Original Research Paper

Establishment and correlation of age specific reference range of psa and psa density in patients of benign prostatic hyperplasia

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Abstract:

Prostate specific antigen (PSA) is a 34-kDa serine protease that is produced by both benign and malignant prostatic epithelial cells. PSA has assumed an increasing role in the diagnosis and management of prostate cancer. Both benign and malignant prostate tissue elaborates PSA; therefore the possibility exists for benign processes such as prostatic hyperplasia.

Aims and objectives:

To estimate serum PSA in 100 patients of Benign Prostatic Hyperplasia (BPH) in various age groups. To estimate the serum PSA in 50 healthy age– matched males. To correlate serum PSA levels in different age groups with volume of prostate gland and prostate density in above 150 cases.

Material and Methods:

The present hospital based observational and analytical study was conducted in the Department of Biochemistry, Government Medical College, Patiala in collaboration with the Department of Urology Rajindra Hospital, Patiala on 100 patients reporting to Department of Urology with diagnosed BPH and presenting with Lower Urinary Tract Symptoms (LUTS), Rajindra Hospital, Patiala.

Results and Conclusion :

With increase in age there was increase in size (volume) of the prostate. PSA values were also increased in patients of BPH. An inverse correlation of PSA with PSAdensity was observed in patients of BPH because volume /size of the prostate was increased with increasing age.

Key Words:

Prostate Specific Antigen (PSA), Prostate Specific Antigen Density (PSAD), Benign Prostatic Hyperplasia (BPH), Lower Urinary Tract Symptoms (LUTS)

Introduction

Benign prostatic Hyperplasia (BPH) is a disease in which the **prostate gland enlarges beyond the normal volume of 20-30 mL as part of the aging process, thus it is common among older men**,[1]BPH causes bladder outlet obstruction (BOO) among affected men and the several symptoms of BPH, which include lower urinary tract symptoms (LUTS), can adversely affect quality of life (QoL). BPH symptoms are classified as storage or voiding. Storage symptoms include urinary frequency, urgency, urgency incontinence, and voiding at night, named nocturia, which can lead to erectile dysfunction (ED)**.**[2] BPH is historically supposed to be a consequence of the ageing process and the abolition of the negative impact of an enlarged prostate in males should be done with the help of medical or surgical treatment. In the last decade, this view has been challenged. BPH-lower urinary tract symptoms (LUTS) should not be considered as an inevitable disease of older men but part of the ageing process which can be treated.[3]

Lower Urinary Tract Symptoms

Lower urinary tract symptoms (LUTS) are categorized into three groups including voiding symptoms (slow stream ,splitting / spraying, intermittency, hesitancy ,straining and terminal dribble), storage symptoms(increased daytime frequency , nocturia , urgency and urinary incontinence) and post micturition symptoms (feeling of incomplete emptying and post micturition dribble)[4]

The symptoms become increasingly common with age, impacting health related quality of life [5]

In the clinical practice guidelines for the diagnosis and treatment of BPH issued by the Agency For Health Care Policy And Research (AHCPR)[6], it was recommended that symptoms of BPH be taken into account

in making treatment recommendations based on a standard symptom questionnaire known as International Prostatic Symptom Score (IPSS)and Quality Of Life Score .

Prostate Specific Antigen

PSA is produced as a proenzyme (proPSA) by the secretory cells that line the prostate glands (acini) and secreted into the lumen, where the propeptide is removed to generate active PSA. The active PSA can then undergo proteolysis to generate inactive PSA, of which a small portion then enters the bloodstream and circulates in an unbound state (free PSA). Alternatively, active PSA can diffuse directly into the circulation where it is rapidly bound by protease inhibitors, including alpha-1-antichymotrypsin (ACT) and alpha-2-macroglobulin [7]

