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PSA and Body Composition by Dual X-ray Absorptiometry (DXA) in NHANES

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Abstract

Background—Obese men are at higher risk for advanced prostate cancer and have a poorer prognosis following treatment. Several studies also report that obese men have lower blood PSA levels, suggesting that obesity may be interfering with the ability to detect early-stage prostate cancer.

Methods—Dual x-ray absorptiometry (DXA) is considered a gold-standard measurement of body composition. We investigated the association between PSA levels and body composition measured by DXA among 1,360 men participating in NHANES (2001-2004), a representative sample of the U.S. male population.

Results—After controlling for age, race, and other factors, PSA concentration was approximately 15% lower for men with the highest level of total mass, lean mass, fat mass, trunk lean mass, and trunk fat mass (all p for trend < 0.05). We then multiplied PSA concentration by estimated plasma volume to calculate the amount of PSA in circulation (i.e., PSA mass). Total body fat mass and fat mass located in the body trunk were not significantly associated with PSA mass, however PSA mass was approximately 10% to 15% higher across low vs. high categories of total body lean mass and bone mineral content (all p-trend < 0.05).

Conclusion—Our results using DXA to measure body composition confirm that a greater body mass, not just fat mass, is associated with a lower PSA concentration. This is consistent with PSA hemodilution within men with a higher body mass index. The separate associations between measured lean and fat mass on calculated PSA mass require further investigation.

Keywords

PSA; prostate cancer; obesity; dual x-ray absorptiometry

Introduction

Most prostate cancer cases in the U.S. are diagnosed at prostate biopsy following a suspicious PSA test. Several studies now report lower PSA levels among obese men [1-3], suggesting the possibility that obesity may hinder the ability to detect prostate cancer at an earlier stage. The two common hypotheses explaining an association between obesity and PSA involve decreased testosterone levels associated with aromatase (CYP19) activity in adipose tissue, and dilution of a fixed amount of PSA in a larger body with a greater plasma volume. However, the strong correlations between anthropometric measures such as BMI and waist circumference and the limited information regarding fat distribution in older men limit our ability to evaluate the relative impact of these two hypotheses. Recently, Rundle

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and colleagues analyzed the association between PSA and total lean mass and fat mass measured by bioelectrical impedance analysis (BIA) among over 8,000 men receiving a routine medical check-up [4]. They found both total lean mass and total fat mass were inversely associated with PSA concentration, suggesting that a greater total body mass, and by extension a greater plasma volume, decreases PSA concentrations via PSA hemodilution.

Further understanding how obesity affects PSA concentration may improve our ability to detect clinically relevant prostate tumors and allow us to evaluate the clinical significance of obesity on prostate cancer detection. We analyzed the association between PSA levels and total body mass, total lean mass, total fat mass, bone mineral content (BMC), trunk lean mass, and trunk fat mass measured by DXA, considered to be a 'gold-standard' method of body composition measurement. We hypothesized that an association between PSA and total fat mass or trunk fat mass would support the steroid hormone metabolism hypothesis, while more generalized association between PSA and total body mass would support the hemodilution hypothesis.

Materials and Methods

Study Population

NHANES uses a complex sampling and weighting scheme to acquire a nationally representative cross-sectional sample of the U.S. civilian non-institutionalized population. The annual sample is based on the selection of U.S. counties, clusters of households, and eligible persons within households. Detailed protocols have been published by the Centers for Disease Control and Prevention National Center for Health Statistics[5]. All procedures were approved by the National Center for Health Statistics IRB, and all subjects provided written informed consent.

Body Composition

Whole body DXA scans were performed during NHANES 1999-2000, NHANES 2001-2002, and NHANES 2003-2004. Scans were acquired using a Hologic QDR 4500 fan beam densitometer (Hologic Inc., Bedford MA) among participants at least 8 years of age, while excluding participants with a self-reported radiographic contrast material (barium) exam in the past seven days, a nuclear medicine test in the past 3 days, weight over 300 pounds, or a height of 6 feet 5 inches or more. All DXA scans were reviewed for quality using a standardized protocol, and data from those DXA scans determined to be invalid or incomplete were reclassified as missing values. This missingness of DXA data was associated with participant age, weight, and height, creating the possibility that analyses of DXA data may be biased to favor the input from participants with the least amount of missing data. To reduce this potential bias, sequential regression multivariate imputation (SRMI) was performed using the module IMPUTE in IVEware (University of Michigan). Detailed protocols describing the methods of imputation, and comparisons of imputed verses measured measures, have been published online [5]. The imputed dataset allows all participants to contribute to the analysis equally and provides a more accurate estimate of standard errors. While the composition of most major body compartments is available, we focused on total body mass (kg), total fat mass (kg), total lean mass without BMC (kg), total BMC (kg), trunk total mass (kg), trunk fat mass (kg), and trunk lean mass without BMC (kg) because these measures provide information relevant to the hormonal vs. hemodilution effects of obesity on PSA concentration.

