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Metformin and Cancer Occurrence in Insulin-Treated Type 2 Diabetic Patients

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OBJECTIVE — Metformin is associated with reduced cancer-related morbidity and mortality. The aim of this study was to assess the effect of metformin on cancer incidence in a consecutive series of insulin-treated patients.

RESEARCH DESIGN AND METHODS — A nested case-control study was performed in a cohort of 1,340 patients by sampling, for each case subject, age-, sex-, and BMI-matched control subjects from the same cohort.

RESULTS — During a median follow-up of 75.9 months, 112 case patients who developed incident cancer and were compared with 370 control subjects. A significantly lower proportion of case subjects were exposed to metformin and sulfonylureas. After adjustment for comorbidity, glargine, and total insulin doses, exposure to metformin, but not to sulfonylureas, was associated with reduced incidence of cancer (odds ratio 0.46 [95% CI 0.25–0.85], $P = 0.014$ and 0.75 [0.39–1.45], $P = 0.40$, respectively).

CONCLUSIONS — The reduction of cancer risk could be a further relevant reason for maintaining use of metformin in insulin-treated patients.

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Several studies have shown that metformin is associated with reduced cancer-related morbidity and mortality (1–4), due to improvement in insulin sensitivity (5) or to the activation of AMP-activated protein kinase (6). In insulin-treated patients, the reduction in insulin doses determined by metformin (7) could theoretically produce a decrease in cancer incidence.

RESEARCH DESIGN AND METHODS

— We analyzed oral hypoglycemic treatments in patients included in a case-control study nested within a cohort of insulin-treated type 2 diabetic patients, which had been designed for the assessment of the effect on cancer incidence of different insulin analogs (8). In brief, 1,340 consecutive type 2 diabetic outpatients (746 women and 594 men, aged [mean ± SD] 63.1 ± 14.9 years) with no history or previous hospitalizations for malignancies, who were living in Florence, Italy, were referred to the University Diabetes Clinics, and started insulin therapy in 1998–2007, were enrolled in the study. Demographic and clinical information was obtained from clinical records, including anthropometric measures, A1C (measured every 3–4 months with high-performance liquid chromatography [Menarini Diagnostics, Florence, Italy]; upper normal limit 5.9%), and serum creatinine, part of routine follow-up. Comorbidity was assessed with the Charlson comorbidity score (CCS), which includes diabetes and its complications and other diseases (9).

Patients with incident cancer up to 31 December 2008 were identified at first hospital admission (from the Regional Hospital Discharge system) or death (from the Mortality Registry of Tuscany) with ICD-9 codes 140–209. A nested case-control study dataset was generated from the cohort study dataset by sampling control subjects from the risk sets. For each case subject, the control subjects (up to five) were chosen randomly from those members of the cohort at risk for the same follow-up time as the case subject. Age, sex, and BMI classes at insulin initiation were considered as additional categorical variables for matching, using Stata 9.0 and the procedure "sttocc." Exposure to hypoglycemic drugs was assessed from enrollment to incident cancer in case subjects and during the corresponding time from initiation of insulin therapy in matched control subjects, retrieving prescriptions from clinical records. If the last available visit had occurred >3 months before the event (or matching date), a telephone contact was attempted to collect further information on subsequent drug use; if the contact was unsuccessful, the patient was assumed to have continued the last reported therapy.

The exposure of case subjects and control subjects to different drugs (proportion of patients exposed, time of exposure, and mean daily dose [MDD], units per kilogram per day) for each compound) was compared using χ^2 and Mann-Whitney tests whenever appropriate. Multivariate analyses were performed with conditional logistic regression, which takes into account the matching structure, using total insulin and glargine MDD and CCS as covariates. All analyses were carried out with SPSS 15.0 and Stata 9.0.