Prostate specific antigen (PSA) is a 34-kDa serine protease that is produced by both benign and malignant prostatic epithelial cells. The physiological function of this enzyme is lysis of the seminal coagulum. In the past decade, PSA has assumed an increasing role in the diagnosis and management of prostate cancer. Both benign and malignant prostate tissue elaborates PSA, the possibility exists for benign processes such as prostatic hyperplasia (BPH), as well as premalignant changes such as prostatic intraepithelial neoplasia (PIN), to interfere with the accuracy of PSA in the detection and staging of prostatic carcinoma.[8]

Factors affecting Normal PSA levels

1. **Age:** In men without prostate cancer, serum PSA reflects the amount of glandular epithelium, which in turn reflects prostate size. **Thus as prostate size increases with increasing age, the PSA concentration also rises; it increases at a faster rate in elderly men**. The normal upper limit of PSA, 4.0, is not always accurate for all ages[9].

   PSA may increase with prostatic hyperplasia; therefore, one would expect that the PSA level should be lower in younger men. The currently used single cut-ofi of 4.0ng/mL underestimates the cancer risk in younger patients and may also result in unnecessary biopsies in older men with benign prostatic hyperplasia.[10, 11]

   As a result, different normal reference ranges may be appropriate based upon a man's age.
2. Body Weight: Weight appears to be associated with PSA concentration. In population-based studies of men without prostate cancer, increasing body mass index (BMI) is associated with a lower mean PSA concentration(BMI= weight in kg/height in m^2) [12].
3. Digital rectal examination (DRE): has minimal effect on PSA levels, leading to transient elevations of only 0.26 to 0.4 ng/mL, and PSA can be measured immediately after DRE.[9]
4. Ejaculation: can increase PSA levels by up to 0.8 ng/ mL, though levels return to normal within 48 hrs .[9]
5. Bacterial prostatitis: may elevate PSA levels, but they generally return to baseline 6 to 8 weeks after symptoms resolve. Asymptomatic prostatic inflammation can also elevate PSA level, but this diagnosis is made on biopsy and so cannot generally be used to defer screening tests.[9]
6. Prostate biopsy : may elevate PSA levels by a median of 7.9 ng/mL within four to 24 h following the procedure. Levels will remain elevated for 2 to 4 weeks. Similarly, a transurethral resection of the prostate **(TURP)** can elevate PSA levels by a median of 5.9 ng/mL. Levels will remain elevated for a median time of approximately 3 weeks. A screening PSA test should not be performed for at least 6 weeks following either of these procedures.[9]
7. Acute urinary retention: may elevate PSA levels, but the levels can be expected to decrease by 50% within 1 or 2 days following resolution. A screening PSA test should not be performed for at least 2 weeks following an episode of acute urinary retention.[9]

   PSA Density: The use of PSA density is based on the premises that a large benign adenoma may contribute to elevated PSA levels even in the absence of cancer. To compensate for BPH and prostate size, transrectal ultrasound (TRUS) has been used to measure prostate volume. **Serum PSA is then divided by prostate volume to give a PSA density, with higher PSA density values (greater than 0.15 ng/mL) being more suggestive of prostate cancer while lower values are more suggestive of benign**

hypertrophy. This seemed a promising concept, subsequent work has shown up limitations of this measurement, while an early study suggested that PSA density was a promising method for distinguishing patients with benign and malignant prostate disease.

The most common cause of an elevated PSA level in the absence of cancer is benign enlargement of the prostate. The concept of PSA density was proposed initially as a means of adjusting for the benign prostate hypertrophy (BPH) component by dividing the serum PSA by the prostate volume (usually estimated by TRUS). Initially, a cut-off ratio of 0.15 was proposed, with a ratio of >0.15 indicative of cancer and <0.15 more likely benign[13]

Its use is relatively limited currently but may provide support for avoiding a repeat biopsy in a patient with a palpable normal prostate and a PSA between 4-10 ng/mL.[14]

Aims and Objectives

To estimate serum PSA in 100 patients of Benign Prostatic Hyperplasia (BPH) in various age groups. To estimate the serum PSA in 50 healthy age– matched males. To correlate serum PSA levels in different age groups with volume of prostate gland and prostate density in above 150 cases.

