Outcome of Obesity on PSA among Male Nigerians without Prostatic Disorders

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ABSTRACT
Background: *Obesity is reported to attenuate serum PSA concentrations, thereby influencing the diagnosis of prostatic diseases. However, most of these reports had emanated from the Caucasian populations.*
Aim: *The study was structured to investigate the effect of obesity on serum PSA among Negroid Nigerian men devoid of prostatic disorders.*
Methods: *This was a descriptive cross-sectional study of 1332 middle-aged and elderly males devoid of prostatic diseases, prospectively conducted in a public tertiary health facility in Nigeria. Clinical, demographic, anthropometric and laboratory variables were obtained from each study participant and analyzed using SPSS version 21. Laboratory analysis was undertaken using standard protocols.*
Results: *The frequency of underweight, overweight, and obesity was 0.9%, 51.4%, and 22.5% respectively. A progressive decrease of serum PSA levels with increasing BMI status was observed among the entire study cohorts. Inverse relationship existed between PSA and BMI (crude beta coefficient:-0.601; $p<0.001$) among the study cohorts which was not significantly influenced by confounders (adjusted beta coefficient:-0.509;$p<0.001$). The inverse relationship was more pronounced among the obese cohorts (crude beta coefficient:-0.539;$p<0.001$; adjusted beta coefficient:-0.530;$p<0.001$) compared to the underweight, normal weight, and the overweight cohorts.*
Conclusion: *The study confirms the inverse relationship between obesity and PSA. Hence, efforts to consider these relationship in the interpretation of PSA results is highly warranted.*
However, more population-based studies are suggested to further explore the influence of obesity on PSA levels across ethnic groups to validate the use of the BMI-adjusted PSA levels as suggested by previous researchers.

Keywords: *Nigeria; Prostate; Obesity; PSA*

INTRODUCTION

Serum prostate-specific antigen (PSA) is the most common tumor marker utilized in the evaluation of prostatic disorders (Catalona, 2014). Since its discovery, serum PSA has revolutionized the screening and diagnosis of prostatic diseases, especially prostate cancer (Banerjee, Iqbal, Kumar, Kambale, & Bavikar, 2016; Wadgaonkar, Patil, Mahajan, & Yengantiwar, 2013). The ease and the low-cost of the PSA assay has been suggested as the single most important factor for the increased detection rates of prostate cancer disease currently been reported from most regions of the world (Eastham, 2017). However, while the tumor marker is organ-specific, it is not disease-specific (Wadgaonkar et al., 2013). It has also been found useful in the screening and diagnosis of other benign conditions of the prostate gland (Kambale et al., 2016; Wadgaonkar et al., 2013; Eastham, 2017).

Various modalities have been suggested to improve the clinical utility of PSA in the evaluation of prostatic diseases as several factors tend to influence its serum level including age, drugs, diet, fasting plasma glucose, hypertension, benign prostatic hyperplasia, and prostate volume (Ayyildiz & Ayyildiz, 2014; Wright & Stanford, 2011; Navin & Loffe, 2017). The use of PSA age-specific reference ranges has been advocated due to the influence of advancing age on the tumor marker (Amadi & Odum, 2018). The use of PSA molecular forms (free, bound), PSA derivatives (PSA velocity, PSA density, PSA mass, free to total PSA ratio, prostate health index), and PSA isoforms have also been suggested to fine-turn the discriminant assessment of malignant and benign conditions of the prostate gland (Ayyildiz & Ayyildiz, 2014).

Currently, some researchers had suggested the use of serum adjusted PSA levels based on the body mass index (BMI) (Loeb et al., 2009; Price, Hamilton, Robertson, Butts, & Freedland, 2008). This is based on the observation by some researchers that increasing obesity status assessed using BMI inversely alters the serum concentrations of PSA (Xiang, Sheng, Ma, & Nan, 2015).

