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Research Article

SERUM TESTOSTERONE AS A MARKER OF RESPONSE TO ANDROGEN DEPRIVATION THERAPY IN METASTATIC PROSTATE CANCER

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ABSTRACT

Objective: Prostate cancer (PCa) is the second most widespread cause of cancer and the sixth foremost cause of cancer death among men worldwide. The sustained presence of particular hormones and growth factors stimulates the prostate, such as other sex accessory tissues, in its growth, maintenance, and secretory function. In the current study, we investigated the association of serum testosterone level and prostate-specific antigen (PSA) level before androgen deprivation therapy in metastatic PCa (mPCa) treated with hormone therapy.

Methods: This retrospective cohort was conducted from July 2017 to December 2019 in the Department of Urology, Post Graduate Institute of Medical Education and Research, Chandigarh on patients diagnosed with mPCa of age >40 years. Total serum testosterone was measured by Electro chemiluminescent immune assay before the treatment. PSA in serum specimens was evaluated.

Results: The mean age was 67.74±8.12 (55–80) years. Serum PSA levels at baseline, 3 months were 530.98±617.28 (ng/dL), and 56.31±89.04 (ng/dL), respectively. The baseline S. testosterone was 288.89±246.53 (ng/mL). Weak negative correlation between the two (p=0.051) As the serum testosterone levels decrease the PSA levels increase and vice-versa. Positive correlation between baseline testosterone and PSA decline (p<0.05). On histopathology, 58.7% (n=71) of the patients had perineural involvement, while 41.3% (n=50) did not have perineural involvement.

Conclusion: We conclude that the effect of testosterone might have a possible role in the assessment of treatment response as assessed by PSA. However, the exact implication and its role in disease assessment need to be examined in a larger prospective cohort.

Keywords: Prostate-specific antigen, S. testosterone, Metastatic prostate cancer, Androgen.

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INTRODUCTION

Prostate cancer (PCa) is the second most widespread cause of cancer and the sixth foremost cause of cancer death among men worldwide. The worldwide PCa burden is expected to grow to 1.7 million new cases and 4,99,000 new deaths by 2030, simply due to the growth and aging of the global population [1]. PCa has become a major health dilemma in the industrialized world during the last decades of the 20th century contributing to three fourth of the registered cases across the globe [2]. Despite the high incidence and mortality rates associated with PCa, little is known about the biological processes that underlie the disease's onset and progression. The sustained presence of particular hormones and growth factors stimulates the prostate, like other sex accessory tissues, in its growth, maintenance, and secretory function.

Given that androgens regulate the prostate, there has long been concern about how androgens may contribute to PCa development. For a healthy prostate to develop, grow, and maintain its mature physiological functions, androgens and the transcriptional programs they activate via binding to the androgen receptor (AR) are essential. Although the precise mechanisms governing the initiation and development of PCa are still unknown, signaling through the AR axis is believed to be important in promoting prostate carcinogenesis [3].

Studies have shown little or no association between serum testosterone concentrations and PCa and also demonstrated there is a limit to the ability of testosterone to simulate PCa growth, PCa has often been associated with low testosterone levels [4,5].

A study stated that "Prostate-specific antigen (PSA) is an androgen-regulated serine protease and member of the tissue kallikrein family of proteases." It is produced primarily by the prostate ductal and acinar epithelium and is secreted into the lumen, where its function is to cleave semenogelin I and II in the seminal coagulum. However, its main significance in oncology is as a biomarker to detect PCa and to assess responses to treatment. A decline in PSA levels in response to androgen deprivation therapy (ADT) is specifically caused in part by tumor cell death, it is also the result of decreased AR-stimulated PSA production by surviving tumor cells. As a result, ADT may in some cases have better effects on PSA production than on tumor survival [4]. However, PSA is limited by its comparative lack of specificity when serum concentration moderately increases (4.0–10.0 ng/mL) [5].

