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Review Article

Diabetes Mellitus is Associated with High Grade and High Stage in Urinary Bladder Cancer

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Abstract

Introduction: Diabetes Mellitus (DM) is increasing worldwide health problems. Several studies have proposed an epidemiological association between DM and bladder cancer. CIS is a high-grade carcinoma with the potential for invasion and metastases. We aimed to reveal association between DM, CIS and tumour characteristics of patients with bladder cancer.

Material and Method: We retrospectively analyzed 615 patients between January 2007 and December 2014 who diagnosed bladder cancer and performed TUR-BT or radical cystectomy. All patients with bladder cancer separated two groups as Non-Muscle Invasive Bladder Cancer (NMIBC) and Muscle Invasive Bladder Cancer (MIBC). Each groups separated two groups inside them as diabetic or non diabetic.

Results: We analyzed 615 patients with bladder cancer. There was statistically significance for relapse frequency was higher in diabetic patients than non-diabetic patients. T, N and M stages were more advance in diabetic patients. Although concurrent CIS is higher in diabetic patients, squamous metaplasias between diabetic and non-diabetic patients were not significant.

Discussion: Diabetes is the critical worldwide health problem that has serious complications that can cause much kind of cancers. We revealed that there is negative effect of diabetes on patients with bladder cancer especially patients with CIS.

Conclusion: Patients with diabetes had advanced stage, grade and concurrent CIS than patients without diabetes. And also, diabetic patients have more recurrent disease than non-diabetic patients.

Introduction

In the United States bladder cancer is fifth most common cancer. In 2016, it is estimated that there will be 76,960 new cases of bladder cancer and an estimated 16,390 people will die of this disease in the USA [1]. Several risk factors have been established for bladder cancer including smoking, using pioglitazone, occupational exposure to aromatic amines and schistosomal infection [2]. Approximately 75% of bladder cancers are non-muscle invasive (Ta, T1 or CIS) at the time of diagnosis. The EORTC scoring system and risk tables predict the short and long-term risks of disease recurrence and progression in individual patients with NMIBC. [3].

Recently, diabetes mellitus (DM) is increasing worldwide health problems. Epidemiological evidence indicates that type 2 DM is a risk factor for several cancers [4-7]. Several studies have proposed an epidemiological association between DM and bladder cancer [8-12].

Carcinoma in Situ (CIS) is a distinct form of NMIBC (non-muscle invasive bladder cancer) that warrants special consideration. CIS is a high-grade carcinoma with the potential for invasion and metastases. High-risk NMIBC, including CIS, fails bladder preservation in approximately 50% of cases [13]. It is well established that those who progress to muscle-invasive bladder cancer on Bacillus-Calmette-Guerin (BCG) have poor outcomes [14].

There is no study in the literature that research association between DM and CIS. In present study, we aimed to reveal association between DM, CIS and tumour characteristics of patients with bladder cancer.

Material and Methods

We retrospectively analyzed 1064 patients between January 2007 and December 2014 who diagnosed bladder cancer and performed TUR-BT or radical cystectomy in our department. 615 patients were included study; remained 449 patients were excluded because of in adequate data. All patients with bladder cancer separated two groups as Non-Muscle Invasive Bladder Cancer (NMIBC) and Muscle Invasive Bladder Cancer (MIBC). Each groups separated two groups inside them as diabetic or non diabetic. All patient and tumour characteristic, TNM stage, CIS, squamous

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Table 1: patient's characteristics.

