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Original Article

Biochemistry Section

Role of Prostate-Specific Antigen (PSA) in Patients with Benign Prostate Hyperplasia

PRIYA DUVEDI[1], HARJINDER SINGH[2], GURDEEP KAUR BEDI[3], MANINDER KAUR[4]

ABSTRACT

Introduction: Prostate-Specific Antigen (PSA) is an organ specific rather than cancer specific hormone. It is a single chain glycoprotein produced by epithelial cells of the prostate gland. Role of PSA in carcinoma of prostate is well defined but its role in other diseases of prostate is not very clear. Increased PSA levels are not essentially associated with prostate cancer, but can also be elevated in conditions other than cancerous lesions, such as prostate inflammation, bacterial prostatitis, Benign Prostate Hyperplasia (BPH) and Urinary Tract Infection (UTI). BPH is the most common benign tumours in men with prevalence ranging from 50% for men in their 50s to 90% for men in their 90s.

Aim: To find the relation of serum PSA levels with age, Prostate Volume (PV) and PSA density in BPH patients.

Materials and Methods: The present hospital-based, cross-sectional study was conducted on 162 BPH patients who consulted to the Urology Department of Rajindra Hospital, Patiala and were prescribed to undergo serum PSA evaluation. The serum PSA levels of these patients were estimated by the Enzyme-Linked Immunosorbent Assay (ELISA). Routine investigations included Complete Blood Count (CBC), serum urea, serum creatinine, Fasting Blood Glucose (FBG), serum PSA and ultrasonography of the kidneys, ureter, bladder and prostate. Correlations were evaluated using Pearson correlation coefficient. All the statistical graphs were plotted using Microsoft Excel 2009. The results p-value <0.001 were considered statistically significant.

Results: No significant association (p=0.445) between serum PSA and age groups of BPH patients was observed. A significant correlation was observed between serum PSA and PV (r=0.59, p-value <0.001) and PSA density (r=0.56, p-value <0.001) in BPH patients.

Conclusion: The present study indicates that there was no association between age specific reference range and serum PSA levels. And PV and PSA density should be considered while interpreting PSA level to improve the diagnostic parameters.

Keywords: Benign prostatic hyperplasia, Prostate specific antigen density, Prostate volume, Urinary tract infection

INTRODUCTION

PSA is a 33-kD (mol.wt: 28,430) protein consisting of a single-chain glycoprotein of 237 amino acid residues, four carbohydrate side-chains, and multiple disulphide bonds. It is a serine protease of kallikrein family [1]. PSA screening test is used for the measurement of prostate growth and detection of early malignancy along with other diagnostic parameters (Ultrasonography, International Prostate Symptom Score) to confirm the diagnosis of prostate diseases [2].

PSA is solely produced in the epithelial cells of the prostate gland. Initially, the proenzyme (proPSA) is secreted by the secretory cells. In the lumen of the prostate, the proPSA is proteolyzed due to removal of pro-peptide group and the structure thus formed, is measureable in blood test. PSA can be increased due to growth of prostatic tissue, inflammation of the prostate, UTI, trauma to the perineal area and male ejaculation [3].

Abnormally higher PSA level can be signal indicating the development of cancer in the prostate gland. However, high levels of PSA can also be found in other conditions that are noncancerous [2]. BPH is a condition in which the prostate gland is enlarged. The development of BPH requires an intact androgen signaling pathway, but androgens alone do not cause the disease. In the absence of cellular proliferation, due to an imbalance between cell death and proliferation, cell accumulates in both the epithelial and stromal compartments leading to hyperplasia. Despite the name 'stromal disease', the site of initiation remains unclear. In BPH, inflammation plays a crucial role in the pathogenesis of the disease via cytokines that promotes cell growth or leads to smooth muscle contraction [4].

Various studies have demonstrated that PSA increases with the age and size of the prostate gland [5-7]. To test these findings, the present study was undertaken to find the association of PSA levels with age, PV and PSA density in benign prostatic hyperplasia.

