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Research Article

Prostate Specific Antigen (PSA) Derivatives for Diagnosis of Prostate Cancer and Benign Prostatic Hyperplasia Subjects in Sokoto, Nigeria

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Abstract

Over the years, many markers have been used for the diagnosis and follow-up of prostate disorders. With its attendant limitations, PSA is the most common marker used. In the present study, PSA ratios; fPSA/cPSA, fPSA/tPSA and cPSA/tPSA were evaluated in 150 prostate cancer (PCa), 200 benign hyperplasia (BPH) patients and 200 controls. Using Mann-Whitney U-Test, free PSA/complexPSA ratio (fPSA/cPSA) was 0. 18±0.01, 0.34±0.02, 0.48±0.02, freePSA/totalPSA ratio (fPSA/tPSA) was 0.19±0.11, 0.34±0.23 and 0.48±0.23 while complexPSA/totalPSA ratio (cPSA/tPSA) was 0.85±0.01, 0.7±0.01 and 0.70±0.01 in PCa, BPH and controls respectively. The difference in the ratios between all the groups are significant ($p<0.01$). Evidence from the current study suggested that, diagnosis and prognosis of prostate disorders can be widened and more steps need to be taken to determine the efficacy of these markers.

Keywords: PSA: Prostate Specific Antigen (PSA) ratios; PCa: Prostate cancer (PCa); BPH: Benign prostatic hyperplasia (BPH); diagnostic value

Introduction

The outstanding successes achieved in the treatment of prostate cancer should be credited to the "golden five" of this era, namely imaging, radiation, chemotherapy, surgery and screening programs [1]. For the past few years, serum PSA estimation has raised quite a cloud when it comes to its effectiveness as a biological marker for the detection of prostate disorders. Its deficiencies have given rise to serious efforts are made to improve its specificity by combining it with other existing biomarkers or discover and define new ones as an adjunct [2]. Serum PSA measurements show variable reliability when it comes to diagnosis of prostate disorders hence stimulating efforts to detect many more markers to aid early detection and treatment.

In men with normal prostate (that is, no cancer, hyperplasia, and no major inflammation/infection), the majority of PSA reflect the mature protein that has been inactivated by internal proteolytic cleavage. In contrast, this cleaved fraction is relatively decreased in prostate cancer and higher in BPH [3]. A number of factors also affect PSA levels in these diseases and should be known before making a decision. These include race, as men without cancer from different ethnic and racial

groups have different average PSA concentrations [4], medications, as Finasteride and Dutasteride, inhibitors of 5-alpha-reductase, produce an approximately 50% or greater decrease in serum PSA [5], rate of PSA change, as elevated serum PSA that continue to rise over time, is more likely to reflect prostate cancer than one that is stable suggestive of BPH or no cancer [6]. Overall, the positive predictive value for PSA >4.0ng/mL is approximately 30%, meaning that slightly less than one in three men with an elevated PSA will have prostate cancer detected on biopsy [7]. PSA levels between 4.0 and 10.0ng/mL, have positive predictive value of about 25% and nearly 75% of cancers detected within this "gray zone" are organ confined , not metastasized and therefore potentially curable by surgery [8].These poses a diagnostic conundrum, and clinicians and patients alike would like definitive answers1.

As the specificity of PSA alone is limited in some patients, there are a number of concern regarding the routine use of this test alone, and alternative strategy would be to improve the methods of detections. Perhaps by identifying novel diagnostic markers to serve as adjunct [9].The aim of the current work was to evaluate the efficacy of PSA ratios derivatives in the diagnosis of PCa and BPH patients in our environment.

Materials and Methods

One hundred and fifty (150) PCa Patients and two hundred (200) BPH patients aged 30-90 years, from the Urology Unit, UsmanuDanfodiyo University Teaching Hospital Sokoto Nigeria, who had undergone Trans rectal Ultra Sonography (TRUS), Digital Rectal Examination (DRE), and/or histologically confirmed and diagnosed to have prostate cancer or BPH were recruited 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. Total and free PSA was estimated by Elisa method [10] and complex PSA value extrapolated mathematically from the two. Accordingly, ratios for fPSA/cPSA, fPSA/tPSA and cPSA/tPSA in PCa, BPH patients and controls were evaluated using Mann-Whitney U-Test calculator obtainable at SciStatCalc website.

The data were analysed statistically using nova, and t-test with SPSS package version 17.

