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Prostate Cancer in Patients with Metabolic Syndrome Is Associated with Low Grade Gleason Score When Diagnosed on Biopsy

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Purpose: Studies on the relationship of metabolic syndrome (MS) and prostate cancer are controversial. We evaluated the association between MS and prostate cancer characteristics in patients who underwent transrectal ultrasound-guided prostate biopsy.

Materials and Methods: From October 2003 to May 2011, patients with a prostate-specific antigen (PSA) value ≥ 4 ng/ml or abnormal digital rectal examination (DRE) result underwent transrectal ultrasound-guided prostate biopsy. MS was diagnosed according to the Adult Treatment Panel III. Clinicopathologic factors including PSA, DRE, prostate volume, age, waist circumference, body mass index (BMI), lipid profiles, fasting blood sugar level, and MS were considered for analysis.

Results: Three hundred fifty-four patients were enrolled (mean age, 68.86±8.95 years; mean PSA, 13.97±20.42 ng/ml). Seventy-five patients (21.2%) had MS and 90 patients (25.4%) were diagnosed as having prostate cancer, including 27 (30%) with MS and 63 (70%) without MS. Total PSA value and prostate volume were significant predictors for prostate cancer. However, MS and BMI were not significantly related to increased cancer risk. Prostate cancer patients with MS had significantly lower Gleason scores (average, 6.63±1.92) than did prostate cancer patients without MS (average, 7.54±1.71; p=0.029).

Conclusions: Presence of MS was associated with a significantly decreased risk of high-grade prostate cancer. A larger, prospective, multicenter investigation is mandatory to clarify the relationship between MS and prostate cancer.

Key Words: *Biopsy; Metabolic syndrome; Prostatic neoplasms*

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INTRODUCTION

The prevalence of prostate cancer is rapidly increasing and prostate cancer is now the 7th most commonly diagnosed cancer in Korea [1]. Factors contributing to this increase include an aging population; westernization of the diet, such as higher intakes of dietary fat, meat, and excessive calories; and the availability of generalized diagnostic tools for prostate cancer. Metabolic syndrome (MS) is the combination of several metabolic abnormalities, including hypertension, dyslipidemia, central obesity, insulin resistance, and glucose intolerance [2]. MS is clearly related to cardiovascular disease or type II diabetes; however, the relationship between MS and malignant diseases is unclear [3]. There are sporadic reports showing that that the incidence and mortality rates of colon cancer, endometrial cancer, and breast cancer are related to the components of MS, such as obesity and insulin resistance [4,5].

Previous studies on the relationship between prostate cancer and MS have reported contradictory results [6-8]. Most previous studies on the association of MS and prostate cancer were conducted in multi-racial groups or non-Korean populations. In this study, we investigated whether there is a relationship between MS and prostate cancer in Korean men who underwent a transrectal ultrasound-guided prostate biopsy.