These researchers had noted in their various studies that the high BMI status attenuates the levels of serum concentration of PSA with the conclusion that it could delay the biopsy and the subsequent diagnostic decisions in the management of prostatic diseases among men of obese status (Harrison et al., 2016). Some of these researchers had recently advocated the use of BMI-adjusted PSA levels to offset the influence of obesity on the serum PSA concentrations (Loeb et al., 2009).

However, some other authors have also reported contradictory findings of the inverse relationship between obesity and PSA in the literature (Sanchez-Bonet et al., 2017; Capitano et al., 2012). While some of these authors had reported nil relationships (Sanchez-Bonet et al., 2017), some others have reported positive relationships (Capitano et al., 2012). Some other authors have also suggested more studies in different ethnicities and regions to further explore the relationship between obesity and serum PSA levels among men at risk of prostatic diseases (Ikuerowo, Omisanjo, Bioku, Ajala, & Esho, 2012).

Epidemiologic report on the relationship between obesity and serum PSA levels in middle-aged and elderly males, who bear the brunt of the diseases of the prostate gland, is scarce among men of Negroid race. Hence, the primary objective of this study was to investigate the relationship between obesity (using BMI as an index of obesity) and PSA among middle-aged and elderly men of Nigerian origin.

MATERIALS AND METHODS

This was a prospective cross-sectional hospital-based study, conducted between January, 2016 and November, 2018 in the University of Port Harcourt Teaching Hospital (UPTH), Nigeria. Approval for the study was granted by the UPTH Research Ethics Committee. Each participant gave informed consent before recruitment. The study protocol was in accordance with the World Medical Association's Declaration of Helsinki which was promulgated in 1964 and subsequently amended in 2000.

During the study period, 1580 middle-aged and elderly males who had presented for routine screening for prostate diseases (prostate cancer, benign prostatic hyperplasia, and prostatitis) were initially enlisted as potential recruits for the study. However, while applying the eligibility criteria, 1332 (84.3%) males who were negative for prostatic diseases during the screening period were eventually enrolled while those with features of prostatic disorders were excluded and referred for further evaluation.

The criteria for inclusion were as follows: males older than forty-five years of age with no irritative or obstructive urinary symptoms, with normal digital rectal examination (DRE) findings, a serum PSA < 4µg/l, normal findings on a trans-rectal ultrasound scan of the prostate gland (TRUS), and normal findings on urine analysis test. Other criteria for exclusion from the study were as follows: non-consenting patients, those who had undergone prostatectomy for benign or malignant prostatic disorders, those with any malignant conditions, those with established diagnosis of diabetes mellitus, chronic renal disease, chronic liver disease or hypertension, and those on medications known to influence serum PSA levels such as the statins, nonsteroidal anti-inflammatory, thiazide, calcium supplement, aspirin, 5α-reductase inhibitors, and exogenous testosterone therapy.

Following informed consent, questionnaires were administered to extract clinical, medical, social, demography and drug intake histories from each participant. The anthropometric variables acquired were weight (kg) and height (m) which were used to calculate the BMI (weight in kg divided by the square of height in meters, kg/m^2).

Each participant was subsequently examined, blood pressure measurement taken and appointment was given to present the next day to obtain a 10-hour fasting venous blood and random urine specimen for laboratory analysis. All specimens were acquired prior to DRE exploration.

Thereafter, each participant was subjected to a trans-rectal ultrasound scan (TRUS) of the prostate. The prostate volume (cm^3) was computed using the modified ellipsoidal formula [0.524 x L (cm) x H (cm) x W (cm)] following the determinations of the TRUS-derived dimensions [cephalocaudal length (L), anteroposterior height (H) and transverse width (W)] of the prostate gland (Aarnink, De la Rossette, Debruyne, & Wijkstra, 1996). The total serum PSA was determined using Enzyme-linked Immunosorbent Assay methods and plasma FPG was determined by the glucose oxidase method. Data were categorized as follows: age was categorized as middle-aged (≤ 65 years) or elderly (> 65 years) while the BMI was categorized as underweight (< 18.5 kg/m^2), normal weight (18.5 – 24.9 kg/m^2), overweight (25 – 29.9 kg/m^2) or obese (> 30 kg/m^2) based on the definition established by the World Health Organization (Lim et al., 2017).

