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Body Composition and Serum Prostate Specific Antigen: A Review and Findings from the Flint Men's Health Study

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Abstract

Recent studies suggest obesity is associated with lower serum PSA, perhaps influencing recommendation for prostate biopsy, potentially explaining part of the observed poorer prognosis among obese men. African American men have the highest rates of prostate cancer and are more likely to die of the disease making early detection a priority in this group. We present findings from the Flint Men's Health Study, a study in African American men, which are consistent with most studies suggesting that overweight men have PSA levels 0.15–0.30 ng/mL lower than those who are not overweight. We have coupled our results with a systematic review of publications in this area.

Keywords

Obesity; Body Mass Index; Waist Circumference; Height; Prostate Cancer; Free PSA; African Americans

INTRODUCTION

The discovery of serum prostate specific antigen (PSA) and its extensive use for the last two decades has dramatically influenced the way prostate cancer is diagnosed and monitored both before and after treatment¹. In spite of this, limitations still exist in the use of the PSA screening for early detection of prostate cancer, which has led to conflicting recommendations in whom to screen and what age to begin screening. Perhaps the most significant issue is the inability to determine a cut-point for "normal" PSA level, resulting in a relatively poor positive predictive value of the PSA screening test^{2, 3}. Results from the end-of-study biopsies performed as part of the Prostate Cancer Prevention Trial (PCPT) indicate poor sensitivity at

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the PSA cut-point of 4.0 ng/mL and no normal threshold as clinically significant prostate cancer was discovered at all PSA levels ^{4, 5}. It has also been suggested that pre-diagnostic PSA no longer adequately predicts important prognostic features, particularly at levels below 10 ng/mL ⁶.

There was some inconsistency in epidemiologic literature published prior to 2000 as to whether obesity is a risk factor for prostate cancer. However, results from recent studies more clearly show obese men present with more advanced stage disease and have a higher risk of recurrence compared to non-obese men ^{7–12}. Studies also indicate obesity is associated with a lower “risk” of early stage/less aggressive disease ^{10, 11, 13}. Debate exists as to the contributing factors that account for the observed poorer outcomes associated with obesity. Is it the result of a more aggressive phenotype due to a distinct underlying biological effect of obesity on prostate cancer initiation and progression, or could it be attributed in part to delayed diagnosis and less successful treatment among obese men ¹⁴?

Findings from the San Antonio center for Biomarkers Of Risk (SABOR) study were the first to demonstrate a strong inverse relation between body mass index (BMI) and total serum PSA level among a population-based sample of healthy men without prostate cancer, suggesting that reliance on PSA testing and the current recommended PSA cutoffs for men in the general population (≥ 4.0 ng/ml) for biopsy referral in obese men may result in protracted progression of disease ¹⁵. A number of subsequent reports support these findings, but studies have not been entirely consistent, as even a prior publication from the SABOR study reported no relation between BMI and PSA levels. Furthermore, there is no definitive knowledge regarding the metabolic and/or hormonal influences which explain the association between obesity and PSA level. If the underlying biology is closely linked to processes connected to increased adipose tissue, BMI is may not be the optimal measure as it does not distinguish fat from lean body mass. There are several other measures of body composition which are valid indicators of adiposity and may be more sensitive in predicting PSA levels. In the current investigation, we examined the relation between BMI, waist circumference, waist to hip ratio (WHR) and height with both total and bioavailable serum PSA concentrations in the Flint Men’s Health Study (FMHS)—a large, population-based study originally designed to evaluate age-specific PSA ranges and prostate cancer risk factors among African American men. In addition, we have conducted a review of the recent literature published in the area of obesity and prostate specific antigen in an effort to synthesize the existing knowledge and discuss the impact of these findings in the context of current and future prostate cancer screening practices.

METHODS

Data Collection

The Flint Men’s Health Study (FMHS) is a cross-sectional community-based study of prostate disease in African-American men. The study design, sampling and methods for data collection have been described in detail previously ^{16, 17}. The protocol was reviewed and approved by the University of Michigan Institutional Review Board. At baseline, 730 men aged 40 to 79, were recruited from a probability sample of age-eligible residents in Flint, Michigan and neighboring communities. All subjects completed an interviewer administered, in-home survey collecting information on demographics, behavioral factors (smoking, alcohol consumption, physical activity), occupational history, family history of prostate cancer, and a complete medical history. Three-hundred seventy-nine men (52%) participated in a clinical examination that included measurement of serum PSA (free and total), digital rectal exam (DRE), transrectal ultrasonography to determine prostate volume, as well as measurement of height, weight, waist and hip circumferences. Exam participants were asked to refrain from sexual activity for at least 24 hours prior to measurement of PSA, and blood draws were performed prior to the DRE to avoid transitory increases in PSA. Men with an elevated total PSA (≥ 4.0 ng/ml) and/or an

