

The Association between Metabolic Syndrome and High-Stage Primary Urothelial Carcinoma of the Bladder

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Key Words

Urothelial carcinoma • Metabolic syndrome • Bladder cancer

Abstract

Recently, metabolic syndrome (MetS) has become an important public health problem, and its prevalence is increasing. MetS is associated with multifactorial diseases. No reports have suggested a relationship between bladder cancer and high blood pressure, and hyperlipidemia has been reported as a possible risk factor. In the present study, we investigated the relationships between the stage and degree of malignancy of bladder cancer and MetS. Furthermore, we investigated the influence of the components of MetS on the results. We retrospectively analyzed the data of 169 patients who underwent transurethral resection of a bladder tumor in our department between January 2005 and March 2011. MetS was significantly associated with a high histological grade ($p < 0.05$). MetS and low high-density lipoprotein were found to be significantly associated with the T stage; no other components of MetS were associated with a high stage or grade. Our results demonstrated that a lack of therapy for patients with low high-density lipoprotein levels could be riskier than was previously thought.

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Introduction

Bladder cancer is the ninth most common cancer in the world, with 430,000 new cases diagnosed in 2012 [1]. In Japan, approximately 6–8 cases per 100,000 people occur each year and the number of patients tends to increase year by year. Cigarette smoking and occupational exposure are the main risk factors for upper tract urothelial carcinoma and urinary bladder cancer. Both genetic and environmental factors are considered to play important roles in the carcinogenesis of bladder cancer [2].

Although these well-established risk factors are directly associated with an increased risk of bladder cancer, the mechanism underlying the development of bladder cancer remains unclear.

Moreover, these factors are not sufficient to explain the differences in the prevalence of urothelial carcinoma of the bladder between ethnicities and genders. The other risk factors should be explored and clarified in order to reduce the incidence of urothelial carcinoma of the bladder.

Recently, metabolic syndrome (MetS) has become an important public health problem, and its prevalence is increasing [3]. MetS is associated with multifactorial diseases, and is characterized by abnormal glucose tolerance, lipid disorders, high blood pressure, and a high

Table 1. Patients and tumor characteristics (n = 169)

Variables	n (%)
Gender	
Male	137 (81%)
Female	32 (19%)
Age (mean ± SD)	73.16 ± 9.99
Pathologic stage	
≤ T1	122 (72.2%)
≥ T2	47 (27.8%)
Histologic grade	
Low grade	84 (49.7%)
High grade	85 (50.3%)
MetS	
Yes	21 (12.4%)
No	148 (87.6%)
Hyperglycemia	67 (38.6%)
Hypertension	68 (40.2%)
Obesity (BMI > 25 kg/m ²)	38 (22.5%)
Low HDL	37 (21.9%)
Hypertriglyceridemia	33 (19.5%)

mortality rate. There are some reports indicating a relationship between the body mass index (BMI) and bladder cancer.

Although no reports have suggested a relationship between bladder cancer and high blood pressure, hyperlipidemia has been reported as a possible risk factor [4].

Although the correlation between MetS and malignant prostate cancer has already been investigated [5], no studies have reported on the correlation between MetS and the clinical stage or degree of malignancy of bladder cancer. In the present study, we investigated the relationships between the stage and degree of malignancy of bladder cancer and MetS. Furthermore, we investigated the influence of the components of MetS on the results.

Materials and Methods

We retrospectively analyzed the data of 169 patients who underwent transurethral resection of a bladder tumor in our department between January 2005 and March 2011. Clinical staging was determined according to the 2002 TNM classification. Ta and T1 tumors were defined as lower stage bladder carcinoma. T2, T3 and T4 tumors were defined as higher stage bladder carcinoma. We evaluated the predictive risk factors for the muscle invasion of urothelial carcinoma of the bladder, including age, sex, BMI, and the high-density lipoprotein (HDL), triglyceride and fasting glucose levels.

Table 2. Comparison of characteristics between patients with or without MetS

Variables	Metabolic syndrome	Non-metabolic syndrome	p
Patients (n)	21	148	
Age (mean ± SD), years	73.14 ± 10.05	73.28 ± 9.99	0.625
BMI (mean ± SD), kg/m ²	26.9 ± 43.4	222.1 ± 3.4	0.005
T stage			0.546
Lower stage (Tis Ta T1)	14 (66.9%)	108 (73%)	
Higher stage (T2 T3 T4)	7 (23.3%)	40 (27%)	0.003
Histologic grade			
Low grade	6 (28.6%)	79 (53.4%)	
High grade	15 (71.4%)	69 (46.6%)	

All of the statistical analyses were carried out on a personal computer using the Ekuseru-Toukei 2015 statistical software package (SSRI, Tokyo, Japan). $P < 0.05$ were considered to indicate statistical significance. The pathological grade was determined according to the 2004 World Health Organization grading system.

