Original Article

Evaluation of the Diagnostic Use of Free Prostate Specific Antigen/Total Prostate Specific Antigen Ratio in Detecting Prostate Cancer

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Abstract

Objective: To assess whether Free/Total prostate specific antigen (PSA) would enhance prostate cancer detection in men with total serum PSA between 2.5 and 10ng/ml.

Methods: This case control study was conducted in the Department of Urology and Renal Transplantation, Jinnah Hospital, Lahore from January 2001 to June 2004. A total of 200 consecutive patients with symptoms of prostate disease, age 60 years or above, and serum PSA level 2.5 to 10.0 were included. Before trans-rectal biopsy of the prostate, a blood sample was taken and total and free PSA levels measured. The results were correlated with biopsy results. All patients had signs of benign prostate disease on digital rectal examination. As a second part of the study, we estimated free prostate specific antigen/total prostate specific antigen ratio (FPSA/TPSA) in 100 local age-matched population who presented to our department with diseases other than that of prostate.

Results: Of the 200 patients included in the study, 122 had free/total prostate specific antigen ratio (FPSA/TPSA) >0.18 and 78 patients had <0.18. Of the later 78 patients, 68 (87%) had cancer. Six of the 122 patients showed malignancy on biopsy. In regard to free/total prostate specific antigen ratio there was statistically significant difference between prostate cancer and benign prostate hyperplasia ($p<0.001$). The sensitivity and specificity of the FPSA/TPSA ratio were 91.9% and 92.1% respectively with 87.2% positive predictive value. The mean total PSA for the benign prostates hyperplasia, prostate cancer and control group were 6.5, 7.2 and 5.2 respectively. FPSA/TPSA ratio in the control group was > 0.42.

Conclusion: Free to total PSA ratio improves early detection of carcinoma of prostate and prevents the patients from unnecessary biopsy (JPMA 55:318;2005).

Introduction

After isolation of prostate specific antigen (PSA) by Wang[1] et al in 1979, its clinical application revolutionized the whole scenario of carcinoma of prostate. PSA proved to be a useful tool for screening, diagnosis and management of prostate cancer.[2] PSA is found in normal, benign hypertrophied and malignant prostate. Non-prostate sources of PSA like breast tissue and periurethral tissue in females have also been identified.[3] A problem with PSA assay is the lack of international standard values. Different manufacturers propose different values of the test according to their controls. Normal value is taken 0-4 ng/ml[4], but patients may have increased value of serum PSA in the absence of prostate cancer with aging.[5,6] In patients with total serum PSA in the range between 4.0-10 ng/ml, the diagnosis of prostate cancer is difficult. Cancer detection rate in PSA ranges 4-10ng/ml, is about 30% and up to 70% respectively.[7] PSA level less then 4.0 ng/ml do not rule out prostate cancer completely.[8] The identification of early prostate cancer is vital in management of prostate cancer especially in men who have mild or vague prostatic symptoms. The diagnostic aid is required for the differentiation of malignant and benign disease.

The substantial overlap in expected value of total PSA (TPSA) may result in unnecessary biopsy of prostate. Recently it has been found that serum PSA exists in several different forms, including free (uncomplexed) and bound to several protease inhibitors (complexed form).[9] The free form is in minority.[10] It has been observed that proportion of free PSA (FPSA) and complexed PSA may differ in prostatic carcinoma and benign lesions. This concept has led to an effort to use this difference of proportion of free PSA to optimize diagnostic performance.

The objective was to evaluate the comparative diagnostic performance of total PSA, free PSA with their ratio in symptomatic patients with total PSA in the range of 2.5-10.0 ng/ml.

Patients and Methods

This study was conducted in the Department of Urology and Renal Transplantation Jinnah Hospital, Lahore between January 2001 to June 2004. A total of 200 consecutive patients with symptoms of prostate disease, age 60 years or above, and serum PSA level 2.5 to 10.0 were included. All patients were evaluated with a detailed medical history, physical and systemic examination. Before trans-rectal biopsy of the prostate, a blood sample was taken, total and free PSA levels were measured by Hyberitech Tandem-R or Tandem MP assay. The results were correlated with biopsy results. All patients had signs of

benign prostate disease on digital rectal examination. As a second part of study we estimated free prostate specific antigen/total prostate specific antigen ratio (FPSA/TPSA) in 100 local age-matched population who presented to our department with diseases other than that of prostate.

The exclusion criteria included all proven cases of carcinoma prostate, previous history of prostate surgery, patients with history of urethral manipulation or with indwelling catheter, patients with a history of diabetes mellitus or other neurological lesions.

Data analysis was conducted with statistical package SPSS version 10.0. The chi-square test was used to compare different values. Moreover specificity, sensitivity and accuracy of diagnostic modalities were also calculated.

Results

The mean age of the 200 patients was 68 ± 10 ranging 60 to 90 years. The most common clinical presentation was lower urinary tract symptoms. This includes increased frequency, nocturia, urgency, hesitancy, intermittency, sense of incomplete evacuation of bladder, dysuria and post voidal dribbling. Haematuria was present in four patients. No other complaints were reported. All patients had normal renal function and benign prostates on digital rectal examination.

