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ASSOCIATION OF OBESITY AND DIABETES WITH SERUM PROSTATE-SPECIFIC ANTIGEN LEVELS IN JAPANESE MALES

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ABSTRACT

Patients with diabetes have been reported to be at an increased risk for cancers of the pancreas, liver, and colon; however, recent studies have suggested that men with diabetes are at a decreased risk for prostate cancer. Previous studies have found that obese men have lower serum prostate-specific antigen (PSA) concentrations than do non-obese men. Further understanding of how obesity and diabetes affect the PSA concentration may improve our ability to detect clinically relevant prostate tumors. This study examined the relationships among serum PSA level, obesity, and diabetes in apparently healthy Japanese males. We analyzed the baseline data from 2,172 Japanese males (age, 56.8 ± 6.1 years [mean ± SD]) who participated in the Japan Multi-Institutional Collaborative Cohort Study. Diabetes was defined as the presence of both a hemoglobin A1c (JDS) of ≥6.1% and a fasting plasma glucose level of ≥126 mg/dL, or a positive medical history. After adjusting for age, the PSA levels were elevated among males with a higher normal BMI (ranging from 23.0 to 24.9) and lowered among men with a BMI of ≥25.0. In the stratified analysis, these significant differences in BMI categories were absent among diabetics. The mean PSA levels were significantly lower in diabetics than in non-diabetics among subjects aged 60 and over. Our findings suggest that the pre-overweight men had increased PSA levels, and the diabetes was associated with a reduction of PSA levels in elderly.

Key Words: Prostate-specific antigen, Diabetes mellitus, Obesity, Body mass index, Epidemiology

INTRODUCTION

Prostate-specific antigen (PSA) levels are affected by many factors that may be unrelated to prostate disease, including age and race.[1)] Patients with diabetes have been reported to be at an increased risk for cancers of the pancreas, liver, and colon;[2)] however, recent studies have suggested that men with diabetes are at a decreased risk for prostate cancer.[3-7)] Indeed, inverse

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associations between PSA levels and diabetes have been reported in recent studies.[8-11]

Multiple studies have found that obese men have lower serum PSA concentrations than do non-obese men.[12-15] Hemodilution may play a major role in the lower serum PSA concentrations among obese men.[16] Although recent reports found no association between body mass index (BMI) and PSA level or percent free PSA,[17-19] the findings were inconsistent.

The incidence of prostate cancer has increased rapidly in the last two decades in most Asian countries.[20] Further understanding of how obesity and diabetes affect the PSA concentration may improve our ability to detect clinically relevant prostate tumors. Positive results may lead to taking obesity or diabetes into account when setting the PSA cutoff value at screening. To our knowledge, no study targeting Japanese males has reported an association of diabetes or obesity with PSA levels in the same population. Thus, in this study, we examined the relationships among PSA levels, obesity and diabetes among apparently healthy Japanese males.

METHODS

We analyzed the baseline data from males in the Shizuoka area who participated in the Japan Multi-Institutional Collaborative Cohort (J-MICC) Study; details of this study have been described elsewhere.[21, 22] Briefly, the J-MICC Study was launched in 2005 by ten research groups throughout Japan, who sought to examine gene-environment interactions in lifestyle-related diseases, especially cancers.

In the Shizuoka area, 5,040 visitors (3,422 males and 1,618 females; age, 35–69 years) to the Seirei Preventive Health Care Center in Hamamatsu were enrolled from January 2006 to December 2007. Their lifestyle, disease history, and family history were surveyed using a self-administered questionnaire. Blood and urine were collected from the participants. Laboratory data, including height, weight, hemoglobin A1c (HbA1c), fasting blood glucose (FBS), and PSA, were obtained at the health check-up. Serum PSA levels were measured using the chemiluminescent enzyme immunoassay method (Abbott Japan, Tokyo, Japan). The Ethics Board of the Nagoya University School of Medicine approved the protocol of this investigation. All patients provided written informed consent.

A total of 2,323 participants (67.9%) had complete PSA data. To remove potentially influential values from the analysis, we excluded subjects with a medical history of prostatitis and prostate cancer, and those whose serum PSA level exceeded 4.0 ng/mL. After excluding 150 participants, the data from the remaining 2,172 men were analyzed (age, 56.8 ± 6.1 years [mean ± SD]; range, 35–69 years). Diabetes was defined as the presence of both an HbA1c of ≥6.1% and an FBS of ≥126 mg/dL, or a positive medical history. HbA1c (%) was estimated as the NGSP equivalent value (%), calculated using the formula HbA1c (%) = HbA1c (JDS)(%) + 0.4%, considering the relationship for HbA1c (JDS)(%) measured in previous Japanese standard substance and measurement methods and HbA1c (NGSP).[23]

BMI was calculated as the weight divided by the height squared. Differences in demographic characteristics were analyzed using the chi-square test, Mantel-Haenszel linear-by-linear chi-square test, and *t*-test. Correlations between the serum PSA levels and other variables were examined by Pearson's correlation analysis.