Statistical analysis was done with SPSS version 21. The continuous data were initially tested for normal distribution using the Shapiro-Wilk test. The non-parametric distributed data were

subsequently logarithmically transformed prior to statistical analysis. The continuous variables were presented as mean ± standard deviations and range. One-way analysis of variance test was used to compare the mean values of more than two continuous variables and Turkey's honestly significant difference test was applied in Post Hoc tests. The categorical variables were presented in numbers and percentages.

Multivariable linear regression analysis was employed to evaluate the relationship between BMI and serum PSA while adjusting for confounders. A p-value of less than 0.05 was chosen as being statistically significant.

RESULTS

This study was conducted at the University of Port Harcourt Teaching Hospital between January 2016 and February 2019. The study population consisted of 1332 ambulatory and healthy middle-aged and elderly males devoid of prostatic diseases.

Table 1 below depicts the mean values with standard deviations and ranges of the non-categorical variables. Specifically, the mean ± SD (range) values of the study cohorts' age, BMI and total serum PSA were 68.89 ± 6.37 years (48 – 82), 28.14 ± 3.99 kg/m^2 (17.10 – 38.40) and 1.74 ± 0.68 (0.4 – 3.70) respectively.

Table 1: Descriptive characteristics of the non-categorical variables

Variables	Mean ± SD	Range
Age (years)	68.89 ± 6.37	48 - 82
Weight (kg)	80.31 ± 10.83	51 - 116
Height (m)	1.69 ± 0.02	1.58 – 1.75
BMI (kg/m^2)	28.14 ± 3.99	17.10 – 38.40
SBP (mmHg)	122.22 ± 7.06	110 - 150
DBP (mmHg)	76.00 ± 5.19	60 - 100
FPG (mmol/l)	4.25 ± 0.75	3.10 – 5.50
tPSA	1.74 ± 0.68	0.4 – 3.70
Prostate Volume (cm^3)	28.15 ± 1.75	23.80 – 33.50

BMI: Body Mass Index; WC: Waist Circumference;
SBP: Systolic Blood pressure; DBP: Diastolic Blood Pressure;
FPG: Fasting Plasma Glucose; tPSA: Total Prostate-specific Antigen.
SD: Standard Deviation

In table 2 below, most of the study cohorts were elderly (n = 837; 62.8%) who were also mostly (n = 1218; 91.4%) in marriage union. Underweight, overweight and obesity BMI status was observed among 0.95 (12), 51.4% (n = 684) and 22.2% (n = 300) of the study cohorts respectively. While normal BMI status was observed among 25.2% of the study cohorts (Table 2).

Table 2: Descriptive characteristics of the categorical variables

Variables	n	%
Age (years)**:**		
≤65 (Middle-aged)	495	37.2
>65(Elderly)	837	62.8
Marital Status**:**		
Married	1218	91.4
Widower	114	8.6
BMI Status (kg/m^2)**:**		
< 18.5 (Underweight**)**	12	0.9
18.5 - 24.9 (Normal)	336	25.2
25 – 29.9 (Overweight)	684	51.4
>30 (Obese)	300	22.5

BMI: Body Mass Index

In Table 3 below, a significant progressive decrease of the mean total PSA levels with a progressive increase in the BMI status was observed among the study cohorts. The mean ± SD of the total serum PSA levels among the underweight, normal weight, overweight and obese study cohorts were 3.40 ± 0.28 µg/l, 2.39 ± 0.68 µg/l, 1.73 ± 0.50 µg/l, and 1.44 ± 0.60 µg/l respectively, which shows a significant decrease with increasing BMI status ($p < 0.05$). A Post Hoc test also shows a significant difference in the mean total PSA levels within the four BMI status sub-groups ($p < 0.05$).

