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Prostate specific antigen (PSA) and sarcosine levels In Patients With Benign Prostatic Hyperplasia (BPH) Disorders In Sokoto, Nigeria

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ABSTRACT

Prostate specific antigens occurs in serum in different molecular isoforms, and serum levels of these isoforms have been introduced as adjuncts for prostate disorder screening to reduce misdiagnosis. Little data exist on the use of these tests for screening patients with BPH . In the current study, serum level of total, free and complex prostate specific antigen (tPSA,fPSAand cPSA) isoforms and serum sarcosine were evaluated in 200 BPH patients and 200 matched controls. tPSA level was 15.13±1.15 ng/ml in BPH patients and 2.75±0.22 ng/ml in controls. fPSA was 2.81±0.16 ng/ml in BPH patients and 0.72±0.03 ng/ml in controls. cPSA was 12.31±1.05 ng/ml in BPH patients and 0.72±0.03 ng/ml in controls. Serum sarcosine was 118.70±1.80 nmol/dl in BPH patients and 64.94±0.81 nmol/dl in controls. The differences between patients and controls in all the analytes are significant (<0.05). In conclusion, the evaluation of these analytes may improve BPH diagnosis and reduce the number of prostatic biopsies in patients with BPH.

Keywords: Prostate Specific Antigen(PSA), PSA Isoforms, sarcosine and Benign Prostatic Hyperplasia (BPH) diagnosis.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is an enlargement of prostate gland that is not cancerous, pressing against and pinches the urethra with eventual weakening of bladder leading to its narrowing and urine retention. Symptoms unrelated to BPH can be caused by bladder problems, urinary tract infections (UTIs), prostatitis or even cancer of the prostate (PCa). Early diagnosis of a disease is important, because the sooner the disease is detected, the better[1].

Prostate specific antigens (PSA) is synthesized in normal prostate epithelium, benign prostate hyperplasia (BPH) and all stages of prostate adenocarcinoma[2]. It is a protein produced only by the prostatic tissue and would seem to be an ideal marker for prostatic disease[3] . In clinical practice, total PSA analysis has been the gold standard in determining the presence of prostate diseases. Varying serum total PSA values are found in patients with normal prostate function, benign prostate hyperplasia (BPH) and prostate cancer[4] and diagnosis with PSA alone is error-prone and cannot distinguish between BPH from malignant disease, nor identify aggressive and indolent types[5].

The majority of PSA produced by the prostate is excreted in the semen but a small proportion ‘’leaks’’ In to the systemic circulation. Unfortunately, many related diseases of the prostate such as BPH and chronic inflammation also caused PSA increased release into the circulation[6].

PSA that reaches the serum in either free or bound to plasma proteins. The most important binding proteins are alpha-1- antichymotripsin (ACT), alpha-2-macroglobulin (A2M), and alpha-1-trypsiinhibitor (API). When it is protein bound, many of the epitopes on the PSA molecule are not available for antibody binding. Indeed, when bound to A2M, PSA is not detectable using the standard method of total PSA estimation[7].

Essentially the same group of men are at risk of BPH, chronic infection and cancer. This has reduced the utility of serum PSA as a diagnostic test for these diseases,. Specific PSA levels would therefore be expected to both increase the pick up of prostate related diseases with better accuracy than total alone[7].

In a new approach to this diagnostic dilemma, the current study was designed to estimate the serum levels of various PSA isoforms and serum sarcosine in patients with BPH and to evaluate whether combination of these biomarkers can improve the diagnosis of patients with the disease and early detection of the prostate disorders

MATERIALS AND METHOD

One hundred and fifty (150) Patients aged 30-90 years, from the Urology Unit Usmanu Danfodiyo

University Teaching Hospital Sokoto Nigeria, who had undergone Transrectal Ultra Sonography (TRUS), Digital Rectal Examination (DRE), and/or histologically confirmed and diagnosed to have BPH were used in the study. Two hundred (200) Control subjects, who were apparently healthy volunteers from among the staff in the hospital and other volunteers were also recruited in the study. Informed consent from all the participants and institutional ethical approval was obtained. Serum sarcosine was measured by the colourimetric method (BioVision Research Products, 980 Linda Vista Avenue, Mountain View, CA 94043 USA).Total and free Prostate Specific Antigen (tPSA,fPSA) was estimated by Elisa method[8] while complexed Prostate Specific Antigen (cPSA) was calculated mathematically by the formula: cPSA = Total PSA - (fPSA).

The data were analysed statistically for the diagnostic performance of the parameters in BPH patients using Anova, T-test and ROC curves in SPSS package version 17

RESULTS AND DISCUSSION

The mean values for serum sarcosine, total PSA, free PSA and complexed PSA in both patients and controls are shown on tables 1. There were statistically significant difference between BPH patients and controls in serum sarcosine, total, free and complexed testosterone levels (<0.05).