MATERIALS AND METHODS

From October 2003 to May 2011, 432 Korean men with a serum prostate-specific antigen (PSA) level ≥4 ng/ml or an abnormal digital rectal examination finding underwent transrectal ultrasound-guided prostate biopsy. Patients who had been diagnosed as having prostate cancer before or who had undergone prostatic surgery and patients taking 5-alpha reductase inhibitors or whose data were insufficient for analysis were excluded. A total of 354 patients were eligible for the investigation. Data were collected retrospectively by reviewing the patients' medical records. Prostate biopsy was performed as an outpatient procedure. Prophylactic oral antibiotics were taken from 2 days before the prostate biopsy until 3 days after the biopsy. A povidone-iodine enema was completed prior to biopsy. Transrectal ultrasound-guided prostate biopsy was performed by using a Falcon ultrasound instrument (BK Medical, Peabody, MA, USA) and 12 cores were obtained. A 16-gauge biopsy needle (magnum 1000; Bard, Byran, CO, USA) and spring-loaded biopsy gun (MG1522; Bard) were used. For pain control, 25 to 50 mg meperidine (Demerol) was injected intramuscularly before biopsy. Biopsy results were classified as benign prostatic hyperplasia, acute or chronic prostatitis, chronic inflammatory atrophy, prostatic intraepithelial neoplasia, atypical small acinar proliferation, or prostate cancer with Gleason score. A biopsy Gleason score ≥7 was regarded as high-grade prostate cancer and a Gleason score <7 as low-grade. All patients received a physical examination including measurement of height, weight, and waist circumference before prostate biopsy. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Fasting serum samples including high-density lipoprotein (HDL) cholesterol, triglyceride, blood glucose, total PSA (tPSA), and free PSA were analyzed. MS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria as follows [9]: 1) high fasting blood glucose level (110 mg/dl), 2) hypertriglyceridemia (150 mg/dl), 3) reduced HDL cholesterol (<40 mg/dl in men and <50 mg/dl in women), 4) high blood pressure (130/85 mmHg) or use of anti-hypertensive drugs, and 5) abdominal obesity (abdomen circumference >90 cm in men or >80 cm in women according to the 2000 World Health Organization criteria for abdominal obesity in the Western Pacific region). At least three of the five criteria needed to be met for a diagnosis of MS. Patients were divided into 2 groups according to presence of MS or diagnosis of prostate cancer. Patients with prostate cancer were subdivided according to Gleason score: Gleason score ≥7 as high-grade and <7 as low-grade prostate cancer groups. By use of multiple logistic regression with the enter method, the statistically significant variables as assessed in the univariate analysis were entered and investigated as predictors of prostate cancer presence versus absence and in a separate model comparing predictors of high-grade versus low-grade prostate cancer among men with cancer on biopsy. The logistic regression analysis was carried out by using data from patients for whom complete data were available. SPSS ver. 18.0 (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis.

RESULTS

The patients' mean age was 68.86±8.95 years, their mean tPSA was 13.97±20.42 ng/ml, their mean prostate volume was 49.23±24.89 ml, their mean waist circumference was 85.15±6.92 cm, their mean weight was 65.93±8.38 kg, and their mean BMI was 23.76±2.71 kg/m^2. Ninety patients (25.4%) were diagnosed with prostate cancer and 75 patients (21.2%) were diagnosed with MS according to the NCEP-ATP III criteria. There was no significant difference in age, tPSA, or prostate volume between the groups with and without MS. Patients with MS had higher values of BMI, waist circumference, fasting blood sugar, and triglyceride, and presented with a lower HDL-cholesterol level, than did patients without MS. Patients diagnosed with prostate cancer had higher age, tPSA, and PSA density (dPSA) than did patients without prostate cancer. Among the 90 patients with prostate cancer, 27 (30%) had MS. At the same time, among the patients without prostate cancer, 18% had MS. Twenty-seven patients had a Gleason score ≤6 and 63 patients had a Gleason score ≥7. Prostate cancer patients diagnosed with MS had a mean Gleason score of 6.63±1.92, which is significantly lower than that of prostate cancer patients without MS (7.54±1.71; p=0.029) (Table 1). Both tPSA and dPSA were higher in patients with a high-grade Gleason score than in those with a low-grade Gleason score. In the logistic regression analysis, high tPSA and small prostate volume were significant predictors for prostate cancer diagnosis (odds ratio [OR], 1.079 and 0.979, respectively). tPSA was significantly related to increasing prostate cancer risk. However, age, presence of MS, and BMI were not significantly related to increasing prostate cancer risk. In the logistic regression analysis, tPSA was significantly related to high-grade prostate cancer (OR, 1.109; p=0.017) (Table 2). Presence of MS was significantly associated with a decreased risk of high-grade prostate cancer (OR, 0.101; p=0.004) (Table 3).

DISCUSSION

The prevalence of MS in Korea, which ranges from 19.8 to 30.9% according to the NCEP-ATP III, has increased up to 28.6% according to the national health nutrition survey in 2001 as compared with the previous survey in 1998 [10]. MS is related to cardiovascular disease or type II diabetes; however, the relationship between MS and malignancy is unclear [3]. It has been reported that the incidence and mortality rates of colon cancer, endometrial cancer, and breast cancer are associated with components of MS such as obesity and insulin resistance [4,5]. Changes in neoplastic metabolism, DNA oxidation damage or repair malfunction, local inflammation, and insulin-like growth fac-

TABLE 1. Characteristics of prostate cancer patients according to presence of metabolic syndrome