abnormal DRE were referred for prostate biopsy. Eleven subjects were diagnosed with prostate cancer as a consequence of the protocol. These cases were excluded as well as those men ($n = 15$) with abnormal DRE and/or total PSA levels ≥ 4.0 ng/ml who did not submit to a prostate biopsy, those with undetectable PSA levels ($n = 3$) based on the assay (Abbott AxSYM polyclonal-monoclonal immunoassay (< 0.1 ng/ml)) or missing anthropometric measures ($n = 2$), leaving a total of 348 men eligible for this analysis.

Statistical Analysis

Analysis was performed using Statistical Analysis System software version 9.1 (SAS Institute, Cary N.C). BMI was calculated from measured weight and height in kg/m^2 . In examining the association between BMI and PSA levels in linear regression analyses, BMI was treated as both a continuous variable and then as a categorical variable in an analysis of variance according to the current Centers for Disease Control (CDC) criteria (normal weight (< 25.0 kg/m^2); overweight (25.0 – 29.9 kg/m^2); and obese (≥ 30.0 kg/m^2)). To facilitate comparison with SABOR results, two additional categories were created that represent morbid or extreme obesity (35.0 – 39.9 kg/m^2 and ≥ 40 kg/m^2), represented in Figure 1. Waist circumference, WHR and height were analyzed as continuous variables and divided into approximate quartiles based on their distributions in the total sample. Since the distributions of both free and total PSA were skewed, a natural log transformation was performed to normalize the distributions and subsequently back transformed to the original scale to facilitate interpretation of results. In some circumstances, the log transformation did not produce normally distributed data. Therefore, non-parametric analysis of variance was used to assess the contribution of body composition measures on variation in log total and log free PSA levels as well as the ratio of free to total PSA (%fPSA) adjusted for age.

RESULTS

The mean age of the 348 FMHS subjects at baseline was 57 years. The distribution of subjects by age and body mass index is described in Table 1. Despite the initial sampling strategy to oversample men in older age groups, just over 60% of participants were younger than 60 at the baseline clinical examination. Approximately 32% of subjects were considered obese and nearly 70% classified as overweight (or obese). The mean waist circumference of FMHS subjects was 38 inches with 30% having a waist circumference of greater than 40 inches (the conventional classification for abdominal obesity¹⁸). The mean total PSA level was 1.36 ng/mL and a mean %fPSA of 27%.

After adjustment for age, BMI was inversely related to both total ($p = 0.03$) and free ($p = 0.009$) PSA concentrations among subjects (Table 2). The geometric mean of total PSA level among men with a BMI of 30 or more kg/m^2 was 0.31 ng/mL lower than those with a BMI of less than 25 kg/m^2 . Although trends by BMI level were similar for free and total PSA concentrations and measures of waist circumference and WHR, those inverse associations were weak. No association was observed between height and PSA concentrations. Likewise, no consistent association was observed between any of the measures gathered and %f PSA. In an effort to replicate the findings of Baillargeon et al.¹⁵, Figure 1 illustrates the relation between PSA concentrations and BMI including the subclasses representing morbidly obese participants. Despite limitations in sample size, our results are remarkably similar to the aforementioned investigation as men with BMI equal to or greater than 40 kg/m^2 had total PSA levels 0.42 ng/mL lower than those with BMI less than 25 kg/m^2 . The monotonic association was less pronounced for free PSA.

COMMENT

The upward trend in the prevalence of obesity has become a major public health concern in this United States. Ogden et al. (18), estimated that 34% of the U.S. adult population in 2004 was considered overweight and 32% obese¹⁹. If current trends are extrapolated into the future, by 2010, more than 40% of the total adult population will be classified as obese²⁰. The prevalence of overweight and obesity in the African American community is particularly staggering, as 45% of the adult population is presently classified as obese¹⁹. An estimated mortality burden of at least 300,000 deaths (all causes) per year and \$90 billion in direct health care costs have been attributed to excess weight and relatively sedentary lifestyle^{21, 22}.