Results

Results of the current work are shown on table 1. The differences in the ratios between all the groups were statistically significant (p<0.01).

Subjects	N	fPSA/cPSA	fPSA/tPSA	cPSA/tPSA
BPH	200	0.34±0.02	0.34±0.23	0.7±0.01
PCa	150	0. 18±0.01	0.19±0.11	0.85±0.01
Controls	200	0.48±0.02	0.48±0.23	0.70±0.01
F		5.758 (6.856)	8.693 (7.306)	11.441 (13.627)
p-value		<0.01	<0.01	<0.01
BPH vsPCa		<0.05	<0.05	<0.05
BPH vs		<0.05	<0.05	<0.05
Control		<0.05	<0.05	<0.05
PCavs Control				

n = sample size

SEM = standard error of mean

BPH = Benign Prostatic Hyperplasia

PCa = Prostate cancer

tPSA = total prostate specific antigen

fPSA = free prostate specific antigen

cPSA = complexed prostate specific antigen

P-Value: significant

Table 1. Mean values of PSA ratios (mean±SEM) in patients and controls.

Discussion

The need for an accurate marker is driven by the fear of unnecessary biopsies on the one hand and the more danger risk of missing a treatable prostate disease on the other. Ongoing efforts are targeted at identifying new serum markers that will have greater diagnostic accuracy and can predict aggressive diseases whose treatment will save lives1. Studies have shown that, the levels of free PSA in the serum act as a more accurate marker for BPH, while the levels of complexes PSA more accurately predict prostate cancer. As PSA is organ specific and not prostate cancer-specific, there is considerable degree of overlap between patients with benign pathologies such as prostatitis, benign hyperplasia BPH or urinary retention [11].

To provide accuracy in prostate disorder detections, we saw an urgent need to identify more prostate disorder biomarkers that can serve as an adjunct in performance characteristics than PSA alone. In the current work, we report the interplay of three PSA derivatives and how their value can be used in the diagnosis and management of prostate disorders. For the first time, we are reporting a coordinated pattern of fPSA/cPSA

and fPSA/tPSA ratios of the studied population in which, highest ratio was observed in controls, followed by BPH patients with lowest ratio seen in PCa patients. We cannot see similar pattern in cPSA/tPSA ratio. Significant variations between the ratios seen in the two groups of patients when compared with controls may interest scientific community in number of ways. First, if validated, these ratios may have diagnostic value, meaning an adjunct to the existing biomarkers used for PCa and BPH patients. Second, can be used as a screening tool as persistent decrease in their level may serve as a pointer towards a disease state, useful in risk stratification in which active surveillance of the affected individuals can be helpful. Thirdly, the wider gap between their ratios observed in BPH vsPCa, patients, and these PSA derivatives may have a promising effect for distinguishing patients with benign and malignant prostate disease. In our community, these ratios may also serve as differential diagnosis that will exclude BPH patients from unnecessary biopsies with attendant consequences of this invasive procedure.

In the current settings, there is no consensus on using any of the PSA modifications, and none of them has been shown to reduce the number of biopsies or improve clinical outcomes [12]. Considerable data however, have shown the potential harms of misdiagnosis and aggressive treatment of prostate disorders [13]. Thus, any choice of PSA value involves a tradeoff between sensitivity and specificity, as shown in many studies. Lower PSA cut-off point would improve test sensitivity; it would also reduce specificity, leading to far more false-positive tests and unnecessary biopsies [14]. The rapid advancements in detection techniques have made it possible to identify a large number of new possible biomarkers, as an ideal biomarker for prostate disorders has not been discovered yet. Sometimes however, just one marker is not enough. This fact gave rise to the idea that the use of multiple markers at the same time as suggested here could provide improved results [15]. We are with the opinion that measurement of different biomarker arrays may give us signatures that could prove to be a very accurate analytical tool for diagnosis, prognosis and patients follow-up [16].

The f PSA/t PSA ratios has been used to improve cancer detection especially when the total PSA is in the normal range (<4ng/ml) and most often to increase the specificity of cancer detection where PSA is in the gray zone (4.1-10ng/ml) [17].

In conclusion, the use of PSA derivatives has the potential to improve upon the current performance characteristics of the PSA test alone. An improved screening test may dramatically reduce the number of men undergoing an unnecessary biopsy and simultaneously enables clinicians to focus on high-risk cases of localized prostate cancer in a population of men likely to benefit from radical intervention [9].

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