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Does prostate specific antigen act as predictor in benign prostatic hyperplasia? An observational study

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***Abstract*---**Background: Benign prostatic hyperplasia (BPH) is associated with increase in prostate volume (PV) and increased epithelial production of prostate specific antigen (PSA). Both, PV and serum PSA, offers a non-invasive guide for identifying patients at high-risk of disease progression and making treatment decisions. Objective: To evaluate the serum PSA concentration and PV in cases of lower urinary tract symptoms (LUTS) secondary to BHP. Methods: Two hundred eligible symptomatic BHP patients with LUTS, were recruited into the study. All relevant history, clinical findings, International Prostate Symptom Score (IPSS) category and digital rectal examination grading were recorded. Blood levels of PSA, blood urea and serum creatinine were estimated followed by abdominal and trans-rectal ultrasonography (USG) to assess the size of prostate, PV, the lobes involved and residual urine volume. The results were compiled and analyzed using statistical software R version 3.6.3. Results: The mean age of the BHP patients was 68.22 ± 9.18 years, with 36% suffering from acute urinary retention (AUR). The mean IPSS, PV and PSA levels were 23.80 ± 5.67, 58.40 ± 18.56 cc and 4.61 ± 1.66 ng/mL, respectively. The mean blood urea and serum creatinine levels were 32.02 ± 6.05 mg/dL and 1.10 ± 0.28 mg/dL, respectively. A significant positive correlation was seen between age and PV (p=0.008), age and PSA (p=0.0002), PV and IPSS (p=0.0001), and PV and PSA (p=0.0001). AUR showed a significant positive association with PSA levels (p=0.016). Conclusion: Patients with serum PSA levels >4 ng/mL are at high risk of developing AUR. PV and serum PSA can be used as predictors of BHP progress (manifested as progressive LUTS and AUR) in Indian men.

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Introduction

Benign prostatic hyperplasia (BPH) is a benign neoplasm, commonly seen in ageing men, characterized by cellular proliferation of the epithelial and stromal elements of the prostate gland, or impaired programmed cell death resulting in cellular accumulation.[1,2] The incidence of BPH begins to rise in the 4th decade of life (30–40%) and increases almost linearly to 70–80% in those above 80 years of age. [3,4] Approximately 50% of those developing histological hyperplasia eventually manifest moderate-to-severe storage and voiding symptoms, collectively called the lower urinary tract symptoms (LUTS).[3,5] This is because the main problem arising out of BPH is obstruction of free flow of urine (due to its anatomic position near the urinary bladder), leading to back pressure effects on the urinary system. These changes lead to detrusor instability or decreased compliance as well as acute urinary retention (AUR). [1,2,4]

BHP is known to be associated with increase in prostate volume (PV), and increased production and leakage of prostate secretory proteins like prostate specific antigen (PSA) (mainly due to subclinical inflammation or microscopic foci of cellular atypia). [6,7] PSA is a glycoprotein secreted exclusively by prostatic epithelium, with a normal serum level of <4 ng/mL in healthy males. [8,9] The serum PSA level and PV of BPH patients has a log-linear relationship that also increases proportionally with age.[10] Serum PSA predicts, with reasonable clinical certainty, the presence of prostate greater than 30 cc.[9,10]

Both, PV and serum PSA, predict the clinical progression of the disease and the response to medical therapy in BPH patients, thus helping in selection of the regimen for medical treatment (alpha-blockers, 5-α reductase inhibitors).[6-12] PV is also useful in determining episodes of AUR as well as predicting the outcome and future need for BPH-related surgery, since rise in PV is associated with greater risk of pharmacotherapy failure.[5,9,13] Hence, evaluation of PV and serum PSA levels offers a non-invasive guide for identifying patients at high-risk of disease progression and making treatment decisions. With this background, the present study was designed with the aim to evaluate the serum PSA concentration and PV in cases of LUTS secondary to BHP.

