

RESEARCH ARTICLE

Association between the Metabolic Syndrome and High Tumor Grade and Stage of Primary Urothelial Cell Carcinoma of the Bladder

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Abstract

Purpose: To compare histopathologic findings of patients who underwent transurethral resection of a bladder tumor (TUR-B) between groups with and without the metabolic syndrome. **Materials and Methods:** We retrospectively analyzed data of 535 patients who underwent TUR-B in our department between October 2005 and March 2011. All patients had primary urothelial cell carcinoma (UCB). Histologic stage, grade, the presence of hypertension, diabetes mellitus, body mass index (BMI), waist circumference, HDL and triglyceride levels were evaluated. The TNM classification was used, with Ta tumor accepted as lower stage and T1 and T2 tumors as higher stage bladder cancers. Also, the pathological grading adopted by the 2004 World Health Organization grading system were applied. Non-invasive papillary urothelial neoplasms of low malignant potential were regarded as low grade. **Results:** Among the total of 509 patients analyzed in our study, there were 439 males (86.2%) and 70 females (13.8%). Metabolic syndrome was significantly associated with high histologic grade, and high pathologic stage ($p < 0.001$). **Conclusions:** The patients with metabolic syndrome were found to have statistically significant higher T stage and grade of bladder cancer. Further studies with more patients are needed to confirm our study.

Keywords: Bladder cancer - metabolic syndrome - urothelial carcinom - diabetes mellitus - grade - stage

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Introduction

Urothelial carcinoma of the bladder is a common malignancy with an estimated 73,510 new cases and 14,880 deaths in 2012 in the United States. Compared to other places in the world, bladder cancer is considered to be a relatively common disease in Europe, North America, and Northern part of Africa (Siegel et al., 2012). Both genetic and environmental factors are considered to play important roles in the carcinogenesis of bladder cancer (Murta-Nascimento et al., 2007). To date, several risk factors, such as paint, smoking and human papillomavirus infection, have been implicated in urinary bladder carcinogenesis (Freedman et al., 2011; Li et al., 2011). Although these well-established risk factors are directly associated with increased risk of bladder cancer, the mechanism of bladder cancer still remains contradictor. These factors can not thoroughly explain the difference in bladder cancer rate between ethnicities and genders. Further researches are needed to explore potential risk factors and clarify the interaction between them.

Metabolic syndrome (MetS) is an important public health problem worldwide, and its prevalence is increasing (Gorbachinsky et al., 2010). MetS characterized by impaired glucose tolerance/diabetes, obesity, high

triglyceride levels, low HDL levels, and hypertension is a multifactorial chronic disease associated with high mortality (Eckel 2007). There are little data on the association between the MetS and risk of bladder cancer, for separate components as well as for MetS factors combined (Calle et al., 2003; Jee et al., 2005; Batty et al., 2005). The association between body mass index (BMI) and bladder cancer has been inconsistent. Some studies have shown an increased risk for high levels of BMI (Samanic et al., 2004; Holick et al., 2007; Koebnick et al., 2008) and several studies have reported no significant association (Samanic et al., 2006; Reeves et al., 2007; Jee et al., 2008; Larsson et al., 2008). A few smaller studies (n cases <500) on hypertension (Grove et al., 1991; Rosengren et al., 1998), cholesterol (Hiatt and Fireman 1986; Haggstrom et al., 2011; Hu et al., 2012) and bladder cancer risk have reported inconsistent associations. Two large studies have investigated glucose levels in relation to risk of bladder cancer, one reported an association with fatal bladder cancer among men (no data reported for women) (Jee et al., 2005), whereas a recent a study from the Me-Can project showed an association between high glucose and risk of bladder cancer among women (Stocks et al., 2009).

Because of these association between bladder

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cancer and the component of MetS, we hypothesized that high pathologic stage and histologic grade at primary urothelial cell carcinoma of the bladder have inconsistent associations with metabolic syndrome. To test this hypothesis, histopathologic findings of patients who underwent transurethral resection of bladder tumor (TUR-B), were evaluated between groups with and without metabolic syndrome.