Mean levels of PSA for subjects with respect to their BMI category or the prevalence of diabetes were compared using a general linear model with age, which may affect serum PSA as a covariate. Serum PSA levels in both diabetic and non-diabetic subjects were also compared using the general linear model with covariates. The interactions between the prevalence of diabetes and age or BMI were tested using a two-way analysis of variance.

All statistical analyses were performed using SPSS software (ver. 18.0 for Windows; SPSS, Chicago, IL, USA). $p<0.05$ was considered to indicate statistical significance in all analyses.

RESULTS

Table 1 provides a description of the analytical study population. The PSA concentrations ranged from 0.1–3.9 ng/mL, and the mean ± SD and median PSA concentration levels were 1.1 ± 0.7, and 0.9 ng/mL, respectively.

Approximately 8.8% of the patients were classified as diabetic (Table 1). The prevalence of diabetes increased with age ($p = 0.001$). In total, 72.2% of the men were in the normal BMI range (BMI 18.5–24.9), with 25.3% classified as overweight (BMI 25.0–29.9) or obese (BMI ≥30), and 2.5% classified as underweight (BMI <18.5). For analysis, the normal BMI category was divided into lower normal (42.5%; BMI 18.5–22.9) and higher normal (29.7%; BMI 23.0–24.9) groups. After adjusting for age, the mean BMI among diabetics was higher than that among non-diabetics (24.1 vs. 23.4; $p = 0.002$).

The mean PSA level increased with age ($r = 0.159$; $p<0.001$). There were negative correlations between BMI and age ($r = –0.096$; $p<0.001$), and there was no significant correlation between PSA and BMI ($r = –0.011$; $p = 0.60$). After adjusting for age and covariates, the men in the BMI category between 23.0 and 24.9 had higher PSA levels than those in the other categories (Table 2).

There was no significant correlation between PSA and HbA1c ($r = –0.006$; $p = 0.78$) or FBS ($r = –0.014$; $p = 0.51$). As shown in Table 3, the PSA level in the diabetics was slightly lower than that in the non-diabetics, and this difference was marginally significant after adjusting for age and BMI (1.05 vs. 1.14; $p = 0.095$). The mean PSA levels of diabetics, with or without diabetes treatment (1.08 vs. 1.09; $P = 0.93$), did not differ. In age-stratified analysis, no significant differences of HbA1c or FBS levels were found between 35–59 years and 60 years or more ($p = 0.313$; $p = 0.847$) in diabetics. The mean PSA levels were significantly lower in diabetics

Table 1 Descriptive characteristics of 2,172 Japanese men aged 35–69 years by diabetes status

		Non-diabetic	Diabetic	*p* *
No. of subjects		1,977	195	–
Age (years)		56.7 ± 6.2	58.3 ± 5.0	0.001
BMI (kg/m^2)		23.4 ± 2.7	24.1 ± 3.1	<0.001
HbA1c (%)		5.2 ± 0.4	6.9 ± 1.2	<0.001
FBS (mg/dL)		99.7 ± 9.6	147.9 ± 42.1	<0.001
Smoking status (%)				
	Current	20.8	28.7	0.020
	Past	47.8	46.7	
	Never	31.3	24.6	
Drinking status (%)				
	Current	77.9	74.5	0.455
	Past	1.3	2.1	
	Never	20.8	23.4	

* The χ^2 test for proportions or *t*-test for continuous variables

Table 2 Mean PSA values for 2,172 Japanese men aged 35–69 years according to BMI measurements

	BMI				*p*
	<18.5	18.5–22.9	23–24.9	≥25	
No. of subjects (%)	53 (2.4)	923 (42.5)	646 (29.7)	550 (25.3)	–
PSA [mean* (ng/mL)]	1.14 (0.10)	1.11 (0.02)	1.21 (0.03)	1.10 (0.03)	0.013
PSA [adjusted mean† (ng/mL)]	1.12 (0.10)	1.10 (0.02)	1.21 (0.03)	1.11 (0.03)	0.023
PSA [adjusted mean‡ (ng/mL)]	1.12 (0.10)	1.10 (0.02)	1.20 (0.03)	1.11 (0.03)	0.024

* Mean (Standard error)
† Mean adjusted for age
‡ Mean adjusted for age and diabetes (yes/no)

Table 3 Mean PSA values for 2,172 Japanese men aged 35–69 years according to their diabetes status