	Total (n=615)		Superficial (n=418)		Invasive (n=197)		p	DM (+) (n=187)		DM (-) (n=428)		p
	N	%	N	%	N	%		N	%	N	%	
Age	64.9	11.4	66.2	12.1	62.4	9.2	<0.001	67.4	9.5	63.9	12.0	<0.001
Sex												
Male	538.0	87.5	365.0	87.3	173.0	87.8	0.862	159.0	85.0	379.0	88.6	0.224
Female	77	12.5	53	12.7	24	12.2		28	15	49	11.4	
Tumor Size	4.0	2.8	3.3	2.5	5.5	2.7	<0.001	4.0	2.8	4.0	2.7	0.992
Tumor Burden	1.9	1.5	2.0	1.4	1.9	1.5	0.420	2.0	1.4	1.9	1.5	0.867
Relapse Frequency	1.0	1.6	0.9	1.6	1.1	1.4	0.143	1.3	1.7	0.9	1.5	0.008
T												
Ta	272	44.2	272	65.1	0	0	NA	60	32.1	212	49.5	<0.001
T1	146	23.7	146	34.9	0	0		63	33.7	83	19.4	
T2	108	17.6	0	0	108	54.8		30	16	78	18.2	
T3	49	8	0	0	49	24.9		16	8.6	33	7.7	
T4	40	6.5	0	0	40	20.3		18	9.6	22	5.1	
N												
N0	521	84.7	402	96.2	119	60.4	<0.001	141	75.4	380	88.8	<0.001
N1	94	15.3	16	3.8	78	39.6		46	24.6	48	11.2	
M												
M0	575	93.5	406	97.1	169	85.8	<0.001	162	86.6	413	96.5	<0.001
M1	40	6.5	12	2.9	28	14.2		25	13.4	15	3.5	
G												
G1	144	23.4	142	34	2	1	<0.001	29	15.5	115	26.9	0.001
G2	151	24.6	149	35.6	2	1		40	21.4	111	25.9	
G3	320	52	127	30.4	193	98		118	63.1	202	47.2	
CIS												
YES	45	7.3	20	4.8	25	12.7	<0.001	21	11.2	24	5.6	0.014
NO	570	92.7	398	95.2	172	87.3		166	88.8	404	94.4	
Squamous Metaplasia												
Yes	51	8.3	7	1.7	44	22.3	<0.001	20	10.7	31	7.2	0.153
No	564	91.7	411	98.3	153	77.7		167	89.3	397	92.8	

metaplasia and recurrens of tumour were analyzed. Incomplete TUR-BT, non-urothelial cancers and recurrent non-muscle invasive bladder cancers were excluded from study.

The clinical staging of the 2009 TNM classification. Papillary tumours confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively. Flat, high-grade tumours that are confined to the mucosa are classified as CIS (Tis). If tumour invades muscular is propria, it is classified as T2. T2 and over stages are accepted as muscle invasive bladder cancer. Also, pathological grading adopted by the 2004 World Health Organization grading system was used.

All statistical analysis was performed by using SPSS17.0 statistical package program. The descriptive statistics we represented as frequencies and percentages for categorical variables and means and standard deviations for continuous variables. The comparisons of the means were examined by independent samples t test, and the relations between categorical variables were investigated by non-parametric chi-square test. For two or more variables, a nova test was applied. A p value 0.05 was accepted statistically significant in comparisons.

Results

We retrospectively analyzed 615 patients with bladder cancer. 418 of these were NMIBC and 197 of MIBC. 187 patients were diabetic and 428 of were non-diabetic. Mean age of all patients were 64, 9±11, 4 years old. 538 (87, 5%) of male and 77 (12, 5%) of female patients. Mean tumour size and tumour burden were 4±2, 8 cm and 1.9±1, 5 respectively. Mean relapse frequency was 1±1, 6 times. T stages for all patients were 272 (44, 2%) of Ta, 146 (23, 7%) of T1, 108 (17, 6%) of T2, 49 (8%) of T3 and 40 (6, 5%) of T4 stages respectively. For N

Table 2: patient characteristics according to the groups.

	Superficial					Invasive				
	DM (+) (n=123)		DM (-) (n=295)		p	DM (+) (n=64)		DM (-) (n=133)		p
	N	%	N	%		N	%	N	%	
Tumor Size	3.2	2.5	3.3	2.5	0.690	5.5	2.9	5.5	2.6	0.994
Tumor Burden	2.0	1.3	2.0	1.5	0.687	1.8	1.4	1.9	1.5	0.819
Relapse Frequency	1.4	1.9	0.8	1.5	0.001	1.1	1.4	1.2	1.4	0.711
T										
Ta	60	48.8	212	71.9		0	0.0	0	0.0	
T1	63	51.2	83	28.1		0	0.0	0	0.0	
T2	0	0.0	0	0.0	<0.001	30	46.9	78	58.6	0.139
T3	0	0.0	0	0.0		16	25.0	33	24.8	
T4	0	0.0	0	0.0		18	28.1	22	16.5	
N										
N0	113	91.9	289	98.0	0.009	28	43.8	91	68.4	0.001
N1	10	8.1	6	2.0		36	56.3	42	31.6	
M										
M0	112	91.1	294	99.7	<0.001	50	78.1	119	89.5	0.033
M1	11	8.9	1	0.3		14	21.9	14	10.5	
G										
G1	28	22.8	114	38.6		1	1.6	1	0.8	
G2	40	32.5	109	36.9	<0.001	0	0.0	2	1.5	NA
G3	55	44.7	72	24.4		63	98.4	130	97.7	
CIS										
YES	9	7.3	11	3.7	0.117	12	18.8	13	9.8	0.076
NO	114	92.7	284	96.3		52	81.3	120	90.2	
Squamous Metaplasia										
Yes	2	1.6	5	1.7	1.000	18	28.1	26	19.5	0.176
No	121	98.4	290	98.3		46	71.9	107	80.5	