Materials and Methods

We retrospectively analyzed data of 535 patients who underwent TURB in our department between October 2005 and March 2011. All patients had primary urothelial cell carcinoma (UCB). Patients with upper urinary tract carcinomas, prostatic stroma invasion or metastatic UCB at diagnosis were excluded from this study. The patients who had CIS, adenocarcinoma or squamous cell carcinoma, Tx on histopathologic results, chemotherapy or radiotherapy were excluded too. Thus, 509 patients (439 men and 70 women) were enrolled in this retrospective study. These were included; tumor number, tumor size, histologic stage, grade, the presence of hypertension, diabetes, body mass index (BMI), HDL and triglyceride levels. Plasma fasting glucose, high-density lipoprotein (HDL) cholesterol levels and triglycerides were measured using enzymatic methods with an autoanalyzer.

The clinical staging of the 2002 TNM classification. T_a tumor was accepted as lower stage bladder carcinoma. T₁ and T₂ tumors were accepted as higher stage bladder carcinoma. Also, pathological grading adopted by the 2004 World Health Organization grading system were used. The patients who had non-invasive papillary urothelial neoplasm of low malignant potential were accepted as low grade papillary urothelial papillary cancer. Metabolic syndrome was defined according to the criteria established in 2005 by the NCEP/ATP III. Metabolic syndrome was diagnosed in those who satisfied at least 3 of the following 5 criteria: waist circumference >88 cm in women and >102 cm in men; triglyceride concentration >150 mg/dL or undergoing treatment for hypertriglyceridemia; HDL cholesterol concentration <40 mg/dL in men and <50 mg/dL in women or undergoing treatment for low HDL-C level; blood pressure >130/85 mm Hg or undergoing treatment for hypertension and fasting plasma glucose level >100 mg/dL or undergoing treatment for hyperglycemia. The institutional review board approved this study, and informed consent was obtained from each participant.

Analyses were completed using Chi-square tests and Logistic regression analysis. All statistical tests were

two-tailed, and statistical significance was defined as $P < 0.05$. All analysis were conducted using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Among the 509 total patients analyzed in our study, there were 439 males (86.2%) and 70 females (13.8%). Demographic analyses and clinicopathologic characteristics were demonstrated in Table 1. Metabolic syndrome was found in 148 (29%) patients. The mean age of patients with the metabolic syndrome group was 59.17 ± 12.34 and non-metabolic syndrome group was 51.11 ± 11.81 years. Tumor pathologic stage were determined lower stage (T_a) and higher stage (T₁ or T₂) in 56% and 44% of patients with metabolic syndrome, respectively. And histopathologic grades low grade and high grade in 65.5% and 34.5% of patients, respectively (Table 2). According to our data, statistically tumor pathologic stage, tumor histologic grade was significantly associated with metabolic syndrome ($p < 0.001$). Also, we compared the relationship of metabolic syndrome parameters with bladder tumor stage and grade (Table 3).

As shown in Table 2, metabolic syndrome was significantly associated with high histologic grade, and

Table 1. The Patients and Tumor Characteristics

| Variables | No (%) |
|--------------------|-------------|
| no of patients | 509 |
| Gender | |
| Male | 439 (86.2%) |
| Female | 70 (13.8%) |
| Age (mean±sd) | 53,45±11.74 |
| Pathologic Stage | |
| T _a | 343 (67.3%) |
| T ₁ | 133 (26.1%) |
| T ₂ | 33 (6.6%) |
| Histologic Grade | |
| Low grade | 391 (76.8%) |
| High grade | 118 (23.2%) |
| Metabolic Syndrome | |
| Yes | 148 (29%) |
| No | 361 (71%) |

