Prostate Specific Antigen Mass Ratio Potential as a Prostate Cancer Screening Tool

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Abbreviations and Acronyms

BMI = body mass index

HOMA = homeostatic model assessment of IR

IR = insulin resistance

PSA = prostate specific antigen

PV = prostate volume

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Study received institutional review board approval.

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Purpose: Studies suggest lowering the threshold of the prostate specific antigen test in obese men due to the hemodilution effect but prostate specific antigen may be affected by prostate volume and insulin resistance, which also increase with obesity. Thus, we examined the combined effect of these factors on prostate specific antigen.

Materials and Methods: We analyzed 3,461 Korean men 30 to 80 years old with prostate volume data available who underwent routine evaluation. We examined the effect of plasma volume, homeostatic model assessment index, prostate volume and body mass index on prostate specific antigen, and prostate specific antigen mass and mass ratio (total circulating prostate specific antigen protein per prostate volume) by the trend test and/or ANOVA after adjusting for age and/or prostate volume.

Results: Body mass index had positive associations with plasma volume, the homeostatic model assessment index and prostate volume (p for trend <0.01). Prostate specific antigen had a positive association with prostate volume and a negative association with plasma volume (p for trend <0.01) but not with homeostatic model assessment index. The adjusted R^2 of prostate volume vs prostate specific antigen was greater than for plasma volume vs prostate specific antigen while for body mass index vs prostate volume it was less than for body mass index vs plasma volume (0.0892, 0.0235, 0.1346 and 0.3360, respectively). Prostate specific antigen mass was not associated with plasma volume or body mass index but it was still associated with prostate volume after adjusting for plasma volume or body mass index (p for trend <0.01). Mean prostate specific antigen mass ratio did not change significantly across body mass index, plasma volume or prostate volume quartiles in men older than 55 years.

Conclusions: It is not logical to lower the prostate specific antigen threshold based on only the hemodilution effect since body mass index related prostate volume enlargement can increase prostate specific antigen in obese men. Another tool is needed and prostate specific antigen mass ratio may be an option.

Key Words: prostate, prostate specific antigen, obesity, insulin resistance, organ size

ALTHOUGH the PSA test is widely used for prostate cancer screening,[1,2] it is not always reliable.[3,4] PSA is influenced by factors unrelated to cancer, such as age, BMI, IR and PV, while other known measures, such as PSA velocity, PSA density and free PSA, are not predictive enough to replace the PSA test.[5,6] Thus, despite its limitations the PSA test remains the

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standard.[1,3,7] We could increase the predictive value of the PSA test if we knew the combined effect of influencing factors on PSA.

Previous studies showed that PSA is positively associated with age and PV, and negatively associated with BMI.[8–21] The negative association between BMI and PSA may be due to low testosterone caused by obesity related hormonal disturbances (decreased sex hormone binding globulin, and increased aromatase and IR)[11–14] or to hemodilution by increased plasma volume.[15–19] Few groups have studied the direct effect of IR on PSA and since most did not simultaneously include plasma volume and IR data, we still do not know whether the negative association of BMI and PSA is due to hemodilution and/or IR. Most groups did not consider PV,[8–18] although it has a strong positive association with PSA.[20,21] The effects of hemodilution and IR on PSA in obese men cannot be accurately evaluated without considering PV since obesity increases plasma volume, IR and PV.

We examined the individual and combined effects of BMI, plasma volume, IR and PV on PSA in a general screening population after adjusting for potentially influencing factors. We also investigated a method that may reflect the effect of prostate cancer on PSA without confounding by other factors.

MATERIALS AND METHODS

Study Population and Data Collection

Of 49,650 Korean men who underwent routine health evaluation at the Healthcare System Gangnam Center of Seoul National University Hospital, Korea, from March 2004 to June 2008 we included in the study 4,083 who were 30 to 80 years old with PV data available. Medication and clinical conditions, such as diabetes mellitus and prostate related problems, were self-reported on a printed form, and a family physician performed an interview regarding current medication and disease status. Anthropometric parameters were measured directly, including height and weight. Blood for serum glucose, insulin and PSA measurements was obtained in the morning after the men fasted at least 12 hours and a radiologist then performed transrectal prostate ultrasound.

Before the study written informed consent was obtained from all participants and the institutional review board approved all procedures. Of 4,083 men with PV data available we excluded from analysis 129 on whom PSA, height, weight or fasting glucose data were missing. We then excluded 485 men with a history of prostate cancer, prostate surgery, a nodular prostate lesion or prostatitis, and those on anti-diabetic medication or any medication such as finasteride that affects PSA. We also excluded 4 men in whom PV was less than 10 ml due to a potential data record error. Finally, we excluded 4 men with serum PSA greater than 15 ng/ml due to a potential data record error and a high chance of prostate cancer or inflammatory prostate disease. That left 3,461 men for available analysis, including 813 with insulin and HOMA index data available. Routine insulin measurement was not started until 2007.

Clinical Variables

BMI was calculated as weight in kg divided by the square of height in m or kg/m^2. The HOMA index was calculated using the HOMA algorithm,[22] glucose in mg/dl $\times$ insulin in μU/ml/405. PSA mass in μg and PSA mass ratio in μg/ml were defined as the total amount of PSA protein in circulation and PSA mass per PV, respectively. Body surface area, plasma volume, PSA mass and PSA mass ratio were estimated using the equations, body surface area in m^2 = body weight in $kg^{0.425}$ $\times$ height in $m^{0.725}$ $\times$ 0.007184,[23] plasma volume in l = body surface area in $m^2 \times 1.670$,[24] PSA mass in μg = PSA in ng/ml $\times$ plasma volume in l[19] and PSA mass ratio in μg/ml = PSA mass in μg/PV in ml.

Statistical Analysis

We used the Pearson correlation test to examine individual associations of age, BMI, plasma volume, HOMA index, PV, PSA, and PSA mass and mass ratio. We divided continuous variables (BMI, plasma volume, HOMA index and PV) into quartiles and used multivariate linear regression to examine associations among PSA, PSA mass, plasma volume, HOMA index, PV and BMI. We also examined changes in PSA and PSA mass by plasma volume and PV quartiles after stratifying each. We tested for trends by regressing outcome variables on the quartile of factor variables on a continuous scale, adjusting for age and/or PV. We then used ANCOVA to examine whether there were differences in mean PSA mass ratio across each BMI, plasma volume and PV quartile. Since the prostate cancer incidence starts to increase significantly in the sixth decade of life and the middle value of age in this study was 55 years, we also divided participants into 2 age groups, including young—30 to 55 and old—56 to 80 years old, and analyzed each.[2]

Due to the skewed distribution of HOMA index, PV, PSA, and PSA mass and mass ratio we log transformed them for normalization before analysis and back transformed obtained data for interpretation. We performed all statistical analysis with STATA®, version 10.0 with 2-sided $p < 0.05$ considered statistically significant.

RESULTS

Baseline Characteristics and Pearson Correlation Test

Table 1 shows study population general characteristics. PSA correlated with age, PV, BMI and plasma volume (each $p < 0.01$). PSA mass correlated with age and PV (each $p < 0.01$). PSA mass ratio correlated with PV, BMI and plasma volume (each $p < 0.05$).

Relationships Among Factors

BMI had positive associations with plasma volume, HOMA index and PV (each p for trend < 0.01). PSA had a positive association with PV and a negative association with plasma volume (each p for trend