Original Article
An inverse association of obesity and prostate-specific antigen in elderly males

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Abstract: Objective: Serum prostate-specific antigen (PSA) test is commonly applied for prostate cancer screening and diagnosis. However, the level of PSA varied in different races and can be influenced by many factors. Previous studies show that obese is related to the PSA level, but the results are highly inconsistent. The aim of this study was to examine the relationships among body mass index (BMI), waist circumference (WC) and serum PSA including PSA density (PSAD) and PSA increasing rate (PSAR) in healthy males, and to investigate whether this relationship was independent to other factors. Methods: Cross-sectional analysis was in men aged from 60 to 85 years (N=4,084) without prostate cancer and had health examination between *August* 2008 and *July* 2014 in a clinical center in Xi'an, China. Obesity (BMI≥27.5 kg/m^2) and overweight (27.5>BMI≥22.5 kg/m^2), the control (WC≤90 cm) and the central obesity (WC>90 cm) were classified according to the WHO criterion respectively. Mean (SD) PSA level, PSAD, PSAR was calculated by categories (the control, overweight, and obesity). The association between BMI, WC and PSA, PSAD, PSAR stratified by age was tested by using multivariate regression models. Results: In the enrolled study population, the prevalence was 55.42% for overweight and 10.22% for obese, 82.65% for the control and 17.35% for central obese. BMI, WC was negatively associated with PSA level (P<0.05), independent to fasting blood glucose (FBG) and prostate volume (P<0.05). BMI was significantly associated with lower level of PSA (P=0.032), in independent of FBG (P=0.021). However, the negative correlation was not statistically significant in age (P=0.063) and PV (P=0.085) adjusted models. BMI was not significantly related to lower level of PSAD, PSAR (P=0.123, 0.307, respectively) after adjusted by age. The multivariate regression results of WC and PSA stratified by age showed similar results. Conclusions: Our results indicate that obesity is associated with a lower level of PSA in healthy males in all age groups, but independent to FPG. With the current obesity epidemic, individual's BMI, WC should be considered, especially BMI. PSA test is applied for prostate cancer screening or diagnose. Despite the inverse association for PSA test would not be available for males older than 60 years, it is suggested that that PSAD or PSAR levels should be selected for estimation.

Keywords: Prostate-specific antigen, body mass index, waist circumference, obesity

Introduction

Nowadays, rapid economic development and industrialization as well as aging society, especially in China, have brought about variation of traditional diets and increasingly sedentary lifestyles. As a result, the prevalence of obesity, especially central obesity has been gradually increased in China. However, numerous studies have indicated that the increasing prevalence of obesity is associated with some common diseases, such as diabetes, cancer, etc. Prostate cancer is the second most common cancer in elderly males all over the world, and it is estimated that one in six males suffered prostate cancer in their lifetime [1]. The incidence of prostate cancer in China, although lower than Western countries, was significantly increased in recent years. In Beijing, the incidence of male prostate cancer increased from 55.3 per million in 2001 to 166.2 per million in 2010, with an average annual growth rate of 9.2% [2]. The increasing of the prostate cancer incidence in China reflects not only the aging of the population, but also the application of more sensitive screening techniques, such as serum prostate-specific antigen (PSA) testing [3]. Recently, PSA test was widely adopted in many countries as a screening tool for cancer screening [4].

Table 1. Characteristics of study participants (N=15, 296)

Variables	Mean ± SD
Age, years	69.96±6.87
PSA, ng/mL	2.63±2.26
PV, mL	29.53±7.86
Height, cm	171.00±5.90
Weight, kg	73.18±10.23
BMI, kg/m²	23.97±2.90
BMI category, N (%)	
Normal weight,	8,056 (52.67)
Overweight	5,849 (38.24)
Obese	1,390 (9.09)
WC category, N (%)	
Non central obese (≤90 cm)	11,389 (74.46)
Central obese (>90 cm)	3907 (25.54)

PSA: prostate specific antigen; PV: prostate volume; BMI: body mass index; WC: waist circumance.

