Comparison between Mean Prostate Specific Antigen Density in menwith Benign Prostatic Hyperplasia (BPH) Following Biopsy and Conventional Value of 0.15ng/ml/cc.

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ABSTRACT

Prostate specific antigen density (PSAD) is a volume corrected prostate specific antigen (PSA). It has been a very useful tool in discriminating between benign prostatic hyperplasia (BPH) and prostate cancer especially in the gray zone of the PSA (4-10ng/ml). The guideline for the diagnosis and treatment of prostate malignancy prescribes 0.15ng/ml per volume of prostate tissue as the cut-off value to enhance diagnostic suspicion of prostate cancer. This study was aimed at comparing the mean value of PSAD in our cohort of patients with the conventional value. Seventy-one patients with histological diagnosis of BPH were evaluated between January 2016 and December 2017. Their clinical information wascollated including bio-data, important findings on history and physical examination, imaging studies and prostate biopsy results. Data were analyzed using the statistical package for the social sciences (SPSS) version 20.0. The patients were aged between 50 and 85 years with a mean age of 64.79±8.09 years. Mean PSA was 4.95±3.24ng/ml, while mean prostate volume and PSAD were 73.20±57.82mls and 0.078±0.55ng/ml/ccrespectively. Using one samplet-test for data analysis, there was significant difference in means (.0716);P-value was set at 0.05. There was a marked difference in means between the PSAD values which was also statistically significant.

Keywords: Benign Prostatic, Hyperplasia, Prostate, Antigen, Density

INTRODUCTION

Mean Prostate Specific Antigen Density (PSAD) isa volume corrected PSA. It is defined as serum PSA divided by the volume of the prostate[1] and it is said to enhance the specificity of Prostate cancer diagnosis especially in the gray zone of the PSA (4-10ng/ml). PSAD complements PSA and digital rectal examination (DRE) in the diagnosis and treatment of Prostate cancer. Many cut-off values for PSAD have been documented in the literature to help discriminate between patients with BPH and Prostate cancer, but Tauro *et al*.[2] Lujan *et al*. [3] and Udeh *et al.* [4] proposed a mean cut-off value of 0.15ng/ml/cc of prostate tissue to minimize false positive results.Despite increased sensitivity and specificity recorded at this cut-off value, Sasaki *et al.*[5] and Lujan et al[3]advocated a shift to 0.18ng/ml/cc since the former value missed 8 cases of cancer and 43% of patients underwent unnecessary prostate biopsies in their study.[5] However, Sarkar *et al*.[6] did not miss any cancer case at the same cut-off value. All these efforts are geared towards achieving 100% sensitivity and an acceptable high specificity to prevent missed cases of cancer and unnecessary prostate biopsy.

PSA is a tumour marker for the diagnosis and treatment of patients with Prostate cancer. Although with acceptable sensitivity, it lacks adequate specificity especially when used as a screening test.[8] It is organ specific but not cancer specific and can be elevated in benign conditions like BPH and Prostatitis. Its value can also be raised after DRE and prostate biopsy. PSA is secreted by the ductal epithelial cells of the prostate and thought to be dependent on prostate volume and the number of epithelial cells in the prostate.[9] Since benign conditions can also produce clinically significant PSA (i.e. above the reference range of 0-4ng/ml) and indicate a need to rule out a malignant lesion, the concept of PSAD had evolved to checkmate unnecessary biopsies based on a conventionally applied guideline for diagnosis and treatment of Prostate cancer.[10]Although this concept is faced with a lot of controversies, some authors have adopted it with close monitoring of their patients in combination with other tools such

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as PSA velocity and free to total PSA ratio to optimize accurate diagnosis while minimizing unnecessary biopsies with its attendant complications. The purpose of this study was to compare the mean PSAD in our cohort of BPH patients with the guideline cut-off value.