MATERIALS AND METHODS

The present hospital-based, cross-sectional study was conducted in the Department of Biochemistry, Government Medical College, Patiala, Punjab, India. About 162 BPH patients consulted to the Urology Department of Rajindra Hospital, Patiala from December 2014 to November 2015 and were required to undergo serum PSA evaluation. Informed written consent was obtained from all the enrolled patients after explaining them the details of the study in their own language. The present study was approved by the institutional ethical committee (Bio/14/546).

Patients' selection was based on exclusion-inclusion criteria.

Inclusion criteria: Patients of more than 50 years of age who were presenting with Lower Urinary Tract Symptoms (LUTS).

Exclusion criteria: Patients below the age of 50 years and patients with carcinoma of the prostate. Patients on any drugs that effect on the level of serum PSA i.e., (5-α-reductase inhibitors) or the history of diabetes, tuberculosis, urinary tract infection and hypertension were also excluded from the study.

Taking all aseptic and antiseptic precautions, 5 mL of blood (EDTA and plain vial) sample was drawn from the median cubital vein. Overnight fasting samples were used for all the investigations. Blood was allowed to clot and samples were centrifuged at 2200-2500 rpm (revolution per minute) for 15 minutes at room temperature. The vials containing separated serum sample were labeled properly and stored at -20°C, if estimations were not done within eight hours of collection of the blood. All the estimations

were carried out within 24 hours of collection of blood samples.

Methods of evaluation: Complete Blood Count (CBC) was done by auto analyser (Transasia Bio-medicals Ltd.,) [8]. Total Serum Protein (TSP) was estimated by the Biuret method, FBG by glucose oxidase method, serum urea by modified Berthelot method, serum creatinine by Brod and Sirota method by using semi-auto analyser [9-12]. Glucose and creatinine were measured at 505 nm. Total protein was at 546 nm and urea was measured at 578 nm. ERBA diagnostics Manheim marketed Transasia Bio-Medicals Ltd., (HP) glucose (979852), urea (120214), creatinine (120246), and total protein (120206) kits were used. The serum PSA levels of these patients were estimated through Sandwich ELISA (enzyme linked immunosorbent assay) by ELISA PSA kit (Cal Biotech Company, PS235T) [13]. Ultrasonography was done for all the patients. Prostate volume was calculated by ellipsoid formula (π/6×height×length×width). Height, length and width of the prostate were measured by transabdominal ultrasonography. Transrectal examination was done to rule out any suspicious lesion in patients with serum PSA >4 ng/mL. PSA density was calculated by PSA/PV.

STATISTICAL ANALYSIS

Data was expressed as Mean±SD. The data was analysed statistically. ANOVA test was used to determine the assocation of PSA with age. Correlations were evaluated using Pearson correlation coefficient. Statistical analysis was done by using GraphPad InStat version 3.00. All the statistical graphs were plotted using Microsoft Excel 2009. p-value <0.001 was considered statistically significant.

RESULTS

Routine investigations (CBC, TSP, FBG, serum urea and serum creatinine) were within normal limit in this study and therefore no statistical test was done for these parameters. The maximum number of patients was in 60-69 years age group with PSA ranging from 0.48-12.06 ng/mL and mean PSA was 3.32±2.67 ng/mL. The changes in PSA levels among different age groups were analysed. No significant difference between the groups on account of PSA parameter (p=0.445) (r= -0.05) was observed [Table/Fig-1].

In BPH patients the mean PSA was 17.85±13.80 ng/mL and the mean PV was 37.20±32.78 mL. The p-value was <0.001 (r=0.59) which was statistically highly significant.

In BPH patients the mean PSA was 17.85±13.80 ng/mL and the mean PSA density was 0.12±0.04 ng/mlcc. The p-value was <0.001 (r=0.56) which was statistically significant.