Recently, some studies reported that levels of PSA are negatively associated with body mass index (BMI), which primarily attributes to the haemodilution effect caused by increased plasma volume [5]; while other studies reported that obese men may have higher normal serum PSA level than non-obese men [6], which affect the validity of PSA tests in prostate cancer screening. As a result, a large number of obese individual without cancer may show positive in PSA screening, which will significantly increase the rate of false positive and cost of health care. Therefore, there is an urgent requirement to understand the relationship between obesity and PSA in healthy and cancer population [7, 8].

The objective of the current study was to investigate the association between body mass index (BMI), waist circumference (WC) and serum PSA, including PSA density (PSAD), as well as PSA increasing rate per year in healthy males. We tried to examine the associated factors between obesity and PSA, including fasting blood glucose (FBG) and prostate volume (PV) [9-11], and to clearify that the relationship between obesity, including central obesity, and serum PSA was independent of other factors in healthy males.

Methods

Patients

A total of 15,296 males aged 60 to 97 years with available PSA data were included, who underwent routine health check-ups in the healthcare center of the Affiliated Hospital of Medical School: Xi'an Jiaotong University, Xi'an, China, from August 2008 to July 2014. Baseline characteristics of studied participants are shown in **Table 1**. As some of these participants underwent health check-ups several times, we only retained the initial screening data and excluded the data for two or more check-ups. The data without age, height, weight, waist circumference, fasting blood glucose, or ultrasonographic examination for prostate were also excluded. After obtaining institutional review board approval, we retrospectively abstracted clinical information from a self-administered questionnaire assessing age, race, medication history, diabetes mellitus history, prostate cancer history, waist circumference, and current height and weight. The consecutive participants volunteered for screening consisting of PSA, FBG, urine routine test and a DRE performed by the urologist. Individuals with history of prostate cancer, active infection or prostate or inflammation with abnormal urinalysis, undergone a DRE in the previous 7 days, undergone a cystoscopy or prostate needle biopsy within a month of testing, with age more than 85 years old, a FPG more than 15 mmol/L, a BMI less than 17.5 kg/m², a PSA levels >15 ng/mL were all excluded, because of a potential data registration error or a high chance of prostate cancer and inflammatory prostate disease. We also excluded the men suspected of having prostate cancer or prostatitis on basis of DRE and ultrasonography, as well as the men who were taking prostate related medication, such as finasteride, which affects PSA [5]. A total of 4,404 men were included in the final analysis. This study protocol was approved by our local clinical research ethics committee.

BMI, serum PSA and other variables

BMI was defined as dividing the weight in kilograms by squared height in meters squared. Limosis vein blood sample was drawn from cubital vein in quiet state after 10-h fasting in the morning for FBG and serum PSA assay. The serum PSA was measured by serum drawn (Access Hybritech PSA assay; Beckman Coulter, Inc., Fullerton, Calif) before DRE. Prostate volume was measured by ultrasonography using the formula for an elliptic volume (π/6× height × width × length). PSA density was calculated as dividing serum PSA (ng/ml) by prostate volume

Table 2. Mean PSA, PV, PSAD and PSAR levels by BMI or WC (N=4,044)

	Normal weight	Overweight	P value	Obese	P value	Non CB	CB	P value
Age (years)	70.13±6.90	69.42±6.58	0.089	68.38±6.58	0.065	70.13±6.18	69.58±6.23	0.084
FBG (mmol/L)	5.61±1.43	5.83±1.53[b]	<0.001	6.11±1.52[b]	<0.001	5.57±1.47	6.04±1.68	<0.001
PSA (ng/ml)	2.70±2.30	2.64±2.26	0.305	2.38±2.07[b]	0.007	2.67±2.3	2.41±2.03	<0.001
PV (ml)	30.03±7.78	29.63±7.76	0.098	28.76±7.89[b]	0.002	29.78±7.74	29.21±7.98	<0.001
PSAD[c](ng/ml²)	9.25±7.57	9.09±7.43	0.405	8.42±6.65[a]	0.034	9.21±7.58	8.44±6.49	0.004
PSAR[c](ng/ml/y)	3.78±3.1	3.77±3.1	0.641	3.42±2.78[a]	0.028	3.79±3.13	3.45±2.72	0.002

[a]$P<0.05$, *difference between overweight, obese and normal weight values;* [b]$P<0.01$, *difference between overweight, obese and normal weight values;* [c]$(\times 10^{-2})$.

