Incretin therapies and risk of hospital admission for acute pancreatitis in an unselected population of European patients with type 2 diabetes: a case-control study

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Summary

Background **Previous studies have yielded conflicting results about the association between incretin therapies and acute pancreatitis. We aimed to compare the occurrence of acute pancreatitis in a population of patients with type 2 diabetes who received incretins compared with those who received other antidiabetic treatment.**

Methods **In our population-based matched case-control study, we extracted information from an administrative database from Piedmont, Italy (containing data for 4·4 million inhabitants). From a dataset of 282 429 patients receiving treatment with antidiabetic drugs for type 2 diabetes, we identified 1003 cases older than 41 years who had been admitted to hospital for acute pancreatitis between Jan 1, 2008, and Dec 31, 2012, and 4012 controls who were matched for sex, age, and time of start of antidiabetic therapy. We compared incretin exposure in cases and controls with a conditional logistic regression model, expressed as odds ratios (ORs [95% CI]). We adjusted all analyses for risk factors of acute pancreatitis, as ascertained by hospital discharge records, and concomitant use of metformin or glibenclamide.**

Findings **The mean age of cases and controls (72·2 years [SD 11·1]) was high, as expected in an unselected diabetic population in Europe. After adjustment for available confounders, use of incretins in the 6 months before hospital admission was not associated with increased risk of acute pancreatitis (OR 0·98, 95% CI 0·69–1·38; p=0·8958).**

Interpretation **Our findings suggest that, in an unselected population, use of incretins is not associated with an increased risk of acute pancreatitis. Larger studies are needed to clarify whether age or type of incretin therapy could affect the risk of acute pancreatitis in patients with type 2 diabetes.**

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Introduction

Incretin-based therapies for type 2 diabetes include two drug classes. The first class, glucagon-like peptide-1 (GLP-1) receptor agonists, includes drugs that mimic the action of native GLP-1, such as the injectable GLP-1 analogues exenatide and liraglutide. The other class includes drugs that delay the catabolism of native GLP-1 mainly through inhibition of the endogenous enzyme dipeptidyl peptidase 4 (DPP-4), thus extending the action of native GLP-1. The DPP-4 inhibitors sitagliptin, vildagliptin, saxagliptin, and linagliptin, in order of their prevalence of use in the market in Europe, are all taken orally. Although cases of haemorrhagic or necrotising pancreatitis have been reported in patients taking these drugs, a clear-cut pharmacoepidemiological association between incretin treatment and increased risk of pancreatic damage has not been shown. Incidence of acute pancreatitis is higher in patients with type 2 diabetes than in the non-diabetic population, irrespective of treatment.[1,2] Further complicating the issue is the fact that several drugs commonly used in the treatment of type 2 diabetes (eg, non-incretin anti-diabetes drugs, statins, and angiotensin-converting enzyme inhibitors) have been reported to increase the risk of acute pancreatitis.[3–5]

After publication of several studies that were criticised because of inadequate statistical power and short duration of follow-up,[6–9] a report by Singh and colleagues[10] provided some evidence for an association between use of incretins and negative effects on pancreatic function. In their case-control study[10] of an administrative database of adults aged 18–64 years with type 2 diabetes in the USA, treatment with two incretins (sitagliptin and exenatide) was associated with increased chance of hospital admission for acute pancreatitis.

To our knowledge, no such analysis has been done on data from European administrative databases that, owing to the universal nature of most European national health systems, encompass the whole population and include all types of available incretins. Therefore, we aimed to assess whether an association exists between incretin therapies and hospital admissions for acute pancreatitis in unselected European patients with type 2 diabetes.

Methods

Study design and participants

In our population-based case-control study, we used regional administrative data from the Piedmont region in northwest Italy, which contains about 4·4 million inhabitants. The population is covered by an automated system of databases that records all drugs dispensed from all regional pharmacies, and hospital discharges reimbursed by the Italian National Health System.

These archives can be linked together by a unique anonymous identifier that is encrypted to protect patients' privacy. Because this automated system is anonymous, ethical committee approval and informed consent were not required.

Procedures

We extracted information from the regional drug prescription database for individuals aged 41 years or older who were dispensed at least one dose of any drug to treat diabetes between Jan 1, 2008, and Dec 31, 2012; incretins were not available in Italy before 2008. We only included residents of Piedmont. To minimise the chance of inclusion of patients with type 1 diabetes, we linked the database to the regional hospital discharge database, which includes all hospital admissions between 1995 and 2012. We excluded individuals who had an International Classification of Diseases, 9th edition, Clinical Modification (ICD-9-CM) code for type 1 diabetes mellitus (250.x1 or 250.x3).