Androgen relation with prostate

Androgens which regulate proliferation, apoptosis, angiogenesis, metastasis, and differentiation. The prostate is stimulated in its growth, maintenance, and secretary function presence of androgens and growth factors. Testosterone and dihydrotestosterone are the two most important androgens in adult men. Testosterone is the major male androgen in circulation, while DTH is the principal androgen in tissues. In healthy adult men, 90% of circulating levels of T is secreted by Leydig cells of the testes. It has been indicated that 5.6% of men aged 30–79 years have a prevalence of symptomatic hypogonadism. It is estimated that by the year 2025, there will be approximately 6.5 million American men 30–80 years of age diagnosed with androgen deficiency [6,7].

Moreover, clinical evidence supports testosterone replacement therapy in hypogonadal patients with erectile dysfunction, which is a frequent complication of treatment for PCa [8]. It was believed for a long time that higher TT contributed to PCa development and caused rapid.

In 1941, Huggins and Hodges showed rapid PCa progression in men who received testosterone and that metastatic carcinoma of the prostate was inhibited by eliminating androgens, through castration. They established PCa as "androgen-dependent." This model suggests that high androgens cause *de novo* PCa or accelerate its growth and low levels are protective [7]. Although these findings appeared indisputable, some literature failed to support this concept. Multiple studies have shown no correlation between endogenous testosterone and PSA. Numerous studies revealed no relationship between TT and PCa risk [9]. Some studies even reported a relationship between low TT and increased risk or grade of PCa [10].

Metastatic disease and PSA

Serum PSA is a well-recognized, highly sensitive tumor marker for PCa. Preliminary data suggest that serum PSA levels measured soon after initiation of hormonal therapy appear to correlate well with clinical outcome [11]. Serial PSA determinations appear to be reliable since there is minimal random fluctuation between measurements in patients with metastatic tumor [12].

Based on unreliable evidence, it is believed that overall survival is poorer in these patients who have low PSA levels compared with patients who have PSA-positive metastatic prostate carcinoma [13]. The pattern of metastatic disease is considered to be unlike the pattern observed in tumors with high PSA levels, with increased numbers of visceral and soft-tissue metastases and a non-typical pattern of bone disease seen [14].

The oligometastatic disease can be defined as the development of three or fewer non-castrate lesions outside of the primary tumor [15]. These can be bone metastases or soft tissue. The concept of oligometastatic disease for all cancers is based on the order of a stepwise progression whereby cancer primarily metastasizes in a restricted way, before acquiring widespread metastatic behavior [16].

PSA with PCa

Data from the PCa Prevention Trial clearly show that the risk for PCa is continuous as PSA increase [17]. No significant differences were noted between cancer and benign groups with consideration to PSA level, PSA density, prostate volume, total testosterone level, or free testosterone level.

ADT role in PCa

ADT is well recognized as a backbone therapy for metastatic PCa (mPCa). Both research and development of increasingly precise assay technologies have enhanced our understanding of androgen production and signaling, and the recent data have suggested that the latest serum testosterone cut-off value of <0.7 nmol/L should be employed. Most clinical trials to date have used the historical 1.7 nmol/L cut-off, but the 0.7 nmol/L cut-off has been associated with improved patient outcomes.

The PSA level is the most valuable tool for monitoring disease status and the treatment response particularly in patients with advanced mPCa, as shown in numerous studies. However, the progression of PCa can sometimes arise in the presence of an undetectable or low serum PSA level.

Morote *et al.* in their recent study stated that serum testosterone has no association with the risk and tumor aggressiveness of PCa [7]. Other recent epidemiologic studies also have found no association between testosterone and PCa. The data are therefore conflicting, on the clinical significance of testosterone level and development of PCa and more so there is a paucity of data in the Indian population.

In the current study, we investigated the association of serum testosterone level and PSA level before ADT in mPCa treated with hormone therapy.