The pathophysiology of obesity may be viewed as an imbalance between energy intake (kilocalories), mechanisms controlling appetite, and energy expenditure. The metabolic consequences of central abdominal obesity include insulin resistance, hyperinsulinemia, glucose intolerance or type-2 diabetes, increased triglyceride levels, increased production of proinflammatory cytokines, elevated C-reactive protein and increased endogenous production of bioavailable sex-steroid hormones. The increased levels of insulin are positively correlated with increased production of bioavailable insulin-like growth factor I (IGF-I) in the liver, fat cells and other organs. IGF-I has been shown to exhibit mitogenic and anti-apoptotic actions that have been associated with risk of solid organ cancers^{23–28}.

Results from a number of epidemiologic investigations suggest that obesity is associated with an increased risk of advanced prostate cancer, biochemical recurrence and death^{29–32}. It has been proposed that the development of aggressive disease among obese men may be due to elevated levels of estradiol relative to testosterone, insulin and insulin-like growth factors and/or altered adipokine concentrations; however, others have attributed these findings to a delayed detection of prostate cancer, related to a difficulty in the palpation of the prostate during clinical examination (DRE) and/or PSA screening in heavy men^{14, 15, 33}.

Thompson et al. (2003) cite the difficulty in determining the appropriate cutoff optimal for distinguishing normal from abnormal PSA values. Although serum PSA elevations greater than 4.0 ng/mL are associated with prostate cancer, the positive predictive value (PPV) of a serum PSA value between 4.0 ng/mL and 10 ng/mL is only 20–30%, with PPV raising to 40–70% for serum PSA values greater than 10 ng/mL³. The PPV of serum PSA values below 4.0 ng/mL are not well defined.

As PSA is only available serum marker for prostate cancer, multiple approaches have been proposed in an effort to increase the sensitivity of the test, including supplementing total PSA concentrations with PSA velocity (the rate of increase in PSA concentration over time) and % fPSA. A post-hoc analysis of prostate cancer risk as a function of PSA level conducted among placebo controls in the Prostate Cancer Prevention Trial (PCPT) who had undergone a prostate biopsy suggests also consideration of DRE findings and family history of prostate cancer in interpreting PSA values before biopsy referral³⁴. The specificity of the PSA test is improved through our understanding the influences of serum PSA among men without disease. The evidence clearly indicates age is a strong predictor of PSA level, serum PSA increasing in a linear fashion with increasing age, so that age-specific normal ranges have been proposed to identify those at a higher probability of having prostate cancer³⁵. Evidence also suggests that PSA level is positively associated with prostate gland volume and higher in African Americans^{36, 37}.

A number of recent studies examining the relation between serum PSA and body mass generally suggest an inverse relation, but the findings are not entirely consistent (Table 3). In 2004, Thompson et al. reported no association between PSA level and BMI among 1,565 healthy men participating in the SABOR study³⁸. However, as previously mentioned, a

subsequent analysis of 2,779 men published from the same study was the first to show age-adjusted PSA concentration decreasing in a linear fashion with increasing BMI ($p < 0.0001$), and the results were reportedly similar across age and race strata. Assuming that the participants from the first study represent more than half the subjects included in the analysis, no explanation was provided by the authors to explain the discrepant findings¹⁵. Following investigations, including the current analysis, report largely similar findings indicating PSA levels 0.15–0.30 ng/mL lower among men with a BMI greater than 30 kg/m² compared to men with a BMI less than 25 kg/m²^{39–42}. However, have others reported no association between BMI and PSA^{43–45}.

Recognizing the limitations of using BMI as a surrogate measure of adiposity, a small number of investigations, including our own, have considered the use of additional measures such as waist circumference (WC) and WHR and have surprisingly not observed similar or stronger relations with PSA levels as BMI^{42, 45}. No significant association between height and total PSA has been observed in any investigation. However, Fowke et al. has shown an association between height and %fPSA, which was not replicated in our data⁴⁰. Using data gathered as part of the National Health and Nutrition Examination Survey (NHANES 2001–2004), Werny et al. reported significant inverse relationships between BMI, weight, WC, total body water (TBW), tricep skinfold and PSA among white men participating in the study. However, no significant associations were reported for measured height, or subscapular skinfold thickness⁴². Our study and others have examined in addition total PSA, PSA velocity and bioavailable or free PSA levels. Our findings are similar to those reported by Fowke et al., indicating that free PSA is inversely associated with BMI, but no relation between BMI and %fPSA. Finally, Kristal et al. found that among PCPT placebo controls, BMI (1 year post-randomization) was unrelated to PSA velocity ($p = 0.84$), but weight gain over the next 6 years was inversely related to change in PSA ($p < 0.02$)³⁹.