Table 3. Regression results on the association of PSA, PSAD and PSA increase per year with BMI and WC

Age group (years)	PSA		PSAD		PSA increase per year	
	β (95% CI)	P Value	β (95% CI)	P Value		P Value
BMI						
Model 1	-0.032 (-0.005, -0.002)	0.032	-0.027 (-0.001, 0.000)	0.073	-0.020 (0.000, 0.000)	0.190
Model 2	-0.028 (-0.047, -0.002)	0.063	-0.023 (-0.001, 0.000)	0.123	-0.015 (0.000, 0.000)	0.307
Model 3	-0.026 (-0.047, 0.003)	0.085	-0.023 (-0.001, 0.000)	0.135	-0.014 (0.000, 0.000)	0.354
Model 4	-0.035 (-0.052, -0.004)	0.021	-0.028 (-0.002, 0.000)	0.060	-0.023 (0.000, 0.000)	0.134
WC						
Model 1	-0.032 (-0.015, 0.000)	0.036	-0.027 (0.000, 0.000)	0.074	-0.019 (0.000, 0.000)	0.202
Model 2	-0.027 (-0.014, 0.001)	0.070	-0.023 (0.000, 0.000)	0.125	-0.015 (0.000, 0.000)	0.325
Model 3	-0.025 (-0.014, 0.001)	0.095	-0.022 (0.000, 0.000)	0.139	-0.013 (0.000, 0.000)	0.380
Model 4	-0.033 (-0.015, 0.000)	0.028	-0.028 (0.000, 0.000)	0.069	-0.021 (0.000, 0.000)	0.159

Model 1: crude; Model 2: adjusted for age; Model 2: adjusted for prostate volume; Model 3: adjusted for fasting blood glucose.

(ml). PSA increasing rate (PSAR) was calculated as serum dividing PSA (ng/ml) by age (year).

Statistical analysis

Descriptive data on study participants' characteristics were expressed as means ± standard deviations (SD) for continuous variables, and percentage (%) for categorical variables. Student's t-test and one way analysis of variance (ANOVA) were applied to compare continuous variables and categorical variables, respectively. Overweight (22.9≥BMI>27.5 kg/m²) and obesity (BMI≥27.5 kg/m²) were classified according to the WHO criterion. Mean (SD) PSA level was calculated by BMI categories (normal weight, overweight, and obesity). And central obesity group (WC>90 cm) and the control group (WC≤90 cm) were also classified according to the WHO criterion. The relationships between BMI, WC and PSA, PSAD, PSAR were examined by using multivariate regression models, and stratified by age, respectively. A *P*

value <0.05 was considered as Statistical significance. All statistical analyses were performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

There were 4,404 men included in current analysis. The mean age was 69.92±6.76 years ranging from 60 to 85. The mean BMI was 24.02±2.8 kg/m², the mean WC was 81.65±9.48 cm and the mean PSA was 2.05±1.63 ng/ml. Enrolled men were classified by BMI categories (control group: 35.04% (N=1,543), overweight: 55.42% (N=2,441) and obese: 10.22% (N=450)), by WC categories (control group: 82.65% (N=3640), central obese: 17.35% (N=764)). The mean serum PSA levels, PV levels, PSAD levels and PSAR by BMI and WC were shown in **Table 2**. There were no significantly different in age between overweight, obese group and the control group (P=0.089, 0.065, respectively). Obese men

Table 4A. Regression results on the association of PSA, PSAD and PSA increase per year with BMI

