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Original Research Article

Role of Prostate Specific Antigen Density (PSAD) in the Detection of Carcinoma Prostate: An Institutional Study

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Abstract

Prostate Specific Antigen (PSA), a member of the human Kallikrein gene family, is a serine protease with chymotrypsin like activity, produced mainly by the epithelial cells that line the acini and duct of the prostate gland. Prostate specific antigen density (PSAD) calculation has been recommended as a more accurate and reliable method for differentiating benign and malignant lesions.

Aims: The present study is undertaken to determine the PSA and PSAD levels in patients of BPH, PIN and carcinoma prostate, and to evaluate the diagnostic efficiency of PSAD in the management of carcinoma prostate and in differentiating patients of early prostate cancer (PIN) from those of BPH.

Materials and Methods: The present study is a hospital based prospective study, undertaken in the department of pathology, Sri Siddhartha Medical College, Tumkur. This study was conducted on 90 transurethral resection of prostate (TURP) and prostate biopsy specimens obtained from patients presenting with complaints of enlargement of prostate in Department of Surgery, SSMC, Tumkur.

Statistical Analysis Used: Data collected was entered in MS Excel spreadsheet and analysed using SPSS version 20.

Results: In benign cases, SPSA was normal in 89.98% of cases. Modest elevation (4.1–10ng/ml) was seen is 10.71% cases. In all the 84 cases, PSA density was within normal range (<0.15ng/ml/cc) and correlated well with the histological pattern.

In PIN cases, SPSA and PSAD were within normal range. All 5 malignant cases show SPSA values is significant zone (>10ng/ml) and PSAD in all the cases were above the cut-off value of 0.15ng/ml/cc.

Conclusion: PSAD offers a simple, readily acceptable, objective and economical approach to the detection of prostatic carcinoma. Further, immunohistochemistry and molecular genetic analysis are suggested.

Keywords: Prostate specific antigen (PSA); Prostatic carcinoma (PCa); Benign prostatic hypertrophy (BPH); Prostate specific antigen density (PSAD); Transurethral resection of prostate (TURP).

Introduction

Benign prostatic hyperplasia (BPH) is the most common neoplastic condition affecting men[1] and is an age related process. It is characterized histologically as a progressive enlargement of the prostate gland resulting from a non-malignant proliferative process that includes both epithelial and stromal elements.[2]

Prostatic intraepithelial neoplasia (PIN) refers to the preinvasive end of the continuum of cellular with cytological changes mimicking cancer.[3] When PIN is associated with elevated PSA, a high incidence of invasive carcinoma is noted on subsequent biopsy.[4]

Prostate specific antigen, a member of the human Kallikrein gene family, is a serine protease with chymotrypsin like activity,produced mainly by the epithelial cells that line the acini and duct of the prostate gland. Disruption of the normal glandular structure by prostatic disease allows greater amounts of PSA to enter the general circulation.[5]

PSA density (PSAD) is defined as the quotient of serum PSA divided by prostate volume. Studies have shown that PSAD was significantly higher in patients with biopsy proven cancer whose PSA values lay between 4 and 10 ng/ml.

PSA is not prostate cancer specific. It is prostate tissue specific and as a result numerous benign condition of the prostate can influence its serum concentration. Due to the tremendous overlap in values of PSA between BPH and carcinoma, combination of digital rectal examination findings, trans rectal ultrasonography along with PSA and PSAD levelsmay lead to the detection of more early, curable prostate cancer.

The present study is undertaken to determine the PSA and PSAD levels in patients of BPH, PIN andcarcinoma prostate to evaluate the diagnostic efficiency of PSAD in the management of carcinoma prostate and in differentiating patients of early prostate cancer (PIN) from those of BPH.

Materials and Methods

The present study is a hospital based prospective study, undertaken in the department of pathology, Sri Siddhartha Medical College, Tumkur. This study was conducted on 90 prostate specimens obtained from patients who underwent transurethral resection of prostate (TURP) & biopsy for enlargement of prostate attending the Department of Surgery & Urology, SSMC&H, Tumkur.

Brief clinical data noted from the case records, which included the age, presenting symptoms, DRE findings, serum PSA levels, USG findings and clinical diagnosis.

Following inclusion and exclusion criteria are adopted in this study.

Inclusion criteria: All types of prostatic specimens including TURP, biopsy and prostatectomy are considered in this study.

Exclusion criteria: Patients with retention of urine due to other causes other than prostatic lesions like urethral stricture and calculi were excluded.

All the prostatic specimens which were sent in 10% formalin were received, weighed and subjected to a careful detailed gross examination. After fixation, the tissues were given for processing. For the first 20g of tissue, four capsules were filled. If the specimen weighed more than 20g then one additional capsule was filled for each subsequent 10g. Paraffin embedded tissue sections from these specimens were used for microscopic study. 4–6 μm thick sections were prepared and stained routinely with H & E stain using standard procedures.