To date, the FMHS is still one of the largest studies of prostate disease among African Americans. The methods of the study are well-suited for this investigation because, as the original goals focused on the examining the distribution of PSA in healthy African American men, efforts were made to reduce both internal (diurnal) and external (DRE, sexual activity) sources of variability. Biopsy referral for abnormal test results and excluding individuals who would not submit for biopsy further reduces the possibility of inclusion of prostate cancer cases in the study population. Furthermore, the impact of studying this relation in the African American community is particularly important in that these men face a poorer prognosis and higher mortality compared to other racial and ethnic groups. This is likely due in part to limited access to medical care and screening for the disease.

There are study limitations which require some consideration in interpreting our results. The cross-sectional design of the study, as is the case for the vast majority of investigations reviewed, is not optimal for establishing a causal relation between obesity and PSA. However, the longitudinal findings by Kristal et al. support a temporal sequence between weight gain and PSA change. A reported 10 pound gain in weight over any single year was associated with a 0.024 ng/mL decrease in PSA adjusting for baseline PSA (PSA at the beginning of the year), age, race and smoking³⁹. In addition, we were limited in our investigation of PSA levels among men characterized as morbidly obese due to the small number of men with BMIs ≥ 35.0 kg/m² ($n = 42$). Our best estimate of the mean PSA concentrations among the heaviest men in our study population align closely with others¹⁵, yet with the imprecision in these estimates one cannot exclude the possibility that PSA levels do not differ from men with BMIs in the normal range.

The underlying biology explaining the relationship between BMI and PSA concentration is poorly understood. The weaker associations observed with WHR and WC may suggest that

the suppression of PSA is not as closely related to the elevated estrogen to androgen ratio observed in men with abdominal adiposity as has been proposed¹⁵. It has also been hypothesized that the association may be explained through effectively a dilution in PSA with an increase in plasma volume observed in obese men³³, a theory supported by the results of Werny et al⁴².

CONCLUSIONS

Taken together, the findings of our study and others suggest a modest decrease in PSA concentrations with increasing body mass among men without prostate cancer. However, the importance of this relation and its contribution to delayed detection and consequently poorer prognosis among obese men diagnosed with prostate cancer is still debatable. One must also consider the screening practices of the individual, competing risk factors and normal physician practice for recommendation of a prostate biopsy in assessing the impact. It has been suggested that we must dispose of the notion that PSA levels are classified as either normal or elevated and men are generally not well-served when biopsy referral is based on conventional cutpoints (>4.0 ng/mL or >2.5 ng/mL)³. We propose that physicians should consider the impact of obesity on PSA and drop the threshold for prostate biopsy. Likewise, Buschmeyer and Freedland have suggested multiplying measured PSA concentrations by a constant among obese men which would depend on the severity of the condition³³, the algorithm determined based on the findings of SABOR¹⁵. In the future, we believe that accounting for body mass in addition to other prostate cancer risk factors in interpreting PSA concentrations and assessing risk may ultimately lead to reductions in prostate cancer mortality among overweight and obese men.

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tPSA = total PSA (in ng/mL)
fPSA = free PSA (in ng/mL)

Figure 1.
The age-adjusted least-squares mean PSA concentrations according to body mass index (with 95% confidence intervals).

Table 1

Selected characteristics and serum PSA among Flint Men's Health Study (FMHS) participants without prostate cancer

Participant characteristic	N (%) or mean (SD)
<i>No. Subjects</i>	348 (100)
Age (in years)	
40 to 49	101 (29.0)
50 to 59	111 (31.9)
60 to 69	89 (25.6)
≥70	47 (13.5)
Body Mass Index (kg/m ²)	
< 25.0 or normal	112 (32.2)
25.0–29.9 or overweight	126 (36.2)
≥30.0 or obese	110 (31.6)
Waist Circumference (inches)	38.0 (6.2)
Hip Circumference (inches)	39.7 (5.4)
Height (inches)	70.0 (2.7)
Waist-to-Hip Ratio	0.95 (0.1)
Total PSA [†] (ng/mL)	1.36 (1.8)
Free PSA [†] (ng/mL)	0.29 (0.2)
% fPSA [‡]	27.0 (10.0)

[†] Raw mean and standard deviation of total and free PSA concentration: Geometric mean for study sample: Total = 0.90 ng/mL

Free = 0.23 ng/mL

[‡] Ratio of free to total PSA concentration

* Excludes missing data

Table 2

Select measures of body composition, total PSA concentration and %f PSA among 348 African American men without prostate cancer at baseline examination.