MATERIALS AND METHOD

This study was conducted retrospectively in the histopathology laboratory for prostate biopsy results and the health records department for patient's case notes between January 2016 to December 2017. They were 71 patients that met the inclusion criteria. Exclusion criteria included patients diagnosed with Prostate cancer, bladder cancer, or urinary tract infection; or patients who had prior urethral instrumentation, prostate biopsy and patients with incomplete clinical information. Information retrieved included findings in the history and physical examination and relevant investigation results such as full blood count, fasting blood sugar, renal function test, PSA and prostate scan with trans-rectal ultrasound scan guided prostate biopsy. Ten (10) to twelve (12) cores of tissues were taken and sent for histopathological analysis. Data collected were entered into a structured proforma. Statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 20.0software. Frequency of variables were determined. Continuous variables were summarized using means and standard deviations. One sample t-test was used to obtain the difference between the means; P-value was set at <0.05.

RESULTS

71 patients with histological evidence of BPH aged between 50 and 85 years were studied. Mean age was 64.79±8.09 years while mean PSA was 4.95±3.24ng/ml. Mean PSAD was 0.078±0.055ng/ml/cc and mean prostate volume was 73.20 ± 57.82mls. Majority of the patients were in their 7th decade of life (43.7%). Retired civil servants were more in number (38.0%). Patients with PSAD <0.15 were 86.0% while those >0.15 were 14.0%. Using one samplet-test statistics, there was a statistically significant difference between mean PSAD recorded in our study and the conventional cut-off value (P-value <0.05) with a mean difference of 0.0716. Prostate volume correlated with PSA, r(71) = 0.40; P<0.05 and inversely with PSAD; r(71) = -0.31 P<0.05

Table 1:
(i) Frequency Table for Age

Age (years)	Frequency (n)	Percent (%)	Cumulative Percent (%)
50-59	18	25.4	25.4
60-69	31	43.7	69.0
70-79	19	26.8	95.8
80-89	3	4.2	100.0
Total	71	100.0	

(ii) Frequency Table for occupation

Occupation	Frequency (n)	Percent (%)	Cumulative Percent (%)
Farming	4	5.6	5.6
Trading	13	18.3	23.9
Business	4	5.6	29.6
Civil Servant	15	21.1	50.7
Retired Civil Servant	27	38.0	88.7
Clergy	8	11.3	100.0
Total	71	100.0	

(iii) Frequency Table for PSAD

Value	Frequency (n)	Percent (%)	Cumulative Percent (%)
<0.15	61	86.0	86.0
>0.15	10	14.0	100.0
Total	71	100.0	

Table 2: Descriptive Statistics for Variables

Variable	Mean	Standard Deviation
Age	64.79	8.092
PSA	4.95	3.247
PSAD	.078	0.055
PV	73.20	57.820

Table 3: Independent t-test

		Test value = 0.15		
Number (n)	Mean	Std. Deviation	Mean Difference	P-value
71	0.078	0.0556	-0.0716	0.000

Table 4: Correlations between Variables

			r	P-value
PV	versus	PSA	0.410	.000*
PV	versus	PSAD	-0.313	.008*
PSA	versus	PSAD	0.565	.000*

*Correlation is significant at P<.05.

DISCUSSION

Prostate specific antigen density is defined as serum PSA divided by the volume of the prostate.[1] It depends on the prostate volume and serum PSA value. PSAD is said to discriminate between BPH and Prostate cancer and many cut-off values have been postulated with different results. Benson *et al.*[10] documented a cut-off value of 0.15ng/ml/cc which currently serves as an international guideline in the diagnosis and treatment of prostate cancer. Benign conditions of the prostate such as BPH can result in elevated PSA mainly due to increased volume of the prostate and application of PSAD as a tool for evaluation obviates the need for biopsy since PSAD remains superior to PSA in the diagnosis of Prostate cancer.[11] The use of PSA alone in prostate cancer diagnosis often leads to over-diagnosis and unnecessary biopsy.[12]Fu-Xiang L *et al.,*[13]using the conventional PSAD cut-off value recorded a sensitivity of 86.6% and a specificity of 71.2% for diagnosis of prostate malignancy while Zlotta et al[14] reported a sensitivity and specificity of 74.3% and 65.9% respectively. Yet Sarkar *et al.*[6] had a 100% sensitivity and 78.38% specificity.These authors further experimented on a PSAD cut-off value of 0.18ng/ml/cc and got a specificity of 91.59% while maintaining 100% sensitivity. All focus is directed on eliminating false positive and negative results especially in the gray zone of the PSA. However, these studies failed to document the histology reports of those missed cancer cases to assess the clinical significance and prognosis of those patients to warrant concerns. The natural history of Prostate cancer is that of a slow growing