All 200 patients had a serum PSA value between 2.5-10 ng/ml. Out of 200 patients 179 (89.5%) had a PSA level > 4.0 ng/ml, 21 patients had a PSA level < 4.0ng/ml. The ratio of free PSA/ total PSA was calculated in all cases. A cut off value of 0.18 was taken as standard. One hundred and twenty two (61%) patients included in the study, had a free/total prostate specific antigen ratio (FPSA/TPSA) >0.18 and 78 (39%) patients had values <0.18 (Table 1).

Table 1. Total serum and percent free PSA for BPH, prostate cancer and control group.

	Number of patients	Mean ± SE	
		Total PSA	% Free PSA
BPH	122	6.5 ± 0.75	22.6 ± 0.55
Ca. prostate	78	7.2 ± 0.59	14.0 ± 0.82
Control	100	5.5 ± 0.65	42.0 ± 0.95

Of the latter 78 patients, 68 (87%) showed malignancy on biopsy while 10 (13%) were free of malignancy. Six of the 122 patients showed malignancy on biopsy. In regard to free/total prostate specific antigen ratio there was statistically significant difference between prostate cancer and benign prostate hyperplasia ($p<0.001$). The sensitivity and specificity of the FPSA/TPSA ratios were 91.9% and 92.1% respectively with 87.2% positive predictive value and negative predictive value was 95.1%. The mean total PSA for the benign prostate hyperplasia, prostate cancer and control group were 6.5, 7.2 and 5.2 respectively. FPSA/TPSA ratio in control group was > 0.42.

In 122 patients with FPSA/TPSA ratio > 0.18 only 6 patients (4.9%) showed malignancy on biopsy. In 21 patients with total PSA between 2.5 - 4.0 ng/ml, 4 showed cancer on biopsy. In control group the FPSA/TPSA ratio was > 0.45. The Gleason scoring was done in patients of carcinoma of prostate. They were subdivided into three group i.e. I Gleason score 2- 4 (47.29%), II Gleason score 5-7 (44.59%), III Gleason score 8-10 (8.10%) (Table 2).

Table 2. Gleason Scoring of Patients with Carcinoma Prostate (n=74).

Gleason score	Number of patients	Percentage
2 - 4	35	47.7%
5 - 7	33	44.7%
8 - 10	06	7.9%

Discussion

Prostate cancer is one of the most common cancer in males. In England and Wales, the annual number of new cases of carcinoma of prostate has increased by 179% between 1971 and 1998.[11] In 2001, there were approximately 198,100 new cases and 31,500 deaths from carcinoma prostate, the number that will continue to rise as the population ages.[12] In Pakistan, the true incidence is not known. In one study, the incidence of carcinoma of prostate in North Western part of Pakistan was less as compared to other malignancies and stands 8th in the list of malignancies.[13] This low incidence may be due to lack of awareness among people, low literacy rate and absence of any screening program for prostate cancer. No age is immune, even younger males may be the victims of prostate carcinoma.[14,15] In this study the majority of the patients were between 60-90 years with a mean age of 68±10 years. A study done in Jamaica showed the mean age at the time of diagnosis was 72 years.[16] Because of this enormous involvement of male population world wide, carcinoma of prostate needs special preference in terms of diagnosis and management.

PSA is very significant in diagnosis of prostate cancer when it is high. But its significance in cancer detection is decreased when serum PSA level is low i.e. 2.5-10ng/ml.[17] Prostate specific antigen occurs in different molecular forms. Most of serum PSA complexes with serum protein inhibitor i.e. 70-90% are bound with alpha 1 antichymotrypsin).[9] Unbound form is called free prostate specific antigen. Nowadays increased number of patients are undergoing prostate biopsy on the basis of serum PSA

testing. Therefore we assessed the ability of FPSA/TPSA ratio to aid biopsy selection. Our results demonstrate the superiority of FPSA/TPSA ratio to total PSA in detection of prostate cancer.

A study conducted in Germany by Stefan and colleagues showed that FPSA/TPSA ratio can better differentiate between patients of carcinoma of prostate and BPH when serum PSA is less than 10.0 ng/ml.[18] Klaus et al showed superiority of ratio of FPSA/TPSA on all other serum tests for early detection of carcinoma of prostate.[19, 20] Overall cancer detection rate was similar to the other study done by Catalona[21] et al and Brawer et al[7] In this study prostate cancer was detected in 19% of men with PSA value of 2.4-4.0 ng/ml. Smith et al[22] and Gann et al[23] also showed similar results. As a result of this study and its comparison with other studies, it can be said that FPSA/TPSA ratio is helpful in detecting prostate cancer in patients with total PSA 2.5-10 ng/ml and prevents the patients from unnecessary biopsy.

On the basis of Gleason scoring, the majority of cases with FPSA/TPSA ratio >0.18 were diagnosed at a less aggressive grade. Southwick et al[24] also reported that higher percentage of free PSA is associated with more favorable histology. The cancer associated with greater than 25% free PSA were more prevalent in older patients and generally were less threatening in terms of grade and value.[25]

The limitation of the study is its small sample size due to difficulty is getting specimens.

Our study revealed that overall diagnostic performance of FPSA/TPSA ratio is better than total PSA. This may lead to a reduction in number of men undergoing unnecessary prostate biopsy.

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