Material and Methods

The present hospital based observational and analytical study was conducted in the Department of Biochemistry, Government Medical College, Patiala in collaboration with the Department of Urology Rajindra Hospital, Patiala on 100 patients reporting to Department of Urology with diagnosed BPH and presenting with Lower Urinary Tract Symptoms, Rajindra Hospital, Patiala.

Inclusion criteria

- Patients of BPH presenting with **Lower urinary tract symptoms (LUTS)**
- Healthy males of various age groups : 41-50 years , 51-60 years,61-70 years, 71-80 years, 81-90 years

Exclusion criteria

- Patients suffering from Urinary tract infection
- Patients of prostatitis
- Patients having stricture urethra
- Clinically diagnosed cases of prostate cancer

Results

There were 20 patients of age groups 41-50 years, 19 patients of age group 51-60 years, 21 patients of age group 61-70 years, 21 patients of age group 71-80 years and 19 patients of age group 81-90 years (Table-1). 52% patients were having PSA<4 ng/ml, 39% were having PSA (4-10) ng/ml and 9% were having PSA>10 ng/ml.

Symptoms with which the patients presented were frequency, nocturia, urgency, straining, weak stream, intermittency, and incomplete emptying. Out of which frequency, nocturia and incomplete emptying were the predominant symptoms.

Age Wise Distribution of Patients in Study Group (BPH) (Table-1)

Age (in yrs)	Study Group (BPH)			
	Total no. of patients	No. of cases in each group		
		PSA<4 (ng/ml)	PSA(4-10) (ng/ml)	PSA>10 (ng/ml)
41-50	20	**19**	0	1
51-60	19	12	5	2
61-70	21	9	9	**3**
71-80	21	10	8	**3**
81-90	19	2	**17**	0
Total	**100**	52	39	9

Hence maximum value of PSA (4-10ng/ml) was observed in age group from 81-90 years.

Reference Range of PSA:

Reference Range and Mean Value of PSA in different Age groups (Table-2)

Age groups (in yrs)	Total no. of patients	Range of PSA (ng/ml)	No. of cases in each group			Mean±S.D (ng/ml)	h value	p value	Significance
			PSA<4 (ng/ml)	PSA (4-10) (ng/ml)	PSA>10 (ng/ml)				
41-50	20	0.20-1.12	19	0	1	3.05±4.21	79.173	<0.001	HS
51-60	19	0.9-2.12	12	5	2	6.64±11.64			
61-70	21	1.3-3.31	9	9	3	**9.17±13.45**			
71-80	21	2.2-4.37	10	8	3	8.63±13.93			
81-90	19	3.18-7.32	2	17	0	5.80±1.78			

The maximum mean value of PSA was 9.17±13.45 in the age group 61-70 years. It was observed that with the increase in age group the range of PSA was increasing and it was highly significant statistically.

Prostate Specific Antigen Density (PSAD)

Mean Value of PSAD in different Age groups (Table-3)

Age groups (in yrs)	Total no. of patients	Range of PSAD	Mean±S.D	t value	p value	Significance
41-50	20	0.05-0.12	**0.09±0.12**	2.372	0.004	s
51-60	19	0.07-0.28	0.17±0.29			
61-70	21	0.03-0.07	0.26±0.43			
71-80	21	0.02-0.08	0.25±0.46			
81-90	19	0.12-0.38	0.12±0.06			

The Minimum value of PSAD was 0.09±0.12 in the age group 41-50 years.It was observed that as the age increases there is variation in the range of PSA Density and PSA Density decreases and it was significant statistically.