Defined reference ranges of PSA isoforms levels when controls were divided age wise 30-40, 41-50, 51-60 and 61-70 age ranges was shows in Table 2 . The distributions shows no significant difference was observed within the age ranges for total, free and complexed PSA levels (P<0.05). Serum sarcosine levels in this groups also showed no significant difference (P<0.05).

Table 1. Mean values of serum level of total, free and complex prostate specific antigen (tPSA, fPSA and cPSA) isoforms and serum sarcosine in patients and controls.

Subjects	n	tPSA (ng/ml)	fPSA (ng/ml)	CPSA (ng/ml)	Serum sarcosine(nmol/dl)
BPH	200	15.13±1.15	2.81±0.16	12.31±1.05	118.70±1.80
Controls	200	2.75±0.22	0.72±0.03	0.72±0.03	64.94±0.81
F		16.767 (22.340)	22.189 (16.767)	15.772 (21.117)	13.627 (11.441)
p-value		<0.01	<0.1	<0.01	<0.01
BPH vs Control		<0.05	<0.05	<0.05	<0.05

n = sample size SEM = standard error of mean

BPH = Benign Prostatic Hyperplasia

tPSA = total prostate specific antigen

fPSA = free prostate specific antigen

CPSA = complexed prostate specific antigen

P value = Significant

Table 2. Age distribution of total prostate specific antigen and other parameters in BPH patients (mean±SEM)

Age category (years)	N (200)	tPSA (ng/ml)	fPSA (ng/ml)	cPSA (ng/ml)	Sarcosine (nmol/dl)
41-50	42	12.24±2.01	2.46±0.32	9.77±1.84	119.95±4.39
51-60	87	14.86±1.66	2.84±0.25	12.03±1.50	117.39±2.87
61-70	46	17.86±3.22	2.99±3.36	14.87±3.04	121.67±3.31
>70	25	16.22±2.27	3.17±0.46	13.45±1.93	115.68±4.59
P-value		<0.05	>0.05	P <0.05	>0.05

n = sample size SEM = standard error of mean

BPH = Benign Prostatic Hyperplasia

tPSA = total prostate specific antigen

fPSA = free prostate specific antigen

cPSA = complexed prostate specific antigen

P <0.05 = significant p>0.05 = not significant

Table 3. Age distribution of total prostate specific antigen and other parameters in controls (mean±SEM)

Age category (years)	n (200)	tPSA (ng/ml)	fPSA (ng/ml)	cPSA (ng/ml)	Sarcosine (nmol/L)
30-40	76	2.39±0.14	0.70±0.04	1.70±0.11	66.02±1.4
41-50	54	2.67±.0.74	0.75±0.05	2.52±0.73	64.54±1.39
51-60	40	2.70±.23	0.73±0.07	1.97±.18	65.35±1.71
61-70	30	3.93±0.86	0.91±0.15	3.02±.72	66.66±3.64
P value		>0.05	>0.05	P >0.05	<0.05

n = sample size SEM = standard error of mean

tPSA = total prostate specific antigen

fPSA = free prostate specific antigen

cPSA = complexed prostate specific antigen

P <0.05 = significant p>0.05 = not significant

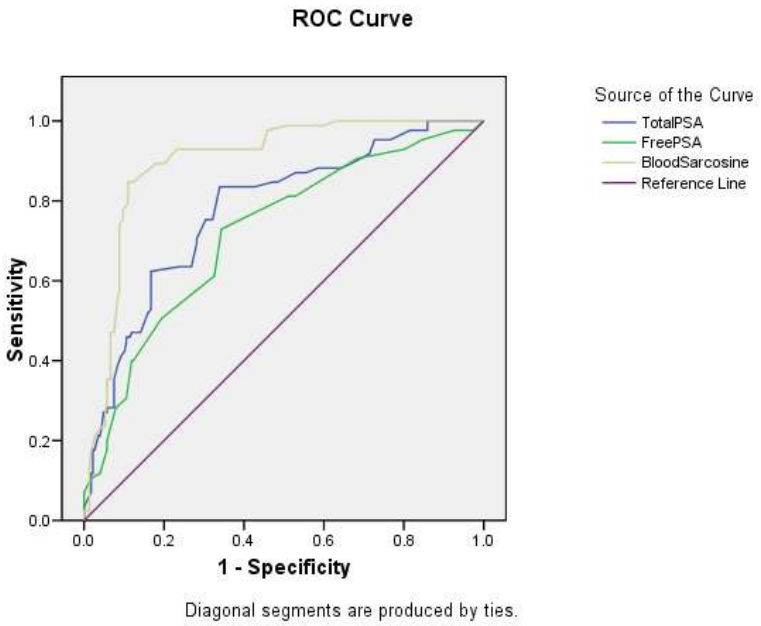

Figure 1:ROC Curve for total PSA, free PSA and Serum Sarcosine for the BPH group in PSA range 0-10ng/ml