PSA

Blood PSA measurement was initiated with NHANES 2001-2002 among men ages 40 years and older using the Hybritech test (Beckman Coulter, Fullerton, CA). Blood was not

collected from participants with hemophilia, recent chemotherapy, or with extensive skin lesions or other counter-indications for blood collection. PSA was not measured among men reporting a current infection or inflammation of the prostate gland, a rectal exam with the past week, a prostate biopsy or cystoscopy within the past month, or a history of prostate cancer. Samples with PSA levels below the assay limit of detection were set to 0.1 ng/ml (n=38). There were 1601 and 1301 men with PSA data from NHANES 2001-2002 or NHANES 2003-2004, respectively.

Statistical Analysis

There were 1383 participants from NHANES 2001-2002 and NHANES 2003-2004 with complete data on PSA, DXA, weight, height, age, and race. We also excluded 23 participants with PSA levels that were greater than 10.0 ng/ml to remove potentially influential values from the analysis, yielding 1360 NHANES participants. PSA concentration was natural log transformed prior to analysis. We used the methods of DuBois and Dubois to calculate body surface area (BSA (m^2) = 0.20247 × $height^{0.725}$ × $weight^{0.425}$) [6], then calculated plasma volume using the ratio of plasma volume to BSA developed by Boer (Plasma volume = BSA × 1.67) [7]. PSA mass (μg) was calculated as PSA concentration × plasma volume. Interpretation of results were unchanged when we calculated BSA using the method of Mosteller[8]. Statistical analyses were performed using IVEware, a SAS callable software application developed to perform analyses on data with multiple imputation while accounting for the weighted and stratified survey design. We calculated mean PSA, plasma volume, and PSA mass within categories of total body mass and other DXA measures categorized at each quartile of the weighted distribution using a linear regression model and controlling for age (continuous) and race. Geometric mean PSA levels are reported. Linear test for trend across categories of each DXA measure was done by testing whether the beta coefficient for the continuous linear variable was equal to zero.

Results

Table 1 provides a description of the analytic study population from NHANES. Age ranged from 40 to 85 years (weighted mean = 55.2 years, standard error = 0.33 years). Race and ethnicity were coded as Mexican American (5.1%), Other Hispanic (3.2%), Non-Hispanic White (78.4%), Non-Hispanic Black (8.9%), and Other (4.4%). PSA concentrations ranged from 0.1 ng/ml to 9.9 ng/ml, and the median and geometric mean blood PSA concentration levels were 0.90 and 0.90 ng/ml, respectively. Approximately 11.8% had previously been diagnosed with diabetes, and 9.4% and 18.0% were regular users of an NSAID or statin, respectively, defined as reporting at least 30 days of use prior to enrollment.

PSA levels were approximately 15% lower among men with the highest vs. lowest categories of total body mass (p-trend =0.006), total lean mass (p-trend = 0.019), and total fat mass (p-trend=0.011) (Table 2). PSA levels were not significantly associated with BMC (p-trend = 0.906). Fat and lean mass in the trunk were investigated to determine the role of centralized fat deposition on PSA. PSA levels were significantly lower with greater trunk total mass (p-trend = 0.023), trunk lean mass (p-trend = 0.023), and trunk fat mass (p-trend = 0.041), although trends were inconsistent for trunk fat mass and trunk lean mass. Differences in PSA concentration between the lowest vs. highest body mass categories were smaller after excluding participants with a PSA level of 4.0 ng/ml or higher. For example, adjusted PSA levels were 0.78, 0.77, 0.72, and 0.72 (p-trend = 0.054) and 0.79, 0.75, 0.73, 0.74 (p-trend = 0.125) across quartile categories of total body mass and total trunk mass, respectively.

All body composition measures were significantly associated with an approximate 25% increase in calculated plasma volume between men with the lowest vs. highest body mass

(all p-trend < 0.001) (Table 2). We calculated an estimate of PSA mass by the product of PSA concentration and plasma volume. PSA mass was not significantly associated with total body fat mass or trunk fat mass, although PSA mass levels tended to be somewhat higher within the higher fat mass categories. PSA mass were significantly higher across categories of lean mass, BMI, and trunk lean mass (all p-trend <0.05), with approximately 10% to 15% higher PSA mass levels across low vs. high categories of lean body mass.