Relation of PSA and PSAD in patients of BPH (Table-4)

Study group	Parameter	Mean ± S.D (ng/ml) (gms)	r value	p value	Significance
BPH	PSA	6.71 ±10.45	0.800	<0.001	HS
	PSAD	0.18± 0.32			

It was observed that there is a negative correlation between PSA and PSA densityi.e. with the **increase in PSA value there was decrease in prostate specific antigen density (PSAD) value in patients of BPH. This was highly significant statistically.**

Discussion: In men without prostate cancer, serum PSA reflects the amount of glandular epithelium, which in turn reflects prostate size.[1]

The serum PSA concentration was directly correlated with patient age and prostate volume, the latter of which is directly related to age. Thus, rather than relying on a single specific range for men of all age groups, it was appropriate to have age – specific reference ranges. These age - specific reference ranges have the potential to make serum PSA a more discriminating tumor marker for detecting clinically significant cancers in older men and to find more potentially curable cancers in younger men.[15]

Our study showed that maximum number of patients belonged to 41-50 years of age group having PSA<4 ng/ml. The range of PSA in different age groups was observed as follows:

Age (in Years)	Range (ng/ml)
41-50	0.20-1.12
51-60	0.9-2.12
61-70	1.3-3.31
71-80	2.2-4.37
81-90	**3.18-7.32**

The age specific ranges have the potential to make serum PSA a more discriminating tumor marker for detecting clinically significant cancers in older men. **Only PSA value has no relation with the age, if the person is having normal prostate size, but when the person suffers from BPH, Prostatitis, Prostate Cancer then size of prostate gets increased which ultimately leads to increased serum PSA levels.**

Present study found that age had a positive correlation with PSA **i.e. with increase in age**, **PSA value was also increased**. This is similar to the study of **RahimifarS. ,**[16]which also found that age was correlated with PSA.

Serum PSA is divided by prostate volume to give a PSA density, with higher PSA density values (greater than 0.15 ng/mL) being more suggestive of prostate cancer while **lower PSA Density values are more suggestive of Benign Prostatic Hypertrophy**. PSAD estimates the PSA secreted per unit volume of prostatic tissue. This is expected to be higher in malignancy.It is known that although benign prostatic tissue secretes more PSA per gram tissue, PSA is confined within the organ because of intact blood basement membrane barrier. Conversely, though carcinoma of the prostate secretes less PSA per gram tissue compared to BPH but due to the distorted blood basement membrane barrier, a greater portion of PSA is released in to the blood stream including the complex forms.[17]

In our study, the mean PSA was 6.71 + 10.45ng/ml and mean PSA Density was 0.18± 0.32. **It was observed that as the age increases there is variation in the range of PSA Density and PSA Density decreases.**

Seamen Ericet al[18]andChungJae Seunget al had also proposed the same study and had showed the similar significant correlation.

Conclusion

In the present studyage specific reference ranges of PSA values were found to be as follows

Age (in Years)	Range (ng/ml)
41-50	0.20-1.12
51-60	0.9-2.12
61-70	1.3-3.31
71-80	2.2-4.37
81-90	3.18-7.32

In patients of BPH as age increases the PSA value also increases. PSAD was found to be decreased with increase in age because volume of prostate gland increases. In our study there was an inverse correlation between PSA and PSAD in patients of BPH.Hence this might help the surgeons toavoid unnecessary repeatedbiopsies in patients with a palpable normal prostate and a PSA between 4-10 ng/mL.PSA density was a promising method for distinguishing patients with benign and malignant prostate disease.The most common cause of an elevated PSA level in the absence of cancer is benign enlargement of the prostate. The concept of PSA density was proposed initially as a means of adjusting for the benign prostate hypertrophy (BPH) component by dividing the serum PSA by the prostate volume (usually estimated by TRUS). Initially, a cut-off ratio of 0.15 was proposed, with a ratio of >0.15 indicative of cancer and <0.15 more likely benign. To conclude estimation of PSA along with measurement of PSA density can help in distinguishing patients of Prostate Cancer from patients of Benign Prostatic Hyperplasia where elevated levels of PSA have been recorded.

Conflict of Interest: None

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