

Correlation Between Serum Prostatic Specific Antigen and Prostatic Volume in Benign Prostatic Hyperplasia

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ABSTRACT

Introduction: Benign prostatic hyperplasia (BPH) is a progressive condition characterized by prostate enlargement accompanied by lower urinary tract symptoms (LUTS). Benign prostatic hyperplasia arises in the periurethral and transition zones of the prostatic gland and represents an inevitable phenomenon for the ageing male population. An estimated 75% of men >50 years of age have symptoms arising from benign prostatic hyperplasia, and 20–30% of men reaching 80 years of age require surgical intervention for the management of BPH. Prostate specific antigen (PSA) is a serine protease produced by the prostate epithelium and periurethral glands in male. Serum PSA elevation occurs as a result of disruption of normal prostatic architecture that allows PSA to diffuse into prostatic tissue and gain access to the circulation. Benign prostatic hyperplasia, prostatic carcinoma and prostatitis are three common diseases where PSA in the serum is raised. **Aims and objectives:** To evaluate the PSA level and To find out the relationship between serum PSA level and the volume of prostate in Benign hyperplasia of prostate. **Material and Methods:** This is a Hospital based prospective study which was conducted in the Department of Surgery at Nepalgunj Medical College Teaching Hospital, Kohalpur, for a duration of 1 year from 13th July 2015 to 12th July 2016. A total of 30 cases were studied. Patients were chosen for the study on the basis of clinical history and DRE. Patient with LUTS symptoms and enlarged Prostate on DRE were further subjected to PSA screening through blood examination and Transabdominal ultrasound for measuring prostatic volume. Patients were explained about procedure and following consent, patients were subjected for TURP under spinal anesthesia/general anesthesia. Specimen was sent to the Department of Pathology, Nepalgunj Medical College for Histopathological evaluation. **Results:** Out of 30 patients, one patient was of 44 years of age, rest of them were above 50 years of age and the mean age was 63.9±8.64 years. All the patients had voiding problems, of which 28 patients (94%) had obstructive symptoms and 27 patients (90%) had irritative symptoms. Most patients had history of nocturia which was present in 24 patients (83%). Mean PSA level was 6.36 ng/ml with a range of 3.2–12 ng/ml. Mean prostate volume measured by TAUS was 60.30 ml. and that by DRE was 38.33 ml. There was statistically significant positive correlation between PSA level and prostate volume measured by TAUS with Pearson's correlation coefficient ($r=0.679$). **Conclusion:** The analysis of present study consisting of 30 patients showed that mean PSA and prostate volume increased with advancing age, and the correlation between PSA and prostate volume estimated by TAUS in BPH as found to be statistically significant ($p<0.05$). DRE underestimated the volume of prostate with a mean difference 21.97ml. The correlation of age of the patient with PSA and prostate volume are ($r=0.128$) and ($r=0.036$) respectively. The above value shows that both are statistically weekly positive but the association between age of patient and PSA seems to be higher in comparison to age of the patient and prostate volume.

Keywords: Benign prostatic hyperplasia (BPH), lower urinary tract symptoms (LUTS), Prostate specific antigen (PSA), Prostate volume (PV), Digital rectal examination (DRE).

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive condition characterized by prostate enlargement accompanied by lower urinary tract symptoms (LUTS). Benign prostatic hyperplasia arises in the periurethral and transition zones of the prostatic gland and represents an inevitable phenomenon for the ageing male population. Benign prostatic hyperplasia is uncommon before age 40, roughly 50% of men develop BPH-related symptoms around 50 years of age. The incidence of BPH increases by 10% per decade and reaches 80% at approximately 80 years of age. An estimated 75% of men >50 years of age have symptoms arising from benign prostatic hyperplasia, and

20–30% of men reaching 80 years of age require surgical intervention for the management of BPH¹. BPH affects both glandular epithelium and connective tissue stroma to variable degrees in which adenosis, epitheliosis and stromal proliferation are seen in differing proportions².

Prostate specific antigen (PSA) is a serine protease produced by the prostate epithelium and periurethral glands in male. Serum PSA elevation occurs as a result of disruption of normal prostatic architecture that allows PSA to diffuse into prostatic tissue and gain access to the circulation. This can occur in the setting of prostate disease and prostate manipulation (prostate massage, prostate biopsy). Benign prostatic hyperplasia, prostatic carcinoma and prostatitis are three common diseases where PSA in the serum is raised³.

