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 0.39 [95% CI 0.25–0.58], 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 “stcox.” 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 χ² 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/m²)           | 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  |
| Fenofibrate           | 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).

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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References

1. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006;29:254–258
2. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005;330:1304–1305
3. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident can-
1. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, Pollak M, Regensteiner JG, Yee D. Diabetes and cancer: a consensus report. Diabetes Care 2010;33:1674–1685
2. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, Hsu L, Hung MC, Hortobagyi GN, Gonzalez-Angulo AM. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 2009;27:3297–3302
3. Kisfalvi K, Eibl G, Sinnett-Smith J, Rozen-gurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. Cancer Res 2009;69:6539–6545
4. Wulffele MG, Kooy A, Lehert P, Bets D, Ogerop JC, Borger van der Burg B, Donker AJ, Stehouwer CD. Combination of insulin and metformin in the treatment of type 2 diabetes. Diabetes Care 2002;25:2133–2140
5. Mannucci E, Monami M, Balzi D, Cresci B, Pala L, Melani C, Lamanna C, Bracali I, Bugaritir M, Barchielli A, Marchionni N, Rotella CM. Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 2010;33:1997–2003
6. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245–1251
7. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zin- man B. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabe-
8. Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R. Diabetes and cancer. En-docr Relat Cancer 2009;16:1103–1123
9. Zakikhani M, Dowling R, Fantus IG, Sonen-berg N, Pollak M. Metformin is an AMP ki-


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