stages, 521 (84, 7%) of N0 and 94 (15, 3%) of N1 stages. For M stages, 575 (93, 5%) of M0 and 40 (6, 5%) of M1 stages. 295 (48%) patient were low grade and 320 (52%) were grade 3 tumours. There were carcinoma in situ in 45 (7, 3%) patients and squamous metaplasia in 51 (8, 3%) patients (Table 1).

In the NMIBC group, mean age was 66, 2±12, 1 year. There were 538 male and 77 female patients. Mean tumour size was 3, 3±2, 5 cm. Mean relapse frequency was 0, 9±1, 6 times. 272 patients were Ta stage and 146 were T1 stage. 402 patients were N0 and 16 patients were N1 stages. Although 406 patients were M0, 12 patients were M1 stages. 291 (98%) patients have low grade tumour, 127 (39, 8%) patients have high grade tumour. There were only 20 (4, 8%) patient with concurrent CIS and 7 (1, 7%) patients have squamous metaplasia in this group. 123 patients were diabetic and 295 patients were non-diabetic. There was statistically significance between diabetic and non-diabetic patients for relapse frequency, T stage, N stage, M stage and grade (Table 2).

In the MIBC group, mean age was 62, 4±9, 2 years. There were 173 male and 24 female patients. Mean tumour size was 5, 5±2, 7cm. Mean relapse frequency was1, 1±1, 4 times. 108 (54, 8%) patients were T2 stages, 49 (24, 9%) patients T3 and 40 (20, 3%) patients were T4 stages. 119 (60, 4%) patients were N0 and 78 (39, 6%) patients were N1 stages. 169 (85, 8%) patients were M0 stages but 28 (14, 2%) patients were M1 stages. 4 (2%) patients have low grade and 193 (60, 2%) patients have high grade tumours. There were concurrent CIS in 25 (12, 7%) patients and squamous metaplasia in 44 (22, 3%) patients. 64 patients were diabetic and 133 patients were non-diabetic. There was only statistically significance between diabetic and non-diabetic patients for N and M stages (Table 2).

For all patients, there was statistically significance for relapse frequency was higher in diabetic patients than non-diabetic patients (p=0, 008). T, N and M stages were more advance in diabetic patients (p < 0, 001). Although concurrent CIS is higher in diabetic patients (p=0, 014), squamous metaplasia between diabetic and non-diabetic patients were not significant (p=0, 047).

Discussion

Diabetes is the critical worldwide health problem that has serious complications that can cause much kind of cancers [8-11]. In the study we retrospectively analyzed patients with bladder cancer. We aimed to show that association between diabetes and bladder cancer. We revealed that there is negative effect of diabetes on patients with bladder cancer especially patients with CIS. Patients with diabetes had advanced stage, grade and concurrent CIS than patients without diabetes. And also, diabetic patients have more recurrent disease than non-diabetic patients.

The possible mechanisms underlying the association of diabetes with bladder cancer risk are uncertain. In type 2 diabetes, insulin resistance leads to a state of hyper insulinemia. Insulin has mitogenic properties and could stimulate tumour growth by increasing bioactive IGF-I, which in turn stimulates cell proliferation and inhibits apoptosis. In the circulation, IGF-I binds mainly to the main IGF binding protein, IGFBP-3. IGF-I and IGFBP-3 may also play a role in the development of bladder cancer [11]. It is reported that DNA damage is a biological link between diabetes and cancer. Diabetes is a state of DNA damage; pathophysiological factors such as oxidative stress in diabetes result in DNA damage; increased DNA damage can cause mutations and these mutations trigger carcinogenesis [12].