Aim of the study

The role of serum testosterone level before ADT as a response marker in mPCa.

1. To evaluate the association of serum testosterone level before ADT and serum PSA response at 3 months after ADT
2. To see the association between serum testosterone and PSA response based on the different grade of PCa and modalities of treatment.

METHODS

After taking proper approval from the Institutional ethical committee this retrospective cohort was conducted from July 1st, 2017, to June 2018 and prospectively between July 1st, 2018, and December 31st, 2019, in the Department of Urology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh.

This study was conducted on patients diagnosed with mPCa and confirming inclusion and exclusion criteria of the study.

All patients of biopsy-proven adenocarcinoma of the prostate with metastasis and age >40 years were included in the study. Patients with a history of chronic liver disease, BMI >30, chronic kidney disease, having any known disease of the hypothalamo-pituitary axis and/or diabetes were excluded from the study.

Methodology

All patients of PCa underwent general physical examination, digital rectal examination, routine investigations including, serum PSA measurement. They underwent staging evaluation which included contrast-enhanced MRI prostate, bone scan or prostate-specific membrane antigen positron emission tomography scan. Prostate biopsies were reported by the department of histopathology and the Gleason score was recorded.

Measurement of serum testosterone level

Total serum testosterone was measured by electrochemiluminescent immune assay before the treatment. In the morning at 8:00 am fasting blood sample (2 mL) was collected in EDTA vial and sent to the Endocrinology laboratory. The food and drug administration recently defined hypogonadism as a serum testosterone level of <300 ng/dL for clinical research trial [18].

Measurement of serum PSA level

PSA in serum specimens, at 8:00 am fasting blood sample (2 mL) was collected in plane vial and sent to Endocrinology laboratory. The normal reference range used for PSA is <4.0 ng/mL. Baseline testosterone and baseline PSA were done for all patients and PSA at 3 months after ADT, the association of serum testosterone with serum PSA response was assessed.

Statistical analysis

Data were statistically evaluated using SPSS v 22 software. The normality of data was checked by Kolmogorov–Smirnov test and expressed as mean plus/minus standard deviation. The proposed test was Student's "t"-test, if given that data holds normality, otherwise Mann-Whitney test was applied. Wilcoxen matched pairs sign ranks test for pair-wise comparison of skewed data was used. To see the statistical difference in serum T level among different stages and Gleason grade of PCa, we used analysis of ANOVA. Correlation between variables was checked using the Pearson coefficient of correlation for normally distributed data and the Spearman correlation coefficient was used for skewed data. A $p \leq 0.05$ was considered statistically significant.

RESULTS

This retrospective and prospective cohort study was conducted in the Department of Urology, Department of Endocrinology, PGIMER,

Chandigarh. During the study, a total of 121 patients were enrolled among which 60 patients were part of a retrospective cohort and 61 patients were in a prospective cohort.

The mean age of the patients with mPCa in the study was 67.74±8.12 years, with a range of 55–80 years. The majority of the patients were between 61 and 70 years of age (53%) followed by >70 years (31%).

The hormonal profile of the patients (n=121) who had mPCa indicated that the overall mean and SD values of serum PSA levels at baseline, 3 months were 530.98±617.28 (ng/dL), 56.31±89.04 (ng/dL) respectively. The baseline S. Testosterone of the cohort was 288.89±246.53 (ng/mL) (Table 1).

There is a weak negative correlation between the two (p=0.051). This means that as the serum testosterone levels decrease the PSA levels increase and vice-versa.

There is a weak positive correlation between baseline testosterone and PSA decline (p<0.05) (Table 2). This means that patients with higher baseline testosterone had a better PSA decline following ADT (Table 2).

The GG groups were compared with respect to their baseline PSA, PSA at 3 months, PSA change, and baseline serum testosterone. There was no significant difference between the two risk groups with respect to the above-mentioned parameters (Table 3).

