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Correlation of Total Serum Prostate Specific Antigen and Prostate Specific Antigen Density with subclinical inflammation in Benign Prostatic Hyperplasia

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ABSTRACT

Background

Serum PSA is an important tumor marker for diagnosis of prostate cancer. However, it can rise in some other benign conditions like benign prostatic hyperplasia (BPH), prostatitis, prostatic infarct, instrumentation, prostate manipulations like examination, transurethral resection and urinary tract infection (UTI). The aim of this study was to find correlation of total serum PSA and PSAD with extent and aggressiveness of subclinical inflammation in BPH.

Methods

This cross-sectional study was conducted on 25 cases of transurethral resection of prostate and open prostatectomy specimens diagnosed with BPH received in time period of July 2022 to June 2023. Cases with clinical signs and symptoms of prostatitis, positive urine culture, diagnosed as prostate cancer, cases with history of previous surgery of prostate and history of instrumentation of urinary tract were excluded. Total serum PSA and prostate weight were measured. PSAD was calculated. Histological inflammation was graded with respect to extent and aggressiveness. PSA and PSAD were correlated with extent and aggressiveness of inflammation.

Results

There was no statistically significant correlation between inflammation extent score and total serum PSA ($p = 0.318$). Also, there was no correlation between inflammation extent score and PSAD ($p = 0.308$). However, there was significant correlation between inflammation aggressiveness score and total serum PSA ($p = 0.011$). Similarly, there was also correlation between inflammation aggressiveness score and PSAD ($p = 0.010$).

Conclusions

Repeat unnecessary biopsies may be avoided in cases with high total serum PSA in presence of glandular epithelial disruption in histological prostatitis.

Keywords: BPH; prostatitis; PSA; PSAD.

INTRODUCTION

Prostate specific antigen (PSA) is the most important test used in the diagnosis and management of prostate cancer.[1] It has the best overall performance in diagnosis of prostate cancer, still its sensitivity and specificity remains low.[2] PSA is prostate specific but not disease specific.[3] The two most important factors limiting the specificity of PSA are benign prostatic hyperplasia (BPH) and acute clinical prostatitis.[2, 4, 5] BPH is an extremely common disorder in men over age of 50.[6] BPH frequently occurs concurrently with prostatitis as evidenced by presence of histological lesions indicating prostatitis in 40-90% cases.[7] Chronic inflammation may even perpetuate chemokine driven development and progression of BPH.[8, 9] Acute and chronic bacterial prostatitis are well known to elevate serum PSA levels in BPH.[4, 9] Correlation of asymptomatic histologic

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inflammation in BPH with serum PSA remains controversial.[5] However, there is a growing evidence regarding correlation of aggressiveness of histologic inflammation in BPH with serum PSA values.[2, 5, 10] Also, men with BPH have overall higher PSA values than men with smaller glands. To factor out the contribution of prostate volume on PSA levels, Prostate specific antigen density (PSAD) is calculated which is ratio between total serum PSA value and prostate volume.[11] In biopsies with elevated PSA and PSAD levels showing inflammation but no evidence of malignancy, reporting of histologic inflammatory infiltrates, especially about the glandular epithelial integrity may avoid repeat unnecessary biopsies.[5] Hence, this study is undertaken to find correlation of intensity and aggressiveness of subclinical inflammation with serum PSA and PSAD levels in BPH cases.

METHODS

This cross-sectional study was conducted in Department of Pathology, College of Medical Sciences and Teaching Hospital. Ethical approval was obtained from COMSTH Institutional Review Committee (Ref No. 2020-090). Total 25 cases of transurethral resection of prostate (TURP) and open prostatectomy specimens diagnosed with BPH whose total serum PSA value and prostate weight (grams) were evaluated before surgery were included in the study received in a time duration of 1 year (Jully, 2022 to June, 2023). Total serum PSA was estimated by Maglumi 2000 (SNIBE) Chemiluminiscent Immunoanalyzer. A value of total serum PSA more than 4.0 ng/ml was considered high.[11] PSAD was calculated as total serum PSA divided by prostate weight.[12] Cases with clinical signs and symptoms of prostatitis, positive urine culture, diagnosed as prostate cancer, cases with history of previous surgery of prostate and history of instrumentation of urinary tract were excluded from the study. Extent and aggressiveness of histological inflammation were graded on a 4 point scale as proposed by Irani et al.[2]

