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Clinical-Bladder cancer

Type 2 diabetes mellitus predicts worse outcomes in patients with high-grade T1 bladder cancer receiving bacillus Calmette-Guérin after transurethral resection of the bladder tumor

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Abstract

Objectives: The aim of this multicenter study was to investigate the prognostic role of type 2 diabetes mellitus (T2DM) comorbidity in a large multi-institutional cohort of patients with primary T1HG/G3 non−muscle-invasive bladder cancer (NMIBC) treated with transurethral resection of the bladder (TURB).

Materials and methods: A total of 1,172 patients with primary T1 HG/G3 who had NMIBC on re-TURB and who received adjuvant intravesical bacillus Calmette-Guérin therapy with maintenance were included. Endpoints were recurrence-free survival and progression-free survival.

Results: A total of 231 (19.7%) of patients had T2DM prior to TURB. Five-year recurrence-free survival estimates were 12.5% in patients with T2DM compared to 36% in patients without T2DM, $P < 0.0001$. Five-year PFS estimates were 60.5% in patients with T2DM compared to 70.2% in patients without T2DM, $P = 0.003$. T2DM was independently associated with disease recurrence (hazard ratio = 1.41; 95% confidence interval = 1.20−1.66, $P < 0.001$) and progression (hazard ratio = 1.27; 95% confidence interval = 0.99−1.63, $P < 0.001$), after adjusting for other known predictive factors such as tumor size, multifocality, T1G3 on re-TURB, body mass index, lymphovascular invasion, and neutrophil-to-lymphocytes ratio.

Conclusions: Given the potential implications for management, prospective validation of this finding along with translational studies designed to investigate the underlying biology of such an association are warranted.

Keywords: High grade; Bladder cancer; High risk; Recurrence; Progression; Diabetes mellitus

1. Introduction

Bladder cancer (BC) represents the seventh most frequent cancer in men and the 17th most frequent cancer in women worldwide [1], with marked geographical differences in its epidemiology. In Europe, age-standardized incidence per 100,000 inhabitants was only 19 and 5 cases in males and females, respectively, while in the world, age-standardized incidence per 100,000 inhabitants was 75.3 and 16.3 per cases in males and females, respectively, in 2012 [2]. Most patients present with non−muscle-invasive bladder cancer (NMIBC) at first diagnosis [3] and are treated with transurethral resection of the bladder (TURB) followed by adjuvant intravesical instillation therapy [4]. Unfortunately, patients with NMIBC treated following current best recommendations show recurrent disease and progressive disease in many as 70% and 30% of cases, respectively [5].

The incidence of type 2 diabetes mellitus (T2DM) has sharply increased worldwide over the past few decades, with an estimated 642 million affected people expected by 2040 [6]. Recently, several studies have shown that T2DM can increase the risk of several cancers, including urological neoplasm's such as BC (Relative risk [RR] = 1.30, 95% confidence interval [CI] = 1.18−1.43) [7,8] and kidney cancer (RR = 1.40, 95% CI = 1.16 −1.69) [9].

On the other hand, there is a controversy regarding the prognostic role of T2DM in diabetic people diagnosed with cancer, with a potential negative influence of T2DM reported in some tumors—e.g., breast cancer [10], and conflicting results obtained in others [11,12].

The aim of this multicenter study was to investigate the prognostic role of T2DM in a large multi-institutional cohort of patients with primary T1 HG/G3 NMIBC treated with bacillus Calmette-Guérin (BCG).

2. Materials and methods

2.1. Patient selection and data collection

Institutional review board approval at each institution was obtained, with all participating sites providing institutional data sharing agreements prior to the initiation of the study. A total of 1,172 patients with primary T1 HG/G3 treated between 1st January 2002 and 31st December 2012 at 13 academic institutions were included and our multi-institutional database was updated to include data regarding T2DM condition. Diabetes was diagnosed based on A1C criteria or plasma glucose criteria, either the fasting plasma glucose or the 2-hour plasma glucose value after a 75-g oral glucose tolerance test, according to the American Diabetes Association guidelines [13]. T2DM condition was considered if patients were under medical treatment before admission for TURB. Comorbidity in each patient was assessed by the Charlson comorbidity index. All patients underwent to induction BCG instillations according to the 6-weekly schedule introduced by Morales et al. [14]. In addition, when indicated, BCG was given in a maintenance schedule for at least 1 year. The maintenance

schedule was generally according to the EAU guidelines at the time [15]. Management and follow-up was previously described in details [15]. In brief, all patients were generally followed with cystoscopy and voiding urine cytology every 3 to 4 months for the first 2 years, every 6 months for the third and fourth year, and annually thereafter. Diagnostic imaging of the upper tract was generally performed at least annually or when clinically indicated. Recurrence was defined as any tumor on follow-up and progression as muscle-invasive BC on follow-up. Endpoints were recurrence-free survival (RFS), and progression-free survival (PFS).

