Association Between Serum Testosterone and Serum PSA Among Men With and Without Partial Androgen Deficiency

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Abstract Serum prostatic specific antigen (PSA) and serum testosterone levels share an undefined relationship with each other, with many conflicting studies showing both positive and negative correlation between them. Our aim was to assess association between serum PSA and serum testosterone in healthy men with normal testosterone levels and men with partial androgen deficiency (PADAM). A cross sectional study was conducted at a teaching hospital setting where serum testosterone and aging male symptom scale (AMS) scores along with PSA were studied in 255 men (> 50 years) with and without PADAM. Mean total testosterone and serum PSA was 9.35 ± 1.33 nmol/L, 1.96 ± 0.76 ng/mL in males with PADAM and 15.30 ± 1.95 nmol/L, 1.85 ± 0.73 ng/mL respectively in males without PADAM. No significant relationship was observed between serum PSA and serum testosterone levels among healthy males irrespective of PADAM in the study population. We suggest, there is no need to adjust PSA values for biopsy decisions according to testosterone levels.

Keywords Testosterone · PSA · PADAM · Aging males

Introduction

Prostate-specific antigen (PSA) is a serine protease, which is produced by prostatic epithelium [1]. PSA, PSA velocity, PSA density and free PSA have long been used as indicators to decide for prostate biopsy in prostate cancer diagnosis. Though, PSA does not come under the category of ideal marker still it is widely used in the diagnosis and the management of prostate cancer [1]. Studies have reported sensitivity and specificity issues with use of PSA as it is neither tissue specific [2] nor cancer specific [3]. Testosterone plays a major role in growth and functional development of prostate gland [4, 5]. It has been postulated that PSA production from prostatic epithelium is under androgenic regulation [6, 7]. However any kind of direct association between the two is still controversial [8]. Serum testosterone has been linked to prostate cancer development and it is observed that disease is controlled after androgen deprivation [9–11]. Studies have reported conflicting results on association between serum PSA and serum total testosterone [1, 4, 12]. A few studies observed a positive correlation between low level of serum testosterone and PSA as seen in hypogonadal men (saturation hypothesis) [12–14]. Males with partial androgen deficiency also show similar signs and symptoms [12]. The diagnosis of partial androgen deficiency of aging males (PADAM) is based upon characteristic signs and symptoms depending on aging males symptom scale (AMS) score [15] and decreased levels of serum testosterone [16, 17] as testosterone deficiency is associated with aging [18].

We aim to understand whether testosterone has any influence on PSA levels in our population and thereby on saturation hypothesis and to study whether there is any need to adjust PSA values as an indicator for prostate biopsy.

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Subjects and Methods

The study was conducted in Batra Hospital and Research Centre, Delhi from January 2014 to December 2014. Approvals were obtained from the Ethical Committee of the hospital. A total of 255 patients aged > 50 years who visited the male health clinic as well the outpatient department and admitted cases of the Department of Urology were enrolled in the study (after applying exclusion criteria). Written informed consent was taken from the participants in the study after explaining them about the study. All the patients were assessed for symptoms and signs suggestive of partial androgen deficiency using aging male symptom scale questionnaire (AMS) [15] which is the most commonly used scale to measure HRQoL (health related quality of life) and symptoms in aging males.

Aging male symptom scale questionnaire comprised of 17 items and the patients rated their answers on the scale of 1–5 each. A composite score of 37 or more was taken as a cut off for deciding PADAM. The questionnaire was made available to the patients in Hindi as well as English. 3 mL blood sample in plain vial was taken from each subject between 0800 and 1100 h for the measurement of total testosterone and total PSA.