Table 1: Mean values of serum PSA levels and serum testosterone

(n=121)	Mean	Median	Standard deviation	Range
PSA baseline	530.98	333.00	617.28	4.07–3996
PSA at 3 months	56.31	12.00	89.04	0.02–567
PSA change	474.67	302.00	563.71	−48.31–3798
S. testosterone	288.89	246.00	246.53	2.50–1302

PSA: Prostate-specific antigen

Table 2: Comparative analysis of serum testosterone with PSA in metastatic prostate cancer

Comparison of S. testosterone	Correlation coefficient (n=121)	p-value
PSA baseline	−0.178	0.051
PSA at 3 months	−0.564	0.000
PSA change	0.178	0.050

PSA: Prostate-specific antigen

Table 3: Comparative analysis of serum PSA and serum testosterone among PCa patients categorized based on Gleason grade

	Gleason grade		p-value
	Intermediate (n=27)	High (n=94)	
PSA baseline			
Median	658.00	376.50	0.241
IQR	804.97	487.00	
PSA at 3 months			
Median	12.00	22.00	0.353
IQR	139.92	119.00	
PSA change			
Median	394.00	252	0.084
IQR	825.08	332.80	
S. testosterone			
Median	328	225	0.366
IQR	294	300	

PSA: Prostate-specific antigen, PCa: Prostate cancer

Our cohort of 121 patients, received various treatment modalities such as ADT alone, ADT with chemotherapy, ADT with chemotherapy, and palliative radiotherapy. The patients were grouped accordingly. There were 27 patients in ADT-only group, 88 in ADT with chemotherapy and 6 patients in ADT with Chemotherapy and Radiotherapy. Comparative analysis between these groups with respect to serum PSA levels and serum testosterone was performed. There was no significant difference between the various treatment groups with respect to their PSA at Baseline, 3 months, PSA Change and S. testosterone (p=0.261, 0.249, 0.471, and 0.583. respectively) (Table 4).

Patients with <4 metastasis and no visceral metastasis were considered an oligometastatic group. 53/121 were in this group. We did a comparative analysis to assess whether there was the difference between the baseline serum testosterone, baseline PSA, PSA response between the two groups. We found that there was no significant difference in baseline PSA, PSA at 3 months, PSA Change, and S. Testosterone between the two groups (p=0.149, 0.627, 0.300, and 0.407, respectively) (Table 5).

DISCUSSION

To examine the same we studied patients of mPCa and analyzed their baseline serum testosterone with their PSA at baseline, 3 months, and change in PSA. We found that patients with higher baseline testosterone had less baseline PSA level before hormonal therapy. It is logical that if low serum testosterone levels are associated with a higher burden of disease which would be reflected in their PSA values, then there should have been a positive correlation. However, although Androgens, PSA, and PCa have been shown to be intimately associated, clinically, neither the total, free nor percent free T values enhance the ability of serum PSA to predict the pathologic tumor volume or stage of disease on an individual basis [19,20]. This finding needs to be validated in a larger prospective cohort. Although majority of our patients were in their 7th decade the baseline testosterone values for the Indian population in the age group in our cohort are not defined.

Another observation in this study was that higher testosterone levels had more PSA decline after ADT (correlation coefficient=0.178 and p=0.05). According to one hypothesis, PCa cells that develop in the presence of a high level of testosterone may contain a high level of AR, which would make them very sensitive to androgen ablation [21]. A cohort study demonstrated that high levels of total serum testosterone levels at the time of diagnosis were associated with aggressive features of PCa, which is consistent with the results of previous studies [22]. ADT to lower the serum testosterone level remains a standard treatment for advanced disease to the present day. A study found that 3 months after the start of endocrine therapy, the PSA value in 26 patients had decreased to below the normal limit, whereas that in 14 patients was above 4.0 ng/mL. Concluding that there was a statistically weak positive significant association between serum testosterone and PSA response [23]. The demonstration that androgen suppression efficiently treats advanced PCa, and the fact that eminent serum androgen levels might predispose people to PCa, have attracted persistent interest. Our findings are in accordance with these studies.