Metabolic syndrome	No (n=63)	Yes (n=27)	p-value[a]
Age (yr)	70.90±9.19	71.59±9.97	0.752
Total PSA (ng/ml)	29.32±45.25	58.85±91.69	0.121
PSA density	0.64±0.80	1.32±2.15	0.117
Prostate volume (ml)	45.69±21.52	46.10±27.66	0.944
BMI (kg/m^2)	22.91±2.07	26.59±2.43	0.000
Waist circumference (cm)	83.42±5.74	91.21±6.99	0.000
Fasting glucose (mg/dl)	113.25±27.78	126.81±39.05	0.065
Triglyceride (mg/dl)	141.21±42.96	155.33±28.63	0.072
HDL cholesterol (mg/dl)	50.74±11.39	46.41±9.13	0.083
Gleason score	7.54±1.711	6.63±1.92	0.029

PSA, prostate-specific antigen; BMI, body mass index; HDL, high-density lipoprotein.
[a]:Student's t-test.

TABLE 2. Odds ratio (OR) and 95% confidence interval (CI) for predicting prostate cancer detection on biopsy

	OR	95% CI	p-value[a]
Prostate cancer detection			
Age	1.024	0.993-1.057	0.133
Total PSA	1.079	1.047-1.111	0.000
Prostate volume	0.979	0.967-0.992	0.001
Body mass index	1.051	0.937-1.178	0.395
Metabolic syndrome	1.733	0.851-3.530	0.130

PSA, prostate-specific antigen.
[a]:Logistic regression analysis.

TABLE 3. Odds ratio (OR) and 95% confidence interval (CI) for a high Gleason score (≥7) among men with prostate cancer on biopsy

	OR	95% CI	p-value[a]
Biopsy Gleason score ≥7			
Age	1.022	0.962-1.085	0.478
Total PSA	1.109	1.019-1.208	0.017
Prostate volume	0.979	0.951-1.007	0.139
Body mass index	1.238	0.974-1.572	0.081
Metabolic syndrome	0.101	0.022-0.473	0.004

PSA, prostate-specific antigen.
[a]:Logistic regression analysis.

tor 1 (IGF-1) may contribute to the relationship between MS and malignant disease [11,12].

Results of previous studies on the relationship between prostate cancer and MS are also controversial [13-16]. Data from an investigation in Finland suggested a positive association between prostate cancer and MS; in that study with 507 prostate cancer cases, patients with at least three metabolic factors showed a 56% increased risk [6,7]. Hammarsten and Hogstedt [17] reported that MS components including hypertension, obesity, dyslipidemia, and hyperinsulinemia are risk factors for the development of clinical prostate cancer and suggested that clinical prostate cancer could be a component of the MS. On the contrary, Tande et al. [8] reported an inverse association; in their study in a large cohort of the Atherosclerosis Risk in Communities study, men with MS showed a 23% reduction in risk of prostate cancer. They hypothesized that this finding reflects a decrease in bioavailable testosterone with the MS and a concomitant reduction in prostate cancer risk. The present study evaluated the relationship between MS and prostate cancer in Korean patients who underwent transrectal ultrasound-guided prostate biopsy. Our results showed that the presence of MS did not significantly increase prostate cancer risk (OR, 1.733; 95% confidence interval [CI], 0.851 to 3.530; p=0.13). De Nunzio et al. [18] showed that MS was not associated with increased prostate cancer risk, but was associated with an increased risk (OR, 3.8; 95% CI, 1.33 to 10.9) of high-grade prostate cancer (Gleason score≥7) in patients with prostate cancer at biopsy. Hammarsten and Hogstedt [17] reported that patients with high-grade prostate cancer and PSA<50 ng/ml were more obese, were more dyslipidemic, and showed a higher plasma insulin level than did those with low-grade prostate cancer and PSA<50 ng/ml. In our results, however, the presence of MS was associated with a significantly decreased risk of high-grade prostate cancer (OR, 0.101; 95% CI, 0.022 to 0.473; p=0.004) (Table 3). Similar to our results, Han et al. [19] reported that prostate cancer patients with MS had a tendency to show a lower Gleason score, but the result was not statistically significant. Lee et al. [13] reported that patients with lower BMI were more likely to have high-grade cancer despite the lack of statistical significance. Moreira et al. [20] showed that diabetes mellitus was associated with a greater risk of high-grade prostate cancer. After stratification by obesity and race, the association was strongest among obese Caucasian men, which suggests that the effect of diabetes on high-grade prostate cancer could be modified by race and obesity. They focused on the complex association among diabetes, serum hormonal levels, and obesity and suggested that compounded effects of lower free IGF-1, lower testosterone in obese Caucasian