Discussion

Our results confirm an inverse relationship between body mass and blood PSA concentration, and provide further evidence for PSA hemodilution among obese men. PSA is produced in prostate epithelial cells in response to androgen receptor activation, and the hormonal hypothesis suggests that known interactions between body adiposity and steroid hormone metabolism, the inflammatory response, or insulin regulation [9] are sufficient to affect PSA expression. Such an effect would be supported if any associations between PSA and body mass were restricted to DXA measures of fat mass. However, Rundle and colleagues previously reported that both lean mass and fat mass estimated by BIA were associated with lower PSA levels, with a somewhat stronger association between PSA and lean mass [4]. Using DXA measures of body composition, we found PSA concentration levels were lower across increasing categories of total body mass, total lean mass, and total fat mass. Additionally, visceral adiposity may be more strongly associated with insulin resistance, lower androgen levels, and inflammation than other fat depots. However, results from prior studies regarding the relationship between waist circumference and PSA concentration are inconsistent [1,4]. We found trunk fat mass and trunk lean mass measured by DXA were each associated with a lower PSA concentration. These consistent relationships from body mass and PSA concentration generalized across lean mass, fat mass, and trunk mass are inconsistent with a hormonal hypothesis.

The hemodilution hypothesis of obesity and PSA is based on the premise that blood PSA concentration is a function of plasma volume as well as PSA expression and PSA leakage into circulation. Unfortunately, plasma volume is not easily measured. Banez and colleagues addressed this challenge by first calculating body surface area with a formula from Dubois and Dubois using weight and height among prostate cancer survivors [6,7,10,11]. PSA mass is calculated as a simple arithmetic function of PSA concentration and plasma volume that is intended to remove the effects of hemodilution and to better capture PSA expression and PSA leakage from the prostate. Analyses from Grubbs et al. [3] used a similar approach among men at risk for prostate cancer, and both studies suggested plasma volume confounded the relationship between BMI and PSA concentration. Similarly, our analyses did not find a significant association between PSA mass and measured total and trunk fat masses. Our results suggest that total fat mass and centralized adiposity do not affect substantially PSA protein expression or PSA leakage from prostate tissue.

Interestingly, while PSA mass was not significantly associated with fat mass, there was a significant increase in PSA mass associated with greater lean mass. There may be several explanations, including the possibility that a person’s height and weight used to calculate body surface area and plasma volume are not fully capturing the effects of lean body mass on plasma volume. Simple calculations using height and weight may reasonably predict body surface area and total body water [12], however the appearance of a positive association between lean mass and greater PSA mass may develop if there is an aspect of height or weight relevant to the relationship between plasma volume and PSA that is not adequately captured in the equation used to calculate BSA. In this situation, with a modest inverse association between body mass and PSA but a strong positive association between body mass and plasma volume, the result of standardizing PSA concentration to plasma

volume would be to induce the appearance of an increasing PSA mass with a greater lean body mass. Indeed, the significant association in our data between BMC and PSA mass but not PSA concentration may be an example. Alternatively, standardizing PSA concentration to plasma volume may uncover some aspect of lean body size that increases PSA expression or PSA leakage from the prostate. Height has been associated with prostate volume [13], and elevated androgen, insulin, IGF-1, growth hormone, or other hormonal levels may also increase PSA expression. Stature has also been associated with prostate cancer risk [14], and the prevalence of latent or undiagnosed prostate cancer may be greater among men with a greater lean body mass. Data and histologic examinations necessary to evaluate these alternatives related hormone levels, latent disease, or analytic plasma volume measurements were not available.

Further research is needed to determine if calculating PSA concentrations adjusted for weight, height, BMI, waist circumference, or plasma volume might be a step toward improving the accuracy of PSA testing to identify potentially lethal tumors. The etiologic relationship between obesity and prostate cancer progression remains an area of clinical interest, and obese men are at greater risk for a diagnosis of advanced prostate cancer [15]. Removing the effect of body mass on PSA levels may improve prostate cancer detection and improve the prognosis of these high-risk men. However, our results also suggest the possibility that standardizing PSA concentration to plasma volume may lead to a higher PSA index among taller men, and the possibility that this process could lead to unnecessarily biopsy and treatment needs consideration. Many factors are known to affect plasma volume, including physical fitness, renal insufficiency, electrolyte levels, dehydration, or standing, sitting, or supine posture, in addition to weight and height [16-18]. The relationships between these factors and PSA are unclear. Although an accurate and feasible method to measure plasma volume to standardize PSA concentrations beyond the applied simple approach is not readily at hand, a refined calculation of plasma volume specific to prostate cancer screening may be needed to improve clinical detection and treatment outcomes, particularly among men with marginal PSA levels in the range of 2.5 to 4.0 ng/ml.

