African Journal of Biochemistry Research Vol. 4(1) pp. 013-016, January, 2010
Available online at http://www.academicjournals.org/ajbr
ISSN 1996-0778 © 2010 Academic Journals

Full Length Research Paper

A study on prostate specific antigen (PSA) with the ratio of free to total PSA

Chavan Atish[1], Suman Diggi Prasad[1], Rawal Mukesh[1], Kandasamy Surendran[2], Sivapatham Sundaresan[3*] and Thangarajan Thangapannerselvem[4]

[1]Department of Biotechnology, School of Bioengineering, SRM University, Kattankulathur, Tamil Nadu, India- 603203, India.
[2]Central Laboratory, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur, Tamil Nadu, India- 603203, India.
[3]Department of Medical Research, SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur, Tamil Nadu, India- 603203, India.
[4]Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur, Tamil Nadu, India- 603203, India.

Accepted 10 September, 2009

Prostate specific antigen (PSA) is a glycoprotein produced as a marker by prostate gland for prostate cancer, benign prostate hyperplasia and prostatitis. Study objective is to evaluate f/t PSA ratio to distinguish the Benign Prostate Hyperplasia (BPH) and prostate cancer patients in and around SRM University. To define the age specific reference ranges of PSA in control and test group at Chennai, India. Healthy men aged 40 - 75 years in and around SRM Medical College and Research Centre, Chennai, India were selected and grouped as control. Blood samples were collected from patients who attended Cancer Hospital, Adiyar underwent rectal examination revealed prostate enlargement. Results of our study showed that they were diagnosed as BPH and as Cancer, using PSA determination. The free to total PSA ratio were decreased significantly in cancer patients than BPH. PSA was increased linearly with age and observations were associated with the claims of National Academy of Clinical Biochemistry guideline reported that the clinical decisions limits should be decreased for younger patients (age below 50) and should be increased for older patients (age above 50). PSA should be used more appropriately to distinguish (BPH) and prostate cancer and to detect cancer prostate at an early stage. The age specific reference ranges and different forms of PSA have the potential to make serum PSA, a more discriminating tumor marker for detecting cancer prostate significantly in men.

Key words: Prostate specific antigen, free PSA prostate cancer, benign prostate hyperplasia, free to total PSA ratio, complex PSA, percentage of free PSA.

INTRODUCTION

Prostate cancer (CaP) is the common malignancy in men globally and ranked second after lung and bronchus cancer with respect to death (Angelis et al., 2007; Katz and Katz, 2008). Serum prostate specific antigen (PSA) has been widely regarded as the most clinically useful marker for the detection of CaP and BPH (Wu, 1994; Brawley et al., 2009). Tumor markers, measurable either in serum or from tissue specimens are generally useful in the detection, screening, staging, prognosis and monitoring therapy (Loeb and Catalona, 2008). PSA was first described in 1971 and purified in 1979 in seminal plasma and the prostate. PSA is a single chain glycoprotein with 240 amino acids having a molecular weight of approximately 34 KDa (Noldus et al., 1997; Singh, 2009). PSA is synthesized by the epithelial cells of prostatic acini and ducts and is secreted as a normal constituent of seminal fluid.

Free to total ratio of PSA (f/t PSA) has been studied to distinguish BPH and CaP and found more specific and sensitive in detection (Woodrum et al., 1998). Measure-

*Corresponding author. E-mail: sundarsivapatham@rediffmail.com. Tel: 044-27455317/ 044-27455701. Fax: 044-27455106/ 044-27453903.

Table 1. Shows the distribution levels of free PSA, total PSA, free to total PSA ratio, complex PSA and % free PSA in control and test group.

Groups	Free PSA (ng/ml)	Total PSA (ng/ml)	Free to total PSA ratio	Complex PSA	Percent free PSA
Control	0.22 ± 0.06	0.67 ± 0.08	0.33 ± 0.08	0.44 ± 0.07	33.85 ± 8.85
Test	1.09 ± 0.69* [a]	4.62 ± 2.85* [a]	0.24 ± 0.07*	3.52 ± 2.31* [b]	24.72 ± 7.59* [b]

* indicate values are statistically significant if the p value ≤ 0.05 (t' test). [a] indicates value are statistically correlated at p value of 0.01 level (Spearmen analysis). [b] indicates value are negatively related between complex PSA and mean percent free SPA was 18% in prostate cancer and 29% in BPH.

ment 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 (Monda et al., 1994). The detection of prostate cancer using a blood test has by many standards changed the face of the disease (Leman and Getzenberg, 2009). Virtually all guidelines regarding screening view PSA and DRE as dichotomous test results, namely, either positive or negative. As such, a man with a PSA level of 4.1 ng/ml is recommended to undergo a biopsy whereas another man with a PSA level of 3.9 ng/ml is considered normal. Similarly, a man with a nodule detected on DRE is recommended to undergo a biopsy regardless of whether his PSA is 0.2 ng/ml or 9.8 ng/ml (Brawley et al., 2009).

