ORIGINAL ARTICLE

FREE/TOTAL PROSTATE SPECIFIC ANTIGEN RATIO AS PREDICTOR FOR PROSTATE CARCINOMA

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ABSTRACT

Background: Prostate-specific antigen (PSA) is a tumor marker helpful in the diagnosis and follow-up of prostate cancer. Objective of the study was to determine Free/total PSA ratio as a predictor of prostate carcinoma.

Material and Methods: This cross-sectional study was carried in the Department of Histopathology, Shaikh Zayed Hospital, Lahore during December, 2006 to July, 2007. Hundred patients were asked to consent for blood sample for PSA analysis. The prostate tissue was preserved in fixative solution (10% buffered) neutral formalin. Multiple sections were stained with Haematoxylin and Eosin and examined microscopically. The demographic variable was age. The research variables were fPSA/tPSA ratio, morphology of prostate, tPSA and fPSA. Frequency and percentage were calculated for categorical whereas mean and standard deviation (SD) for numeric variables. The findings were recorded in proforma. Histopathology was taken as gold standard. The data was entered in SPSS version 10 and analyzed accordingly.

Results: Mean TPSA was found to be higher in carcinoma cases (25.7±21.6 ng/mL) and was lower in the benign cases (12.7±6.9 ng/mL). Moreover, a majority of the carcinoma cases had serum PSA >10 ng/mL. Using a free-PSA "cut-off" of 25% to differentiate between benign and malignant prostate enlargement.

Conclusion: This study concludes that there is highly significant increase in tPSA level in cases of prostate carcinoma whereas fPSA/tPSA ratio significantly increases in BPH cases as compared to prostate carcinoma. Therefore fPSA/tPSA ratio can be a useful predictor for early detection of prostate carcinoma.

KEY WORDS: Free prostate- specific antigen; Prostate; carcinoma.

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INTRODUCTION

Prostate carcinoma is a significant cause of morbidity and mortality. It's the most common malignancy amongst men.[1] It has become one of the leading male cancers in Asian countries as well.[2] Prostate carcinoma has a wide spectrum of biological behaviour between indolent and aggressive. Earlier diagnosis of prostate carcinoma is helpful in potentially curable cases.[3] The magnitude of the problem is not known for Pakistan.[4]

In comparison to many malignancies prostate carcinoma is generally considered slow growing.[5] The complexity in the prostate carcinoma is that it is not easy to predict the clinical course of the carcinoma for different individuals. About 50% of men with prostate carcinoma have clinically advanced disease at the time of initial diagnosis. One third of remaining 50% with organ confined disease actually have micrometastatic disease at time of surgery.[3]

Many tests are used to aid in the diagnosis but on their own, none of the individual test can be expected to provide accurate assessment of disease stage. Gleason's grading system in the biopsy is clinically useful in directing further studies and treatment. What is urgently required is some type of diagnostic method which can be combined with the histological grading, in order to identify the prostate carcinomas, thus requiring immediate therapeutic intervention at the time of initial diagnosis.[3,5]

In 1979, a tissue specific antigen was isolated from prostate using gel electrophoresis and was called as Prostate specific antigen (PSA). The standard PSA reference range is 0-4 nanograms per milliliter [ng/ml].[6] Results under 4 ng/ml are usually

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considered normal. Different ranges of total PSA are used for individuals with prostate disease i.e mildly elevated (4 to 10ng/ml), moderately (10 and 20 ng/ml) and highly elevated (>20 ng/ml). The higher the PSA level, the more likely is the possibility of carcinoma prostate. The PSA is called a biological marker.[7]

PSA exists in serum in multiple forms: complexed to alpha-1-anti-chymotrypsin (PSA-ACT complex), unbound (free PSA), and enveloped by alpha-2-macroglobulin (not detected by immunoassays). In men with a normal prostate, the majority of free PSA in the serum reflects the mature protein that has been inactivated by internal proteolytic cleavage. In contrast, this cleaved fraction is relatively decreased in prostate cancer (Ca prostate). Thus, the percentage of free or unbound PSA is lower in the serum of men with Ca prostate (and conversely, the amount of complexed PSA is higher) compared with those who have a normal prostate or BPH. This finding has been exploited in the use of the ratio of free to total PSA and complexed PSA (cPSA) as a means of distinguishing between Ca prostate and BPH as a cause of an elevated PSA.[8]

Objective of the study was to determine free/total PSA ratio as a predictor of prostate carcinoma.

MATERIAL AND METHODS

It was a comparative cross-sectional study, conducted in the Histopathology Department at Shaikh Zayed Hospital (Federal Postgraduate Medical Institute) in collaboration with Departments of Urology and National Health Research Complex Lahore from December, 2006 to July, 2007. The sample size was 100 patients with prostate disease, selected through consecutive sampling technique.

Male patients aged 40 years or above with symptomatic prostate disease attending the Department of Urology and patients with abnormal digital rectal examination (DRE) indicating hard or nodular prostate and undergoing needle prostate biopsies, transurethral prostate resection chips, as well as suprapubic prostatectomy specimens were included in this study. While patients having ejaculated 2 days prior to having a PSA test, patients on medication for BPH, baldness and herbal supplements and patients having DRE before blood sample was taken were excluded from the study.