Prostate volume (PV) varies widely throughout man's lifetime, and in the course of different prostatic diseases, including

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benign prostatic hyperplasia (BPH). Both PV and serum prostate-specific antigen (PSA) are key predictors of clinical progression and response to medical therapy in patients with BPH, thus helping to select the regimen for medical treatment (alpha-blockers, 5-alpha-reductase inhibitors (5-ARI), or their combination⁴.

In normal person, the serum concentration of PSA are proportional to the volume of prostatic epithelium, but the release of PSA from BPH is three fold that from the normal prostate and in carcinoma of prostate the release of PSA is thirty fold. PSA is elevated approximately 0.12ng/ml/g of BPH tissue. Thus, patients with enlarged glands due to BPH may have elevated PSA levels^{5,6}.

The ratio of PSA to gland volume is termed as PSA density. The positive predictive value of PSA density is slightly higher than the use of a PSA level >4 ng/ml in several series (30–40% versus 20–30%). Instead of adjusting the PSA to total prostate volume, some have advocated adjusting it to transition zone volume (PSA transition zone density)⁶.

The concept of PSA density (PSAD) has been described as, the PSA value (ng/ml) divided by the prostate volume (ml). PSA levels associated with a small prostate may have prostate cancer while the same value of PSA in a man with a large prostate may indicate BPH. It has been suggested that a PSAD greater than 0.15 is associated with 25% incidence of cancer, and a PSAD less than 0.10 is associated with 5% incidence of cancer⁷.

During the past two decades, the development of highly specialized ultrasound equipment has allowed the application of this imaging technique in the diagnosis, treatment and follows up of prostatic disease, particularly BPH. Transabdominal ultrasound measurement of prostate volume is consistent and correlated to transrectal prostate volume when the bladder volume is less than 400ml. The maximum prostatic protrusion occurs when bladder volume is between 100 and 200ml. It is thus recommended that the transabdominal ultrasound measurement of prostatic protrusion should be carried out at bladder volumes between 100 and 200 ml and should be avoided at the extremes of bladder volumes⁸.

There is paucity of data regarding reports of PSA level in Benign hypertrophy of prostate and its relationship with volume of prostate in Nepal particularly in this region of country. Therefore this study was conducted to estimate serum PSA level and its relationship with volume of prostate.

MATERIAL AND METHODS

This is a Hospital based prospective study which was conducted in the Department of Surgery at Nepalgunj Medical College Teaching Hospital, Kohalpur, for a duration of 1 year from 13th July 2015 to 12th July 2016. Patients were chosen for the study

on the basis of clinical history and DRE. Patient with LUTS symptoms and enlarged Prostate on DRE were further subjected to PSA screening and Transabdominal ultrasound for measuring prostatic volume. Patients were explained about procedure and following consent, subjected for TURP under spinal anesthesia/general anesthesia. Specimen was sent for Histopathological evaluation.

Grades of prostatic enlargement on DRE

Grading of prostate volume was categorized using the grading scale ranging from 0 to 4+.⁹

- (1) Normal gland (20 g); about the size of a chest nut _____ 0.
- (2) Enlarged prostate gland (about 25 g); about the size of a plum and occupies a bit < 1/4th of the rectum lumen _____ 1+.
- (3) Enlarged prostate gland (about 50 g); about the size of a lemon and fills somewhat >½ of the rectum _____ 2+.
- (4) Enlarged prostate gland (about 75 g); about the size of an orange and fills approximately three-fourth of the rectal diameter _____ 3+.
- (5) Enlarged prostate gland (about 100 g); may attain the size of a grape fruit and fills so much of the rectal lumen that adequate examination is difficult _____ 4+.

PSA ESTIMATION

Blood sample was drawn before prostatic manipulation, waited at least for 24 hrs. After the manipulation. 5 ml of venous blood was collected in blood collecting tube. Standing at room temperature, centrifuging, separating serum part. PSA was estimated by chemi luminescence immunosorbent assay (CLIA), a solid phase two-site immunoassay. Transabdominal ultrasound was used to measure prostatic volume at Radiology Department. Patients with minimal bladder volume of 100 to 200 ml were subjected to USG for near correct estimation of prostate volume by USG¹⁰.