Serum testosterone levels were measured using VIDAS automated immunoanalyser (*BioMérieux, France*) based on ELFA technique (enzyme linked fluorescent assay) and serum total testosterone between 12.13 and 36.75 nmol/L was taken as normal. Serum total PSA was measured using COBAS E 601 immunoassay analyser (*Roche Diagnostics, USA*) based on ECLIA technique (electrochemiluminescence immunoassay). Patients with pathological andropause were excluded from the study. Confirmed cases of prostate cancer, persons with palpable prostate nodule and people with PSA more or equal to 4 ng/mL were also excluded. All the known cases of diabetes mellitus, heart disease, any form of kidney or liver diseases were also excluded from the study as they are known to contribute to erectile dysfunction as well alter the circulating levels of PSA and testosterone [19, 20]. A total of 255 men (> 50 years) were recruited for the study who were further divided into Group A and Group B. Group A comprised of subjects with PADAM (AMS total score of 37 or more and serum testosterone < 12.13 nmol/L) and Group B comprised of subjects without PADAM (AMS total score < 37 and serum testosterone > 12.13 nmol/L). Both the groups were again subdivided into groups based on age and comparisons were studied for age, serum testosterone and serum PSA levels.

Statistical analysis was done using SPSS software version 16. Data was expressed as mean $\pm$ standard deviation. Students *t* test was used to compare age, testosterone and

PSA levels between the two groups. Pearson correlation test was applied to estimate association between testosterone and PSA levels (with PSA being dependent variable). *p* values of less than 0.05 were considered significant.

Results

The characteristics of the study population are summarized in Table 1. The mean age was 62.48 ± 3.38 years in group A and 59.73 ± 2.59 years in group B (*p* value = 0.01). Mean total testosterone in group A was 9.35 ± 1.33 nmol/L, (range: 6.06–12.05 nmol/L) and mean total testosterone in group B was 15.30 ± 1.95 nmol/L (range: 12.25–22.1 nmol/L). There was significant difference between the two groups in relation to total testosterone levels (*p* value = 0.001).

The mean serum PSA value in group A was 1.96 ± 0.76 ng/mL and in group B was: 1.85 ± 0.73 ng/mL. This did not show any statistically significant difference (*p* value = 0.50). No correlation was found between serum testosterone and serum PSA levels in group A (*r*: 0.08, *p* value = 0.35) as well as group B (*r*: -0.06, *p* value = 0.49) (Table 2). Figures 1 and 2, illustrate the relation between testosterone and PSA levels between group A and group B respectively with testosterone being the independent variable. Further no association was found between testosterone and PSA levels in both the groups combined (Fig. 3) (*r* = -0.09, *p* value = 0.12). In the subgroups also no association was seen [(group A1 (*r* = -0.03, *p* value = 0.80) group A2 (*r* = -0.11, *p* value = 0.27), group B1 (*r* = -0.05, *p* value = 0.62) and group B2 (*r* = -0.11, *p* value = 0.51)].

Discussion

We investigated the effect of testosterone levels on PSA values in subjects with symptoms of partial androgen deficiency as well as in healthy men. Our study did not show any association between PSA and serum testosterone levels in both healthy as well as men with PADAM. Even age wise analysis did not reveal any relationship between the two. Further the mean of serum PSA levels did not show any statistically significant difference (*p* value = 0.50). We observed a significant difference between the mean of ages in the two groups (*p* value = 0.01) indicating that the men who were classified as having PADAM were older as compared to the eugonadal men. This is in alignment with the argument that as the age advances there is a gradual and progressive

Table 1 Comparison between subjects with PADAM (Group A) and without PADAM (Group B)

Variable	Group A (139)			Group B (116)		
	A1 50–60 years (N = 48)	A2 > 60 years (N = 91)	Total (N = 139)	B1 50–60 years (N = 81)	B2 > 60 years (N = 35)	Total (N = 116)
Age	59.16 ± 0.99	64.24 ± 2.8	62.48 ± 3.38	58.32 ± 1.53	63 ± 1.18	59.73 ± 2.59
PSA (ng/mL)	1.79 ± 0.78	2.04 ± 0.79	1.96 ± 0.76	1.86 ± 0.75	1.81 ± 0.71	1.85 ± 0.73
Testosterone (nmol/L)	9.26 ± 1.28	9.39 ± 1.36	9.35 ± 1.33	15.53 ± 2.01	14.77 ± 1.73	15.30 ± 1.95

Table 2 Correlation between PSA and testosterone in Group A (PADAM) and Group B (without PADAM)

Group	PSA (ng/mL) Mean ± SD	Total Testosterone (nmol/L) Mean ± SD	<i>p</i> value	<i>r</i> value
A (N = 139)	1.96 ± 0.76	9.35 ± 1.33	<i>p</i> = 0.35	<i>r</i> = 0.08
B (N = 116)	1.85 ± 0.73	15.30 ± 1.95	<i>p</i> = 0.49	<i>r</i> = − 0.06

p < 0.05 considered significant, Group A = PADAM, Group B = Without PADAM

Fig. 1 No association is present between two variables in PADAM associated group **Fig. 2** No association is present between two variables in group without PADAM

decline in serum testosterone levels at the rate of 1–2% per year, beginning in the third decade of life [18, 21].

