ORIGINAL ARTICLE

COMPARISON OF PROSTATE-SPECIFIC ANTIGEN RATIOS – RESOLVING THE UROLOGIST'S DILEMMA IN NIGERIAN MEN WITH PROSTATE CANCER AND BENIGN PROSTATIC HYPERPLASIA

Authors

Eyam Sunday Eyam[1], Eyam Lilian Eberechukwu[2], EneAsuquo Bassey[1], OgarekpeYeonun Mba[3], BabatopeOluwakorede Ayodele[3]

Affiliations

1. Department of Chemical Pathology, Faculty of Basic Clinical Sciences, University of Calabar.
2. Department of Public Health, Faculty of Allied Medical Sciences, University of Calabar.
3. Department of Chemical Pathology, University of Calabar Teaching Hospital, Calabar.

Email Contacts

Eyam Sunday Eyam Corresponding author, Email: dr.eyam@yahoo.com
Eyam Lilian Eberechuwu, Email: lilyeyam@yahoo.com
Ene Asuquo Bassey, Email: asuquoene@unical.edu.ng
OgarekpeYeonun Mba, Email: yeonunogarekpe@yahoo.com
Babatope Oluwakorede Ayodele, Email: drkoredesurg@gmail.com

ABSTRACT

Background
Differentiating prostrate diseases using PSA is difficult because PSA changes are not prostate disease-specific which is the Urologist's dilemma in the diagnosis of prostate cancer (PCa) making it necessary to find ways of improving PSA sensitivity.

Objective
The study analyzed the molecular forms of PSA and compared the ability of their ratios to differentiate between BPH and PCa in Nigerian men.

Materials and method A cross-sectional descriptive multi-centred study that consecutively recruited 120 patients from the urology clinics of Lagos University and University of Calabar Teaching Hospitals in Nigeria. Thirty participants each with BPH and PCa were recruited from each centre over one year. Treatment-naïve Patients were histological confirmed for PCa and their Sera analyzed for cPSA, fPSA, and tPSA using WKEA ELISA kits and read off with 2100 STAT FAX microplate reader.

Results
The interquartile ranges were 0.53-0.85 and 0.04-0.20 with medians of 0.67 and 0.14 for PCa and BPH respectively. p-Value= .001. On the other hand fPSA to tPSA ratios for PCa and BPH had interquartile ranges of 0.03-0.26 (median 0.16) and 0.63-0.88 (median 0.74) respectively. cPSA to total PSA ratio ROC AUC was 0.68 at a cutoff of less than/equal to 33%, with a sensitivity of 57.6% and specificity of 71.2% against fPSA to tPSA ratio which had ROC AUC of 0.66 at a cutoff of less than/equal to 26% with a sensitivity of 80.3% and specificity of 52.5% to differentiate between PCa and BPH.

Conclusion
Both cPSA to tPSA ratio and fPSA to tPSA ratio are good parameters that improve the early differentiation of PCa from BPH. However, cPSA to tPSA ratio outperformed fPSA to tPSA ratio in terms of specificity and therefore may improve the differentiation of PCa from BPH.

Keywords
Prostate cancer, Benign prostatic hyperplasia, Complexed PSA, Free PSA,Total PSA, Nigerian men

INTRODUCTION

The prevalence of prostate cancer (PCa), like most other diseases, varies across ethnic and racial divides worldwide.[1, 2] This is thought to be a result of differences in genetic make-up, environment, diet, and lifestyle.[3, 4] It is the most commonly diagnosed cancer among African men, majority of whom are diagnosed at advance stages.[4] Incidence among Nigerian men is 127/100000 male population.[5] Benign prostatic hyperplasia (BPH) on the other hand, is common among the ageing Nigerian male population and constitutes a lot of health and economic burden on patients with a prevalence of 25.35% noted in a study that was carried out in the South-Eastern part of Nigeria.[6] Differentiating between these two common prostate diseases has become the urologists' dilemma in Nigeria, due to the deficiencies inherent in the routine diagnostic methods. More and more research is being done to improve the differentiating ability of various methods but these studies are carried out mostly in Caucasian and African-American populations which do not necessarily represent or reflect other ethnicities especially the indigenous African population.[7] For decades now, total prostate-specific antigen (tPSA) has been a useful biomarker tool for early diagnosis of prostate diseases but is not sufficiently disease-specific to differentiate between PCa and BPH.[8] This is due to the overlap in values in both conditions using 4.0ng/mL as the cutoff value. [9] In a recent study in Nigeria, it was noted that among patients with PCa disease, 20% of them had tPSA values below10.0 ng/mL, while another 10% had values below 4.0ng/mL.[10] Studies have also shown that at the conventional cut-off value of 10.0 ng/mL as a distinctive limit between malignant and benign prostate tumours, there was a 65% false positive increase in serum PSA concentrations in non-malignant prostate conditions.[11, 12] These aberrations support the need for further researches to enhance the differentiation of PCa and BPH, especially in Nigerian men.[10, 13] This will improve early diagnosis, promote appropriate patient selection for appropriate and prompt treatment modalities and prevent the sequelae of advance disease often associated with delayed diagnosis.