Prostatic volume was measured using ellipsoid formula.

Ellipsoid formula (V) = length x height x width x 0.52. (V = volume of prostate). PSAD was then calculated by PSA (ng/ml) divided by prostatic volume (ml).⁷

All patients included in the study underwent transurethral resection of prostate. Following surgery the tissue resected were sent for histopathological examination to confirm the diagnosis of BPH and to exclude those patients with prostatic carcinoma. Bivariate correlation and regression analysis was done by using SPSS 20.0 for windows. P value of <0.05 was taken as statistically significant.

RESULT

A total of 30 patients were included in the study. Age of patients ranged from 44-82 years with mean age of 63.9 years (SD±8.64). The distribution of patient according to age group is shown in Table I.

Age group	No of patients	Percent
< 50	1	3.3
50 -59	7	23.3
60-69	12	40
70-79	8	26.7
>80	2	6.7
Total	30	100

Table I: Age distribution of patients (N=30)

PSA(ng/ml)	No of patients	Percent
<4.0	1	3.3
4.0- 10.0	27	90.0
>10.0	2	6.7
Total	30	100.0

Table II: Frequency distribution of PSA (N=30)

Prostate volume (gm)	No of patients	Percent
25 (1 +)	19	63.3
50 (2 +)	6	20
75 (3 +)	5	16.7
Total	30	100

Table III: Frequency distribution of prostate volume by DRE (N=30)

Model	Sum of Squares	Df	Mean Square	F	Sig.	p value
Regression	35.411	1	35.411	.465	.501 ^b	<0.05
Residual	2131.289	28	76.117			
Total	2166.700	29				

Table VI: Correlation of PSA and age

		Age in years	USGV	p value
Age in years	Pearson Correlation	1	.036	<0.05
	Sig. (2-tailed)		.852	
	N	30	30	
USGV	Pearson Correlation	.036	1	
	Sig. (2-tailed)	.852		
	N	30	30	

Table VII: Correlation between age and USGV

Prostate volume (gm)	No of patients	Percent
40-59	14	46.7
60-79	12	40
>80	4	13.3
Total	30	100

Table IV: Frequency distribution of Prostate volume by TAUS (N=30)

	PSA	USGV	p value
PSA	Pearson Correlation	1	.679**
	Sig. (2-tailed)		.000
	N	30	30
USGV	Pearson Correlation	.679**	1
	Sig. (2-tailed)	.000	
	N	30	30

** .Correlation is significant at the 0.01 level (2-tailed).

Table V: Correlation between PSA and USGV

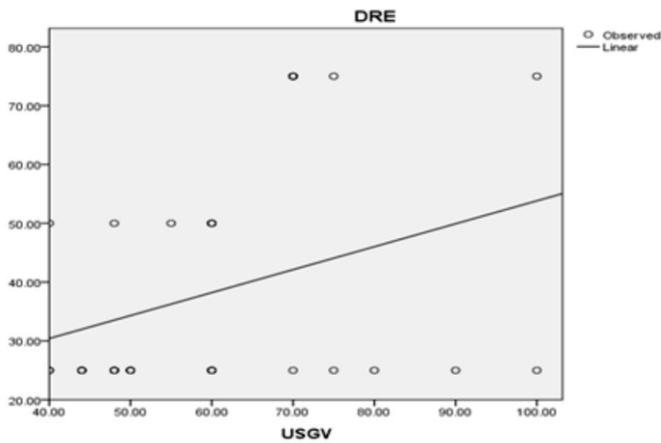


Figure 1: Correlation of prostate volume by DRE and TAUS

PSAD	No of patients	Percent
0.06	1	3.3
0.07	5	16.7
0.08	1	3.3
0.09	7	23.3
0.10	2	6.7
0.11	3	10.0
0.12	4	13.3
0.13	5	16.7
0.17	1	3.3
0.19	1	3.3
Total	30	100

Prostate specific antigen density (PSAD)

Table VIII: Distribution of PSAD (N=30)

PSA value ranged from 3.2-12 ng/ml with mean PSA of 6.36 ng/ml (SD±1.9). Out of 30 patients, 27 patients (90%) had PSA level in between 4.0 – 10.0 ng/ml. One patient (3.3%) had PSA less than 4 ng/ml whereas only 2 patients (6.7%) had PSA level more than 10 ng/ml as shown in table II.