tumour of which may not manifest clinically throughout the lifetime of the sufferer. Moreso, age of these patients were not mentioned together with the number of biopsy cores taken which could have also affected cancer detection especially when cores were few. Besides our concerns raised above, Oesterling LE *et al.*[15] noted that PSAD varies with age and as a component of the equation, Kleer E et al[16] reported an approximately 10% error in prostate volume measurement using transrectal ultrasound scan (TRUS). Moreover, there is about a three-fold difference in the ratio of epithelium to stroma between prostates,[17] while prostate volume and as a follow up with serum PSA, varies between races.[18,19] Prostate volume has been noted to be lower in the Japanese population than in whites with more PSA per unit Prostate volume recorded in the Japanese men.[19] This also emphasizes the need to incorporate racial and ethnic differences in making decisions about PSAD cut-off values.

The mean age of our patients was 64.79 ± .09 years (Table 2) similar to another study in Nigerian men with BPH[20] and lower than a study of Italian men with the same condition.[21] The peak incidence occurred in the 7th decade of life. This was also recorded among Indian men.[20] Mean PSA was 4.95±3.24ng/ml (Table 2) which was higher than mean PSA in another study even with a similar mean age.[22] Mean PV was 73.20 ± 57.82mls (Table 2) in gross excess of the Indian study reflecting an increase in PSA as PV increases, background racial and ethnic differences notwithstanding.[22] We noted that 86.0% of patients had PSAD value <0.15ng/ml/cc while the remaining14.0% had PSAD > 0.15ng/ml/cc [Table 1(iii)]. The latter group had smaller prostates that magnified PSAD at a given PSA. Here, prostate biopsy could not completely rule out foci of malignancy, the study being retrospective, but they will be followed up with repeat DRE, PSA and repeat biopsy where indicated. Mean PSAD was 0.078 ± 0.55ng/ml/cc (Table 2). Other authors recorded values between 0.17-0.27ng/ml/cc.[23-25] Their mean PV was also lower than in our study which can account for the higher value of PSAD for a given serum PSA.[23] Our patients were noted to have a higher prostate volume thereby reducing the PSAD at a given serum PSA. Again, they were hospital based who only presented with severe symptoms and advancing age accounting for the high Prostate volume since most studies had already documented a positive correlation between Prostate volume and age.[15,23,26]

Comparing mean PSAD with the standard guideline value, there was a significant difference in means with a mean difference of -0.0716 (P-value<0.05) (Table 4). This implies that our men have larger prostates and relatively lower levels of serum PSA which therefore accounts for the lower mean PSAD value. We will need a longitudinal study to characterize and probably determine our local cut-off value to prevent misdiagnosis and most importantly deploy PSA velocity, PSA total and free ratio as adjuncts, to better discriminate between BPH and Prostate cancer prior to prostate biopsy, when indicated. Prostate volume correlated inversely with PSAD (Table 4); meaning that the higher the Prostate volume the lower the values of PSAD.

Some limitations of this study include the retrospective nature which did not allow verification of true absence of malignancy. A pre-biopsy prostate multi-parametric MRI was not done because this facility is not available at the index hospital. Being a hospital based study, we may have used patients with larger prostates than the mean in the general population. However, we consider our study to be informative enough to promote and stimulate future research in this area.

CONCLUSION

PSAD has been one of the tools that can be used to discriminate between BPH and Prostate cancer especially in the gray zone of PSA. In our study, there was a significant difference between mean PSAD and the guideline cut-off value suggesting bigger prostate volumes that produce comparatively less PSA. Further study is needed to standardize our local value since the conventional cut-off value is already influenced by contending variables such as ethnic and racial factors apart from differences in the methodology, study design as well as age and number of patients studied.

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