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RESEARCH ARTICLE

Study of Free and Total PSA levels in Patients with Benign Prostatic Hyperplasia and Carcinoma Prostate

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ABSTRACT

The usefulness of PSA as an early detector of prostate cancer by itself is questionable owing to overlap in PSA values seen in patients with Benign Prostatic Hyperplasia (BPH) and in those with organ confined prostate cancer. Several workers used Free PSA levels to improve the specificity of Prostate Specific Antigen (PSA) for Prostate cancer. We studied 70 cases who presented in Surgical OPD with complaints of frequency, urgency of urination and hesitancy. They were tested for Free and Total PSA levels by chemiluminescent assay. Other biochemical markers tested were serum calcium, acid phosphatase and alkaline phosphatase. Along with this histopathological examination of prostatic biopsies was done. In our study of 70 cases it was found that the mean serum levels of Free PSA, Total PSA and free /total PSA ratio in BPH patients were 2.43±1.10, 8.51±5.20, 0.32±0.09, while in carcinoma patients mean serum levels were 1.59±0.55, 66.83±58.29, 0.04±0.03. In control groups of 30 patients mean serum levels were 0.68±0.56, 1.95±1.24 and 0.34±0.15. The results showed that mean Free PSA, Free /total PSA ratio was significantly decreased in carcinoma patients as compared to BPH patients. Total PSA levels were significantly increased in carcinoma as compared to BPH patients. A negative correlation was between Free/Total PSA ratio and histopathological findings. In our study clinical, biochemical parameters were correlated with biopsy report. Our study concluded that the Free PSA and free/Total PSA ratio were decreased in carcinoma prostate as compared to benign prostatic Hyperplasia (BPH). Total PSA levels were significantly increased in carcinoma prostate. So free/total PSA ratio helps in distinguishing between BPH & Carcinoma Prostate. Cut off value of free/total PSA ratio was 0.14 in our study. Patients above this cut off were BPH and below this were Carcinoma prostate. Above findings correlated with the biopsy report. We concluded that patients with prostate cancer have a greater fraction of bound PSA and a lower percentage of free PSA than in men without prostate cancer. There was a negative correlation found between free/total PSA ratio and the histopathologic findings. Lower the ratio higher is the grade of malignancy. Therefore in clinical practice Free/Total PSA ratio is crucial parameter which helps the clinicians to decide if a biopsy is necessary or not. It is also helpful to screen the patients in the grey zone & helps in diagnosing prostate carcinoma cases which are usually missed.

KEYWORDS

BPH, Carcinoma Prostate, free/Total PSA Ratio

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INTRODUCTION

Prostate- Specific Antigen (PSA) is a glycoprotein that is produced by the prostate gland, the lining of the urethra, and the bulbourethral gland .PSA was first described in

1971 and purified in 1979[1] in seminal plasma and prostate.[1]Normally very little PSA is secreted in the blood. Increase in glandular size and tissue damage caused by benign prostatic hypertrophy, prostatitis, or prostate cancer may increase circulating PSA levels. The prostate gland is a pear shaped glandular organ that lies directly under the bladder and encloses the upper section of urethra .It is approximately 20-25g in a young man & 30g in an older man. Traditionally it has been divided into anterior, middle, posterior and two lateral lobes by drawing divergent lines from centrally located urethra. A division that correlates better with the physiologic and pathologic features of the organ is into an inner (periurethral) and an outer (cortical) zone. The inner zone is the primary site for nodular hyperplasia whereas the outer zone is the site of predilection for the ordinary adeno carcinoma arising from peripheral ducts and acini.[2]

During ejaculation, the prostate gland adds up to 40gm of a milky secretion to the ejaculate in which prostate specific antigen (PSA), a protein formed by the prostate gland, is present in high concentration. Prostatic secretions are slightly acidic with a pH around 6.4. The acidity serves to neutralize vaginal alkalinity and prolong the life span of spermatozoa.PSA liquefies semen promoting sperm motility, and serves to dissolve cervical mucus. PSA present in low concentrations in the blood, but the concentration increases with prostate irritation, prostatic infection & benign prostatic hyperplasia (BPH)[3]. PSA useful tumour marker is a glycoprotein consisting of 93% aminoacids and 7% carbohydrates. It is worthwhile to mention that PSA is a glycoprotein as a marker by prostate gland for Prostate Cancer, Prostatitis and BPH.PSA is very similar to kallikrein, which is androgen dependent and produced in epithelial and glandular tissue .PSA exists in the blood in two forms. Most PSA in the blood is bound to serum proteins (alpha 1 anti chymotrypsin), some of which are inhibitors of the serine protease activity of PSA. Further PSA is also present as free PSA. Total PSA is the sum of both bound and free PSA; however, free PSA is measured only if total PSA is increased. PSA is primarily a tissue specific marker. With increasing age, enlargement of the prostate gland is common and in most cases it is benign. It often leads to unpleasant symptoms such as increased urinary frequency, urgency, hesitancy, sensation of incomplete bladder emptying.