	Diabetic			Non-diabetic	*p*§
	Treatment (–)	Treatment (+)	All		
All					
No. of subjects	111	84	195	1,977	–
PSA [mean* (ng/mlL)]	1.09 (0.07)	1.08 (0.08)	1.08 (0.05)	1.14 (0.02)	0.286
PSA [adjusted mean† (ng/mL)]	1.06 (0.07)	1.05 (0.08)	1.06 (0.05)	1.14 (0.02)	0.101
PSA [adjusted mean‡ (ng/mL)]	1.06 (0.07)	1.05 (0.08)	1.05 (0.05)	1.14 (0.02)	0.095
60 yrs>					
No. of subjects	68	56	124	1,356	–
PSA [mean* (ng/mL)]	1.05 (0.08)	1.14 (0.09)	1.09 (0.06)	1.07 (0.02)	0.770
PSA [adjusted mean† (ng/mL)]	1.03 (0.08)	1.11 (0.09)	1.07 (0.06)	1.07 (0.02)	0.880
PSA [adjusted mean‡ (ng/mL)]	1.03 (0.08)	1.11 (0.09)	1.06 (0.06)	1.07 (0.02)	0.946
≥60 yrs					
No. of subjects	43	28	71	621	
PSA [mean* (ng/mL)]	1.15 (0.12)	0.96 (0.15)	1.07 (0.09)	1.29 (0.03)	0.024
PSA [adjusted mean† (ng/mL)]	1.15 (0.12)	0.97 (0.14)	1.07 (0.06)	1.29 (0.03)	0.028
PSA [adjusted mean‡ (ng/mL)]	1.15 (0.12)	0.95 (0.14)	1.08 (0.09)	1.29 (0.03)	0.022

* Mean (Standard error)
† Mean adjusted for age
‡ Mean adjusted for age and BMI
§ *p* values between all diabetic subjects and non-diabetic subjects

than in non-diabetics among subjects aged 60 or over (1.07 vs. 1.29; p = 0.02). The interaction between the prevalence of diabetes and age was significant (p=0.03).

The age-adjusted mean PSA levels in both diabetics and non-diabetics were higher in the BMI category between 23.0 and 24.9 than in those of the other categories (Fig. 1). These differences were marginally significant among non-diabetics (p = 0.056), but not among diabetics (p = 0.163). The interaction between the prevalence of diabetes and BMI was not significant (p=0.53).

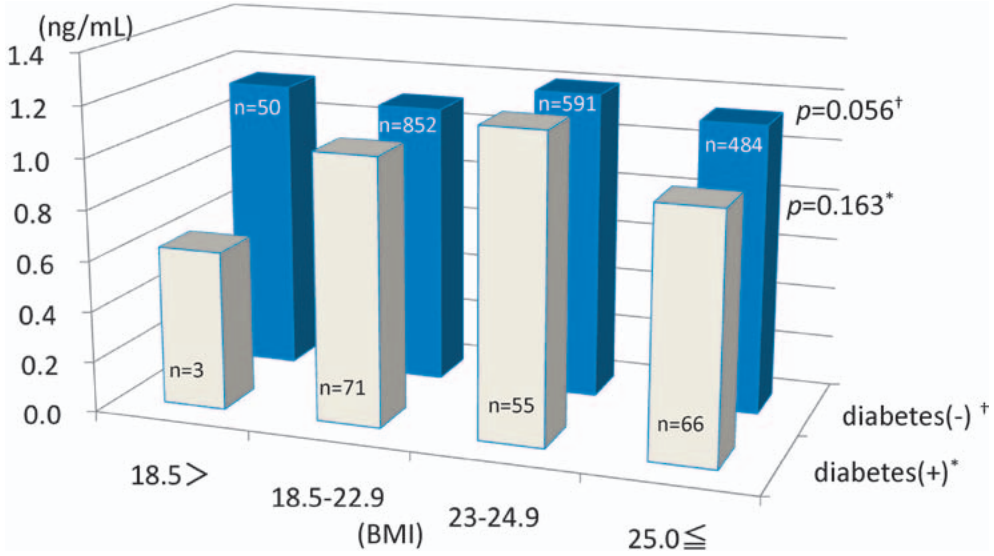

Fig. 1 The age-adjusted mean PSA values according to BMI and prevalence of diabetes among the 2,172 Japanese men

DISCUSSION

Our findings show that PSA levels were increased among men with a higher normal BMI and were decreased among men with a BMI of 25.0 or higher after adjusting for age. In the stratified analysis, these significant differences in BMI categories were absent among diabetics. After adjusting for age and BMI, the mean PSA levels were significantly lower in diabetics than in non-diabetics among men aged 60 and over. There was no significant difference in PSA levels of diabetic men, whether or not they were receiving diabetic treatment.