DISCUSSION

Present study found that age was not associated with PSA. PSA did not increase or decrease with respect to age strata in BPH patients. In our study highest range of PSA (0.48-12.06 ng/mL) was in 60-69 years age group and lowest range of PSA (2.07-5.6 ng/mL) was in 90-93 years age group. The maximum numbers of patients were in the age group 60-69 years which was similar to the study of Deori R et al., [7]. In contrast to our study, Mosli HA et al., Casey RG et al., and Deori Ret al., demonstrated that age was significantly (p-value <0.001) correlated with PSA and PSA levels increased with age [5-7]. According to Casey RG et al., age specific reference ranges were introduced to increase the specificity and sensitivity of a PSA. According to their study, increased PSA reflect the increase prevalence of pathology rather than a physiological process of ageing [6]. Deori R et al., demonstrated that BPH is age related and the prevalence increases with increasing age [7]. The risk of prostate cancer is high when the total PSA is more than 10 ng/mL and conversely low in patients with a total PSA is less than 4 ng/mL. The range of 4 to 10 ng/mL represents the 'grey zone' [14]. The age specific range of serum PSA levels makes it more efficient tumour marker for detection of clinical cancer in elderly men. In BPH patients, the size of prostate increases which ultimately leads to elevated serum PSA levels. Due to lack of well-documented sensitivity and specificity data,

Authors	Age groups (in yrs)	Range of PSA (ng/mL)	p-value	r-value
Mosli HA et al., and Abdel-Meguid TA et al., [5]	40-49	0.18-4.2	<0.001*	0.32
	50-59	0.43-5.6		
	60-69	0.27-10		
	70-79	0.34-10		
	80-89	0.4-3.1		
Casey RG et al., [6]	30-39	0.71-1.65	0.001	NA
	40-49	0.73-2.17		
	50-59	0.88-2.63		
	60-69	1.01-3.25		
	70-89	1.43-4.96		
Deori R et al., [7]	Below 50	0.39-1.26	0.001	0.49
	50-59	0.42-2.80		
	60-69	0.28-4.61		
	70-79	2.18-8.76		
	80-89	1.30-2.54		
Present study, 2015	50-59	0.57-10.10	0.445	-0.05
	60-69	0.48-12.06		
	70-79	0.6-11.20		
	80-89	0.11-11.73		
	90-93	2.07-5.6		

[Table/Fig-2]: Correlation of PSA with age groups in various studies [5-7].
*p<0.001 statistically significant. PSA: Prostate specific antigen

several investigations were undertaken to study the ability of PSA to differentiate between benign processes [Table/Fig-2] [5-7].

PV levels fluctuate significantly throughout man's lifetime, and in the course of different prostatic diseases including BPH. The mean PSA in the present study was 17.85±13.80 ng/mL and the mean PV was 37.20±32.07 mL [Table/Fig-3] [5,7,15,16]. PSA and PV were significantly (p-value <0.001) associated which was almost similar to other studies. Mosli HA et al., demonstrated PV and PSA are key predictors of clinical progression, response to medical treatment and prostate-related events in patients. Levels of PV and PSA were highly variable among different ages. Age was found to be significant but had weak positive correlations with PV and PSA. Only PSA and PV showed a significant and strong positive correlation (r=0.44) [5]. Park DS et al., also reported that PSA levels not only had a strong correlation with PV, but they were also a strong predictor of PV in a large scale Korean screening cohort

Age groups (in yrs)	Total no. of patients	Range of PSA (ng/mL)	No. of cases in each group			Mean±S.D (ng/mL)	f value	p-value
			PSA<4 (ng/mL)	PSA (4-10) (ng/mL)	PSA>10 (ng/mL)			
50-59	31	0.57-10.10	23	7	1	3.07±2.54	0.935	0.445
60-69	70	0.48-12.06	48	21	1	3.32±2.67		
70-79	50	0.6-11.20	34	15	1	3.21±2.24		
80-89	8	0.11-11.73	3	4	1	5.00±4.33		
90 – 93	3	2.07-5.6	2	1	0	3.25±1.82		

[Table/Fig-1]: Correlation of PSA in BPH patients among different age groups.
Normal value of PSA <4 ng/mL. PSA: Prostate specific antigen; ANOVA test was used to calculate f and p-value.*p-value <0.001, statistical significant

Name of the author	Mean±S.D of PSA (ng/mL)	Mean±S.D of PV (mL)	p-value	r-value
Mosli HA et al., and Abdel-Meguid TA et al., [5]	17.04±12.05	35.17±30.01	<0.001*	0.44
Park DS et al., [15]	1.49±1.50	29.9±14.2	<0.001*	0.26
Putra IB et al., [16]	4.13±2.62	47.58±21.33	<0.001*	NA
Deori R et al., [7]	2.3±1.5	43.0±22.4	<0.001*	0.93
Present study, 2015	17.85±13.80	37.20±32.07	<0.001*	0.59

