10.1053.paor.2001.0292 available online at http://www.idealibrary.com on IDEAL

ARTICLE

Increased Incidence of Diabetes Mellitus in the Patients with Transitional Cell Carcinoma of Urinary Bladder

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The progression of bladder cancer to invasive disease is highly dependent on its ability to penetrate basement membrane of urothelium. Studies on diabetic nephropathy have shown a reduction in proteoglycan content of the glomerular basement membrane. Based on the well-known fact that proteoglycans are one of the main components of basement membrane and extracellular matrix we assessed the relationship between diabetes mellitus, bladder cancer incidence and its behavior. These studies include 252 patients with microscopically confirmed transitional cell carcinoma of bladder, and 549 patients with other urological disorders who served as controls. The prevalence of diabetes mellitus in each group was assessed. The group of patients suffering from transitional cell carcinoma was divided according to etiological risk factors such as cigarette smoking, diabetes and patients that were non-smokers and did not suffer from diabetes mellitus. We assessed the features of bladder cancer behavior in each group. Logistic regression model estimation for statistical analysis was used, with transitional cell carcinoma as a dependent binary variable and age, sexes smoking and diabetes as independent variables. Statistical significance was considered at two levels: $p \leq 0.001$ and $p \leq 0.05$. Odds ratio (OR) adjusted to age, sex, cigarette smoking, diabetes mellitus and 95% Confidence Interval (CI) were calculated for TCC. In the TCC group 22.2% of the patients suffered from diabetes mellitus. In the control group 10.38% suffered from diabetes mellitus. Logistic regression analysis, OR and 95% CI showed a statistically significant relationship between diabetes and TCC. These data are comparable only with smoking (OR – 2.3; 95% CI – 1.6 – 3.5 and OR– 1.58; 95% CI – 1.08 – 2.4 correspondingly). Based on these data we suggest that diabetes mellitus may be considered an etiological risk factor for bladder cancer development. (Pathology Oncology Research Vol 7, No 1, 56–59, 2001)

Keywords: Urinary bladder, transitional cell carcinoma, diabetes mellitus

Introduction

Approximately 95% of neoplasm of the bladder is of urothelial origin. The epithelial tumors, most of that are malignant, are of interest for many reasons. These are rather common tumors: there are some 38.000 new cases of bladder cancer each year in the United States, and 10.000 deaths from the disease. There is now substantial evidence that a long prodrome of widely dispersed mucosal epithelial hyperplasia and progressive atypia antedates the appearance of these neoplasms.[1]

A number of environmental factors increase risk of bladder cancer, such as: cigarette smoking,[2] occupational exposure to beta-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, and 4,4-diaminobiphenyl.[3] Bladder cancers occur among workers after a mean exposure of approximately 20 years, accounting for up to a 50-fold increased incidence in those exposed. As mentioned, there is increased incidence of bladder cancer in patients harboring Schistosoma haematobium in their bladders.[4] Certain metabolites of tryptophan-kynurenine, and cyclophosphamide, increase the risk of bladder cancer.[5,6]

Received: August 18, 2000; *revised:* Dec 5, 2000; *accepted:* Dec 20, 2000

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 1219-4956/01/010056+04 $ 12.00/0

Transitional cell carcinoma of urinary bladder is one of the commonest urologic malignancies. This statement challenged the urologists to seek the potential etiological factors promoting the onset of urothelial tumors. The ominous features of bladder cancer are dependent on the tumor's ability to destroy basement membrane and progress to invasion. What determines the activation and deployment of these biochemical activities are unclear.[7] Proteoglycan degradation with consecutive release of cytokines and growth factors is one of the events involved in this process.[8,9] Degradation of Heparan Sulphate Proteoglycan (HSPG), one of the main components of basement membranes and extracellular matrix, is closely correlated with tumor development and metastasis at other sites, such as mouse lymphoma and melanoma.[10,11]

5-hexyl-2-deoxyuridine (HudR) was shown to inhibit the conversion of glucosamine to UDP-sugars. Consequently various glycoconjugates were affected; especially the synthesis of heparan sulfate was reduced. It is noteworthy that HudR inhibited the synthesis of glycosaminoglycans in tumor cells with high metastatic capacity.[12] Significant reduction of glomerular basement membrane's HSPG was noted in the patients with diabetic nephropathy. This is probably caused by such metabolic factors as glucose and insulin – like growth factor.[13]

We explored in a retrospective manner the prevalence of diabetes mellitus among patients with transitional cell carcinoma (TCC) of urinary bladder and compared these data with those obtained in the control group. We also tried to reveal predictive features of tumor behavior in diabetic patients in order to evaluate the possible etiological role of diabetes mellitus in bladder cancer development.