MATERIALS AND METHOD

It was a cross-sectional descriptive study involving one hundred and twenty male patients aged between 50 and 80 years consecutively recruited from two tertiary hospitals, University of Calabar Teaching Hospital, Calabar in South-South Nigeria and Lagos University Teaching Hospital, Idi-Araba, Lagos in South-West Nigeria. Thirty treatment-naive patients with a histologically confirmed diagnosis of prostate cancer (PCa) and thirty treatment-naive patients with benign prostatic hyperplasia (BPH) were recruited from the urology clinics of the two centres making a total of sixty patients from each centre. Ethical approval was obtained from the health research ethics committee of the two centres separately and the study lasted for one year. Four millilitres of blood was collected into SST vacutainer tubes from each patient using multipurpose sample needles and the serum was divided in aliquots into two separate cryotubes and stored at a temperature of -80^{o}C. Analyses for complexed PSA, free PSA and total PSA were done using WKEA ELISA kits and absorbancies read off with 2100 STAT FAX model microplate reader.

RESULTS

The levels of total PSA, free PSA and complexed PSA were non-parametrically distributed hence interquartile range was implored during analysis as shown in table I. Total PSA levels were lower in BPH than in PCa with median values of 8.40 (3.80-15.00) and 19.35 (10.57-72.50) respectively. Levels of free PSA were higher in BPH with a value of 6.00(2.60-12.90) compared to levels in PCa with a value of 2.60(0.80-4.80). Complexed PSA on the other hand had values of 0.85(0.52-1.17) and 15.80(7.70-40.15) in BPH and in PCa respectively. The Mann-Whitney U-test showed the P-values of tPSA, fPSA, and cPSA to be statistically significant at $P < 0.05$.

Table I
showing interquartile range (IQR) i.e. 25-75 percentile of tPSA, fPSA, and cPSA.

Variable	BPH N= Median (IQR)	PCa N= Median (IQR)	p-Value
tPSA	8.40 (3.80-15.00)	19.35 (10.57-72.50)	< 0.005
fPSA	6.00 (2.60-12.90)	2.60 (0.80-4.80)	
cPSA	0.85 (0.52-1.17)	15.80 (7.70-40.15)	

The medians of free prostate-specific antigen to total prostate-specific antigen ratio (fPSA/tPSA) and complexed prostate-specific antigen to total prostate-specific antigen ratio (cPSA/tPSA) were statistically compared as shown in Table 1. The median fPSA/tPSA ratio was 0.74 for benign prostatic hyperplasia (BPH) with an interquartile range (IQR) of 0.63-0.88 and 0.16 with IQR of 0.03-0.26 for prostate cancer (PCa), p = .001. The median cPSA/tPSA ratio for BPH was 0.14 with an IQR of 0.04-0.20 and 0.67 for PCa with an IQR of 0.53-0.85, p = .001.

Table 1:
Median interquartile ranges of ratios of fPSA/tPSA, cPSA/tPSA and fPSA/cPSA.

Variable	BPH N=60 Median IQR	PCa N=60 Median IQR	p-value
fPSA/tPSA	0.74(0.63-0.88)	0.16(0.03-0.26)	.001
cPSA/tPSA	0.14 (0.04-0.20)	0.67(0.53-0.85)	.001

Figure 1: ROC of fPSA/tPSA ratio and cPSA/tPSA ratio???