Prostate volume was estimated by DRE. Prostate volume by DRE ranged from 25-75 gm, mean prostate volume by DRE was 38.3 ml (SD±19.4). 19 patients (63.3%) had grade 1+ (25 gm), 6 patients (20%) had grade 2+ (50 gm) and only 5 patients (16.7%) had grade 3+ (75 gm). Almost more than half of patients had grade 1+ prostate enlargement. There was no patient with prostate enlargement grade 4 + as shown in table III.

All patients were subjected to transabdominal ultrasound. The volume of prostate is shown in Table IV. Prostate volume ranged from 40 ml to 100 ml, with mean prostate volume 60.3 (SD±16.8).

The mean difference of prostate volume by TAUS and DRE was 21.9 ml. DRE tend to underestimate prostate volume in comparison to TAUS.

There was moderately positive correlation between PSA and prostate volume estimated by Transabdominal ultrasound with Pearson's correlation coefficient $r=0.679$. The correlation was statistically significant ($p<0.01$).

There was a very weak correlation between PSA and age in years with Pearson's Correlation coefficient $r=0.128$. There was a very weak correlation between age and prostate volume by TAUS with Pearson's coefficient $r=0.036$.

Prostate specific antigen density in 30 patients with BPH was also calculated. Out of 30 patients, 7 patients (23.3%) had PSAD 0.09. The mean PSAD was 0.10 (SD±0.02).

DISCUSSION

BPH is most common benign tumour in men, and its incidence is age related. The prevalence of histological BPH in autopsy studies rises from approximately 20% in men aged 41-50. To 50% in men aged 51-60, and to >90% men older than 80. Although clinical evidence of disease occurs less commonly, symptoms of prostatic obstruction are also age related. At age 55, 25% of men report obstructive voiding symptoms. At age 75, 50% of men complain of a decrease in force and caliber of their urinary stream¹¹.

Most of the workers have shown that there is a strong relationship of age with PSA and prostate volume^{12,13,14}. however, a few workers observed a weak relationship of age with PSA and prostate volume.^{3,4}

The present study is the analysis to address the interrelationship among age, serum PSA and prostate volume in a small cohort of men without prostate cancer. This study involved serum PSA estimation using the same method, and all prostate volume measurements were done by TAUS, thus assuring good reproducibility of the results. The most important finding is that there is an age-dependent relationship between serum PSA and prostate volume. Knowing a patient's age and serum PSA allows clinicians to determine whether the patient has prostatic enlargement as well as the degree of enlargement with reasonable certainty.

Prostate volume (PV) is perhaps the most extensively studied risk factor for BPH progression. Men with a PV of ≥ 30 mL are more likely to have moderate-to-severe symptoms (3.5-fold increase), decreased flow rates (2.5-fold increase), and urine retention (three- to four-fold increase) than are men with a PV < 30 mL. So, PV information has become more and more important because the PV strongly predicts BPH-related morbidity such as acute urinary retention and the need for

surgery. Because PV is strongly related to serum PSA in men with no evidence of prostate cancer, it was suggested that serum PSA can be used to estimate the degree of prostate enlargement accurately enough for it was a useful tool in therapeutic decision making¹⁵.

Generally, the typical method of measuring PV is Transrectal ultrasound (TRUS) (Stravodimos et al., 2009).¹⁶ But, TRUS is relatively painful. Moreover, TRUS is also not cost-effective and routine evaluation of patients with BPH. In our setting, TRUS may not be available everywhere. Additionally, DRE is simple to perform and practical for estimating the PV, but it has been revealed that DRE underestimates the real prostate size¹⁵.

Roehrborn and associates have introduced the concept of PSA as a surrogate measurement for prostate volume in patients with clinical BPH and LUTS¹³. However, Partin et al. (1990) have suggested that serum PSA does not correlate with prostate volume in BPH¹⁷. This study also support a positive relationship between PSA and prostate volume (Table V). There are evidence to suggest that a reasonable linear correlation exists not only in patients with LUTS and clinical BPH, but also in a large series of patients with histologically proven BPH. These data are comparable to recent correlations by Bosch et al. and others, between PSA and prostate volume noted in patients with clinical BPH and LUTS, with the correlation coefficient (r) ranging from 0.37 to 0.58^{13,18,19}.