men, and lower insulin from diabetes perhaps created a very poor growth factor environment leading to the selection of aggressive tumors. Barnard et al. [7] suggested that hormone-resistant prostate cancer can occur earlier in the case of obesity-induced hormonal changes including decreased levels of total testosterone, free testosterone, and sex hormone binding globulin and increased levels of estradiol.

Insulin resistance, which is a fundamental component of MS, plays an important role in malignant formation regarding the intracellular insulin receptor or intrinsic hormone metabolism. In particular, insulin and IGF-1 facilitate cell proliferation and suppress apoptosis [21]. Animal studies have also revealed that removal of IGF-1 receptor or lowering of the IGF-1 level decreases malignant formation [22]. An epidemiologic investigation also linked increasing IGF-1 level to prostate cancer [23] and supported the suggestion that overactivity of male hormone levels induced by insulin resistance, increased IGF-1 level, and decreased IGF binding protein level would also be related to prostate cancer.

It has been suggested that evaluating MS as a single condition may be an inappropriate approach to investigating prostate cancer risk. Specifically, combining all the multiple components of the syndrome into a single variable may confound or obscure the independent effects and interactions of these metabolic components on prostate cancer risk [24]. Unfortunately, our study did not analyze the association between each component of MS and prostate cancer because of a lack of information, which is major limitation of retrospective review. On the basis of previous reports, however, the association of MS with a significantly decreased risk of high-grade prostate cancer in our study might result from a change in the sex steroid pathway or circulating levels of cytokines such as leptin and adiponectin [24]. Although the exact function of androgen and estrogen in prostate cancer development is not definite, it has been suggested that low total and free testosterone are inversely associated with low-grade prostate cancer but positively associated with high-grade prostate cancer. A possible explanation for this relation is that high-grade prostate cancer is more aggressive and may be more androgen-independent than low-grade tumors, thereby continuing to progress despite the relative lack of testosterone [25]. Circulating levels of cytokines such as leptin and adiponectin have been preliminarily associated with prostate carcinogenesis. Leptin stimulates the *in vitro* growth of androgen-insensitive prostate cancer cells, and increased serum leptin levels are associated with larger, high-grade, and more advanced tumors. Adiponectin showed antitumor activity via inhibition of angiogenesis, and lower adiponectin serum levels are associated with high-grade and more advanced prostate cancer. Chronic prostatic inflammation as observed in patients with MS is associated with a milieu rich in proinflammatory cytokines, inflammatory mediators, and growth factors, which may lead to an uncontrolled proliferative response with rapidly dividing cells that are more likely to undergo mutation, as observed in cancer [24]. This investigation had limitations, including the retrospective review and lack of prostatectomy Gleason scores, which limited the statistical power and generalizability of our results. In addition, in our study, information on each primary component of MS could not obtained, and thus an analysis of the relationship between each component of MS and prostate cancer was not performed. Despite these limitations, however, our results showing that the presence of MS was not significantly related to increasing prostate cancer risk but was associated with a significantly decreased risk of high-grade prostate cancer could play a role in disclosing the link between MS and prostate cancer. Further prospective studies in larger patient groups with long-term follow-up as well as basic research are needed to clarify the relationship between the components of MS and prostate cancer and to evaluate the possible implication of MS prevention on prostate cancer development.

CONCLUSIONS

The results of our study suggest that high tPSA and small prostate volume are significant predictors for prostate cancer diagnosis. However, age, presence of MS, and BMI were not significantly related to increasing prostate cancer risk. Furthermore, the presence of MS was significantly associated with a decreased risk of high-grade prostate cancer. A larger, prospective, multicenter investigation is needed to clarify the relationship between MS and prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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