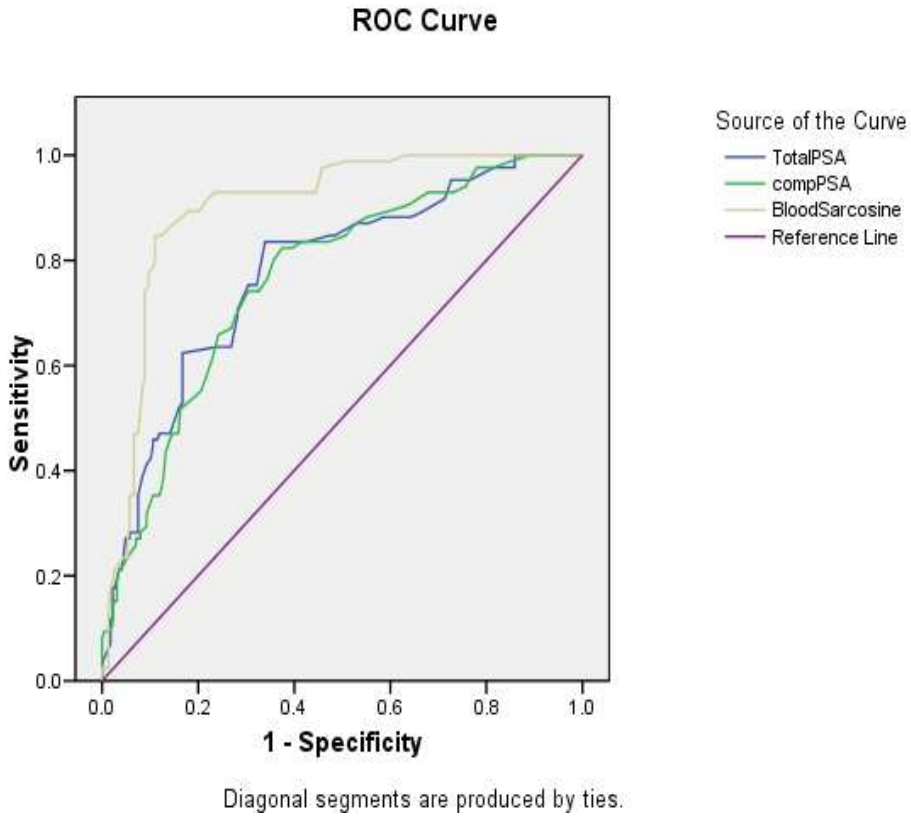

Figure 2:ROC Curve for total PSA, Complexed PSA and Serum Sarcosine for the BPH group in PSA range 0-10ng/ml