[Table/Fig-3]: Correlation of PSA with prostate volume (PV) in various studies [5,7,15,16].
*p<0.001 statistically significant. PV: Prostate Volume; PSA: Prostate specific antigen

[15]. PSA is an organ-specific biomarker of the prostate that increases on disruption of the normal anatomic prostatic tissue due to malignant or benign prostatic diseases. In Indonesian men with BPH, both PV and PSA increased with age and PV was found to be significantly correlated with PSA [16]. In a study by Deori R et al., changes in PV and serum PSA vary among different ages. PSA and PV demonstrated a significant and strong positive correlation (r=0.93) [7]. The mean PSA in our study was more than the two studies (Putra IB et al., and Deori R et al.,) may be due to sample size of the study population.

In the present study, PSA and PSA density was significantly correlated (p-value <0.001) in BPH patients which was similar to other studies [Table/Fig-4] [17-19]. PSA density is an accurate predictor for adverse pathology prediction. The accuracy and potential improvement in sensitivity and specificity associated with the use of PSA density are limited by several factors. PSA density is able to better reflect biologic differences between prostate cancer and BPH, enhancing diagnostic discriminative power for the population with PSA levels in the 'grey zone' [17]. PSA density is a derivative measure that involves dividing the serum PSA specificity by adjusting for that component of the serum PSA that may arise from benign elements. The largest determinant of prostate size is the transition zone, with expansion resulting from the development of benign prostatic hypertrophy [18]. Kuppusamy S et al., found that PSA density value improves the diagnostic performance of total PSA level, especially in the range of 4.01 to 30.00 ng/mL as the incidence and cancer detection was quite low. An increased cut-off value

Name of the author	Mean±S.D of PSA (ng/mL)	Mean±S.D of PSA density (ng/mlcc)	p-value
Sfoungaristos S and Perimenis P, 2012 [17]	13.26±12.69	0.38±0.33	0.001
Yang T et al, 2017 [18]	14.71±16.57	0.28±0.31	<0.001*
Kuppusamy S et al, 2018 [19]	9.35±5.26	0.23±0.15	0.001
Present study, 2015	17.85±13.80	0.12±0.04	0.001

[Table/Fig-4]: Assocation of PSA with PSA density in various studies [17-19].
*p<0.001 statistically significant. PSA: Prostate specific antigen

PSA density (>0.19) and Digital Rectal Examination (DRE) eliminates the need of multiple biopsies and helps in diagnosis of cancer [19].

In our study, no correlation was observed between serum PSA and advancing age in BPH patients, but prostate size was found to be significantly correlated with serum PSA. Therefore, before interpreting PSA values, prostate size and PSA density should be taken into consideration.

LIMITATION

Further studies with larger sample size and age-matched control group are required to validate our findings and to improve the diagnostic performance of PSA while examining the relationship between prostate volume, PSA density and patient age.

CONCLUSION

The age of BPH patients was not correlated with PSA levels. PSA did not increase or decrease among different age groups in this study. Therefore the age of the patients should not be taken into consideration while interpreting PSA levels. PSA density increases the diagnostic value of PSA. PSA and prostate volume were significantly correlated in BPH patients. Increase in prostate volume is associated with increased serum PSA level. PSA levels depicts approximate prostate volume, and may have clinical potential in the management of patients with BPH.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate, Department of Biochemistry, Government Medical College, Patiala, Punjab, India.
2. Professor and Head, Department of Urology, Government Medical College, Patiala, Punjab, India.
3. Associate Professor, Department of Biochemistry, Government Medical College, Patiala, Punjab, India.
4. Professor and Head, Department of Biochemistry, Government Medical College, Patiala, Punjab, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Harjinder Singh,
Professor and Head, Department of Urology, Government Medical College, Patiala-147001, Punjab, India.
E-mail: dr.hsingh.uro@gmail.com

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