2.2. Statistical analysis

Association of type 2 diabetes with categorical variables was assessed using χ^2 tests; differences in continuous variables were analyzed using Mann-Whitney *U* test. Kaplan-Meier method was used to estimate RFS and PFS; log-rank tests were applied for pair wise comparison of survival. Univariable and multivariable Cox regression models addressed associations with RFS and PFS, adjusting for the effects of known clinicopathologic prognostic features. Harrell's concordance index (*c* index) was applied to evaluate the performances of the survival models. All *P* values were 2-sided, and statistical significance was defined as a $P < 0.05$. Statistical analyses were performed using MedCalc 9.2.0.1 (MedCalc software, Mariakerke, Belgium) and PASW 18 software (PASW 18, SPSS, Chicago, IL).

3. Results

3.1. Baseline clinicopathologic features

A total of 231 (19.7%) of patients had documented T2DM prior to TURB. The features evaluated in the study included gender, smoking status, tumor multifocality and dimension, presence of carcinoma in situ, high-grade T1 disease on re-TUR, lymphovascular invasion (LVI), body mass index (BMI), and neutrophil-to-lymphocytes ratio (NLR). Detailed clinical and pathological characteristics of the patients are summarized in Table 1.

3.2. Association of T2DM with disease recurrence and progression

Within a median follow-up of 47 months (95% CI = 45–48), 203 (87.9%) of the 231 patients with T2DM

Table 1
Association of clinic and pathologic features with type 2 diabetes in 1,172 patients treated with maintenance BCG after primary T1G3.

	All cohort	No type 2 diabetes	Type 2 diabetes	*P* value
Age mean years (SD)	70.3 (9.81)	70.2 (9.87)	70.4 (9.61)	0.90
Gender, *n* (%)				
Male	974 (83.1)	813 (86.4)	161 (69.7)	**0.001**
Female	198 (16.9)	128 (13.6)	70 (30.3)	
Smoker, *n* (%)				
No	332 (28.4)	175 (29.2)	57 (24.7)	0.19
Yes*	840 (71.6)	666 (70.8)	174 (75.3)	
Multifocality, *n* (%)				
Single	650 (55.5)	510 (55.2)	140 (60.6)	0.09
Multiple	522 (44.5)	431 (44.8)	91 (39.4)	
Size, *n* (%)				
<3 cm	414 (35.3)	343 (36.4)	71 (30.7)	0.12
≥3 cm	758 (64.7)	598 (63.6)	160 (69.3)	
Concomitant CIS, *n* (%)				
No	1014 (86.5)	805 (85.5)	209 (90.5)	0.06
Yes	158 (13.5)	136 (14.5)	22 (9.5)	
T1 G3 on re-TUR, *n* (%)				
No	876 (74.7)	716 (76.1)	160 (69.3)	**0.03**
Yes	296 (25.3)	225 (23.9)	71 (30.7)	
LVI, *n* (%)				
No	992 (84.6)	807 (85.7)	185 (80.1)	**0.04**
Yes	180 (15.4)	134 (14.3)	46 (19.9)	
BMI mean (SD)	26.7 (3.91)	26.4 (3.9)	27.7 (3.71)	**0.001**
NLR, *n* (%)				
<3	379 (32.4)	342 (36.3)	37 (16)	**0.001**
>3	793 (67.6)	599 (63.7)	194 (84)	

BCG = bacillus Calmette-Guérin; BMI = body mass index; CIS = carcinoma in situ; LVI = lymphovascular invasion; NLR = neutrophil-to-lymphocytes ratio; NMIBC = non–muscle-invasive bladder cancer; SD = standard deviation; TUR = transurethral resection of bladder tumor.

* includes former and current smokers. Bold values indicate statistical significance.