Strengths of this study include the use of DXA to provide direct measures of total and trunk lean and fat masses in a nationally representative sample of men. Limitations include a cross-sectional study design, the possibility that there may be latent undiagnosed prostate cancer within the study population, and that a portion of DXA data were imputed to prevent bias derived from the analysis of nonrandom missing data. Most PSA levels were below the level of clinical suspicion, and there were few severely obese men available for analysis due to technical difficulties of performing such DXA scans.

Conclusions

PSA concentration was significantly although moderately lower among men with increased body mass as measured by DXA, regardless of lean or fat composition or deposition in the trunk. This is consistent with PSA hemodilution among obese men. Further research is needed to determine the best method to extend these results to prostate cancer screening protocols.

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Table 1

Description of analytic study population (n=1360 men) from NHANES (2001-2004)

Factor	Level	Weighted %
Age	40-49	38.1%
	50-59	30.4%
	60-69	16.9%
	70-79	10.6%
	80 or more	4.0%
Race	Mexican American	5.1%
	Other Hispanic	3.2%
	White	78.4%
	Black	8.9%
	Other	4.4%
BMI	25 or less	21.7%
	25-29	45.2%
	30 or more	33.1%
PSA	0.1 – 2.0	82.8%
	2.1 – 4.0	12.3%
	4.1 – 10.0	4.9%
Diabetes	Ever diagnosed	11.8%
NSAID use	30 days or more	9.4%
Statin use	30 days or more	18.0%

Table 2

Body Composition and PSA Concentration, Plasma Volume, and PSA Mass

Body Composition	Category	N	Weighted %	PSA concentration (ng/ml)*	Plasma Volume (l)*	Plasma PSA Mass (μg)*
Total Body Mass (kg)	42.4 – 78.0	447	24.9%	0.86	3.00	2.58
	78.0 – 88.5	343	24.9%	0.86	3.27	2.82
	88.5 – 99.4	287	25.5%	0.80	3.47	2.78
	99.5 – 174.6	284	24.7%	0.76	3.78	2.86
			p-trend	0.006	<0.001	0.030
Total Lean Mass* (kg)	28.1 – 53.7	468	24.7%	0.86	3.01	2.58
	53.9 – 59.4	333	24.7%	0.85	3.28	2.79
	59.5 – 65.4	286	25.4%	0.78	3.47	2.70
	65.5 – 100.6	274	25.2%	0.78	3.79	2.95
			p-trend	0.019	<0.001	0.003
Total Fat Mass (kg)	8.0 – 21.0	433	25.0%	0.87	3.03	2.63
	21.1 – 26.2	348	25.3%	0.84	3.25	2.71
	26.3 – 32.3	316	25.3%	0.83	3.45	2.86
	32.4 – 74.1	293	24.4%	0.77	3.70	2.83
			p-trend	0.011	<0.001	0.293
Total BMC (kg)	1.3 – 2.3	422	25.0%	0.82	3.14	2.57
	2.4 – 2.6	331	24.5%	0.86	3.34	2.86
	2.7 – 2.9	308	25.3%	0.78	3.47	2.70
	3.0 – 5.8	299	25.2%	0.84	3.66	3.07
			p-trend	0.906	<0.001	0.021
Trunk Total Mass (kg)	21.0 – 38.9	424	24.8%	0.87	3.01	2.57
	39.0 – 44.6	360	25.3%	0.84	3.27	2.86
	44.7 – 51.1	296	25.4%	0.81	3.46	2.70
	51.2 – 94.0	279	24.5%	0.79	3.76	3.07
			p-trend	0.023	<0.001	0.031
Trunk Lean Mass (kg)	15.6 – 27.0	457	24.7%	0.88	3.02	2.67
	27.1 – 29.8	328	24.4%	0.84	3.29	2.74
	29.9 – 32.6	304	25.6%	0.72	3.49	2.50

Body Composition	Category	N	Weighted %	PSA concentration (ng/ml)*	Plasma Volume (l)*	Plasma PSA Mass (μg)*
	32.7 – 51.8	271	25.3%	0.82	3.78	3.07
			p-trend	0.023	<0.001	0.007
Trunk Fat Mass (kg)	2.4 – 10.8	397	25.2%	0.84	3.04	2.54
	10.9 – 14.0	343	25.0%	0.85	3.24	2.75
	14.1 – 17.7	318	24.7%	0.84	3.44	2.89
	17.8 – 42.4	302	25.1%	0.78	3.69	2.86
			p-trend	0.041	<0.001	0.138

* All values adjusted for age, race, statin or NSAID use for at least 30 days, and a prior diabetes diagnosis. Geometric mean PSA concentration and PSA mass are reported.