The worrisome conclusion of observations from a study is that screening with PSA using a single upper limit of normal of 4.0 ng/ml may carry a risk of detecting many cancers too late to enable radiation or surgery to cure the disease.

In order to evaluate the effect of total and free form of PSA, free to total PSA ratio on age and to distinguish BPH and CaP, the study was chosen among SRM Hospital, Kattankulathur and Cancer Institute, Adiyar.

MATERIALS AND METHODS

Sample collection

Healthy men aged 40 - 60 years from the area in and around SRM Medical College Hospital and Research Centre, SRM University, Kattankulathur were selected and grouped as control at 2009. Test group of untreated patients who attended SRM Hospital and Cancer Institute, Adiyar, Chennai were enrolled for the study. Individuals who had no history of previous or concomitant malignancies and no acute illness within the last three months were clinically identified. Serum samples were collected prospectively from untreated patients who attended SRM Hospital and Research Centre, Kattankulathur and Cancer Institute, Adiyar, Chennai. The control group includes the men with ages between 40 to 70 years. Blood samples were allowed to clot for one hour at room temperature, were centrifuged at 2000 rpm for 10 min. The study was approved by inter departmental ethical committee and carried out in accordance with procedure, including informed consent of all participants. Blood sampling was performed before the other diagnostic procedures like imaging technique. Serum samples were stored at -20°C.

Biochemical analysis

Free and total PSA were analyzed with Diagnostic Biochem Canada (DBC) kits. Complexed PSA (cPSA) and percent PSA were estimated from free and total PSA values of control and test groups. The samples were analyzed for free PSA and total PSA by using the ANTHOS ELISA reader and washer made in Austria.

Statistical analysis

Data were expressed as mean ± SD and values are statistically significant if the p value at 0.05 level. Data's were analyzed using the statistical software SPSS 16.0 for student's t- test and correlation was calculated by Spearmen one tailed test and the values are significant if the p value is at 0.01 level.

RESULTS AND DISCUSSION

Table 1 describes the distribution of total PSA, free PSA and free to total ratio of PSA among the control group and test group. The highest total PSA was 10.0 ng/ml and lowest was 1.2 ng/ml in test group. The total and free PSA mean was increased in test group when compared to control group significantly at P value 0.05 level. The highest free PSA mean was 2.48 ng/ml and lowest mean was 0.2 ng/ml in test group. Free to total PSA ratio was decreased in test group when compared to control group significantly at P value 0.05 level. The lowest f/t ratio was 0.11 and highest was 0.33. Total and free PSA were correlated significantly at 0.01 level.

Table 1 also signifies the levels of complexed PSA (cPSA) and percent free PSA in control and test group. The highest value of cPSA was 8.06 and the lowest was 1.03. The levels of cPSA were significantly elevated in test group then control. Percentage of free PSA was found to be decreased among cancer patients than BPH. The mean value of percentage free PSA of cancer patients was 18% and the mean value of percentage of free PSA of BPH was 29%. cPSA was negatively related to percentage of free PSA.

Figures 1 and 2 show the distribution of total PSA, free PSA in test group against age respectively. Serum PSA levels gradually increase with age in men over 40 years old (Chen et al., 1996). The reference range of PSA with age has been proposed with the expectation that their implementation increase cancer detection rates in younger men. PSA plays a cardinal role in all aspects of

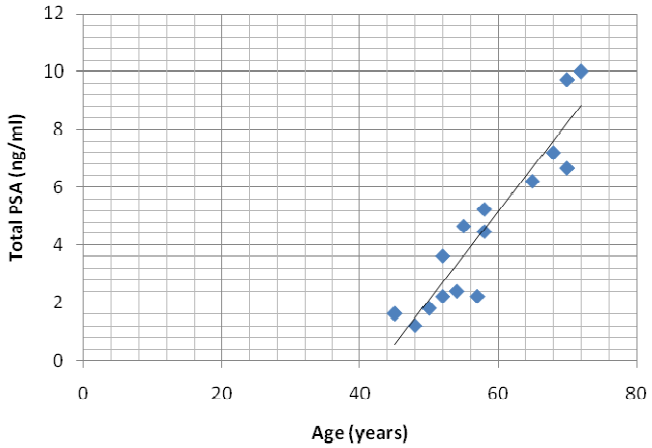

Figure 1. Graph showing age specific total PSA (ng/ml) among test group.