Materials and Methods

This hospital-based, cross-sectional, observational clinical study was conducted at the Department of General Surgery, Private Medical College, Karad, Maharashtra, India from July 2015 to July 2017 (2 years), after obtaining ethical clearance from the Institutional Review Board. In a power-based approach, for an effect size of 0.408, confidence interval (CI) of 95%, power of 80%, and two-sided alternative, the minimum sample size required was found to be 190. For convenience, a sample size of 200 was selected for the study.

Two hundred male patients diagnosed with BPH with LUTS, including voiding symptoms (hesitancy, poor flow, intermittent stream, dribbling, poor bladder emptying, urine retention) and storage symptoms (increased frequency, nocturia, urgency, urge incontinence), were recruited into the study, after obtaining written informed consent from them. The study excluded patients with prostate carcinoma (known, or diagnosed during work up/on histopathology postoperatively), PSA levels >10 ng/mL (to reduce the likelihood of occult prostate cancer), acute prostatitis, previous history of prostate surgery, treatment with alpha-blocker and/or 5-alpha reductase inhibitors and need of additional procedures for associated clinical entities (like vesical calculus, bladder diverticula, renal failure, recurrent UTI).

All relevant history and clinical findings (from general, systemic and genitourinary examinations) were recorded for all the patients. Depending on the signs and symptoms, the patients were categorized as per the International Prostate Symptom Score (IPSS)[14,15] into mild, moderate and severe, and the treatment modality determined accordingly (medical with alpha-blocker and/or 5-alpha reductase inhibitors, or surgical trans-urethral resection of the prostate). Digital rectal examination (DRE) was done in all the cases to reveal the extent of prostate enlargement and the lobes involved, and accordingly divided into 3 grades - Grade I (prostate is just palpable and upper limit is easily reached), Grade II (prostate is well palpable and the upper limit is reached with difficulty), and Grade III (upper limit of the prostate cannot be reached).[16]

Biochemical estimations of serum levels of PSA, blood urea and serum creatinine were done in the Biochemistry Laboratory of the same hospital, including all routine blood investigations, using blood withdrawn from the patients through venipuncture, under aseptic precautions. PSA was measured by radioimmunoassay method. Abdominal and trans-rectal ultrasonography (USG) were done at the Department of Radiology at the same hospital, in order to sonographically assess the size of prostate, the lobes involved and residual urine volume.

Statistical analysis

Data was collected, compiled & analyzed using statistical software R version 3.6.3 and Microsoft Excel. Categorical variables were represented by frequency tables. Continuous variables were given in the mean ± SD form. Correlation was done to find the relationship between two quantitative variables. Categorical data were compared using chi-square test. Pearson's correlation test was used to study the correlation between continuous variables. p-value ≤0.05 was considered significant.

Results

The study consisted of 200 male patients, with a mean age of 68.22 ± 9.18 years. Table-1 and -2 present the frequency distribution and the average values of the various age and clinical parameters. Around 36% of the patients were found to suffer from acute urinary retention (AUR). Further, 68% of the participants had an IPSS between 20-35 (indicating severe disease) with a mean IPSS of 23.80 ±

5.67. The mean PV in this cohort was 58.40 ± 18.56 cc, with 64% of the patients having a PV >50 cc. Most patients (59%) had their PSA levels between 4-10 ng/mL, with a mean value of 4.61 ± 1.66 ng/mL. The mean blood urea and serum creatinine levels were 32.02 ± 6.05 mg/dL and 1.10 ± 0.28 mg/dL, respectively.

Table-3 summarizes the correlation between the various study parameters. Age showed a significant positive correlation with both, PV (p=0.008) and PSA (p=0.0002), implying that PV and PSA levels increased with an increase in age, and were lower in younger males. PV also showed a significant positive correlation with both, IPSS (p=0.0001) and PSA (p=0.0001), implying that IPSS and PSA levels increased with an increase in PV.

Table-4 depicts the association of AUR with other study parameters. AUR showed a significant positive association with PSA levels (p=0.016), implying that the PSA levels increased in the presence of AUR. The odds of AUR being present were 2.2 times more in cases with PSA >4 ng/mL than in those with PSA ≤4 ng/mL (with a significant p-value of 0.01 and CI of 1.14-4.32). However, AUR showed no significant association with age (p=0.078) and PV (p=0.845).

