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ARTICLE

Diabetes Mellitus and Bladder Cancer – An Epidemiological Relationship?

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An epidemiological association between diabetes mellitus and transitional cell carcinoma of the bladder has been proposed. This study looked retrospectively at 125 patients with transitional cell carcinoma of the bladder as a study group and 80 other hospital patients with conditions not specifically associated with diabetes mellitus as a control group. Diabetic patients had an increased, significant odds ratio for bladder cancer compared with non diabetics even after adjustment for smoking and age [OR: 2.69 p=0.049 (95% CI 1.006-7.194)] A history of smoking OR 2.16 p=0.013 (95% C.I. 1.175-3.964) is a significant independent association with transitional cell carcinoma of the bladder as is age: p=0.001 OR 1.07. We propose potential pathogenic pathways for transitional cell carcinoma of the bladder in diabetic patients based on altered integrin and cadherin distribution in urothelial cells in diabetic patients. A larger study is planned to confirm an association between diabetes mellitus and transitional cell carcinoma of the bladder. (Pathology Oncology Research Vol 9, No 1, 30–31, 2003)

Keywords:

Introduction

A postulated association between diabetes mellitus (DM) and bladder transitional cell carcinoma (TCC bladder) has been casually observed for many years. Kravchik et al[1] have conducted a recent case control study in Israel (n=801) which demonstrated a statistically significant odds ratio of 2.3 (incidence of diabetes mellitus in bladder carcinoma group versus incidence of DM in control group). The incidence of bladder cancer in that case group was 22%. A study by Rische et al[2] primarily investigating dietary factors in bladder cancer also found an association between diabetes mellitus (onset after age 20) and bladder cancer with an odds ratio of 1.65 (p=0.019). No further association was found with insulin or oral hypoglycaemic use.

We have attempted to look for an epidemiological association between diabetes mellitus and transitional cell carcinoma of the bladder. The link between history of smoking and TCC bladder was also investigated.

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Materials and Methods

The study was based on a retrospective case control design. The study group consisted of 134 patients at Bedford General Hospital over the age of 60 with transitional cell carcinoma of the bladder who had pathology specimens taken between January 2000 and September 2001as identified from pathology records. Information taken from comprehensive medical records included age, sex, history of smoking (either current or previous), and diabetes mellitus (insulin dependent-IDDM or non insulin dependent-NIDDM). Other known risk factors were also recorded including occupational risks, use of oral anticoagulants, cyclophosphamide, recurrent cystitis and renal tract calculi. The control group consisted of patients (n=80) presenting to the hospital, in this case the general dermatology clinics, with a similar age and sex distribution. Statistical analysis was carried out using logistic regression to study the effect of diabetes on the risk of bladder cancer adjusted for age and smoking.

Results

Of the 134 patients in the study group, 9 were excluded from further calculations due to risk factors for TCC bladder other than diabetes mellitus, smoking or age.

In total, 23 of the remaining 125 patients in the study group had IDDM or NIDDM representing 18.4%. In non-smokers, the figure was 10 of 59 subjects or 16.9%. This compared with the control group where 7.5% (6 of 80) of all patients had NIDDM (none with IDDM). With regard to smoking, 52% (65 of 125) of patients had a history of tobacco usage in the study group compared with 34% of the control group.

Logistic regression was then carried out to take into account smoking and age as confounding variables. Diabetes mellitus remains a significant association when smoking and age are considered: OR 2.69 p=0.049 (95% CI 1.006-7.194). Both a history of smoking OR 2.16 p=0.013 (95% C.I. 1.175-3.964) and increasing age OR 1.07 p=0.001 (95% C.I. 1.030-1.112) are significant independent risk factors for bladder cancer.

Discussion

This preliminary study attempts to ascertain whether an epidemiological association may exist between diabetes mellitus and transitional cell carcinoma (TCC) of the bladder. Regression analysis shows an increased odds ratio of 2.69 between diabetes mellitus versus non diabetics and TCC of the bladder, with a significant p-value of 0.049. This p value may have fallen further if the cases and controls were exactly age matched. Smoking was also found to be a significant independent variable OR 2.16 p=0.013. This latter figure correlates well with previous studies.[3,4] Increasing age was a significant but low risk factor for TCC bladder OR 1.07 p=0.001. Our study differs from previous investigations in that the Bedford population has a high incidence of tobacco use and habitats an area of former industrial usage (although this was primarily brick and iron making).

The mechanism by which diabetes mellitus contributes towards bladder carcinoma remains uncertain. However, a considerable amount of work has been dedicated into looking at structural changes in urothelium in diabetic nephropathy. Cadherins are a family of membrane glycoproteins involved in cell to cell adhesion . Singh et al[5] looked at cadherin distribution and quantity in rat renal cells exposed to glycated proteins and found a decrease in both cadherin amount and distribution. In addition, they were able to demonstrate that resultant basement membranes were more permeable to insulin and albumin. Reduced expression of the subtype e-cadherin has been associated with poor outcome in bladder cancer patients and has been shown to correlate with increased tumour invasion.[6-8]

Integrins are another class of transmembrane glycoproteins implicated as receptors for extracellular matrix components. Various studies have demonstrated changes in integrin distribution with diabetic nephropathy[6,8] though the exact role of various subtypes is unknown. Normally, alpha 6 beta 4 integrin co-localises with the hemidesmosomal anchoring complex which attaches basal epithelial cells to the underlying substratum The loss of interaction between collagen VII and alpha 6 beta 4 integrin has been implicated in bladder cancer.[10] Jin et al[11] found an increased expression of alpha 6 integrin subunits on endothelial glomerular renal cells in diabetic patients.

In conclusion, this small study has again highlighted a potential association between diabetes mellitus and transitional cell bladder cancer. We have postulated a novel hypothesis for an etiological association between diabetes mellitus and bladder cancer. Larger studies are required to confirm the association between bladder cancer and diabetes mellitus. Future meta-analysis of multiple studies would add greatly to the case.

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