The moderately positive correlation of PSA and prostate volume observed in this study may be due to the dissimilarities between the databases. While previous studies have examined only patients with clinically diagnosed BPH, This study represents patients with histologically proven BPH. The observation in present study is in conformity with findings of other worker indicating the prevalence of clinical BPH and LUTS match the prevalence of histological BPH²⁰. The differences between histologically and clinically derived databases may indeed be explained by the diverse etiologies of LUTS in a given population.

Among many factors that contribute to prostate enlargement in BPH, the two most well known etiologic factors were aging and androgen²¹. Consistent with the theory that aging is an etiological factor of BPH, the observation made in this study showed a trend of increasing median PV with advancing age (Table VII). This increasing PV with aging is accompanied with an increasing trend of PSA with age (Table VI). This observation is consistent with other studies^{12,13,14,22,23}. The correlation between age and PV in present study is the weakest ($r=0.036$) which was similar to the result of the study done by Mosli et al. in Saudi men⁴. Consistent with results from other studies, PSA was positively correlated with age in present study. However, the correlation is the weakest ($r=0.12$) compared with results from other studies^{13,14,23,24}. Similar weak correlation was found in

some of the studies done to correlate PSA and age^{3,4,15}. The difference may be attributed to a selection bias. The age of our patients was not evenly distributed across the age range; about 40% of the patients were aged between 60-69 years. The uneven age distribution may have accounted for the difference in statistical analysis. There is a possibility that if we had enrolled more patients who were older in age the correlation between age and PSA might have become significant.

PSA has been suggested as an estimator for PV^{13,24}. This is supported by the fact that prostatic epithelial cells are responsible for circulating PSA, and several studies had documented a positive correlation between PSA and PV^{14,22,25}. Hochberg et al.²² in 2000 reported a correlation coefficient of 0.33-0.41 in a series of white patients. Similar studies done by Roehrborn et al. and others showed a positive significant correlation coefficient between PSA and PV^{13,14,23,24}. The findings of this showed a similar but moderately positive correlation with a correlation coefficient of ($r=0.679$, $p<0.01$) (Table V). The corresponding studies had a similar study design. The recent study by Putra et al. in 2016 suggested that difference between the degree of correlation of age with PV and age with PSA is probably attributable to the ethnic or geographical factors that may influence prostatic growth²⁶.

PSAD cut off value of 0.15 as reported by other workers was consistent with the result of this study. The indication of prostatic biopsy and chances of being malignancy beyond the level of 0.15 as reported in the previous studies^{7,27,28} is similar to this study. Mean PSAD was 0.10 and no case had PSAD more than 0.15.

There is paucity of report from this part of Nepal showing the relationship between PSA and PV and we couldn't find any report to show the efficacy of PSA at predicting more precise PV in Nepalese man. Because of the ability to obtain more accurate estimates of the PV without the help of more expensive, invasive diagnostic evaluations, PSA would give a more reasonable contribution in the proper management of patients with BPH.

The present findings suggest that PSA is a good indicator of prostatic volume, but there appears to be a weak relation among Age with PSA and prostate volume. The results of the analyses presented here characterize the average prostate volume given PSA level and age based on the clinical trial population studied. Caution should be exercised in attempting to predict precisely an individual patient's prostate volume given his age and PSA because the error associated with the predicted prostate volume for an individual patient is greater than that associated with the predicted average prostate volume. In addition, PSA and prostate volume measurements vary appreciably with use of different measurement techniques, each with its own measurement error and variability, and there are inherent differences among clinical

practice settings that also will increase the uncertainty of prediction for individual patients. The relationship may not be applicable to patients with different characteristics from those in the clinical trials, so that the graphs may not be appropriate for patient populations and clinical settings different from those studied. Nonetheless, these relationships are likely to be useful as an aid in approximating average prostate size for men with given levels of serum PSA and age. However, larger and multicentric studies is suggested which will give more useful result.

CONCLUSION

The mean PSA and prostate volume increased with advancing age, and the correlation between PSA and prostate volume estimated by TAUS in BPH as found to be statistically significant ($p < 0.05$). DRE underestimated the volume of prostate with a mean difference 21.97ml. The correlation of age of the patient with PSA and prostate volume are ($r=0.128$) and ($r=0.036$) respectively. The above value shows that both are statistically weekly positive but the association between age of patient and PSA seems to be higher in comparison to age of the patient and prostate volume.

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