Discussion

This study was conducted to evaluate the serum PSA concentration and PV in cases of LUTS secondary to BHP. It was found that serum PSA levels >4.79ng/mL and PV >59.87 cc, together with age >68 years and severe IPSS grading, were strongly associated with an increased risk of progression of LUTS and AUR in BHP patients.

The results of the present study resonate with those of various other researches. The age distribution seen is mirrored in the findings of Deori et al, Mohamed et al and McConnell et al (mean age 64.1 years, 69.4 years and 64 years, respectively).[17-19] The mean serum PVA concentration is also similar to that found by Milonas et al (4.96 ng/mL) and Vesely et al (3.9 ± 4.2 ng/mL).[20,21] The mean PV is akin to the findings of McConnell et al (55cc) and Milonas et al (58.1 cc).[19,20] Milanos et al (23.57) and Mohamed et al (27.5) also found the mean IPSS values closer to the current study.[18,20]

The significant positive correlation of age with PV and PSA was also found to be in concordance with the studies of Deori et al (r=0.34 and p=0.03 for age/PV; r=0.49 and p=0.001 for age/PSA).[17] Chung et al also concluded that the log serum PSA level and log PV were linearly related to age, such that the increase in log PSA and log PV per year of age was estimated to be 0.0307 and 0.0117, respectively, corresponding to a 35.9% and 12.4% increase in serum PSA and PV with each decade of life, respectively.[5] This implies that PV and PSA levels increased with an increase in age, and were lower in younger males.

Roehrborn et al noted a strong log-linear relationship between PV and serum PSA, in line with the present study.[9] A similar relationship between PV and PSA was suggested by Deori et al (r=0.93, p<0.001).[17] Vesely et al, too, reported that PV correlated positively with PSA (r=0.54, p<0.0001).[21] Chung et al identified that PSA had good predictive value for various PV thresholds.[5] Mochtar et al also

reported that the PSA threshold predicting PVs of > 30 and 40 mL were 2.0 and 2.5 ng/mL, respectively, while it was around 4ng/mL in the present study.[22] A significant relationship between PV and IPSS was confirmed by Vesely et al and Gyasi-Sarpong et al ($p<0.05$), who deduced that each unit increase of age, PSA and PV influenced 15.6%, 2.3% and 4.8% change in the symptom score, respectively.[21,23]

The significant association of AUR with PSA levels also found resonance in the studies of Mohamed et al and Milanos et al.[18,20] Laniadoet et al studied 302 BHP patients with LUTS and found that PSA was significantly associated with bladder outlet obstruction ($p< 0.001$; $r^2=0.07$). If the PSA was >4 ng/mL, mild or definite bladder outlet obstruction was likely (89%), whereas if the PSA was <2 ng/ mL, there was about a one-third chance each of no, mild and definite bladder outlet obstruction.[24] Roehrborn et al also identified serum PSA and PV as significant predictors of AUR and the subsequent need for BPH-related surgery ($p<0.05$), while the present study did not find this association to be significant with PV.[9] These studies suggest that the opportunity to reduce the risk of AUR and invasive surgery in men with LUTS, bladder outlet obstruction and AUR is now possible from assessing their PSA levels.[5,9,25]

Symptomatic BPH does not progress in all patients; therefore, progression modifying intervention is not always warranted. To tailor therapeutic and or preventive approaches appropriately, it is valuable to differentiate patients at high risk of progression from those at lower risk. PV and serum PSA could be useful in predicting this disease progression in BPH with LUTS, when considered in conjunction with other clinical indicators. Hence, patients with raised PV and PSA may benefit from close monitoring and may be good candidates for pharmacotherapy to arrest the disease process. On the other hand, patients with a small prostate gland, low serum PSA, and bothersome LUTS may benefit most from symptomatic treatment, but should be periodically monitored to assess changes in clinical status. The strong predictive utility of PV and PSA combined with the fact that they, unlike other clinical markers of BPH status, can be accurately, non-invasively and easily measured, render them as important tools for optimizing outcomes for BPH patients.[26]