The relationship between serum testosterone levels and serum PSA and prostate cancer, is a continuing controversy. There have been many studies in the past that have

Fig. 3 No association is present between PSA and testosterone in total subjects

found either weak positive association or no association at all between serum testosterone and serum PSA levels [4, 7, 22]. Some studies have found positive correlation between PSA and serum testosterone levels in hypogonadal men [12, 23]. This has been explained by “Saturation Hypothesis” which says that at a low testosterone level maximum androgen receptor saturation is achieved in the prostate tissue [24]. Thereafter as the testosterone concentration increases towards normal levels it has very little effect on testosterone dependent prostate function like PSA levels [13, 14]. Based upon Saturation hypothesis some authors have suggested the use of PSA as a marker of testosterone concentration to confirm hypogonadism [12]. However in our study no such association was noticed even at low levels of testosterone as in PADAM (hypogonadal) men.

The importance of finding an association between serum testosterone and serum PSA levels is to find out the impact of testosterone level on deciding benchmark for prostate biopsy at various PSA levels in these two groups. A recent review of the literature on total testosterone and the subsequent risk of prostate cancer [8] revealed contradictory findings. Out of the 45 studies examined in this review 18 showed positive relationship with low levels of testosterone, 17 studies with high total testosterone, and 10 showed no relationship at all. Again there has been controversy with impact of high or low serum testosterone on the prognosis of prostate cancer. In African American patients with high serum levels of testosterone, biopsy is recommended at PSA levels of 2.5 ng/mL [25] and others have reported low serum testosterone level association with worse clinical and pathological determinants of prostate cancer [26, 27].

Understanding the association between testosterone and PSA also becomes important while considering testosterone replacement therapy (TRT) among hypogonadal men. Some studies reported the rise in PSA after TRT and there by risk of prostate cancer [28]. Others have reported that the rise in PSA after TRT is only minimal and stabilizes after the normalization of testosterone levels

(saturation hypothesis). Therefore the risk of cancer prostate in these individuals is not more than that of general population [29, 30]. Hypogonadism is considered to be a risk factor for cancer prostate and TRT further adds to this risk. However in our study where no association was found between low levels of testosterone (hypogonadal men) and PSA, one can consider TRT to be safe in the treatment of hypogonadism.

In the present study we thus investigated the effect of testosterone levels on PSA values to determine whether testosterone levels may dictate adjustment of normal ranges of PSA level. We found no significant relation between PSA and testosterone levels in either of the two groups and hence it is suggested that serum testosterone levels do not have an impact on the PSA levels. Thus our findings suggest that in practice there is no need to adjust PSA values according to the serum testosterone levels.

Our study is different from other studies as the relationship between testosterone and PSA was evaluated in healthy Indian men and hypogonadal men with PADAM for the first time. Most of the previously conducted studies were based upon men receiving testosterone replacement therapy. However determination of free and bioavailable testosterone levels and intraprostatic levels of testosterone was not done. This is the limitation of the study.

Conclusion

Despite the major role played by testosterone on control and progression of prostate cancer no similar impact was seen on the serum PSA levels. Our findings suggest that serum testosterone levels do not appear to significantly influence serum PSA levels among healthy males (> 50 years) as well as hypogonadal men. Hence we, do not suggest to use serum PSA as a predictor of testosterone deficiency. This may question the role of PSA as an emerging tool for confirming hypogonadism. Also TRT should be considered safe in hypogonadal men as no

correlation was found between low levels of testosterone and PSA as well as normal levels of testosterone and PSA.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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