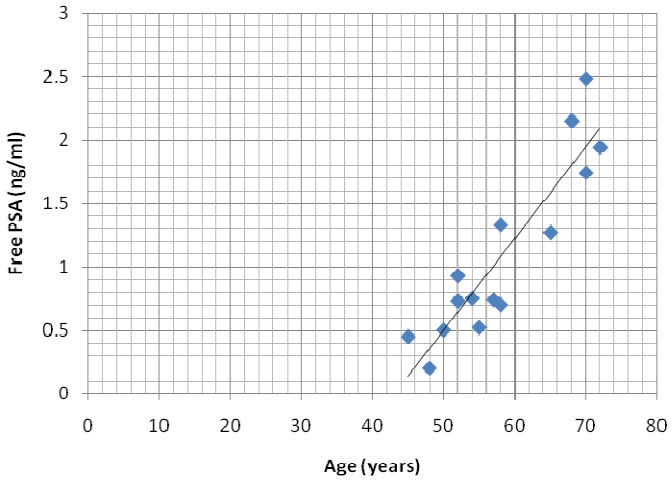

Figure 2. Graph showing age specific free PSA (ng/ml) among test group.

management of prostate cancer (Daniëlle et al., 2008). The recommended follow up testing of high risk individuals initially screened at 40 years of age depends on PSA result. Those with PSA levels < 1 ng/ml would resume testing at 5 years interval and those with levels > 1 but < 2.5 ng/ml would be tested annually, while those with levels ≥ 2.5 ng/ml would be evaluated further and considered for biopsy (Catalona et al., 1995).

When f/t PSA was analyzed among the patients with CaP it showed significantly low f/t PSA levels than those without CaP (Yamamoto and Maruyama, 2008). The use of high cutoff points of f/t PSA resulted in high sensitivity. When the cutoff point of f/tPSA was set at < 15%, sensitivity were 82.0%, while this value increased to 96.0%, at the cutoff point < 20%, indicating that f/t PSA would be useful to improve sensitivity and be able to predict the outcome of prostate cancer (Frempong et al., 2008; Vutuc et al., 2009).

As data mounted that percent free PSA offered improved specificity over the use of total PSA alone in the range of 4 - 10 ng/ml, it also become evident that percent free PSA might provide improved sensitivity at total PSA values less than 4.0 ng/ml (Yoshimo et al., 2008). Catalona et al. (1998) studied a population of men with PSA values restricted to 2.6 - 4.0 ng/ml are benign prostates on examination.

Percent free PSA predicted cancer in men and that over 80% of the cancers so detected were organ confined (Leman and Getzenberg, 2009). Vashi et al. (1997) examined the use of percent free PSA to trigger biopsy in the range of 3 - 4 ng/ml total PSA. A free PSA cut point of 19% allowed detection of 90% of the cancers in these men and resulted in a 73% biopsy rate and 44% cancer detection rate.

A direct relationship has been demonstrated between preoperative serum PSA and tumor volume as determined from radical prostectomy specimens (Kabalin et al., 1995). As a general rule, as prostate cancer progresses it produces more PSA. Our results confirmed the findings that the f/t PSA ratio is statistically different between control and patients. Gann (1997) have suggested men with PSA between 2 and 3 ng/ml have 5.5 fold higher risks for prostate cancer. National Academy of Clinical Biochemistry recommends validating the medical decision limit for each free and total PSA (Lilja et al., 2004; Vickers and Lilja, 2009). Using more intensive screening in younger men with lower PSA levels will result in the detection of predominantly low–grade, potentially inconsequential cancers. Conversely, using higher levels of PSA to prompt a biopsy in older men will result in significantly higher rates of aggressive cancer going undetected. The risks of using PSA age–related cutoff values for PSA instead of incorporating all risk variables is that younger men are increasingly likely to be diagnosed with inconsequential tumors, whereas older men may ultimately be found to have aggressive, potentially lethal cancers that are diagnosed too late to allow curative treatments to be given (Brawley et al., 2009).

Efforts made to detect cancer in patients with intermediate or low PSA are justified because 40% of confined CaP is expected to occur in patients with PSA from 4 to 10 ng/ml, we conclude that the free to total PSA ratio may be helpful for differential diagnosis of BPH and CaP. Long term multicancer trials to determine the impact of prostate cancer screening on survival are needed to establish the incidence and mortality owing to prostate cancer (Luderer et al., 1995).

REFERENCES

Angelis GD, Rittenhouse HG, Mikolajczyk SD, Shamel LB, Semjonow A (2007). Twenty years of PSA: From prostate Antigen to Tumor Marker, Rev. Urol. 9(3): 113-123.