Inflammation

0 – No inflammatory cells

1–Scattered inflammatory cell infiltrat

2–Non confluent lymphoid nodules

3–Large inflammatory areas with confluence of infiltrate

Aggressiveness

0–No contact between inflammatory cells and glandular epithelium

1–Contact between inflammatory cells and glandular epithelium

2–Clear but limited (<25% of examined material) glandular epithelial disruption

3–Glandular epithelial disruption on >25% examined material

Age, PSA (ng/ml), PSAD, inflammation score and aggressiveness score were entered in Statistical Package for Social Sciences (SPSS) version 20. Age of presentation, PSA level and weight were expressed as mean ± Standard deviation (SD). Correlation of total serum PSA and PSAD with extent and aggressiveness of inflammation was sought using one way analysis of covariance (ANOVA) test and p value < 0.05 was considered statistically significant at 95% confidence interval, in which further Tamhane post hoc test was applied to see pairwise comparison of groups contributing to the statistical significance

RESULTS

A total of 25 cases of TURP or open prostatectomy specimens were included in the study period. Age of the patients ranged from 57 to 92 years with a mean ± SD of 74.4 ± 8.3 years. Total serum PSA ranged from 0.75 to 29.14 ng/ml with a mean ± SD of 6.33 ± 7.22 ng/ml. 11 (44.0%) cases had PSA value >4 ng/ml. Weight of the prostate ranged from 32 to 186 grams with mean ± SD of 66.0 ± 32.8 grams. All 25 cases had some evidence of histological inflammation. 5 (20%) cases had score 1 inflammation (scattered inflammatory cell infiltrate), 14 (56%) cases had score 2 inflammation (nonconfluent lymphoid nodules) and 6 (24%) cases had score 3 inflammation (confluent lymphoid nodules). There was no statistically significant correlation between inflammation and total serum PSA value as p value was > 0.05 (Table 1).

Table 1. Correlation between Total serum PSA and Inflammation score. (n = 25)

Inflammation score	No. of cases	PSA (ng/ml)			
		Mean	SD	Minimum	Maximum
1	5 (20)	2.3	2.43	0.75	6.59
2	14 (56)	6.65	7.24	0.83	29.14
3	6 (24)	8.96	9.17	1.01	26.3
Total	25 (100)	6.33	7.22	0.75	29.14
p = 0.318					

In the aggressiveness of inflammation scoring, 2 (8%) had score 0 (no contact between inflammatory cells and glandular epithelium), 11 (44%) cases had score 1 (contact between inflammatory cells and glandular epithelium) and 12 (48%) had score 2 (clear but limited (<25% of examined material) glandular epithelial disruption) (Figure 1).

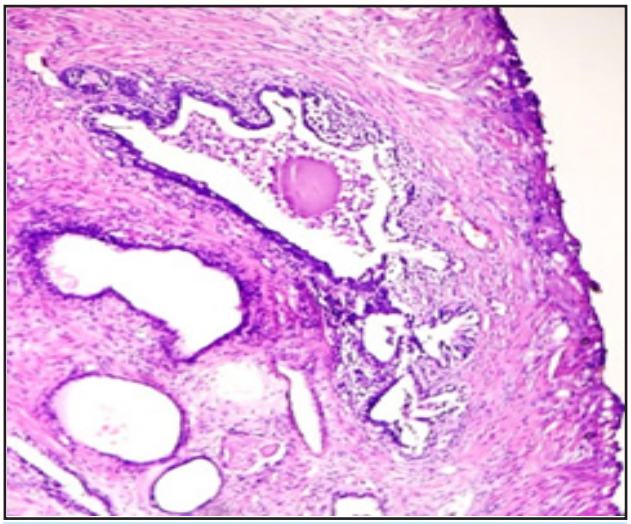

Figure 1. Glandular epithelial disruption by inflammatory infiltrate (H and E X100).

There was statistically significant correlation between aggressiveness score and total serum PSA value as p value was < 0.05 (Table 2).

Table 2. Correlation between Total serum PSA and Aggressiveness score. (n = 25)

Aggressiveness score	No. of cases	PSA (ng/ml)			
		Mean	SD	Minimum	Maximum
0	2 (8)	0.79	0.57	0.75	0.83
1	11 (44)	2.72	1.57	1.07	6.59
2	12 (48)	10.57	8.55	1.01	29.14
Total	25 (100)	6.33	7.22	0.75	29.14
p-value= 0.011					

On further application of Tamhane post hoc test, the mean difference between total serum PSA level at all aggressiveness score levels was significant (Table 3).