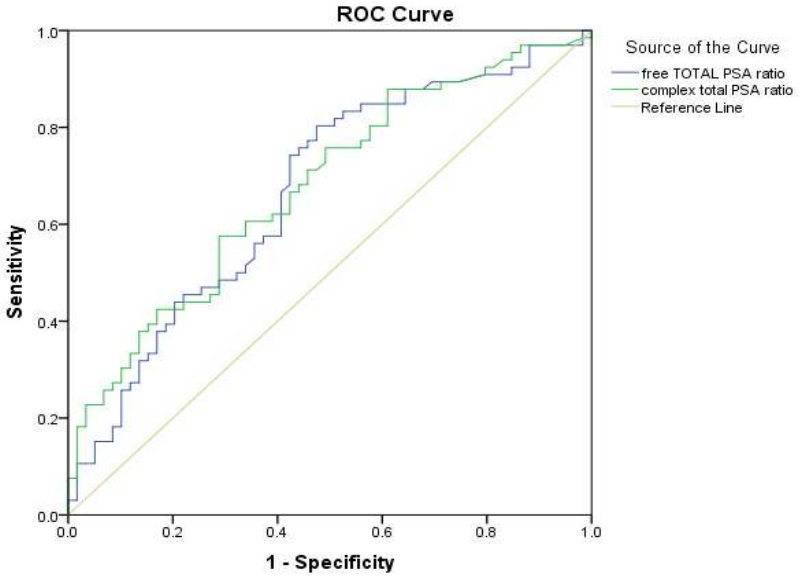

Figure 1 shows receiver operating characteristic curve (ROC) analyses of complexed PSA to total PSA ratio and free PSA to total PSA ratio were compared in their ability to detect prostate cancer as shown in the figure above. The complexed PSA to total PSA ratio showed the ROC area under the curve (AUC) to be 0.68 witha sensitivity of 57.0% and specificity of 71.2% at a cutoff of less than/equal to (≤) 33% against free PSA to total PSA ratio with ROC AUC of 0.66, a sensitivity of 80.3% and specificity of 52.5% at a cutoff of 25%.

TABLE II: Table of ROC analyses of cPSA/tPSA ratio and fPSA/tPSA ratio.

Variable	Sensitivity(%)	Specificity(%)	Cutoff(%)	AUC	p-value
fPSA/tPSA	80.3	52.5	≤ 0.26	0.66	0.001??
cPSA/tPSA	57.6	71.2	≤ 0.33	0.68	0.001???

DISCUSSION

Total prostate-specific antigen (PSA) has been the major biochemical tool in use for the screening, diagnosis, and follow-up of patients with prostate diseases especially prostate cancer (PCa) in Nigeria. However, because of its lack of prostate disease specificity, many other modalities have been explored to improve the differentiation of PCa from other benign prostate diseases including benign prostatic hyperplasia (BPH). Most studies have focused attention on the use of percentage-free PSA to differentiate between PCa and BPH when PSA values are in the grey zone between 4.0ng/mL and 10ng/mL. This work set out to compare the differentiating ability of the ratio of complexed Prostate-specific antigen to total Prostate-specific antigen (cPSA/tPSA) with the ratio of free Prostate-specific antigen to total Prostate-specific antigen (fPSA/tPSA) in the diagnosis of PCa and BPH in Nigerian men.

Results obtained in this study demoonstrated the benefit of using ratios of the molecular forms of PSA in the differential diagnoses of prostate diseases. The results revealed that there was a statistical difference between complexed PSA to total PSA ratio compared to free PSA to total PSA ratio in improving the differentiation between PCa and BPH which was similar to other studies done in the past[17] [18]..However, the result was at variance with another study which showed a greater receiver operating characteristics curve - area under the curve (ROC-AUC) for free to total PSA ratio than complexed to total PSA ratio and in which a larger sample size was employed.[14]The study further revealed that complexed to total PSA ratio was more specific in detecting PCa than BPH while the free to total PSA ratio was more specific in detecting BPH than PCa. The study was in agreement with other studies that revealed that the lower the free to total PSA ratio the more likely the presence of PCa.[9] Going further, the study showed that the higher the complexed to total PSA ratio the greater the likelihood of the presence of PCa.

In all, the study showed that the determination and use of ratios of molecular forms of PSA (complexed PSA to total PSA ratio and free PSA to total PSA ratio) greatly improves the specificity of detecting and differentiating PCa from BPH and may greatly reduce and prevent the unnecessary biopsies carried out on Nigerian men with equivocal total PSA values and no obvious clinical signs of malignant disease. It may also reduce the time of decision-making in determining treatment modality by early and appropriate categorization of the patient to a definite diagnosis to administer the prompt and appropriate intervention.

CONCLUSION

The determination of ratios of molecular forms of PSA may improve the detection and differentiation of PCa and BPH in patients who are in the subclinical state of disease with equivocal values of total PSA. It may be of economic value and early treatment benefit to patients if clinicians request free or complexed PSA along with total PSA at the point of first contact with the patient thus reducingor eliminating the onset of complications that could arise following a delay in making accurate treatment decisions.

CONFLICT OF INTEREST

There is no disclosure of anyconflicting interest regarding this research work.

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