All the sections were subjected to detailed microscopic examination.

Blood samples for total SPSA estimation were collected on ambulatory basis i.e. at the time of admission prior to the examination of the prostate, by venipuncture. The blood was sent to biochemistry laboratory in a plain vacutainer. Serum was separated. Samples were stored at 2°C–8°C till the time assay was carried out for a maximum period of 2 days.

Quantitative estimation of total SPSA was done with fully automated chemiluminescent Immunoassay method. Sensitivity of this method is 0.01 ng/ml. Normal reference range is < 4.00 ng/ml. 4.01 to 10.00 ng/ml were classified as borderline.

Prostate specific antigen density (PSAD) was calculated by dividing serum PSA values with prostate volume as determined by ultrasonography. Cut-off value was taken as 0.15 ng/ml/cc.

Results

The present study deals with various histological evaluations of prostate tissue specimen and correlation with preoperative ambulatory total serum PSA levels and assessing prostate specific antigen density. During the period of present study, 90 prostatic specimens were analyzed in the Department of Pathology, Sri Siddhartha Medical College, Tumkur.

Out of 90 prostatic specimens received, 84 cases were benign lesions, one case was low grade intraepithelial neoplasia along with nodular hyperplasia (NH), and prostatic malignancy was diagnosed in 5 cases. Incidences of benign lesions were 94.5% and malignant lesions were 5.5% in this present study.

Histopathological examination was carried out in all 90 cases, further to know the variable components in benign prostatic hyperplasia, premalignant lesion and prostatic carcinoma. An attempt was made to find out the relationship between prostatic lesions and preoperative total serum PSA and PSAD levels.

Total serum PSA values obtained were grouped into three categories i.e., 0–4 ng/ml (Normal zone), 4–10 ng/ml (gray zone) and more than 10 ng/ml (significant zone). Volume of the prostate was assessed by ultrasound examination and PSA density was calculated and analyzed.

Significant numbers of patients (76 cases) were found to have total SPSA of 0–4 ng/ml (normal zone) and 8 cases showed PSA level of 4–10 ng/ml (gray zone) range (Table 1).

Table 1: Distribution of NH patients with respect to total SPSA levels.

Total SPSA (ng/ml)	No of Cases	Percentage
0–4 (normal zone)	76	90.4%
4–10 (gray zone)	08	9.52
>10 (significant zone)	–	–

PSA Density in Nodular Hyperplasia: In all 84 cases, PSAD was within normal range, i.e. 0.15ng/ml/cc with a mean average value of 0.0058 ng/ml/cc. Even in cases where PSA was in gray zone, the PSAD was within normal range. PSAD correlated well with the histopathological pattern.

Prostatic Intraepithelial Neoplasia: NH was associated with low grade PIN in one case, which shows epithelial crowding and stratification, the nuclei were enlarged with anisonucleosis and nuclear chromatin was apparently normal. PSA level was 3.1 ng/ml and PSA density was 0.068. Thus values were within normal range (Table 2).

Table 2: Correlation of PSA levels & PSA density with PIN.

No of Cases	PSA Levels (ng/ml)	PSA density
01	3.1	0.068

Carcinoma Prostate

Microscopic features: Five cases of prostatic carcinoma were identified in the present study. All of them were adenocarcinomas involving the prostate. All of them showed one or more of the different growth patterns and were categorized depending on the predominant growth pattern (according to Gleasons scoring system).

All 5 case showed PSA values in significant zone (>10 ng/ml). PSA density in all the cases were above normal value (normal value being 0.15 ng/ml/cc) (Table 3).

Table 3: Correlation of prostatic carcinoma with PSA levels & PSA density.

Case No.	Age (Years)	Histopathological diagnosis	PSA (ng/ml)	Prostate Volume (grams)	PSA Density (ng/ml/cc)
9	68	Well differentiated adenocarcinoma	11.83	50	0.236
23	76	Moderately to poorly differentiated	20	45	0.444
31	70	Moderately to poorly differentiated	13.8	52	0.265
35	70	Moderately to poorly differentiated	18.2	55	0.330
46	75	Moderately to poorly differentiated	32.8	52	0.630

Discussion

Nodular hyperplasia is a common condition in males over 50 years, and prostate cancer can develop in the same population. Prostate specific antigen, the best marker for prostate cancer, is also produced by benign epithelial cells, and there is an overlapping phenomenon between both conditions. The better we understand the relationship between NH and PSA, the higher will be the discrimination power of PSA measurement as a marker for prostate cancer.6 This study was undertaken to evaluate the various histological lesions in the prostatic specimens and to study the relationship between PSA, PSAD and prostatic lesions.