RESULTS

— The 112 patients with incident cancer (gastrointestinal, 29; lung, 16; pancreatic, 14; and other, 53) during a median follow-up of 75.9 (range 27.4–133.7) months (case subjects) were compared with 370 control subjects. A significantly lower proportion of case subjects were exposed to metformin and sulfonylureas during follow-up. Among

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Table 1—*Characteristics of case and control subjects*

	Case subjects	Control subjects	*P* value
n (male/female)	112 (60/52)	370 (189/181)	0.64
Age (years)	68.9 ± 9.9	68.0 ± 10.0	0.41
BMI (kg/m^2)	28.1 ± 5.3	28.2 ± 5.1	0.78
Duration of diabetes (years)	8.4 (0.3–20.9)	10.0 (0.6–21.0)	0.28
Current smokers	25 (22.5)	66 (17.8)	0.39
Exposure to drugs during follow-up			
Biguanides	20 (17.9)	158 (42.7)	<0.001
Fenformin	0 (0.0)	8 (2.2)	0.12
Metformin	20 (17.9)	150 (40.5)	<0.001
Insulin secretagogues	0 (0.0)	0 (0.0)	—
Glimepiride	0 (0.0)	28 (7.6)	0.003
Gliclazide	3 (2.7)	13 (3.5)	0.67
Glibenclamide	14 (12.5)	55 (14.9)	0.53
Chlorpropamide	1 (0.4)	6 (1.6)	0.56
Repaglinide	2 (1.8)	41 (11.1)	0.02
Acarbose	0 (0.0)	8 (2.2)	0.12
Length of exposure (months)			
Metformin	24.0 (9.0–44.0)	29.0 (20.0–75.0)	0.69
Sulfonylureas	27.5 (7.0–46.0)	23.0 (15.0–43.0)	0.56
Mean daily doses (mg/kg · day)			
Metformin	16.0 (11.8–21.4)	18.5 (10.3–31.0)	0.40
Glyburide	0.05 (0.03–0.10)	0.08 (0.04–0.10)	0.75

Data are means ± SD, *n* (%), and median (range).

those exposed, the length of exposure to sulfonylureas was greater in case subjects than in control subjects, whereas no such difference was observed for metformin. MDD for metformin and glyburide did not differ between case subjects and control subjects (Table 1).

In a multivariate model, with adjustment for CCS, glargine MDD, and total MDD of insulin, exposure to metformin was associated with reduced incidence of cancer (OR 0.46 [95% CI 0.25–0.85], $P = 0.014$; 0.37 [0.15–0.92], $P = 0.032$, and 0.55 [0.23–1.32], $P = 0.18$, in men and women, respectively), whereas sulfonylurea treatment was not (0.75 [0.39–1.45], $P = 0.40$). When cancer occurred within 12 months of follow-up of enrollment and matching control subjects were excluded, the ORs for cancer were 0.53 [0.26–1.06], $P = 0.074$ and 0.86 [0.42–1.79], $P = 0.69$, for any exposure to metformin and sulfonylureas, respectively; the corresponding figures for exposure >12 months during follow-up were 0.30 [0.14–0.66], $P = 0.003$ and 0.70 [0.34–1.41], $P = 0.31$, for metformin and sulfonylureas, respectively.

CONCLUSIONS — The present results confirm previous findings on the protective effect of metformin with respect to malignancies (1–3). Interestingly, this effect was evident even after adjustment for insulin doses, suggesting that the protective action of metformin cannot be entirely attributed to its insulin-sparing effects. Although insulin has mitogenic properties (10) and metformin reduces insulin requirements in type 2 diabetic patients (7), the decrease in insulin doses determined by metformin does not explain the observed reduction of cancer incidence. This result supports the notion of other mechanisms, independent of insulin dose (6,11,12). It is possible that patients not receiving metformin have a greater incidence of cancer due to comorbidities; the adjustment for a comorbidity score does not eliminate completely the possibility of a prescription bias. Conversely, the protective effect of sulfonylureas did not retain significance in multivariate analysis, suggesting that the higher proportion of sulfonylurea-treated patients among control subjects could be either due to lower comorbidity or metformin cotreatment. The possibility of misdiagnosis of diabetes type in some case subjects should be considered.

Current recommendations suggest a trial of metformin, unless contraindicated, in all insulin-treated type 2 diabetic patients (13). This recommendation is motivated by the beneficial effects of metformin on insulin sensitivity, insulin doses, and glucose control. Beyond all those effects, the reduction of cancer risk could be a further relevant reason for maintaining use of metformin in insulin-treated patients.

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