Metformin (1, 1-dimethylbiguanide hydrochloride), an oral biguanide agent, has been widely used for the treatment of type 2 diabetes [13]. Epidemiological studies also revealed that metformin indeed decreased the incidence of cancer and cancer-related mortality in diabetic patients compared with those treated with other anti diabetic agents. Recent study demonstrated that metformin could exert a protective effect on disease recurrence in patients with non-muscle invasive bladder cancer [14]. Metformin has been shown to inhibit proliferation in some cancer cell lines through activation of the AMPK pathway. Metformin treatment leads to activation of AMPK and inhibition of the MTOR signalling pathway in bladder cancer cells. It is the AMPK-mediated MTOR inhibition that is supposed to be the crucial factor responsible for the antitumor properties of metformin [15]. Although diabetes promotes cancer, metformin treatment can prevent cancer development.

A recent study about association between metformin use and bladder cancer reported that there was not statistically significance

between metformin use and bladder cancer. In this study, metformin was administered in the treatment of 32 patients with a history of bladder cancer, and their results were compared with those of 33 patients with bladder cancer recurrence. But there was no difference about tumour recurrence between the two groups [16].

We could not evaluate the effect of metformin on these patients. Because our study was retrospective and we could not reach the data of patient's medicine that use for diabetes from our hospitals patients record system. We consider that is the limitation of our study.

Up to date, lots of studies showed that diabetes have negative effects on patients with much cancer about survive. Diabetic patients, especially type 2 diabetes have more advanced tumour stage; grade and less survive than non-diabetic patients for many kinds of cancer. 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 that could cause cancer [17]. But, any study was reported about association between diabetes and CIS.

Coughlin et al. in a large prospective mortality study related to a cohort of 1.2 million Americans and a follow-up of 16 years (CPS II), suggested that DM may be an independent risk factor for bladder cancer-related deaths in men (RR 1.43, 95% CI 1.14–1.80), with an elevated although not significant rate in women (R.R 1.30, 95% CI 0.85-2.00) [18].

Mackenzie ET all reported that risk of bladder cancer was elevated among those with a history of diabetes patients, in particular, those taking oral hypoglycaemic or insulin. Additionally, the association increased with duration of diabetes [19].

In the study of Wolcott et al showed that nearly 186,000 persons representing five ethnic groups, with 918 cases of urothelial cancer diagnosed over a median 10.7 years of follow-up, a self-reported diagnosis of diabetes was associated with a statistically significant 25% increased risk of urothelial cancer [20].

In our study we found that diabetic patients have more concomitant CIS than non-diabetic patients. So, these diabetic patients have more aggressive tumour than non diabetic patients. As we know, patients with CIS can be progress into invasive tumour. And also Diabetic patients have more advanced stage, grade and more lymph node or distant metastasis than non-diabetic patients. Diabetic patients with NMIBC have more relapse than non-diabetic NMIBC patients, but there was no statistically significance between diabetic and non-diabetic patients in patients with MIBC. Interestingly in our study we revealed that in the NMIBC group, 11 (8, 9%) patients were diabetic and have distant metastasis. Only 1 (0, 3%) patients was non diabetic and have distant metastasis. That was statistically significant ($p < 0, 001$). Although 10 (8, 1%) diabetic patient with NMIB have lymph node metastasis patients, 6 (2%) non-diabetic patients with NMIBC have lymph node metastasis. Limitation of our study, association between duration of diabetes mellitus and bladder cancer is unknown. Control of diabetes can play major role over the cancer parameters. We could not record patients' diabetes mellitus history and follow-up.

Conclusion

We can propose that diabetes mellitus may play critical role in progression of bladder cancer. Patients with bladder cancer, either NMIBC or MIBC, can be affected negatively from diabetes mellitus. Diabetes mellitus can worsen progression of cancer to inhibit the apoptosis by different ways. Bladder cancer incidence is increasing day by day in today's industrialized world. And also, diabetic patients are increasing, too. It is more often observed bladder cancer and diabetes concomitancy. This concomitance can worsen disease progression and shorten patient's survival. We suggest that patients with both diabetes mellitus and bladder cancer must follow more frequently and carefully.

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