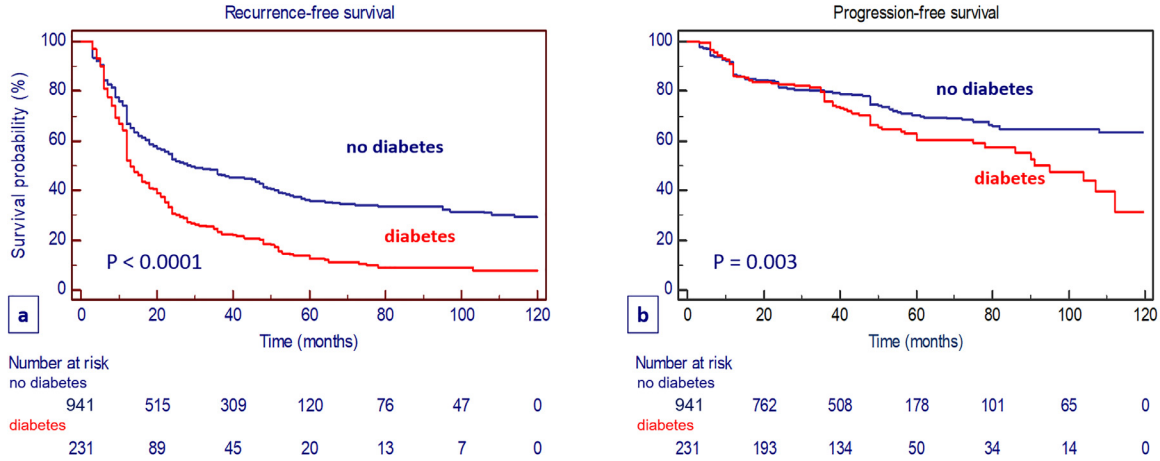

Fig. 1. Comparison of recurrence-free survival (A) and progression-free survival (B) according to type 2 diabetes status in 1,172 patients with primary T1 HG/G3 non−muscle-invasive bladder cancer.

experienced disease recurrence compared to 586 (62.1%) patients without T2DM, $P < 0.001$. Five-year RFS estimates were 12.5% in patients with T2DM compared to 36% in patients without T2DM, $P < 0.0001$ (Fig. 1A). Multivariable Cox regression analyses revealed that T2DM was as an independent predictive factor associated with worse RFS (hazard ratio [HR] = 1.41; 95%CI = 1.20−1.66, $P < 0.001$) together with smoking status (HR = 0.82; 95%CI = 0.85−0.90, $P = 0.01$), tumor size ≥3 cm (HR = 1.29; 95%CI = 1.11−1.51, $P = 0.01$), high grade on re-TURB (HR = 1.34; 95%CI = 1.14−1.57, $P = 0.003$), LVI (HR = 1.30; 95%CI = 1.07−1.57, $P < 0.001$), higher BMI (HR = 1.12; 95%CI = 1.10−1.15, $P < 0.001$) and higher NLR (HR = 1.10; 95%CI = 1.08−1.13, $P < 0.001$; Table 2). Furthermore, 44 (19%) patients with T2DM had recurrence within 6 months after BCG initiation compared to 145 (15.4%) patients without T2DM ($P = 0.21$), while 58 (42.6%) compared to 305 (33.5%) patients with vs. without T2DM had tumor recurrence within 12 months after BCG initiation ($P < 0.0001$). Eighty eight (38.1%) of the 231 patients with T2DM experienced disease progression compared to 265 (28.2%) patients without T2DM, $P = 0.004$. Five-year PFS estimates were 60.5% in patients with T2DM compared to 70.2% in patients without T2DM, $P = 0.003$ (Fig. 1B). Multivariable Cox regression analyses revealed that T2DM was as an independent predictive factor associated with worse PFS (HR = 1.27; 95%CI = 0.99−1.63, $P < 0.001$) together with other clinic-pathological factors such as tumor size, carcinoma in situ, high-grade disease on re-TURB, LVI, BMI, and NLR [16] (Table 2). The *c* indices for RFS and PFS models were 0.81 and 0.78, respectively.

4. Discussion

In this study, we investigated the predictive role of pre-existing T2DM in patients diagnosed with high-grade

Table 2
Multivariable Cox regression analyses predicting disease recurrence and progression of 1,172 patients treated with BCG after primary T1 HG/G3 NMIBC.

Variables	Recurrence			Progression		
	HR	95%CI	*P*	HR	95%CI	*P*
Age cont.	0.99	0.98−1	0.13	0.99	0.98−1	0.27
Gender (male vs. female)	0.98	0.8−1.19	0.85	1.48	1.10−1.97	0.62
Smoking (yes vs. no)	0.82	0.75−0.90	**0.01**	1.41	1.06−1.97	0.08
Size (<3 vs. ≥ 3) cm	1.29	1.11−1.51	**0.001**	1.53	1.15−1.96	**0.001**
Multifocality (single vs. multiple)	1.14	0.98−1.32	0.07	1.2	0.95−1.51	0.11
Concomitant CIS (no vs. yes)	1.07	0.86−1.32	0.51	1.97	1.51−2.58	**0.001**
T1 HG/G3 on re-TUR	1.34	1.14−1.57	**0.003**	1.54	1.22−1.94	**0.003**
LVI (no vs. yes)	1.30	1.07−1.57	**0.001**	1.53	1.18−2.01	**0.001**
Type 2 diabetes (yes vs. no)	1.41	1.20−1.66	**0.001**	1.27	0.99−1.63	**0.001**
CCI cont.	1.11	1.05−1.17	0.06	1.41	1.02−1.98	0.08
BMI cont.	1.12	1.10−1.15	**0.001**	1.04	1.00−1.07	**0.001**
NLR cont.	1.10	1.08−1.13	**0.001**	1.08	1.01−1.12	**0.001**

BCG = bacillus Calmette-Guérin; BMI = body mass index; CCI = Charlson comorbidity index; CI = confidence interval; CIS = carcinoma in situ; HG = high grade; HR = hazard ratio; LVI = lymphovascular invasion; NLR: neutrophil-to-lymphocyte ratio; NMIBC = non−muscle-invasive bladder cancer; *P* = *P* value; TUR = transurethral resection of bladder tumor. Bold values indicate statistical significance.