PSA = Prostate Specific antigen, **BPH**= Benign Prostatic Hyperplasia

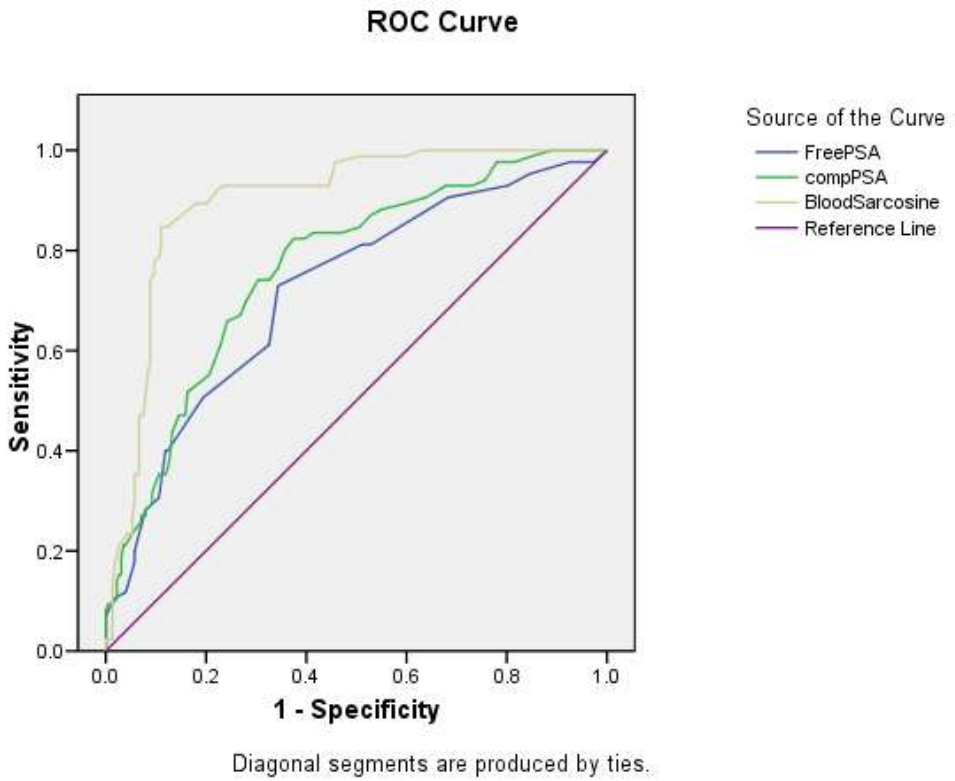

Figure 3: ROC Curve for free PSA, Complexed PSA and serum Sarcosine for the BPH group in PSA range 0-10ng/ml

PSA = Prostate Specific antigen, **BPH**= Benign Prostatic Hyperplasia

Despite the fact that almost all men may develop symptoms associated with benign prostatic hyperplasia within their lifetimes, no molecular markers for the disease or its likelihood to progress have been established. A marker of this type could be used to stratify patients into subpopulations as well as to identify individuals whose disease is most likely to progress[9].The use of serum-based prostate-specific antigen (PSA) has revolutionized the detection of prostate disorders and dramatically changed the course of these disorders. PSA by itself has limited specificity, and cannot distinguish between early stage prostate cancer and benign prostatic hyperplasia (BPH), resulting in many unnecessary biopsies. As serum total prostate-specific antigen (tPSA) lack clear thresholds balancing specificity and sensitivity for the early detection of BPH, continuous efforts are being made to discover new BPH markers[10].

In the current study, we aimed at evaluating the levels of three PSA isoforms and sarcosine, as an aid to the diagnosis of patients with BPH. Investigation of the structural heterogeneity of PSA revealed that some distinct forms are more frequently associated with PCa and others with BPH[11]. An important observation is the fact that tPSA and cPSA concentrations did not differ significantly between men with and without BPH. We found here, no any significant difference in the mean

levels of tPSA and cPSA (<0.05), in all the age groups, indicative of stability of these isoforms despite age variations. Our results also indicated that the major molecular species PSA isoforms found in BPH patients are total, followed by complexed with the lowest concentration in free isoform. Almost same pattern was observed in the controls as well. PSA was reported to comprise heterogeneous molecules differing in primary structure and in glycan composition. Structural variability exists among PSA forms in serum, seminal plasma, and hyperplastic or cancerous tissues[12]. These variability can be used to improve diagnostic chances, especially as using different experimental approaches, more than 30 immunoreactive isoforms have been separated from serum, seminal plasma, or prostate tissue[11]. Our findings showed that a single marker is unable to predict the presence of BPH. However, might be of additional value in combination with other markers.

With the increasing prevalence of BPH, comes the demand for a panel of molecular biomarkers that can confidently identify and monitor disease progression[13]. Biomarker panel is needed to identify symptomatic BPH and provide an insight into an individual patient clinical state, with the ability to detect symptomatic BPH before the onset of complication which often tend to be irreversible[7]. Furthermore, a panel of markers that could differentiate between symptomatic BPH and asymptomatic BPH and allow physicians to confidently treat patients with different levels of treatment aggression. Ultimately, Clinics and Laboratories would require a panel of markers that monitors the progression of BPH and would provide additional benefit by acting as an internal monitor to guide treatment decisions[13].

As new approaches to identifying panel of molecular markers as attempted in this study, further study is needed to clearly define the definitive value of PSA isoforms in BPH detection and their ability to modify the number of men undergoing prostate biopsy. The use of molecular forms of PSA has drastically renewed clinical research in enhancing the specificity in tPSA ranges. It is hoped the use of the PSA and its isoforms can significantly improve specificity compared with tPSA, with minimal loss of sensitivity in detecting PCa. Hence, this current study is aimed also at reawakening the interest in availing the populace the opportunity for proper assessment and diagnosis to prevent unnecessary biopsies. The findings of the study therefore suggests that the tPSA and %fPSA measurements be requested simultaneously.

CONCLUSION

the findings of the present study showed that PSA is significantly higher in the patient study groups than the controls. Free PSA measurement can as well enhance the specificity of the total PSA value, while reducing the number of unnecessary biopsies. Combination of these biomarkers

may serve as a vital tool in identifying men with clinically insignificant prostate disorders who could be candidates for active surveillance. It is being recommended that the parameters be considered and included in the list for routine screening and monitoring of patients at risk.

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