Consent was taken from patients. Blood samples were drawn. All prostate specimens were properly preserved in fixative solution (10% buffered) neutral formalin or with 95% methanol in properly labeled containers indicating the patients name, age and medical record number. Tissue taken from the specimen was processed and paraffin embedded tissue blocks were made as per standard techniques. Multiple sections with thickness range 3 -5 micrometers, stained with Haematoxylin and Eosin were made and examined microscopically. In the laboratory the specimen was examined grossly to observe the various macroscopic features. The demographic variable was age in years. The research variables were levels of tPSA, fPSA, fPSA/tPSA ratio and morphology of prostate. The morphology of the prostate had two attributes BPH and carcinoma. fPSA/tPSA ratio and morphology of prostate were categorical whereas age, tPSA, fPSA were numeric variables. Frequency and percentage were calculated for categorical whereas mean and standard deviation (SD) for numeric. The findings were recorded in proforma. Histopathology was taken as gold standard. The data was entered in SPSS version 10 and analyzed accordingly.

RESULTS

Out of 100 patients, Ca prostate cases were 30(30%) and benign prostate hyperplasias (BPH) were 70(70%).

Table 1: Descriptive statistics in levels of total prostate specific antigen (tpsa) and free prostate specific antigen (fPSA) in prostate diseases (n=100).

S.No	Variables	Mean ± SD	95% CI	Max-Min
1	Age in years	63.06±7.35	61.6-64.5	79-50
2	tPSA	16.45±14.52	13.57-19.3	85.67-1.5
3	fPSA	28.84±13.47	26.17-31.5	99.56-8.5

Key:
CI = Confidence Interval

Table 2: Inferential statistics in levels of total prostate specific antigen (tPSA) and free prostate specific antigen (fPSA) in prostate diseases (n=100).

S.No	Variables	BPH(n=70)	Ca prostate (n=30)	t-test	p value
1	Age in years	62.34±6.6	64.73±8.8	-0.154	0.13
2	tPSA	12.7±6.9	25.7±21.6	-4.6	P<0.01*
3	fPSA	34.4±11.8	16.1±6.5	7.95	P<0.01*

*Statistically significant

The mean age of the patients was 63.06±7.35 (95%CI; 61.6 to 64.5) Years. The range of age was 29 years. Averages, ranges and 95% CI of tPSA and fPSA of patients are given in table 1.

Age difference was not statistically significant between BPH and Ca prostate (t-value = -0.154, P=0.13). tPSA was significantly lower in BPH than Ca prostate (t=-4.6; p<0.01) whereas fPSA was significantly higher in BPH than Ca prostate (t=7.95, p<0.01) as given in table 2.

DISCUSSION

Early diagnosis of Ca prostate is an important issue among urologists and pathologists. PSA is a very useful marker in the early detection and also for monitoring effects of therapy of Ca prostate.[9] In the present study 40% of Ca-prostate cases were diagnosed in age group 70-79years, and 36% in age group 50-59 years showing increase incidence as age advances. This is similar to study conducted by Battikhi[10] in Jordan who also found out relationship of increasing serum PSA value and Ca prostate with advancing age (p value <0.005).

The mean PSA level in Ca prostate cases was higher than BPH patients, same results are reported by Lojanapiwat et al.[11] The reason is that normal prostate histology is distorted that allows PSA to diffuse into the prostatic tissue and gain access to the circulation. The mean PSA in Ca prostate cases also increased with age.[12] Therefore BPH and Ca prostate cases show higher levels of PSA. Only in advance stages of carcinoma of prostate, the total PSA exceed the gray zone. Thus the specificity of PSA as a tumor marker is limited. The determination of the proportion of free PSA has been widely used to improve the specificity of PSA, especially in “gray zone”, in which the serum PSA values for BPH and Ca commonly overlap. It has been observed that in BPH the free PSA exceeded 25% cutoff value; but in Ca the free to total PSA was reversed.[12,13]

In the present study an inverse relationship was found between percent free PSA and total PSA. Men with Ca prostate have a greater fraction of serum PSA complexed to α-1-antitrypsin (ACT) resulting in “a lower percentage of free PSA , than men without Ca prostate”. The reason for the fact was given by Bjartell et al[14], that possibly extra ACT is produced by cancerous compared to benign epithelial cells.

It was observed that most of the BPH cases had f/t ratio >25, while most of the Ca prostate cases had f/t ratio <25. These findings were conformed by the different studies that free/total PSA ratio significantly improved the ability to differentiate between Ca prostate and patients having BPH, as compared to total PSA only. [15-17]

It was thus proved that measuring the free serum PSA with total PSA, can improve the specificity (i.e. the ability to detect true negative cases) of Ca prostate screening in patients with increased total serum PSA levels and consequently unnecessary biopsies can be avoided. [18, 19]

CONCLUSION

There was significant increase in tPSA level in cases of Ca prostate whereas fPSA levels were significantly higher in BPH cases as compared to Ca prostate. Therefore, free to total PSA ratio is useful predictor for early detection of Ca prostate.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

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