Table 2. Comparison of Characteristics between Patients with or without Metabolic Syndrome

| | Metabolic Syndrome | Non-Metabolic Syndrome | p value |
|-------------------------------------------------|--------------------|------------------------|---------|
| no of patients | 148 (29%) | 361 (71%) | |
| Age (mean±sd) | 59.17±12.34 | 51.11±11.81 | <0.05 |
| BMI (mean±sd) | 28,93±2,89 | 27,35±2,93 | <0.05 |
| T Stage | | | |
| Lower stage (T _a) | 83 (56%) | 260 (72%) | |
| Higher stage(T ₁ or T ₂) | 65 (44%) | 101 (28%) | <0.001 |
| Histologic Grade | | | |
| Low grade | 97 (65.5%) | 294 (81.4%) | |
| High grade | 51 (34.5%) | 67 (18.6%) | <0.001 |

Table 3. Comparison between Parameters of MetS with Stage and Grade

| | Lower stage | Higher stage | p value | Low Grade (G1) | High Grade (G3) | p value |
|--------------------------------------|-------------|--------------|---------|----------------|-----------------|---------|
| Abd. obese (M>102,W>88) ^a | 117 (69.7%) | 51 (30.3%) | 0.496 | 127 (75.6%) | 41 (24.4%) | 0.243 |
| DM ^b | 93 (56.4%) | 72 (43.6%) | <0.001 | 109 (66.1%) | 56 (33.9%) | <0.001 |
| Hypertension ^c | 126 (67.4%) | 61 (32.6%) | 0.537 | 139 (74.3%) | 48 (25.7%) | 0.183 |
| Cholesterol ^d | 92 (63%) | 54 (37%) | 0.142 | 108 (73.9%) | 38 (26.7%) | 0.096 |
| Triglyceride ^e | 142 (65.7%) | 74 (34.3%) | 0.184 | 156 (72.2%) | 60 (27.8%) | 0.064 |

^aWaist circumference >88 cm in women and >102 cm in men; ^bFasting plasma glucose level >100 mg/dL; ^cBlood pressure >130/85 mm Hg; ^dHDL cholesterol concentration <40 mg/dL; ^etriglyceride concentration >150 mg/dL or undergoing treatment for hypertriglyceridemia

high pathologic stage, whereas age, gender, other than metabolic syndrome were not.

Relationship of patients with metabolic syndrome and components of metabolic syndrome with T stage and grade shown at Table 3. As its seen metabolic syndrome and diabetes mellitus (DM) have a significantly association with T stage and grade but other components (abdominal obesity, high blood pressure, cholesterol and triglyceride) did not associated with high stage or grade.

Discussion

In this study, we retrospectively reviewed the patients undergoing TUR-B at our institution between October 2005 and March 2011, comparing those with metabolic syndrome to those with no components of the syndrome to assess its potential association on bladder cancer aggressiveness. This study showed that primary urothelial carcinoma of bladder with metabolic syndrome is associated with higher tumor stage and histologic grade.

The classic metabolic syndrome is characterized by visceral obesity, insulin resistance, low HDL-cholesterol, high triglycerides, high blood pressure. Insulin resistance and hyperinsulinemia are the cornerstone of metabolic syndrome and are also factors for some cancers. The correlation between obesity and increased bladder cancer or bladder recurrence risk need further research to better clarify the potential mechanism (Eckel 2007; Borena et al., 2011; Currie et al., 2012; Lee et al., 2012; Liu et al., 2012).

Best to our knowledge, the relationship between obesity and diabetes, especially type 2 diabetes, is definite. Obese people tend to suffer from diabetes. The role of obesity in the process of carcinogenesis is probably similar to that of diabetes. It is well-known that type 2 diabetes is related to insulin resistance, and up-regulated serum level of IGF-1. IGF-1 could stimulate proliferation and inhibit apoptosis, which could ultimately result in cancer. Previous epidemiological studies implicated that type 2 diabetes mellitus and IGF-I played an important role in the development and mortality of prostate, lung, liver and colorectal cancers. Evidence of links with bladder cancer has been presented (Qin et al., 2013; Yang et al., 2013). Another case-control study detected higher levels of IGF-I in bladder cancer cases than that in controls which was statistically significant (Zhao et al., 2003). The role of IGF-I in the development of bladder cancer was also evaluated via in vivo studies which demonstrated similar results (Dunn et al., 1997).