Material and Methods

The study group included 252 patients with microscopically confirmed TCC of urinary bladder, who were treated in our departments. There were 202 men and 50 women. For men, the mean age at diagnosis was 71.5 years and for women the mean age at diagnosis was 73 years. The control group comprised 549 patients with similar age and sex distribution, treated for other urological problems, not connected with malignancies.

All subjects were interviewed personally if they ever were diagnosed with diabetes mellitus (either insulin-dependent or non-insulin dependent). To assess the possible impact of diabetes mellitus on TCC cancer incidence and behavior, the study group was divided into 3 groups: diabetics, smokers and non-diabetics/non-smokers. We did not enroll in the study patients with diabetes mellitus that also smoked cigarettes (because of statistical insignificant number, – 5 patients). None of the patients were involved in industrial works connected with exposure to known carcinogens. In order to reveal special features of cancer behavior in the different subgroups we compared the data according to: tumor grade and stage on the first medical presentation, and recurrent disease.

A logistic regression model was used for statistical analysis, with bladder cancer as a dependent binary variable and age, sex, smoking and diabetes mellitus as independent variables. Statistical significance was considered at two levels: $p \leq 0.001$ and $p \leq 0.05$. Odds ratio (adjusted to age, sex, cigarette smoking, diabetes mellitus) and 95 % Confident Interval were calculated for cancer of bladder.

Results

Of the 252 consecutive patients with TCC 56 (22,2 %) suffered from diabetes mellitus, 51 (20,24 %) were cigarette smokers and 145 (57,56 %) patients never smoked cigarettes and had no history of diabetes. ***Table 1*** summarizes the staging of disease on the first medical presentation. In the control group of 549 patients without TCC only in 57 (10,38 %) the diagnosis of diabetes mellitus was confirmed. So, the incidence of diabetes mellitus in the study group was twice that of the control group.

Table 2 summarizes the age distribution of the patients in the study group: diabetic group was the oldest, (n = 47; 83,9 % of patients over 65 years old), the age prevalence was almost equal in the cigarette smokers group.

Recurrent disease was noted in 16 (28.6%) of diabetic group patients, 25 (49 %) in the group of smokers, and 35 (24 %) in the patients that are non-smokers and without diabetes mellitus (***Table 3***). Diabetic patients had less ominous tendency for BCG treatment failure then cigarette smokers (n 12 / 56; 21.4 % vs. n16 / 51; 31.4 %), but more resistant to BCG treatment disease than patients without history of cigarette smoking (n23 / 145; 15.9%).

Table 1. **Staging of bladder TCC on the first medical presentation**

Stage and Grade	*Diabetics*	*Smokers*	*Non-diabetics/ Non-smokers*
Ta	24	25	81
T1	21	17	32
T2	11	9	32
Total number	56 (22.2%)	51 (20.24%)	145 (57.56%)

Table 2. **Age distribution in the different groups of patients with TCC**

Age	*Diabetics (n56)*	*Smokers(n51)*	*Non-diabetics/non-smokers (n145)*
41–65	9 (16.1%)	22 (43.1%)	38 (26.2%)
66–90	47 (83.9%)	29 (56.9%)	107 (73.8%)

Table 3. **Recurrence of bladder TCC disease**

Stage of disease	*Diabetics (n16)*	*Smokers (n25)*	*Non-diabetics/non-smokers (n35)*
Ta	8	11	16
T1	7	14	17
T2	1	–	2
Failures of BCG treatment	12/16	16/25	23/35

Table 4. **Odds Ratio (O.R.) and 95 % Confidence Interval (C. I.) for TCC**

	O.R.	*C.I.*
Age	1.06	1.04–1.07
Sex	1.15	0.8–1.7
Smoking	1.58	1.08–2.4
Diabetes mellitus	2.34	1.6–3.5

Logistic regression analysis reported statistically significant association of diabetes mellitus with bladder cancer (p – 0.0001 vs. p – 0.000 for age and p – 0.0127 for smoking). Odds ratio (OR) and 95 % Confidence Interval (95% CI) also emphasized statistically significant relationship between diabetes mellitus and bladder cancer: OR – 2.34; 95 % CI – 1.6 – 3.5. These data are comparable only with smoking: OR – 1.58; 95 % CI – 1.08 – 2.4 (*Table 4*).