Thus, the goals of BPH treatment could include reduction of PV and PSA levels, which would reflect relieving of LUTS. Serum PV and PSA have been found to be reduced by 40-50% after 3-6 months of BHP treatment with finasteride.[27] Therefore, this study establishes PV and serum PSA concentrations as predictive markers in cases of LUTS secondary to BHP. However, this study has its limitations in using a single center, observational approach with a limited sample size. Also, a limitation of PSA as a tumour marker is demonstrated in the substantial overlap in its values between benign and malignant prostatic diseases.[28] Hence, multicentric, prospective studies with a larger sample size and longer follow-up periods are encouraged to validate the results and more definitively establish the role of PV and PSA as predictors of the severity, outcome and management of BPH.

Conclusion

PV and serum PSA can be used as predictors of BHP progress (manifested as progressive LUTS and AUR) with sufficient accuracy, to be useful for therapeutic, especially medical, management in Indian men. Patients with serum PSA levels >4 ng/mL are at high risk of developing AUR, and hence, are indicated for initiation of pharmacotherapy.

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Table Legends

Table 1: Frequency distribution of the various study parameters
Table 2: Distribution of the average values of the various study parameters
Table 3: Correlation between the various study parameters
Table 4: Association of acute urinary retention with other parameters

Table 1
Frequency distribution of the various study parameters

Parameters	**Frequency (n=200) and Percentage**
Age (years)	
<60	30 (15)
60-69	76 (38)
70-79	70 (35)
≥80	24 (12)
Acute urinary retention (AUR)	
Present	72 (36)
Absent	128 (64)
International Prostate Symptom Score (IPSS)	
0-7	0 (0)
8-20	64 (32)
20-35	136 (68)
Ultrasonographic prostate volume (USG - PV) cc	
21-30	19 (9.5)
31-50	53 (26.5)
51-80	100 (50)
>80	28 (14)
Prostate specific antigen (PSA) ng/mL	
0-2	16 (8)
2.01-4	66 (33)
4.01-10	118 (59)
>10	0 (0)

Table 2
Distribution of the average values of the various study parameters

Parameter	Mean ± SD	Median	Minimum	Maximum
International Prostate Symptom Score (IPSS)	23.80 ± 5.67	24.00	12.00	33.00
Grades of prostatic enlargement	2.46 ± 0.70	3.00	1.00	4.00
Hemoglobin (g%)	13.51 ± 1.91	13.50	9.10	19.40
Blood urea (mg/dL)	32.02 ± 6.05	32.00	20.00	49.00
Serum creatinine (mg/dL)	1.10 ± 0.28	1.10	0.00	2.30
Prostate specific antigen (ng/mL)	4.61 ± 1.66	4.65	1.30	8.80
Prostate volume (cc)	58.40 ± 18.56	60.00	27.00	110.00
Urine analysis - Red blood cells per high power field (cells/hpf)	0.64 ± 1.22	0.00	0.00	5.00
Urine analysis - Pus cells per high power field (cells/hpf)	3.16 ± 2.64	3.00	0.00	9.00

Table 3
Correlation between the various study parameters

Parameter 1	Parameter 2	Correlation coefficient (r)	p-value
Age	Prostate specific antigen	0.257	0.0002*
	Prostate volume	0.186	0.008*
Prostate volume	International Prostate Symptom Score (IPSS)	0.416	0.0001*
	Prostate specific antigen	0.815	0.0001*

***:** Significant

Table 4
Association of acute urinary retention with other parameters

Parameters	Acute urinary retention		p-value
	Present	Absent	
Age (years)			
<80	63	121	0.078
≥80	9	7	
Prostate specific antigen (ng/mL)			
≤4	21	61	0.016*
>4	51	67	
Prostate volume (cc)			
≤50	26	48	0.845
>50	46	80	

*: Significant