Brawley OW, Ankerst DP, Thompson IM (2009). Screening for Prostate Cancer. CA Cancer J. Clin., 59(4):264-273. Epub 2009 Jun 29.

Catalona WJ, Partin AW, Slawin KM (1998). Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter Clin. Trial JAMA. 279: 1542-1547.

Catalona WJ, Smith DS, Wolfert R, Wang T, Rittenhouse H (1995).Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening. JAMA. 274(15): 1214-1220.

Chen YT, Luderer AA, Thiel RP, Carlson G, Cony CL, Soriano TE (1996). Using proportions of free to total prostate-specific antigen, age, and total prostate-specific antigen to predict the probability of prostate cancer. Urology, 47: 518-524.

Daniëlle BP, Andrea L, Monique G, Erik R (2008). Why determine only the total prostate-specific antigen, if the free-to-total ratio contains the information? Ann. Clin. Biochem., 45: 270-274.

Frempong MT, Aboah K (2008). Correlation of serum free/total prostate specific antigen ratio with histological features for differential diagnosis of prostate cancer. J. Med. Sci., 8: 540-546.

Gann PH (1998). Interpreting recent trends in prostate cancer incidence and mortality. Epidemiol., 8: 117-120

Kabalin JN, McNeal JE, Johnstone IM, Stamey TA (1995). Serum prostate specific antigen and the biologic progression of prostate cancer. Urology, 46: 65-70.

Katz A, Katz A (2008). The top 13: what family physicians should know about prostate cancer. Can. Fam. Phys. Rev. 54(2): 198-203.

Leman ES, Getzenberg RH (2009). Biomarkers for prostate cancer. J. Cell. Biochem., Jun 8..

Lilja H, Semjonow A, Sibley P, Babaian R, Dowell B, Rittenhouse H, Sokoll L (2004). NACB: Practice guidelines and recommendations for use of tumor markers in the clinic prostate cancer (Section 3B).

Loeb S, Catalona WJ (2008). What to do with an abnormal PSA Test. Oncologist, 13: 299–305.

Luderer AA, Chen YT, Soriano TF, Kramp WI, Cuny C, Sharp I, Smith W, Petteway J, Brawer MK (1995). Measurement of the proportion of free to total prostate-specific antigen improves diagnostic performance of prostate-specific antigen in the diagnostic gray zone of total prostate-specific antigen. Urology, 46: 187-194.

Monda JM, Barry MJ, Oesterling JE (1994). Prostate specific antigen cannot distinguish stage 1a (A1) prostate cancer from benign prostatic hyperplasia. J. Urol., 151: 1291-1295.

Noldus J, Chen Z, Stamey T (1997). Isolation and characterization of free form prostate specific antigen (f-PSA) in sera of men with prostate cancer. J. Urol., 158: 1606–1609.

Singh JC (2009). Cut-off value for PSA: do we need a change?. J. Postgrad. Med., 55(2): 150-151.

Vashi AR, Wojno KJ, Henricks W, England BA, Vessella RL, Lange PH, Wright GL, Schellhammer PF, Weigand RA, Olson RM, Dowell BL, Borden KK, Oesterling E (1997). Determination of the “reflex range” and appropriate cut points for percent free-PSA in 413 men referred for prostatic evaluation using the AxSYM system. Urology, 49(1): 19-27.

Vickers AJ, Lilja H (2009). Prostate cancer: Estimating the benefits of PSA screening. Nat. Rev. Urol., 6(6): 301-303.

Vutuc C, Waldhoer T, Lunglmayr G, Hoeltl W, Haidinger G (2009). PSA testing in Austria: induced morbidity and saved mortality. Eur. J. Cancer Prev., 18(5): 377-380.

Woodrum DL, Brawer MK, Partin AW, Catalona WW, Southwick PC (1998). Interpretation of free prostate specific antigen clinical research studies for the detection of prostate cancer. J. Urol. (Suppl), 159: 5-12.

Wu JT (1994). Assay for prostate specific antigen (PSA). Problems and possible solutions. J. Clin. Lab. Anal. 8: 51-62.

Yamamoto S, Maruyama T (2008). Diagnostic efficacy of free to total ratio of prostate-specific antigen and prostate-specific antigen velocity, singly and in combination, in detecting prostate cancer in patients with total serum prostate-specific antigen between 4 and 10 ng/ml. Int. Urol. Nephrol., 40: 85–89

Yoshimo K, Yasuhide K (2008). Free-to-total prostate-specific antigen (PSA) ratio contributes to an increased rate of prostate cancer detection in a Japanese population screened using a PSA level of 2.1 -10.0ng/ml as a criterion. Int. J. Clin. Oncol., 13: 229-232.