Table 3. Comparison of mean total serum PSA level with aggressiveness scores. (n = 25)

Aggressiveness score		Mean difference in total serum PSA ng/ml (I-J)	Significance
I	J		
0	1	-1.93	0.007
	2	-9.78	0.007
1	0	1.93	0.007
	2	-7.85	0.027
2	0	-9.78	0.007
	1	7.85	0.027

There was no statistically significant correlation between inflammation score and PSAD as p value was > 0.05 (Table 4).

Table 4. Correlation between PSAD and Inflammation score. (n = 25)

Inflammation score	No. of cases	PSAD (Total serum PSA (ng/ml) / prostate weight in grams)			
		Mean	SD	Minimum	Maximum
1	5 (20)	0.043	0.05	0.012	0.132
2	14 (56)	0.101	0.078	0.017	0.291
3	6 (24)	0.117	0.107	0.019	0.296
Total	25 (100)	0.093	0.083	0.012	0.296

There was statistically significant correlation between aggressiveness score and PSAD value as p value was < 0.05 (Table 5).

Table 5. Correlation between PSAD and Aggressiveness score. (n = 25)

Aggressiveness score	No. of cases	PSAD (Total serum PSA (ng/ml) / prostate weight in grams)			
		Mean	SD	Minimum	Maximum
0	2 (8)	0.016	0	0.016	0.017
1	11 (44)	0.055	0.034	0.012	0.132
2	12 (48)	0.141	0.094	0.019	0.296
Total	25 (100)	0.093	0.083	0.012	0.296
p-value= 0.010					

On further application of Tamhane post hoc test, the mean difference between total serum PSA level at all aggressiveness score levels was significant (Table 6).

Table 6. Comparison of mean PSAD with aggressiveness scores. (n = 25)

Aggressiveness score		Mean difference in PSAD (I-J)	p-value
I	J		
0	1	-0.038	0.012
	2	-0.125	0.002
1	0	0.038	0.012
	2	-0.086	0.029
2	0	0.125	0.002
	1	0.086	0.029