PSA is produced in prostate epithelial cells in response to androgen receptor activation. The hormonal hypothesis suggests that known interactions between body adiposity and steroid hormone metabolism, the inflammatory response, or insulin regulation, are sufficient to affect PSA expression. Androgens have been implicated in prostate tumorigenesis. Men with diabetes had significantly lower serum testosterone concentrations than did non-diabetic men according to a previous study.[24] Wallner et al.[10] assessed the associations between type 2 diabetes and changes in serum PSA levels, and suggested that Caucasian men with type 2 diabetes experienced smaller increases in serum PSA levels as they aged compared with men without diabetes. These findings seem to be in line with reports that patients with type 2 diabetes are at a decreased risk for prostate cancer.[25] Men with a higher BMI also have larger plasma volumes, which could decrease serum concentrations of soluble tumor markers.[26] It has been suggested that the larger vascular volume in obese men causes a dilution effect, decreasing the serum PSA.[13, 26]

Hutterer et al.,[17] Thomson et al.,[18] and Kristal et al.[19] found no statistically significant relationship between BMI and PSA. In other studies, BMI was inversely associated with PSA levels.[13, 15] Chia et al.[1] indicated an inverse association between BMI and PSA levels, especially among 70- to 79-year-old Chinese men with a BMI >25.0. Each 1 kg/m^2 of BMI gain per year was associated with a –0.011 ng/mL change in PSA concentration. Price et al.[14] showed that obesity (BMI >30) was associated with decreased PSA levels in a multiethnic cohort of participants. Kubota et al.[27] found an inverse but weak relationship between BMI and PSA in

Japanese participants from a large cohort study based on health check-ups. Hence, this association remains controversial.

Several studies found a lower serum PSA level among those with diabetes; Müller et al.[8] analyzed data from a large population-based cohort study in Germany in which the participants were aged 50 to 74 years and had a 17% prevalence of diabetes. They reported that more severe forms of diabetes were associated with lower PSA levels. Werney et al.[9] analyzed data from American men aged ≥40 years in the National Health and Nutrition Examination Survey, and found that those subjects with self-reported diabetes had a 21.6% lower geometric mean PSA level than did those without diabetes. Fukui et al.[11] showed that serum PSA levels were lower in patients with type 2 diabetes than in healthy men among Japanese males aged 50–79 years.

Our results partially confirm the inverse correlations between PSA levels and BMI, or diabetes described above. The lower BMI (mean = 23.4) and prevalence of diabetes (8.8%) in this study may be related to our weak associations. In this study, the mean age of the subjects was in the 50s. Many previous studies obtained results from subjects whose mean ages were in the 40s or 60s. PSA levels are influenced by a number of demographic, lifestyle, and health characteristics, all of which deserve careful attention in the interpretation of test results.[8] The association between BMI and PSA may vary according to population characteristics.[17] Our findings were consistent with those of Kubota et al.,[27] in which men with a higher normal BMI (23–24.9) showed the highest mean PSA levels in all BMI categories. This BMI range may be likely to increase the PSA levels among apparently healthy Japanese, even though the biological mechanism is unknown. Prostate weights and volumes were not considered in our analysis. These factors might affect the results in which men with a BMI below 23.0 showed lower PSA levels than those in men with higher-normal BMI. Most studies analyzed data on subjects with BMI less than 25.0 as one category. There has been insufficient evidence to discuss the association between PSA and BMI or diabetes in non-obese men. Taken together, further study is therefore needed to investigate the association of diabetes and obesity with PSA levels using a longitudinal study design.

Limitations of this study include the fact that there were proportionally fewer subjects in the diabetes group than would be included in a case-control study. Thus, the statistical power to analyze the impact of diabetes on PSA levels may have been decreased. We did not measure prostate weights and volumes which affected the PSA level. These factors were not considered in our analysis. Furthermore, because all subjects were health check-up examinees, mild cases of diabetes were likely to be included in the study population. We could not analyze the data by the treatment duration and diagnosis period of diabetes because of the lack of this information, although the mean PSA level of the diabetics whether or not they were being treated did not differ. The treatment duration and diagnosis period of diabetes may affect our findings, that a reduction of PSA levels in diabetics was found among elderly men. Finally, it is possible that men with underlying prostate disease could have been included in this study, although we excluded subjects with evident prostate disease and those whose serum PSA level exceeded 4.0 ng/mL.

In conclusion, our findings suggest that PSA levels were elevated among pre-overweight men and were lower among overweight and obese men, and that diabetes was associated with a reduction of PSA levels in the elderly.

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