Discussion

As it was shown in the previous studies glycosaminoglycans and proteoglycans play a major role in protecting bladder epithelial cells from harmful urinary constituents, carcinogens, tumor cellis adherence and implantation.[14,15,16] One of them, HSPG, is the main component of basement membrane (including glomerular basement membrane) and extracellular matrix (ECM). Its heparan sulphate chains bind growth factors and cytokines, protecting them from degradation in the ECM. Degradation, of these chains caused by heparanase activity, induces growth factor release and elicits wound repair, inflammation, and assists tumor development and metastasis as mouse lymphoma and melanoma.[10,11] The same events of proteoglycans degradation with consecutive release of epidermal growth factor have been shown to take place in bladder cancer .[7,18,19]

Studies dedicated to the mechanisms involved in diabetic nephropathy pathophysiology demonstrated a decreased staining of HS in the glomerular basement membrane. It was proposed that metabolic factors such as glucose and insulin – like growth factor (IGF-1) lead to decreased HS production and increased degradation. These processes were observed in patients either with insulin dependent diabetes mellitus or non-insulin dependent diabetes mellitus.[13] The process of glycosaminoglycan degradation may take place in bladder urothelium, predisposing it to carcinogen exposure, tumor cell adherence and implantation. Some studies, dedicated to the mechanisms of bladder cancer development, revealed that hyaluronidase, an endoglycosidase, degrades glycosaminoglycans and promotes bladder cancer progression and metastasis.[20]

Increased IGF-1 in the diabetic patients stimulates cellular proliferation and inhibits apoptosis.[21] The administration of IGF-1 resulted in a shortened latency period and more rapid growth of the tumors. These effects were particularly noticeable in tumors resulting from those cells that expressed higher levels of the IGF-1 receptors.[22]

In this study we observed significantly increased incidence of diabetes mellitus in the group of patients with TCC. It was twice that of the control group and common incidence in the world.[23,24] An a alternative explanation for this observation is age-related prevalence of both: diabetes mellitus and bladder TCC. The diabetic group was the oldest in our study. However, several lines of evidence argue against this explanation. First, we found that statistical analysis reported a statistically significant association of diabetes mellitus and bladder cancer. Second, as we have emphasized previously, smokers who suffered from diabetes mellitus were excluded from the study. Consequently, we could exclude a possible impact of smoking on this group of patients. Nevertheless, the relationship between diabetes mellitus and cancer incidence in this group is comparable with the generally accepted etiology of TCC, including cigarette smoking. And lastly, the tendency to the ominous and progressive disease in the diabetic group was higher when compared to the group of non-smokers without diabetes mellitus.

In conclusion, our data provide support for the hypothesis that diabetes mellitus is associated with increased incidence of transitional cell carcinoma of bladder. These findings provide evidence for the hypothesis that endoglycosidases may promote tumor progression. However, it remains unclear whether diabetes is an independent causal factor of bladder TCC.

References

1. *Cotran RS, Kumar V, Robbins SL, et al:* Pathologic basis of disease, 5th ed, WB Saunders Co, Philadelphia, Pennsylvania, 1994.
2. *Hayes RB, Friedell GH, Zahm SH, et al:* Are the known bladder cancer risk factors associated with more advanced bladder cancer? Cancer Causes Control 4:157-162, 1993.
3. *Schulte PA, Ringen K, Hemstreet GP, et al:* Risk factors for bladder cancer in a cohort exposed to aromatic amines. Cancer 58:21-56, 1986.
4. *Silverman DT, Hartge P, Morrison AS, et al:* Epidemiology of bladder cancer. Hematol Oncol Clin North Am 6:1-30, 1992.