PSA is produced in the epithelial cells of prostate. Disruption of this epithelium in inflammation or benign prostatic hyperplasia, may lead to diffusion of antigen into the stromal tissue around the epithelium & is the cause of elevated blood levels of PSA in these conditions.

Benign Prostatic Hyperplasia is the usual name applied to a common benign disorder of the prostate that, when extensive results in varying degrees of urinary obstruction, sometimes requiring surgical intervention.

The disease represents a nodular enlargement of the gland caused by hyperplasia of both glandular and stromal components. These results in an increase in the weight of the organ well beyond the 20g regarded as normal for adult individuals.

The clinical evidence of this disease is only 8% during the fourth decade, but it reaches 50% in the fifth decade and 75% in the eight decade. It has been estimated that the process begins before the age of 30 and that its doubling time progressively increases from 43 yrs in the early stage (third to fifth decade) to over 100 years in late stage(patients beyond 70 yrs old). It has been established that prostatic nodular hyperplasia occurs only in individuals with intact testes and that it is an androgen dependent disorder.[2]

Grossly variously sized nodules with grey to yellow colour and a granular appearance are seen projecting above the cut surface. Microscopic appearance shows stromal proliferation, and dilated, Cystic glands containing corpora amylacea.[2] Carcinoma of prostate is second only to lung cancer as a leading cause of cancer related deaths. Hormonal factors appear to play a role in the development of prostate carcinoma. The disease does not occur in enunchs castrated before puberty and its incidence is low in patients with hyper estrogenism resulting from liver

cirrhosis. It has been estimated that 5-10% of prostatic carcinomas have genetic link. There is no convincing evidence that patients with nodular hyperplasia are at an increased risk for the development of prostatic carcinoma. Skillful rectal examination remains a practical and efficient method for the detection of prostatic carcinoma. Transrectal ultrasonography can detect carcinomas as small as 5mm in diameter; however it will miss up to 30% of the prostatic tumours that are isoechoic and has not proved an efficient tool for screening.

PSA is secreted by all but the most undifferentiated prostatic tumours. The average prostatic carcinoma produces ten times or the amount of PSA produced by normal tissue. Serum determination of PSA has all but replaced the time honored determination of Prostatic acid phosphatase. Mild serum elevations of PSA can be seen with nodular hyperplasia, but levels above 4ng/ml call for serial determination, with the performance of a biopsy if they continue to rise. Almost half of patients with prostatic carcinomas have levels over 10ng/ml. Most prostatic carcinomas arise in the peripheral zone, whether posteriorly, laterally, or anteriorly with sparing of the periurethral zone.

Grossly the tumour is grey or yellowish, poorly delineated, firm area. Microscopy shows well-differentiated tumour composed of medium sized irregular shaped glands showing various patterns like papillary, hypernephroid and comedo carcinoma appearance.[2]

The usefulness of PSA as an early detector of prostate cancer by itself is questionable owing to overlap in PSA values seen in patients with BPH and in those with organ confined prostate cancer. Several workers[4] used Free PSA levels to improve the specificity of PSA for PCa.

Free to Total PSA ratio (f/t PSA) has been studied to distinguish BPH & CaP and found more specific[1] and sensitive in detection. Measurement of PSA provides essential information about the efficacy of surgery or radiation therapy helps establish the possibility of residual disease local or distant and provides a useful adjunct in the evaluation of therapeutic response.

MATERIAL AND METHODS

Weprospectively studied seventy patients (35 of benign prostatic hyperplasia and 35 patients of carcinoma prostate) who presented to the OPD and IPD of Padmashree Dr D.Y. Patil Medical College. Hospital and research centre, Pune. The study period was from July 2012-September 2014. Study design was as a prospective & control study.