NMIBC treated with BCG by reviewing a large dataset with adequate follow-up and found that prior history of T2DM was significantly associated with a greater risk of disease recurrence and disease progression to muscle-invasive BC, as well as with overall and cancer-specific survival.

T2DM is a systemic endocrine and metabolic disease with a rapidly increasing incidence worldwide, especially in developing countries [6]. Several studies have shown that, compared to the general population, patients with T2DM have a significantly higher incidence of malignant neoplasms, such as breast, endometrial, liver, pancreatic, colorectal, and urinary tract cancer, including BC [7-12]. A 42% increased risk of developing renal cell carcinoma has been estimated for patients with T2DM [17], while a recent meta-analysis revealed that diabetic individuals have an increased incidence and mortality for BC compared to nondiabetic individuals [8].

T2DM is closely associated with obesity, and an association between high BMI and an increased risk of progression and of residual high-grade disease after TURBT was reported in a large cohort of NMIBC patients [18,19]. Furthermore, an association between metabolic syndrome and primary refractoriness to BCG therapy has also been recently reported [20].

The underlying biologic mechanisms linking diabetes with BC are yet to be fully elucidated [21-24]. Biological factors such as hyperinsulinemia associated with insulin resistance and the secretion of insulin-like growth factor-1 (IGF-1) have been investigated for their ability to stimulate cell proliferation [25,26]. Indeed, insulin is a powerful growth factor involved in carcinogenesis through promoting cell proliferation, alone or in combination with IGF-1 [24]. Hyperinsulinemia can increase the amount and the bioactivity of IGF-1 through inhibition of IGF binding protein-1 and this leads to the stimulation of cell proliferation and differentiation. On the other hand, hyperinsulinemia is involved in the inhibition of cell apoptosis, and these effects may promote the development of cancer [25]. In addition, high levels of insulin and IGF-1 also increase the secretion of vascular endothelial growth factor and upregulate the expression of vascular endothelial growth factor, which induces tumor angiogenesis, leading to tumorigenesis and metastasis [26]. Other possible mechanisms are related to hyperglycemia, which has been suggested as a plausible explanation for diabetes-induced carcinogenesis. Both cohort and case-control studies have shown a positive relationship between hyperglycemia and the risk of developing cancer, suggesting that high glucose levels may exert direct and indirect effects upon cancer cells to promote proliferation [27,28].

Many recent evidences suggest that chronic inflammation in T2DM should be considered as a hallmark of carcinogenesis, as a result of insulin, IGF-1, proinflammatory cytokines, oxidative stress, and growth factors' effects [29]. This is reported also for BC, whose initiation and progression could be strongly affected by the low-grade systemic inflammation which characterized T2DM [30].

Recently, the emerging role of the immune cells is under investigation in the pathogenesis of BC. Indeed, a protumor effect has been attributed to the innate immune system while the adaptive immune system seems to play an antitumor effect [31]. Moreover, some reports suggest that resistance to intravesical treatment with BCG could be associated with the presence of the aggregation of tumor-associated macrophages and regulatory T cells (Tregs) in the tumor microenvironment [32,33]. In a mouse model, intravesical sequential treatment has been able to suppress the resistance to BCG through the enhancement of antitumor immunity, mainly represented by the induction of NK cells, and inhibition of tumor-associated macrophages and Tregs [34]. Dysregulation of innate immunity associated with an increased inflammatory response is a common complication of diabetes [35], therefore a role for T2DM in contributing to the failure of BCG could be suggested.

The present study has several limitations due to its retrospective design. First, we lack data on diabetic therapies. In addition data on the potential impact of laboratory data such as glucose, insulin, C-peptide, HbA1c, and IGFs levels were not available, as well as we did not consider the duration of DM which may affect cancer clinical outcome. Finally, diabetes-associated diseases assessment was not available, so we cannot consider these as variables in statistical analysis. Moreover, the multicentric design of the study implies that different surgical methods and pathological evaluations were included.

5. Conclusions

History of T2DM was predictive of an increased risk of recurrence and progression in patients with primary T1 HG/G3 NMIBC. Prospective validation of this finding along with translational studies designed to investigate the underlying biology of such an association are warranted.

Conflicts of interest

The authors declare no conflict of interest.

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