	Normal weight	Overweight		Obese		Per BMI increase (treat BMI as a continuous variable)	
		β (95% CI)	P Value	β (95% CI)	P Value	β (95% CI)	P Value
PSA							
Model 1	Referent	-0.016 (-0.093, -0.038)	0.417	-0.030 (-0.079, 0.156)	0.522	-0.161 (-0.007, -0.005)	<0.001
Model 2	Referent	-0.015 (-0.094, -0.040)	0.429	-0.033 (-0.079, 0.169)	0.483	-0.157 (-0.007, -0.005)	<0.001
Model 3	Referent	-0.022 (-0.109, -0.029)	0.257	0.010 (-0.112, 0.139)	0.985	-0.154 (-0.007, -0.005)	<0.001
Model 4	Referent	-0.010 (-0.082, -0.048)	0.609	0.000 (-0.121, 0.119)	0.830	-0.164 (-0.007, -0.005)	<0.001
PSAD							
Model 1	Referent	-0.011 (-0.030, 0.001)	0.556	0.038 (-0.002, 0.005)	0.421		
Model 2	Referent	-0.012 (-0.003, 0.001)	0.521	0.044 (-0.002, 0.006)	0.352		
Model 3	Referent	-0.012 (-0.003, 0.001)	0.521	0.026 (-0.003, 0.005)	0.587		
Model 4	Referent	-0.009 (-0.003, 0.002)	0.659	0.007 (-0.003, 0.004)	0.877		
PSAR							
Model 1	Referent	-0.009 (-0.001, 0.001)	0.646	0.039 (0.000, 0.002)	0.421		
Model 2	Referent	-0.009 (-0.001, 0.001)	0.654	0.042 (0.000, 0.002)	0.370		
Model 3	Referent	-0.014 (-0.001, 0.001)	0.476	0.020 (-0.001, 0.002)	0.674		
Model 4	Referent	-0.003 (0.000, 0.001)	0.873	0.007 (-0.001, 0.002)	0.888		

Model 1: crude; Model 2: adjusted for age; Model 2: adjusted for prostate volume; Model 3: adjusted for fasting blood glucose.

Table 4B. Regression results on the association of PSA, PSAD and PSA increase per year with WC

Age group (years)	Control WC	Central obesity		Per WC increase (treat WC as a continuous variable)	
		β (95% CI)	P Value	β (95% CI)	P Value
PSA					
Model 1	Referent	-0.003 (-0.037, 0.034)	0.929	-160 (0.000, 0.000)	<0.001
Model 2	Referent	-0.002 (-0.036, 0.038)	0.963	-0.156 (0.000, 0.000)	<0.001
Model 3	Referent	-0.008 (-0.042, 0.033)	0.821	-0.153 (0.000, 0.000)	<0.001
Model 4	Referent	-0.027 (-0.049, 0.022)	0.453	-0.162 (0.000, 0.000)	<0.001
PSAD					
Model 1	Referent	0.012 (0.000, 0.001)	0.739		
Model 2	Referent	0.017 (0.000, 0.001)	0.629		
Model 3	Referent	0.007 (-0.001, 0.001)	0.840		
Model 4	Referent	-0.012 (0.000, 0.001)	0.746		
PSAR					
Model 1	Referent	0.004 (0.000, 0.000)	0.914		
Model 2	Referent	0.009 (0.000, 0.001)	0.794		
Model 3	Referent	-0.002 (0.000, 0.000)	0.964		
Model 4	Referent	-0.020 (0.000, 0.000)	0.584		

Model 1: crude; Model 2: adjusted for age; Model 2: adjusted for prostate volume; Model 3: adjusted for fasting blood glucose.

had significantly lower serum PSA, PV, PSAD and PSAR (P=0.007, 0.002, 0.034, 0.028, each age group, respectively) than those of the control group. Comparing with the men in control as well as overweight groups, obese men had significantly higher FBG levels (P<0.001). There was no significantly different in age between the central obese group and the control group (P=0.084, each age group, respectively). The central obese men had significantly lower serum PSA, PV, PSAD and PSAR (P<0.001, <0.001, 0.004, 0.002; respectively) but significantly higher FBG level (P<0.001) than those in the control group.