Table 3: Distribution of the mean ± SD values of BMI and PSA based on BMI status

BMI Sub-groups	BMI (kg/m^2) Mean ± SD	PSA (µg/l) Mean ± SD
A. Underweight	17.46 ± 0.27	3.40 ± 0.28
B. Normal weight	23.85 ± 1.07	2.39 ± 0.68
C. Overweight	27.88 ± 1.50	1.73 ± 0.50
D. Obese	33.98 ± 2.23	1.44 ± 0.60
p value	< 0.001*	< 0.001*
Post Hoc Test‡	A vs B: p < 0.001*	A vs B: p < 0.001*
	A vs C: p < 0.001*	A vs C: p < 0.001*
	A vs D: p < 0.001*	A vs D: p < 0.001*
	B vs C: p < 0.001*	B vs C: p < 0.001*
	B vs D: p < 0.001*	B vs D: p < 0.001*
	C vs D: p < 0.001*	C vs D: p < 0.001*

*Statistically significant; ‡Turkey's honestly significant difference test
SD: Standard deviation; BMI: Body Mass Index

Table 4 below depicts the result from linear regression analysis of the relationship between total serum PSA as a dependent variable and BMI (Model 1: Crude) while adjusting for age, FPG, marital status, and prostate volume (Model 2). The analysis confirms the inverse relationship between PSA and BMI (crude beta coefficient: -0.601; p< 0.001) among the entire study cohorts (n = 1320) which was not significantly influenced by age, FPG, marital status, and prostate volume in adjusted (adjusted beta coefficient: -0.509; p < 0.001) linear logistic regression analysis.

The inverse relationship also existed among the normal weight, overweight, and the obese cohorts which was not also significantly influenced by the confounders (age, FPG, marital status, and prostate volume) as shown (Table 4).

No significant relationship existed between PSA and BMI in both crude and adjusted regression analysis among the underweight cohorts which could be due to the limited number of participants (n = 12) in this cohort (Table 4).

However, there was an observed progressive increase in the magnitude of the inverse relationship between PSA and BMI as the BMI status increases from the normal weight cohorts (crude beta coefficient: -0.202; p < 0.001; adjusted beta coefficient: –0.146; p= 0.003) to the overweight cohorts (crude beta coefficient: -0.496; p< 0.001; adjusted beta coefficient:– 0.448; p<0.001) and to the obese cohorts (crude: Beta -0.539; p< 0.001; adjusted: Beta – 0.530; p<0.001) in both the crude and adjusted linear logistic regression analysis (Table 4).

Based on the stratified BMI status as shown (Table 4), the magnitude of the inverse relationship between PSA and BMI was more pronounced among the obese cohorts (crude beta coefficient: -0.539; p< 0.001; adjusted beta coefficient: –0.530; p<0.001) compared to the underweight, normal weight, and the overweight cohorts in both the crude and adjusted linear regression analysis.

Table 4: Linear regression models of the relationship between BMI and PSA among the study cohorts (n = 1332) with PSA as the dependent variable

Study group, n	Beta Coefficients	p value
Overall cohort, n = 1332		
Model 1	-0.601	< 0.001*
Model 2	-0.509	< 0.001*
Underweight, n = 12		
Model 1	-0.071	< 0.111
Model 2	-0.020	0.744
Normal weight, n = 336		
Model 1	-0.202	< 0.001*
Model 2	-0.146	0.003*
Overweight, n = 684		
Model 1	-0.496	< 0.001*
Model 2	-0.448	< 0.001*
Obese, n = 300		
Model 1	-0.539	< 0.001*
Model 2	-0.530	< 0.001*

*Statistically significant; SE: Standard Error;
Model 1: Crude
Model 2: Adjusted for age, FPG, Marital Status, and Prostate Volume