In this study, 90 prostatic specimens were analyzed.These formed 5% of the total surgical specimens received during the study period.

Correlation of PSA values in prostatic lesions

PSA is elevated by any change that disrupts the normal architecture of the prostate which allows diffusion of protease into the micro vascular circulation.

PSA is the most important and clinically useful biochemical marker of the prostate because it is produced by and is specific for prostatic tissue.[7]

The PSA values were divided into 3 groups 0–4ng/ml,4–10 ng/ml and >10 ng/ml and analyzed according to age and clinical diagnosis. In the present study, 84 cases were benign lesions (94.5%) out of which a significant number of patients,i.e. 89.28% were found to have total SPSA of 0–4ng/

Table 4: Association between BPH & serum PSA values.

Authors	No. Pts	% pts with PSA values in Specified Range		
		0.0–4.0 (ng/ml)	4.1–10.0 (ng/ml)	>10.1 ng/ml
Ercole et al[8]	357	79%(282)	18(64)	3(11)
Oesterling et al[9]	72	47(34)	43(31)	10(7)
Armitage et al[10]	91	53(48)	35(32)	12(11)
Hudson et al[11]	168	79(133)	19(32)	2(3)
Present study	84	89(75)	10(09)	–

ml (normal zone) and 10.7% showed PSA level of 4–10 ng/ml (gray zone) range (Table 4). The age distribution was between 40–90 years. Majority of cases were in 7th & 8th decade (66.66%) with PSA range of 0–4 ng/ml and 10.71% of cases were in the gray zone (4–10 ng/ml).

PSA values in prostatic adenocarcinoma

The prevalence of prostate cancer (PCa) is high and increases with age. PSA screening has impacted the detection of PCa and is directly responsible for a dramatic decrease in stage at diagnosis, with over 80% of PCa being localized to the prostate. Gleason score and stage at the time of diagnosis remain the mainstays to predict prognosis.[12] In the present study, all 5 cases show PSA values in the significant zone i.e. >10 ng/ml with mean PSA value of 19.32 ng/ml.

PSA density

To improve the differentiation between benign and malignant causes of PSA-elevation, additional parameters such as PSA density are frequently used. PSA density relates serum PSA level to the prostate volume, usually calculated with transrectal ultrasound (TRUS). It is an estimate of the PSA secreted per unit volume of prostatic tissue. This is studied to be higher in cases of prostatic carcinoma. A level below 0.15 ng/ml/cc is more suggestive of NH than prostate carcinoma.[13]

In the present study, total SPSA values and PSAD of malignant lesions were significantly higher when compared to benign lesions and correlated with histologic grade of tumor (Table 5). In the present study, PSAD was within normal range i.e.0.15 ng/ml/cc in all the benign lesions with a mean average of 0.0058 ng/ml/cc. In all malignant cases, PSAD was above the normal value and the mean average was 0.381 ng/ml/cc.

Table 5: Correlation of PSA density in prostatic lesions in different studies.

Authors	Benign Lesion		Malignant Lesion	
	No Cases	Mean PSAD	No Cases	Mean PSAD
Benson et al[14]	20	0.044	41	0.581
Present study	85	0.0058	05	0.381

The present data indicates that simple measurement of SPSA can be used efficiently as a prescreening test to distinguish BPH and prostate cancer and to detect at an early stage. The results suggested that PSAD combined with PSA was more efficient in distinguishing BPH and prostate cancer.

All 5 malignant cases show SPSA values in significant zone (>10 ng/ml) and PSAD in all the cases were above the normal value. Study done by Sfoungaristos et al. shows similar results and an optimal cutoff of 0.15 was established for PSAD in the study.[15] Previous studies done also supported the use of PSAD in evaluating patients with "gray zone PSA" with a PSAD cutoff level of 0.15. In a recent study by Aminsharifi A et al. the performance of different cutoff points ranging from 0.05 to 0.15 ng/ml/cc was evaluated and an optimum PSAD cutoff of 0.08 ng/ml/cc was suggested.[16]

Conclusion

PSA estimation with PSAD is the initial test in men older than 50 years. PSAD offers a simple, readily acceptable, objective and economical approach to the detection of prostatic carcinoma. Further, immunohistochemistry and molecular genetic analysis are suggested. Screening protocols and awareness programs need to be instituted.A comprehensive histopathological study of prostatic biopsy specimens should be done to confirm the diagnosis of NH, PIN and prostatic carcinoma. Keeping in mind the cost-effectiveness and simple clinical application, PSAD is a popular PSA derivative even in the era of modern biomarkers.

Conflicts of interest: There are no conflicts of interest.

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