Table 3 shows the multivariate regression results of BMI and PSA, stratified by age. BMI was significantly associated with lower level of PSA (P for trend =0.032) and in independent of FBG (P for trend =0.021). However, the negative correlation was not statistically significant in age (P for trend =0.063), PV (P for trend =0.085) adjusted models. BMI was not significantly associated with lower level of PSAD, PSAR (P for trend =0.123, 0.307, respectively) after adjusted by age. Similar results were also found in the multivariate regression results of WC and PSA, stratified by age, PV and FBG.

Table 4A shows that the overweight or obese individuals had lower PSA levels comparing to the referent weight individuals. However, the difference was not statistically significant in both crude and age adjusted models. It can be seen that obese was significantly associated with higher level of PSA in both FPG and PV adjusted models. The overweight individuals had lower PSAD, PSAR levels comparing to referent weight individuals, but independent with FPG and PV. Nevertheless, the difference was not statistically significant. **Table 4B** shows similar result in the multivariate regression results of WC and PSA. The multivariate regression results of BMI and PSA shows that BMI was significantly associated with lower level of PSA (OR: -0.032, 95% CI: (-0.050, -0.002)); P for trend =0.032), in independent of FBG (P for trend =0.021) step wised by WC and BMI, while BMI or WC was not significantly associated with PSAD, PSAR, including age, PV and FBG.

When BMI was treated as a continuous variable, the increasing rate of BMI was associated with a decrease of PSA by 0.112 ng/mL. When WC was treated as a continuous variable, the increasing rate of WC was associated with a decrease of PSA by 0.033 cm. There was a negative association between BMI or WC and PSA, PSAD and PSAR (P<0.001, 0.001, respectively) with a board line significance, but independent to FPG and PV.

Discussion

In this large study of 4404 males older than 60 years without prostate cancer, it can be investigated that obese men including central obesity have lower PSA, PSAD and PSAR. There was an inverse association between BMI, WC and serum PSA levels, but independent of FPG and

PV. When BMI and WC were considered as a continuous variable, the above negative association was strongly significant. Moreover, our data showed that levels of PSA might be negatively associated with BMI, rather than WC.

Although the exact relationship between obesity and PSA or prostate cancer is unclear, previous studies have shown an inverse relationship between serum PSA levels and BMI in other populations. In a recent report about 3,000 healthy men from the San Antonio Center for Biomarkers of Risk of prostate carcinoma (SABOR) demonstrated that high BMI was associated with lower PSA levels after controlling age and race [12]. Two studies about Asian populations also reported an inverse association between BMI and PSA [13, 14]. However, the study conducted in Korea only found such inverse association in men younger than 60 years of age. Comparing with previous studies, our study had much larger sample size and was controlled with other factors such as FPG and prostate volume. In addition, the inverse relationship between BMI, WC and PSA was found in young, middle-aged and old (over 60 years) Chinese males in this study.

The mechanisms behind the inverse association of BMI, WC and PSA are up to now unclear. Obesity is featured with multiple metabolic disorders and may influence PSA in several pathways. There are two hypotheses for the mechanism. The first one is hemodilution hypothesis which suggests that obesity could lead to the increasing of plasma volume and hemodilution, and reduction of circulation PSA levels [15]. This hypothesis 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 [16]. The second one is steroid hormone metabolism hypothesis. It is highly likely that obesity influence the PSA level through multiple pathways. Obesity might alter levels of multiple hormones and growth factors (e.g. testosterone, estrogens, leptin, insulin and insulin-like growth factor 1) with competing effects on prostate growth and size [17]. For obese individuals, a high amount of adipose tissue could improve aromatase activity, leading to the increasing of cyclic estrogen levels [18]. We speculate that this result might be due to regulating via androgen, estrodiol from adipose tissue, growth factors for obesity.