5. *Wilkens LR, Kadir MM, Kolonel LN, et al:* Risk factors for lower urinary tract cancer: the role of total fluid consumption, nitrites and nitrosamines, and selected foods. Cancer Epidemiol Biomarkers Prev 5:161-166, 1996.
6. *Asten P, Barrett J, Symmons D:* Risk of developing certain malignancies is related to duration of immunosuppressive drug exposure in patients with rheumatic diseases. J Rheumatol 26:1705-1714, 1999.
7. *Liu BC, Liotta LA:* Biochemistry of bladder cancer invasion and metastasis. Urol Clin North Am 19:621-627, 1992.
8. *Jackson RL, Buch SJ, Cardin AD:* Glycosaminogycans: molecular properties, protein interaction, and role in physiological processes. Physiol Rev 71:481-539, 1991.
9. *Ruoslahti E, Yamaguchi Y.* Proteoglycans as modulators of growth factor activities. Cell 64:867-869, 1991.
10. *Vlodavsky I, Eldor A, Haimovitz-Friedman A, et al:* Expression of heparanase by platelets and circulating cells of immune system: possible involvement in diapedesis and extravasation. Invasion Metastasis 12:112-127, 1992.
11. *Nakajima M, Irimura T, Nicolson GL:* Heparanases and tumor metastasis. J Cell Biochem 36:157-167, 1988.
12. *Timar J, Diczhazi C, Bartha I, et al:* Modulation of heparan-sulphat/chondroitin-sulphate ratio by glycosaminoglycan biosynthesis inhibitors affects liver metastatic potential of tumor cells. Int J Cancer 62:755-761, 1995
13. *Tamsma JT, van den Born J, Bruijn JA, et al:* Expression of glomerular extra cellular matrix components in human diabetic nephropathy: decrease of heparan sulphate in the glomerular basement membrane. Diabetologia 37:313-320, 1994.
14. *Uehling DT, Kelly E, Hopkins WJ, et al:* Urinary glycosaminoglycan levels following induced cystitis in monkeys. J Urology 139:1103-1105, 1988.
15. *Parsons CL, Boychuk S, Hurst R, et al:* Bladder surface glycosaminoglycans: an epithelial permeability barrier. J Urol 143:139-142, 1990.
16. *Bodenstab W Kaufman J, Parsons CL:* Inactivation of antiadherence effect of bladder surface glycosaminoglycans by a complete urinary carcinogen (N-Methyl – N – Nitrosourea). J Urol 129:200-201, 1983.
17. *Messing EM, Hanson P, Ulrich P, et al:* Epidermal growth factor interaction with normal and malignant urothelium: in vivo and in situ studies. J Urol 138:1329-1335, 1987.
18. *Messing EM:* Clinical implication of the expression of epidermal growth factor in human transitional cell carcinoma. Cancer Res 50:2530–2537, 1990.
19. *Kristensen JK, Lose G, Lund F, Nexo E:* Epidermal growth factor in urine from patients with urinary bladder tumors. Eur Urol 14:313–314, 1988.
20. *Lokeshwar VB, Lokeshwar VB, Young MJ, et al:* Identification of bladder tumor-derived hyaluronidase: its similarity to HYAL1. Cancer Res 59:4464-4470, 1999.
21. *Attia N, Caprio S, Jones TW, et al:* Changes in free insulin-like growth factor-1 and leptin concentrations during acute metabolic decompensation in insulin withdrawn patients with type 1 diabetes. J Clin Endocrinol Metab 84:2324-2328,1999.
22. *Butler AA, Blakesley VA, Poulaki V, et al:* Stimulation of tumor growth by recombinant human insulin-like growth factor-I (IGF-I) is dependent on the dose and the level of IGF-I receptor expression. Cancer Res 58:3021-3027, 1998.
23. *Kamel HK, Rodriguez-Saldana J, Flaherty JH, et al:* Diabetes mellitus among ethnic seniors: contrasts with diabetes in whites. Clin Geriatr Med 15:265-278, 1999.
24. *Sinclair AJ:* Diabetes in the elderly: A perspective from the United Kingdom. Clin Geriatr Med 15:225-37, 1999.