	N (%)	Total PSA [‡] (ng/mL)	P-value *	Free PSA [‡] (ng/mL)	P-value *	% fPSA	P-value *
BMI							
Normal (<25.0 kg/m ²)	112 (32.2)	1.05		0.25		26.0	
Overweight (25.0–29.9 kg/m ²)	126 (36.2)	0.95		0.23		27.2	
Obese (≥30 kg/m ²)	110 (31.6)	0.74	0.03	0.19	0.009	28.1	0.35
Waist Circumference							
< 34 inches	78 (22.4)	1.02		0.25		25.8	
34 to 37.5 inches	97 (27.9)	0.92		0.23		27.8	
37.6 to 41 inches	88 (25.3)	0.92		0.23		27.7	
> 41 inches	85 (24.4)	0.81	0.26	0.20	0.20	26.9	0.56
Waist to Hip ratio							
< 0.91	79 (22.7)	1.05		0.26		25.9	
0.91–0.95	95 (27.3)	0.77		0.22		29.2	
0.96–1.00	102 (29.3)	0.91		0.21		25.9	
> 1.00	72 (20.7)	0.94	0.11	0.22	0.17	27.3	0.14
Height							
< 68 inches	78 (22.4)	1.03		0.24		25.7	
68 to 69.9 inches	88 (25.3)	0.87		0.23		29.0	
70 to 71.9 inches	99 (28.5)	0.85		0.21		27.0	
≥ 72 inches	83 (23.8)	0.89	0.73	0.22	0.95	26.5	0.23

[‡] Geometric mean of total and bioavailable PSA concentrations rounded to two significant digits

* p-value corresponding to age-adjusted difference in log transformed PSA and %fPSA comparing all groups

Table 3

A summary of findings from studies of body composition and prostate specific antigen (PSA) levels in men without diagnosis of prostate cancer.

First Author (year of publication)	Study Population	Measure(s)	Findings	Comments
Ku et al. (2002) ⁴³	6,005 men 40–59 yrs	BMI	BMI 20.47 (OR ^a = 1.55 (0.99,2.41)) BMI 20.48–27.09 (referent) BMI 27.10 (OR ^a = 0.79 (0.45– 1.39))	Age only predictor of having a PSA > 2.5ng/mL in multivariable analysis
Thompson et al. (2004) ³⁸	1,565 men ≥20 yrs	BMI	No reported variation in PSA by BMI No reported modification by race or family history, however regression lines appear to differ between races	SABOR ^b study
Baillargeon et al. (2005) ¹⁵	2,770 men ≥20 yrs	BMI	Inverse linear association with PSA (p<0.0001) No reported modification by race/ ethnicity (data not shown)	SABOR ^b study
Kristal et al. (2005) 39	9,459 men ≥55 yrs	BMI	Inverse association with PSA (p<0.0001) No association with PSA velocity ^d	PCPT ^c placebo controls
Ochiai et al. (2005) 44	653 men median age 62 yrs	BMI, BSA weight, height	BSA inversely associated to PSA (p<0.05) PSA unrelated to BMI, weight, height	BMI, BSA, height available on 478 subjects
Barqawi et al. (2005) ⁴¹	4,458 men median age 60 yrs	BMI	BMI inversely associated with total and complexed PSA	PCAW ^e
Fowke et al. (2006) 40	299 men 40–79 yrs	BMI, height	BMI inversely associated with PSA among men <60 yrs (p = 0.02) and free PSA (p = 0.04), but not % fPSA (p = 0.49) Height unrelated to PSA	Subset of SSCS ^f study Comparison of Caucasian and African American men
Fowke et al. (2007) 45	380 men ≥40 yrs	BMI, WHR, WC, height	PSA unrelated to BMI, WC, height, but positively associated with WHR (p = 0.04)	
Werny et al. (2007) 42	2,396 men ≥40 yrs	BMI, WC, height, weight skinfold ^g TBW	BMI inversely associated with PSA among whites, Hispanics, but not blacks TBW inversely associated with PSA among whites, blacks, but not Hispanics	NHANES ^h (2001–2004)

^a Age-adjusted odds ratio predicting probability of having a PSA >2.5 ng/mL;

^b San Antonio study of Biomarkers Of Risk;

^c Prostate Cancer Prevention Trial

^d % change per year;

^e Prostate Cancer Awareness Week 2003 National Screening Program;

^f Southern Community Cohort Study;

^g Tricep and subscapular thickness;

^h National Health And Nutrition Examination Survey;

KEY: BMI=Body Mass Index (kg/m²); WHR=Waist/Hip ratio; WC=Waist Circumference; BSA=Body Surface Area (sqrt[m*kg/3600]); TBW=Total Body Water