Additionally, diabetes was also found to be related to an increased risk of urinary tract infection (Funfstuck et al., 2012) and urinary tract calculi (Chen et al., 2012), which was associated with various histologic types of bladder cancer, such as transitional cell carcinoma (Chow et al., 1997; Jankovic and Radosavljevic n.d.).

Little is known about possible pathways between hypertension and cancer (Stumpe, 2002). Previous studies were based on much smaller study populations (Grove et al., 1991; Hole et al., 1993; Rosengren et al., 1998) the largest study to date was based on 69 cases and reported no association (Grove et al., 1991). A study with 1585 cases, investigated the relationships between

hypertension, hypertension medication and bladder cancer risk in a population-based case control study conducted in Los Angeles, and found a reduced risk of bladder cancer among hypertensive subjects who did not use antihypertensives or diuretics regularly and this reduction in risk was limited to smokers and carriers of the GSTM1-null genotype.

Cholesterol and triglycerides have previously been studied in much smaller cohorts. The largest study to date (303 cases) reported a small nonsignificant decrease in risk for high cholesterol levels (Hiatt and Fireman 1986). To the best of our knowledge, no previous studies have examined triglyceride levels in relation to bladder cancer risk, but triglyceride levels have been linked to risk of cancer at other sites in some studies, for example, colon and breast (Cowe and Hardy 2006).

So as we told before there are little data on the association between the MetS and risk of bladder cancer. When we have an attentive look at this and similar studies, we can see that most of the bladder cancer is related to a risk. We have assessed the relationship of the aggressiveness of metabolic syndrome and its parameters on T stage and grade through an evaluation among the patients that we had operated because of bladder cancer. In addition, we have foreseen that when these parameters are considered individually, the metabolic syndrome might cause different consequences with a synergy.

According to our hypothesis, in most of the parameters of metabolic syndrome, the results that we had considered as not related, when assessed individually, have been found seriously meaningful, when they are considered as metabolic syndromes. The metabolic syndrome is not only a situation that hosts the components. The combination of these components indicates the impact on the metabolism and malignancy in the metabolic syndrome, especially on insulin resistance and hyperinsulinemia, which are the corner-stones.

The strong side of this study is its nature not being a meta-analysis study that was carried out by identifying the population over the criteria of metabolic syndrome by studying on hypertension, cholesterol, diabetes of the patients individually, but by involving the patients having a metabolic syndrome within the population consisting of the patients that applied TURB because of bladder tumor within our own department.

This study had some deficiencies. First of them was its being retrospective and the limited number of patients involved in the study. It is unavoidable to state that the post follow up period as important as the pathology in the follow-up of the patients involved in the study and the aggressiveness of the tumor.

Secondly, the factors that are definitely attested to be effective on bladder cancer risk (such as smoking, exposure to the renal calculus, urinary tract infection, and schistosome parasite) were not included in the study. When considered in terms of the quality of life, smoking and its duration, which can be related to the metabolic syndrome.

Third, our results were based on the experience of a single institution in Turkey with a <600 patients with primary NMIBC, and there are substantial differences in bladder cancer incidence and mortality rates between

Western countries and Turkey. Therefore, relationship between bladder tm and metabolic syndrome should be validated through massive studies worldwide.

Although the absolute risks of bladder cancer are low among individuals with metabolic syndrome parameters, our results have important clinical and public health significance. On the basis of the most recent epidemiological analysis using the American Heart Association/National Heart, Lung, and Blood Institute 2005 guidelines, similar to those of National Cholesterol Education Program/Adult Treatment Panel III, slightly more than one-third (35%) of adults in the U.S. could be characterized as having the metabolic syndrome.

In conclusion, metabolic syndrome is a multifactorial originated disease which contains impaired glucose tolerance/diabetes, obesity, high triglyceride levels, low HDL levels, and hypertension. All these components may have effect on tumor carcinogenesis in similar pathways. In our study patients with metabolic syndrome were found to have statistically significant higher T stage and grade at bladder cancer. Further studies with more patients are needed to confirm our study

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