 ± 21.27 grams. A weak but statistically significant negative correlation was seen between serum Testosterone and prostatic volume ($-0.45, p < 0.001$). Volumes of prostate showed a positive and statistically significant correlation with total PSA ($0.430, p < 0.001$) and free PSA ($0.372, p < 0.001$). In the second group of patients with total PSA > 4 ng/ml, free PSA showed a statistically significant but weak negative correlation with PSA ($-0.156, p = 0.005$) but there was no correlation between Testosterone and total PSA ($-0.006, p = 0.913$).

Discussion

It is a well-accepted fact that Testosterone and PSA share a common ground. Testosterone is essential for the normal growth and

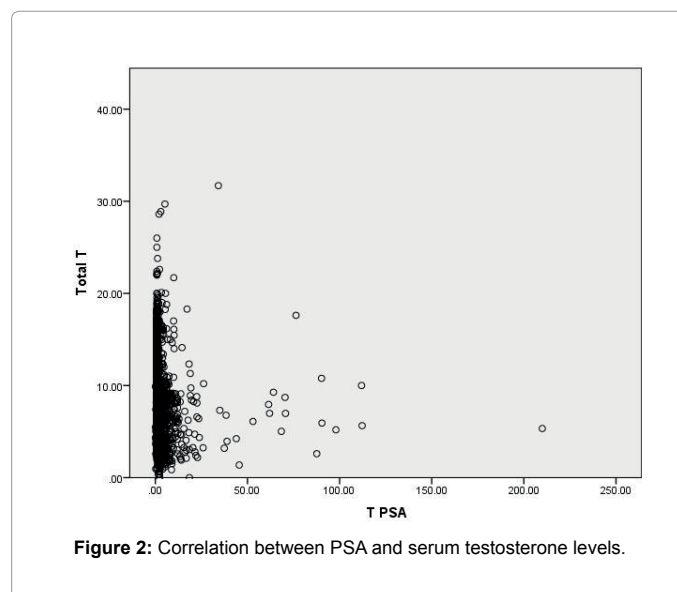


Figure 2: Correlation between PSA and serum testosterone levels.

development of the prostate gland and PSA correlates well with the volume of the prostate. The possibility of an association has been the research question for many studies and there have been attempts in the past to review this correlation in many ways among healthy population, patients with prostatic conditions and in patients with hypogonadism. Unfortunately these studies were based on small sample sizes and many of them did not address the association in a relevant population. With these deficiencies in mind the present study was designed in a scenario of LUTS due to benign prostatic enlargement (BPH) where PSA and Testosterone have both been shown to share the stage and influence the symptoms. Ideally correlation between two parameters should be studied in a large cohort of healthy population but since its application is most useful in patients with LUTS due to prostatic enlargement we chose subset as the most relevant and ideal population for the study.

The relation between Testosterone and PSA has been tested in various ways. The initial and ideal way has been to assess the levels of each in large populations and analyse how the levels vary with respect to each other. The other way to establish the relation is to supplement testosterone and then assess the variation in PSA. The study of association between PSA and Testosterone dates back to 1992 when Hanash and Mostofi demonstrated that prolonged parenteral androgen therapy for 1 year resulted in the hypersecretion of prostate specific antigen (PSA) [1]. The authors emphasized the need of a similar study in a larger population of men. In 1994, Aus. et al. [2] Studied 120 patients symptomatic for BPH but found no statistically significant influence of Testosterone and/or age on serum-PSA or PSA density in these patients. Douglas et al. studied effect of Testosterone in 10 hypogonadal men on PSA and found that neither Prostate Specific Membrane Antigen nor PSA expression was Testosterone-dependent [3]. Monath et al. also failed to find correlation between Testosterone and PSA, even when corrected for age and weight in 150 healthy men [4]. Mermall et al. pointed out that circadian variations in PSA and Testosterone could be causative for lack of association and collected Testosterone samples on a 3 hourly basis from 11 men but found that within-day variation in PSA was of little diagnostic significance and did not prevent accurate clinical classification when a single specimen is used, even though a circadian pattern did exist [5].