MetS was diagnosed in patients who satisfied at least 3 of the following 5 criteria: 1) BMI > 25 kg/m²; 2) triglyceride concentration > 150 mg/dl or undergoing treatment for hypertriglyceridemia; 3) HDL cholesterol concentration < 40 mg/dl or undergoing treatment for a low HDL-C level; 4) blood pressure > 130/85 mmHg or undergoing treatment for hypertension; 5) fasting plasma glucose level > 100 mg/dl or undergoing treatment for hyperglycemia.

Results

Among the 169 patients who were analyzed in our study, 137 were male (81%) and 32 were female (19%). The patient and tumor characteristics are shown in table 1. MetS was found in 21 (12.4%) patients. The mean ages of the patients in the MetS group and the non-MetS group were 73.14 ± 10.05 and 73.28 ± 9.99 years, respectively ($p = 0.625$).

The pathological stages of the tumors were lower (Tis, Ta, T1) in 66.7% of the patients with MetS and higher (T2, T3, T4) in 23.3% of the patients with MetS. The histological grades of tumor were low and high 65.5 and 34.5% of the patients, respectively (table 2). The relationships between MetS (and the components of MetS) and the T stage and grade are shown at table 3.

According to our data, the pathological stage of the tumor was significantly associated with low HDL ($p < 0.05$). As shown in table 2, MetS was significantly associated with a high histological grade ($p < 0.05$). MetS

Table 3. Comparison between parameters MetS with stage and grade

Variables	Lower stage	Higher stage	p	Lower grade	Higher grade	p
Patients (n)	122	47		85	84	
Obesity (BMI > 25 kg/m ²)	23 (18.9%)	15 (31.9%)	0.068	16 (18.8%)	22 (15.5%)	0.251
Hyperglycemia	47 (38.5%)	20 (42.6%)	0.631	32 (37.6%)	35 (41.7%)	0.593
Hypertension	48 (39.3%)	20 (42.6%)	0.703	33 (38.8%)	35 (41.7%)	0.706
Low HDL	21 (17.2%)	17 (36.2%)	0.008	16 (18.8%)	21 (25%)	0.332
Triglyceride	16 (13.1%)	8 (17%)	0.514	12 (14.1%)	21 (25%)	0.074

and low HDL were found to be significantly associated with the T stage; no other components of MetS were associated with a high stage or grade.

Discussion

In the present study, we retrospectively reviewed the patients who have been treated by transurethral resection of a bladder tumor to assess the association between the components of MetS and the aggressiveness of urothelial carcinoma of the bladder. Our study demonstrated that primary urothelial bladder carcinoma with MetS could become a risk factor for the malignant potential of urothelial carcinoma of the bladder.

Why is MetS associated with bladder cancer malignancy? MetS could decrease insulin sensitivity and induce a permanent state of excess insulin secretion [6]. Moreover, our reports have demonstrated that a low HDL level could be a risk factor for the upstaging of urothelial carcinoma of the bladder.

Although the reports about the association between low HDL levels and arteriosclerosis are common, reports about the association between low HDL levels and malignant disease are rare. This is the first report to demonstrate an association between the components of MetS and the aggressiveness of urothelial carcinoma of the bladder. MetS could be associated with the malignant potential of urothelial carcinoma of the bladder due to the excess secretion of insulin [6]. The fact that the excess secretion of insulin can become a risk factor for malignant potential in some organs is well known [3]. However, the reason why a low HDL level could be a risk factor for the upstaging of urothelial carcinoma of the bladder is unknown.

Indeed, our study could not demonstrate whether low HDL levels are directly related to the upstaging of urothelial carcinoma of the bladder. However, low HDL

levels could be related to the excess secretion of insulin. After all, the mechanism through which low HDL levels induce the upstaging of urothelial carcinoma of the bladder might be same as the mechanism by which MetS induces the worsening of the pathological stage of urothelial carcinoma of the bladder. One possibility is that the stimulation of insulin via insulin receptors could activate the PI3/Akt pathway, which could induce carcinogenesis and cell proliferation.

Many patients with low HDL levels have no symptoms of diabetes mellitus, and some show excess insulin secretion. Physicians tend to diagnose these patients with mild metabolic disorder, and to not consider them to have an increased risk of malignancy. However, physicians should take care, as this condition may be associated with a worsening of urothelial carcinoma of the bladder. On the other hand, physicians should also keep in mind that a low HDL level can worsen a patient's metabolic disorder; without proper treatment, this has the potential to lead to MetS and a worsening of urothelial carcinoma of the bladder.

Most patients with of low HDL levels are thought to show no symptoms; such conditions tend to be detected by blood tests for other diseases. Our results demonstrated that a lack of therapy for patients with low HDL levels could be riskier than was previously thought.

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