We further examined weather serum testosterone levels were any different between various ISUP risk groups, the presence or absence of perineural invasion as found on histology. We did not find any significant difference in testosterone levels, serum PSA levels at baseline, 3 months between them. A study examining 455 men observed that low serum testosterone was not prognostic of biochemical recurrence, tumor volume, or disease progression, but that it was allied with Gleason 4–5 disease (odds ratio [OR] 2.4, 95% CI: 1.0–5.7; p=0.048) [24]. Our findings are in contrast with this study, however, we had not specifically defined or analyzed based on low vs high testosterone.

Other comparative analysis based on oligometastasis and non-oligometastasis PCa, visceral and bone metastasis and with various treatment modalities such as ADT only, ADT with Chemotherapy and ADT

Table 4: Comparative analysis of various treatment modalities versus serum PSA level and serum testosterone in metastatic prostate cancer

	Treatment modalities			
	ADT only (n=27)	**ADT+Chemotherapy (n=88)**	**ADT+Chemo+Radiotherapy (n=6)**	
PSA baseline				
Median	299.92	379.50	846.96	0.261
IQR	629.00	589.01	466	
PSA at 3 months				
Median	45.00	12.00	220.00	0.249
IQR	113.00	116.50	210.0	
PSA change				
Median	244.86	259.46	480	0.471
IQR	514.08	342.55	636.00	
S. testosterone				
Median	298	230	178	0.583
IQR	276	329	401	

PSA: Prostate-specific antigen, ADT: Androgen deprivation therapy

Table 5: Comparative analysis of oligometastasis and non-oligometastasis prostate cancer with serum PSA and serum testosterone

???	**Oligo metastasis (n=53)**	**Non-oligo Metastasis (n=68)**	**p-value**
PSA baseline			
Median	331	433	0.149
IQR	475	642	
PSA at 3 months			
Median	15	68	0.627
IQR	107.00	138.50	
PSA change			
Median	217	273	0.300
IQR	288.20	390.42	
S. testosterone			
Median	280	232	0.407
IQR	258	332	

PSA: Prostate-specific antigen

along with Chemo as well as Radiotherapy then it was observed that there was no association found between serum PSA and serum testosterone. In 2016, Porcaro *et al*. found that high testosterone levels predicted an increased risk of Gleason score upgrading (OR, 1.06; p=0.027) [25]. An animal study by Morgentaler and Traish stated that "Beyond a certain serum testosterone concentration, androgens have a restricted ability to stimulate PCa growth. Subsequent increases in serum testosterone levels beyond that concentration did not stimulate the prostate because the binding capacity of the intra-prostatic ARs had been saturated" [26].

Mikkola *et al*. studies have demonstrated that low, rather than high, testosterone levels at diagnosis were associated with various markers of poor prognosis, including an advanced pathological stage, higher Gleason scores, higher PSA levels, seminal vesicle invasion, and positive surgical margins [17]. They also reported that pre-treatment testosterone level in patients without mPCa was not higher than those with metastasis [17]. A pre-existing low serum testosterone level might selectively affect the growth of less androgen-dependent cancer cells, which might be more resistant to subsequent androgen withdrawal. To our knowledge, reports of the association between serum testosterone and the disease prognosis besides those of the western countries are very limited [27]. Our study further adds to the controversial effects of serum testosterone on PCa treatment and progression.

Our study has various limitations.

1. Small Sample size of our study (121 patients)
2. Retrospective cohort and the inherent bias associated with it
3. Shorter follow-up period (follow-up period of 3 months is too short to assess the true oncological outcomes).

CONCLUSION

We conclude that the effect of testosterone might have a possible role in the assessment of treatment response as assessed by PSA. However, the exact implication and its role in disease assessment need to be examined in a larger prospective cohort.

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