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RESEARCH POINTERS

Metformin and reduced risk of cancer in diabetic patients

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Metformin, widely given to patients with type 2 diabetes, works by targeting the enzyme AMPK (AMP activated protein kinase), which induces muscles to take up glucose from the blood. A recent breakthrough has found the upstream regulator of AMPK to be a protein kinase known as LKB1.[1 2] LKB1 is a well recognised tumour suppressor. Activation of AMPK by metformin and exercise requires LKB1, and this would also explain why exercise is beneficial in the primary and secondary prevention of certain cancers.[3] We hypothesise that metformin use in patients with type 2 diabetes may reduce their risk of cancer.

Participants, methods, and results

We tested this hypothesis using record linkage databases developed in Tayside, Scotland: a diabetes clinical information system (DARTS) and a database of dispensed prescriptions (MEMO).[4] We did a pilot case-control study using previously validated methods.[5]

From 314 127 people who were resident (or died) in Tayside in 1993-2001, 11 876 had been newly diagnosed with type 2 diabetes. Of these, 923 were subsequently admitted to hospital with an ICD-9 or ICD-10 (international classification of diseases, 9th or 10th revision) diagnostic code for malignant cancer in study period (for which first admission occurred at least one year after diagnosis of diabetes). The index date of these cases was the date of first admission. We generated random controls from the diabetic population (two for each case); patients without cancer matched for age, year of diagnosis, and sex, and we gave them matching index dates.

We collated information about use of metformin for all cases and controls and calculated unadjusted odds ratios using conditional logistic regression (taking matching into account). The proportions of cases and controls for whom confounding data were available were smoking 73%, body mass index 62%, blood pressure 67%, and postcode rank for material deprivation 99%. We categorised continuous variables into quartile groups, with missing values forming a separate category. We adjusted odds ratios for these possible confounders.

More than half of the patients with cancer (488; 53%) were men. Mean age was 73 (standard deviation 9.8) years and mean duration of diabetes was 8.5 (6.4) years. More than a third (336; 36.4%) of the cases had been given at least one prescription for metformin in the year before their index date compared with 732 (39.7%) of the controls. The unadjusted odds ratio was 0.86 (95% confidence interval 0.73 to 1.02). The unadjusted odds ratio for any exposure to metformin since 1993 was 0.79 (0.67 to 0.93).

We also investigated total duration of exposure (time between first and last metformin prescription), total number of prescriptions, and total amount of metformin dispensed since January 1993 (table). Adjustment did not greatly affect the risk estimates, indicating no substantial confounding effects.

Comment

Taking metformin may be associated with reduced risk of cancer in patients with type 2 diabetes, and a biologically plausible mechanism exists. Of particular interest is the suggestion of a dose-response relationship (table).

The strengths of the study were its population based sampling, the objective method used to define metformin exposure, detailed dispensed prescribing histories available for patients, and adjustment for confounders. Because this is a pilot observational study, however, we must consider alternative explanations. We used a crudely defined case series of cancer patients. The index date used for the cases was their date of first admission to hospital for cancer. If cases' actual dates of diagnosis of cancer were much earlier, this could affect clinicians' prescribing.

We are planning a large cohort study linked to a cancer registration database. We will identify a more tightly defined case

Metformin use in patients with type 2 diabetes and controls in Tayside, Scotland, 1993-2001

	No (%)			
	Cases (n=983)	Controls (n=1846)	Unadjusted odds ratios (95% CI)	Adjusted odds ratios (95% CI)
Exposure during year before index date:				
No	587 (63.6)	1114 (60.4)	1.00	1.00
Yes	336 (36.4)	732 (39.7)	0.86 (0.73 to 1.02)	0.85 (0.71 to 1.01)
Any exposure to metformin since January 1993:				
No	547 (59.3)	996 (54.0)	1.00	1.00
Yes	376 (40.7)	850 (46.0)	0.79 (0.67 to 0.93)	0.77 (0.64 to 0.92)
Duration (days):				
0	547 (59.3)	996 (54.0)	1.00	1.00
1-634	127 (13.8)	282 (15.3)	0.81 (0.64 to 1.02)	0.80 (0.62 to 1.02)
635-1806	143 (15.5)	273 (14.8)	0.93 (0.74 to 1.17)	0.92 (0.72 to 1.17)
>1806	106 (11.5)	295 (16.0)	0.62 (0.47 to 0.80)	0.56 (0.43 to 0.74)
Total prescriptions dispensed:				
0	547 (59.3)	996 (54.0)	1.00	1.00
1-11	127 (13.8)	282 (15.3)	0.82 (0.65 to 1.04)	0.82 (0.64 to 1.04)
12-31	122 (13.2)	281 (15.2)	0.77 (0.61 to 0.99)	0.75 (0.58 to 0.97)
>31	127 (13.8)	291 (15.8)	0.76 (0.60 to 0.98)	0.73 (0.56 to 0.94)
Total amount of metformin dispensed (mg):				
0	547 (59.3)	996 (54.0)	1.00	1.00
14 000-672 000	130 (14.1)	279 (15.1)	0.84 (0.67 to 1.06)	0.83 (0.65 to 1.06)
673 000-964 000	138 (15.0)	279 (15.1)	0.88 (0.69 to 1.10)	0.86 (0.68 to 1.10)
>964 000	108 (11.7)	292 (15.8)	0.63 (0.49 to 0.82)	0.57 (0.43 to 0.75)

What this paper suggests

Metformin may reduce the risk of cancer in patients with type 2 diabetes

What research is needed now

A more rigorous cohort study, before experimental work is initiated

series of specific cancers, with more precise dates of diagnosis, to explore this further.

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Competing interests: AME-S has received fees for lecturing from Merck-Lipha (manufacturer of metformin).

Ethical approval: Tayside Committee for Medical Research Ethics.

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