DISCUSSION

PSA is a serine protease synthesized by epithelial cells lining the prostatic ducts and acini into the prostatic ductal system finally into the semen. Its function is to cleave and liquefy seminal coagulum after ejaculation. Normally, only a minute amount circulates in the serum. In most laboratories, a serum level of 4 ng/ml is used as a cutoff between normal and abnormal.[11, 13] Since its introduction in the late 1980s, most prostate cancers are detected at an earlier stage, much earlier before the emergence of clinically evident disease which usually represent locally advanced or metastatic disease.[14] PSA is organ specific but not cancer specific. It may also be elevated in some other benign conditions like BPH, prostatitis, prostatic infarct, instrumentation, prostate manipulations like examination, transurethral resection and urinary tract infection (UTI). Some physiological conditions like increasing age, vigorous exercise and ejaculation can also increase PSA levels.[10, 11, 13] Because of this, several refinements in the estimation and interpretation of PSA values are used. One such refinement is estimation of PSAD which is ratio between total serum PSA value and volume of prostate gland. PSAD can be estimated by total serum PSA divided by weight of prostate gland as measured by transrectal ultrasonography. Men with BPH have higher total serum PSA values than men with smaller glands. Measurement of PSAD factors out contribution of benign prostatic tissue to serum PSA levels.[11, 12] BPH also termed as nodular hyperplasia by Moore, is a nodular enlargement of gland caused by hyperplasia of both glandular and stromal components within the transitional and periurethral zones resulting in increase in weight of gland well beyond 20 grams which is considered as normal for adult individual. Incidence is only 8% in fourth decade, but it reaches 50% in fifth decade, 75% in eighth decade and affects almost all men by ninth decade.[6, 15] Prostatitis is inflammation of prostate gland which can fall into several categories like acute and chronic bacterial prostatitis, chronic abacterial prostatitis and granulomatous prostatitis. Acute bacterial prostatitis is caused by organisms similar to those causing urinary tract infections (UTI). Clinically, it is characterized by fever, chills and dysuria. On rectal examination prostate is boggy and tender. Chronic bacterial prostatitis may present with low back pain, dysuria and perineal and suprapubic discomfort or may be sometimes asymptomatic but with history of recurrent UTI. Chronic abacterial prostatitis is the most common form of prostatitis seen today which has no history of recurrent UTI and bacterial cultures are negative.[11] Acute prostatitis is rarely seen in surgical specimens. Chronic prostatitis is more common, but it is important to distinguish the true infectious process from inconsequential mononuclear infiltrates often seen in chronic abacterial prostatitis which frequently accompanies nodular hyperplasia.[15] Inflammation is a histological finding associated with BPH in almost all prostate specimens whether it is biopsy, surgical or autopsy specimen even in the absence of clinical prostatitis.[5, 10] Present study was carried out on 25 prostate biopsies (both open and transurethral resection) diagnosed with BPH. Clinical prostatitis, instrumentation of urinary tract and adenocarcinoma were ruled out. Total serum PSA and PSAD were correlated with extent and aggressiveness of inflammation according to scoring system by Irani et al.[2] Age of the patients ranged from 57 to 92 years with a mean ± SD of 74.4 ± 8.3 years in the present study. In similar studies conducted by Irani et al.[2], Kandirali et al.[16], Song et al.[5], and Schatteman et al.[10], age ranged from 53 to 95 years with a mean of 67.9 years, 52 to 80 years with a mean of 64.7 years, 40 to 88 years with a mean of 69.2 years and 44 to 92 years with a mean of 66.9 years respectively. In present study, total serum PSA ranged from 0.75 to 29.14 ng/ml with a mean ± SD of 6.33 ± 7.22 ng/ml. Similarly, in study conducted by Irani et al.[2] mean total serum PSA was 7.2 ng/ml, in study conducted by Kandirali et al.[16], total serum PSA ranged from 0.91 to 66.20 with mean of 12.66 ± 10.73 ng/ml, in study conducted by Song et al.[5], total serum PSA ranged from 0.37 to 72.85 with mean of 8.39 ng/ml, in study conducted by Schatteman et al.[10], total serum PSA ranged from 0.3 to 43.0 with mean of 6.0 ngl/ml and in study conducted by Ozden et al.[17], mean

total serum PSA was 5.2 ng/ml. All 25 cases had histological inflammation in present study. Similarly, in studies conducted by Irani et al.[2], Schatteman et al.[10] and Nickel et al.[18], inflammation was present in all the cases. In the present study both total serum PSA and PSAD did not correlate with extent of inflammation ($p > 0.05$). However, both total serum PSA and PSAD correlated with aggressiveness of inflammation ($p < 0.05$). In study conducted by Irani et al.[2], total serum PSA correlated with aggressiveness of inflammation but not with extent. In study conducted by Kandirali et al.[16], both total serum PSA and PSAD correlated both with extent and aggressiveness of inflammation. In study conducted by Song et al.[5], serum PSA correlated with aggressiveness of inflammation. In study conducted by Schatteman et al.[10], serum PSA correlated with aggressiveness and not with extent of inflammation. In study conducted by Ozden et al.[17], serum PSA correlated with aggressiveness score. However, in study conducted by Nickel et al.[18], serum PSA did not correlate with amount, degree or pattern of inflammation. In a study conducted by Piovesan et al.[19], histological evidence of chronic prostatitis was present in 78% cases only and moreover, when they compared PSAD in two different groups: one with inflammation and one without inflammation, there was no significant difference. However, in study conducted by Nadler et al.[20], they concluded that prostate volume and inflammation were the two most important factors contributing to serum PSA level in men without prostatic carcinoma. Chronic inflammation, like acute can also increase serum PSA level, but its effect is not as well established and studied as it is for acute prostatitis.[21] Moreover, the relationship between histological inflammation and serum PSA remains controversial.[16] Most of the studies have established relationship between aggressiveness of inflammation and serum PSA level including the present study.[2, 5, 10, 16, 17] The theory of leakage due to glandular epithelial disruption morphologically may be the most plausible explanation of rise in serum PSA.[5]

CONCLUSIONS

Asymptomatic histological prostatitis can contribute to rise in serum PSA level. Aggressiveness of inflammation is more important contributor of such rise. Hence, inclusion of such morphological finding in biopsy report and careful interpretation may avoid repeat unnecessary biopsies.

Conflict of interest: None

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