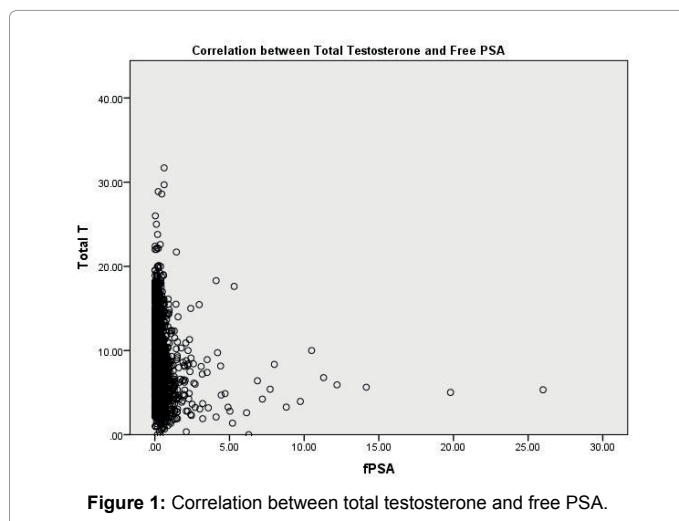


Figure 1: Correlation between total testosterone and free PSA.

Literature also offers studies that tried to assess the correlation in the other way. Cooper et al. administered Testosterone in 31 subjects and monitored the prostate volume and PSA levels but despite significant elevations in serum total and free Testosterone, healthy young men did not demonstrate increased serum or semen PSA levels, or increased prostate volume [6]. Based on a study of 65 men Gustafsson et al. also observed that there was no relationship between PSA and Testosterone [7]. El-Sakka AI et al. in 2005 studied the effect of Testosterone replacement on PSA level in 187 hypogonadal men for one year [8]. There was no significant association found between PSA level and the duration of Testosterone replacement therapy in their study population. This confirmed the earlier findings of Douglas on a larger population of patients. Thus by the beginning of the 21st century a number of small studies were done to establish the relationship between PSA and Testosterone in every possible way but the need for larger and better defined studies was identified.

In 2010, Favilla et al. found that the severity of LUTS was associated with total Testosterone but there was no significant correlation derived between PSA and Testosterone in patients with BPH [9-11]. In a large series of symptomatic and healthy men by Corona et al. in 2010, PSA was found to be unrelated to Testosterone concentration [10]. Only in severely low Testosterone was there a decrease in PSA. Even in patients who received Testosterone replacement, PSA levels were found to remain stable after normalization of Testosterone for 5 or more years. The increase in PSA was only mild and did not vary on the basis of the mode of replacement, age or baseline PSA and Testosterone.

The effect of Testosterone supplementation on LUTS has also been studied by Pearl et al. [12,13]. When Testosterone therapy was given in hypogonadal men, LUTS improved best in those with PSA more than 4.0 ng/ml. Ko et al. found that Testosterone therapy improved symptoms of LUTS in patients of BPH who were not on any medications without causing a rise in PSA [14]. Our study made an attempt to find the natural correlation in this previously unaddressed pool of population by providing the typical clinical scenario where it can be applied. We divided our population based on an arbitrary PSA value of 4 ng/ml. We chose this value as it also represents a trigger for biopsy and we were interested to find if estimation of Testosterone in such patients could be put to clinical use. We found that those with higher PSA had lower mean Testosterone levels but there was no significant correlation between total PSA and Testosterone especially in patients with PSA >4 ng/ml. Only free PSA showed a significant weak negative correlation across all values of PSA.

The present study tries to fill the lacunae and settle down the controversies in available literature and emphasizes certain accepted facts. The study is based on a large sample size of clinically relevant patients where the correlation really matters, but may not necessarily represent the general population. The weak point of the present study is its retrospective nature and the severity of LUTS has not been taken into account. Since negative biopsy does not identify all cases with prostate cancer, the current patient population may include patients with prostate cancer leading to LUTS. Despite these pitfalls the study emphasizes that while there is a correlation between PSA

and Testosterone it varies with the level of PSA and is unlikely to be significant enough to put to clinical use and draw conclusions.

Conclusions

While there is a statistically significant negative correlation between Testosterone and free and total PSA in adult patients with LUTS at PSA levels <4 ng/ml, the association dwindles as PSA levels rise. A larger series focussed on detection of prostate cancer and hypogonadism using PSA in conjunction with Testosterone as a marker may be warranted to determine the clinical usefulness of Testosterone such as to screen prostate cancer and PSA to predict hypogonadism.

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