DISCUSSION

The index study was an attempt to examine the relationship between BMI and PSA among healthy middle-aged and elderly males devoid of any clinical, laboratory and radiologic features of prostatic diseases. We had also, in this study, excluded those participants with any medical or surgical conditions including those on any medications that have been suggested in the literature to influence the PSA levels in men. Following our analysis, we had observed a progressive decrease of plasma PSA with a corresponding increase in the BMI status among the study cohorts. There was also a significant inverse correlation, more pronounced among the obese cohorts, between BM and PSA which was not attenuated with tested confounders in the present study. These findings are in accord with a number of similar studies in the literature (Dada, Soriyan, Okpara, & Onyenekwu, 2018; Soe et al., 2017; Parker, Hart, Blonigen, Lindsell, & Barret, 2012). In Nigeria, a recent cross-sectional study had also documented significant lower PSA levels among the overweight and obese participants compared to ideal weight controls with a significant negative correlation between the total serum PSA levels and BMI among the overweight, obese and ideal weight control participants (Dada et al., 2018). Though this recent Nigerian study was limited by its small sample size and the inability of the researchers to adjust for potential influence of age and prostate volumes that are major determinants of serum PSA concentrations in men (Dada et al., 2018). In a recent retrospective study reported from South Korea and conducted among men over fifty years of age, the authors had also documented a decreasing trend of PSA levels as the BMI status increases among their study participants with a corresponding inverse relationship between BMI and PSA levels observed following correlation and linear regression analysis (Soe et al., 2017). In a similar study reported from the United States of America, the authors had also reported a statistically significant 0.026 decrease in PSA levels for every unit increase in the BMI status of their study participants (Parker et al., 2012).

However, some other investigators had reported contrasting findings to this study (Capitano et al., 20120. This could be related to the differences in the study population characteristics which are reported to influence PSA (Hutterer, et al., 2007).

The plausible biological mechanism of these reported inverse relationship between BMI and PSA in most studies is still poorly understood. However, some theories have been suggested in the literature (Kubota et al., 2011; Fowke & Mathews, 2010; Castro-Fernandez et al., 2000; Xiang, Feng, Ye, Chang, & Ye, 2012).

The first suggestion is the hemodilution theory which posits that the increasing BMI status occasions increased plasma volume which ultimately dilutes the PSA concentration in the process (Kubota et al., 2011). The second suggestion is the steroid hormone hypothesis which posits that the increased BMI tend to be associated with low testosterone and raise estrogen levels due to improved aromatase activity in the altered adipose tissues (Foeke & Mathews, 2010). The associated low testosterone levels due to the high BMI status decreases the androgen growth influence on the prostate tissues, thereby leading to the reduction of serum PSA levels (Fowke & Mathews, 2010; Castro-Fernandez et al., 2000). The third suggestion is based on the high BMI-induced altered status of some prostate tissue growth factors such as leptin, insulin and insulin-

like growth factor-1 (IGF-1) which negatively impacts on the prostate gland growth and size, thereby altering the PSA levels in the process (Xiang et al., 2012).

The strength of the study lies in its large sample size, prospective design, and the exclusion of participants with various factors reported to influence serum PSA levels among adult males. However, the conduct of the study had some limitations that are worthy of note. All of our study cohorts were of Negroid race, therefore findings may not be applicable to men of other races. We could not also prove with certainty that the study participants were truly devoid of prostatic diseases since prostate biopsy investigation was not carried out on them owing to ethical issues and financial constraints.

However, all the participants were all ambulatory healthy men with no clinical, laboratory and radiological features of any benign or malignant diseases of the prostate gland. Finally, the study was single-center hospital-based research which might not be representative of the entire general population of our region.

CONCLUSION

In the current clinical practice, serum PSA level is the major and most common biomarker currently in use to make a prostate biopsy decision during the investigation of prostatic diseases especially prostate cancer disease.

Hence, the low PSA levels observed in obese status with increased BMI is likely to delay and hinder diagnostic decisions. This may explain the negative correlation frequently documented between obesity and PSA-dependent prostate cancer diagnosis. This may also be the plausible reason for the positive relationship reported between obesity and the various documented adverse clinic-pathologic features of neoplastic diseases of the prostate gland.

It is, therefore, very imperative that further measures to explore this relationship with elaborate population-based studies to validate the use of the BMI-adjusted PSA values as currently being advocated by some investigators (Loeb et al., 2009).

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