In current study, we observed an inverse association between obesity and PSA, especially BMI and WC as a continuous variable in crude and age, FBG or PV adjusted models. However, at the same time, it is found that obesity, including central obesity, might have no significant effect on serum PSA levels after age adjusted and PSAD and PSAR for males older than 60 years, in which age group it is well known that prostate cancer is very common. We speculate that the significantly negative correlation between obesity and PSA might be disturbed by the following factors: Firstly, in the prospective cohort study of Caucasian men, ages 40-79, serum PSA levels increased at a rate of 3.6% per year. Older men had more rapid increasing rate in serum PSA than younger ones, and men without diabetes had more rapid increases serum PSA levels. Hypertension, however, was not associated with rate of change in serum PSA levels [19]. Hence, considering the age interference, exclusive obesity might not influence the level of PSA for Chinese males. Secondly, we suspected obese elder with complicated BPH symptom might lead to an unconspicuous result for the influence of obesity on PSA levels for Chinese males. It is well known that BPH is frequently seen in males older than 60 years. About 60% of men aged over 50 years have histological evidence of BPH and, after age 70, the proportion increases to 80% [20]. The study for Korean conducted by Lee et al. [21] showed PV was positively correlated with BMI and WC, and WC was an independent risk factor for BPH (OR 3.37, 95% CI 1.08-10.5, p=0.037). The study for Chinese found that overweight and obese males have increased age-adjusted risk of BPH [22]. However, according to our result, PV have a negative association with BMI and WC. We speculate that the obese subjects of more than 60 years underwent BPH might attribute to the limited medical conditions in northwest of China, lack of the early detection of prostate disease knowledge, long-term drinking, as well as chronic urinary tract infection and MS. In fact, in the past decades, many different groups have investigated the influence of obesity on the development of BPH with conflicting results [23-25]. BPH and chronic urinary tract infection may have a conflicting effect on serum PSA for males in northwest of China. Finally, the diseases along with obese individual varied with ethnicities, lifestyle, age, functional androgen levels [26, 27], which may lead to the result that the elder had taken all kinds of medicines for interrupting serum PSA levels or for PSA balance, which should be clarified in further study.

Our study had several advantages. Firstly, the sample size is large. We had data from 4,404 healthy males with age ranging from 60 to 85. Such a large sample size and wide age range allow us to have good power for stratified analysis, particular by age groups. Secondly, important factors, including FBG, were collected, which may influence the relationship between BMI, WC and PSA. Hence, we were able to explore influence from these factors. As we known, no previous studies have controlled the factors of FBG, PV, or both of them in their analyses. Thirdly, we found the inverse association between obese, including central obesity, and PSA might not be not available males older than 60 years, in which age group it is well known that prostate cancer is very common.

There are also several limitations for this study, including the cross-sectional design, no information on important lifestyle factors, and other medical history, such as blood pressure medication. It may not be possible to generalize our results to all races, because only the northwest males in China, almost all Han race, were sampled, while BMI tends to be lower in Asian men than in Western men [28]. However, as the trends in BMI and PSA level for Western men are not different [29, 30], a more general application of our results might be acceptable. In addition, we have not excluded all subjects with prostate cancer, because biopsies were not taken for all participants. However, the prevalence of prostate cancer in eastern Asia is not high [31]. We would clarify the reason why overweight, obese and central individuals had not statistically significant comparing with referent weight or WC individuals for the black in **Table 4**, which should be investigated in the future. We have excluded subjects with PSA levels >15 ng/mL, while 98% of the study population had a PSA level <4 ng/mL. We also excluded people with abnormal ultrasound findings from ultrasonographic imaging for all participants. The probability of included cancer individual is very low.

Conclusion

A higher BMI, WC is associated with a lower level of PSA in healthy elderly males in all age

group, but independent to FBG and PV. When PSA is applied to screen prostate cancer, BMI should be considered to avoid a missed diagnosis. With the current obesity epidemic, individual's BMI, WC should be considered when PSA test was used for prostate cancer screening or diagnose. Despite the inverse association for PSA test would not be available for males older than 60 years, it is suggested that that PSAD or PSAR levels should be selected for estimation.

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Disclosure of conflict of interest

None.

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