The proposal of the study was put forth in the meeting of Ethical committee of the institute and necessary permissions and clearance was obtained. An informed consent was also obtained from the study population which consisted of two groups of males aged more than 50 yrs. Male patients above the age of 50 years who presented with urinary complaints and showed prostatic enlargement on Ultrasonography were included in the study. Those patients with diabetes, hypertension, stroke, any history of major surgery were excluded from the study. Under all aseptic precautions about 5 ml of venous blood will be collected in a plain bulb and allowed to clot for one hour at room temperature, centrifuged at 2000 rpm for 10 min. Serum was separated and analyzed immediately for Free PSA, Total PSA. Biopsy samples were processed in Histopathology section of Pathology and reports were collected. Free and total PSA levels were assayed by Chemiluminescent assay.

RESULTS

In our study, it was found that the mean serum levels of Free PSA, Total PSA and free /total PSA ratio in BPH patients were 2.43±1.10, 8.51±5.20, 0.32±0.09, while in carcinoma patients mean serum levels were 1.59±0.55, 66.83±58.29, and 0.04±0.03.

In control groups mean serum levels were 0.68±0.56, 1.95±1.24 and 0.34±0.15. The results showed that mean Free PSA, Free /total PSA ratio was significantly decreased in carcinoma patients as compared to BPH patients.

Total PSA levels were significantly increased in carcinoma as compared to BPH patients. A negative correlation was between Free/ Total

PSA ratio and histopathological findings. In our study clinical, biochemical parameters were correlated with biopsy report.

Our study concluded that the Free PSA and free /Total PSA ratio were decreased in carcinoma prostate as compared to BPH.

Total PSA levels were significantly increased in carcinoma prostate.

So free/total PSA ratio helps in distinguishing between BPH & Carcinoma Prostate.

In our study cut off value of free/total PSA ratio is 0.14.Patients above this cut off were BPH and below this were Carcinoma prostate.

Above findings correlated with the histopathology report.

DISCUSSION

Prostate-specific antigen is a glycoprotein that is produced by the gland. The determination of serum prostate specific antigen has become an essential tumour marker for diagnosis, evaluation of treatment & follows up of patients with prostate conditions such as prostate cancer, acute prostatitis and benign prostatic hyperplasia. Due to biological nature of PSA, its serum values may be elevated even in benign prostatic diseases.

The most important reason to measure PSA in blood is to screen for prostate carcinoma in men over the age of 50. In addition to screening, free to total PSA ratio helps to determine the relative risk of prostate cancer. Therefore some urologists recommend using the free to total PSA ratio to help select which men should undergo biops. The total PSA range of 4-10ng/ml has been described as diagnostic gray zone, in which the free: total PSA ratio helps to determine the relative risk of prostate carcinoma.

The current prospective study was conducted with the aim to estimate Free PSA, Total PSA Free/Total PSA ratio in patients with benign prostatic hyperplasia & Carcinoma Prostate and correlate with the histopathology report.

In the present study age wise distribution in control group is 68.07± 7.95, while in benign prostatic hyperplasia it was 64 ± 4.92 and in carcinoma prostate 68.26± 5.82. There was no significant difference in the age wise distribution among all the three groups.

Mean values of Free PSA levels in benign prostatic hyperplasia were 2.43±1.10ng/ml ,in carcinoma prostate were 1.59±0.55ng/ml as compared to 0.68±0.56 ng/ml in the control group .The result was statistically highly significant.($p<0.0001$).

Free PSA is significantly raised in patients with benign prostatic hyperplasia whereas in Carcinoma Prostate it is reduced.

In Carcinoma Prostate most of the PSA is in bound form therefore fraction of free PSA reduces.

PSA produced from cancerous cells appears to escape an enzymatic processing that cleaves the bond between PSA & its binding proteins. Therefore men with prostate carcinoma have a greater fraction of bound PSA & a lower percentage of free PSA.

In our study the mean total PSA values were 8.51±5.20 ng/ml and 66.83±58.29 ng/ml in benign prostatic hyperplasia and carcinoma prostate respectively.

In the control group total PSA values were 1.95±1.24 ng/ml Test was statistically highly significant ($p<0.0001$). Mild rise of PSA values in BPH and grossly elevated serum PSA levels was observed in adenocarcinoma prostate.

Similarly mean value of Free to total PSA ratio in benign prostatic hyperplasia and Carcinoma Prostate was 0.32±0.09 and 0.04±0.03 respectively. Control group showed 0.34±0.15.

Test was statistically significant with $p < 0.0001$. In the present study free/total PSA ratio is reduced in carcinoma prostate as compared to benign prostatic hyperplasia. Histological grades of prostate biopsy showed a negative correlation with free/total PSA ratio in our study.

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