To identify cases, we identified all patients from the database with type 2 diabetes who had at least one discharge for acute pancreatitis, defined as a ICD-9-CM code 577.0 discharge diagnosis[11] at any time after the first exposure to antidiabetic drugs (ie, date of dispensation). For patients with more than one acute discharge for pancreatitis, we only included the first episode (ie, the hospital admission closest to Jan 1, 2008). We included residents of Piedmont discharged from any hospital outside the region (2·1%) because information on exposure to dispensed drugs is available for all patients residing in the region.

To identify controls, we randomly selected four controls from the same population source for each case, matched for year of birth, sex, and year of first exposure to antidiabetic drugs. Matching was done by the study statistician (RP) by use of an automated computer program. Patients with acute pancreatitis (ie, cases) were ineligible for resampling as controls.

We used the regional drug database to identify cases and controls who had been prescribed incretins at any time in the 6 months before the date of hospital admission. We used the hospital admission date of cases to calculate exposure windows for controls. Incretins were selected according to the anatomical therapeutic chemical (ATC) classification system; ATC codes A10BH01 and A10BD07 (sitagliptin), A10BH02 and A10BD08 (vildagliptin), A10BH03 (saxagliptin), A10BX04 (exenatide), and A10BX07 (liraglutide) were considered.

We defined potential confounders from the regional hospital discharge database as hospital admissions up to 5 years before the index date for the following disorders: chronic or acute pancreatitis, excluding the episode of the index case (ICD-9-CM 577); gallstones, including diagnosis of either cholelithiasis (ICD-9-CM 574, 575·2) or cholangiography (ICD-9-CM 51·10–51·11) or cholecystectomy (ICD-9-CM 51.2); alcohol misuse (ICD-9-CM 303); hypertriglyceridaemia (ICD-9-CM 272); obesity (ICD-9-CM 278); and biliary tract (ICD-9-CM 156) or pancreatic cancers (ICD-9-CM 157). Previous hospital admissions for cardiovascular diseases (ICD-9-CM codes 410-414, 430-438, 440-448), and diabetic retinopathy (ICD-9-CM 3620) were regarded as proxies of severity of diabetes.

From the regional drug database, we also included individuals who were treated with metformin (ATC codes A10BA02, A10BD02, A10BD07, A10BD08, and A10BD05) or glibenclamide (ATC codes A10BB01 or A10BD02) in the 6 months before hospital admission.

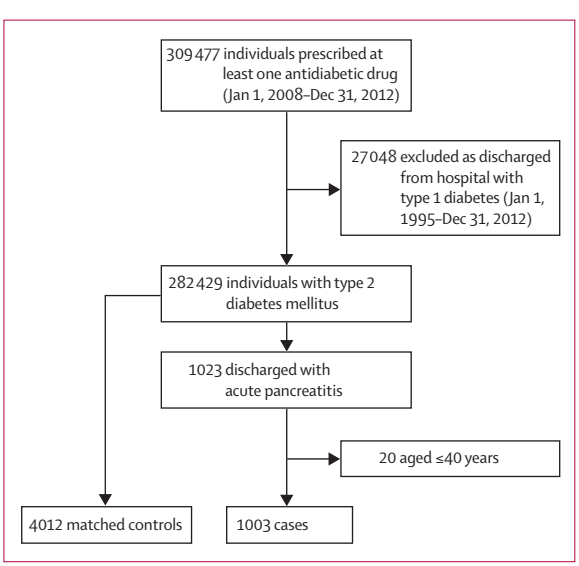

Figure: **Study profile**

Statistical analysis

We calculated the proportions of categorical variables in cases and controls, and assessed differences in baseline characteristics with the χ^2 test. We estimated the risk of acute pancreatitis associated with dispensation of any incretins by fitting conditional logistic regression models, expressed as odds ratios (ORs) and corresponding 95% CIs.

We adjusted the statistical models for the aforementioned confounders. Confounders included in the final model were past history of pancreatitis, gallstones, alcohol use, hypertriglyceridaemia, obesity, biliary tract or pancreatic cancer, cardiovascular disease, and metformin or glibenclamide use.

We did two different sensitivity analyses. First, we assessed the use of incretins at any time before hospital admission. We subsequently excluded from the study population all individuals who had a hospital discharge for acute pancreatitis from Jan 1, 2003, to Dec 31, 2007. We excluded individuals who started antidiabetic drug treatment after Jan 1, 2008, if they were admitted to hospital for acute pancreatitis in the 5 years before the date of start of drug therapy. Thus, only individuals with incident acute pancreatitis in 2008–12 were defined as cases.

All analyses were done with SAS PHREG procedure, version 9.2.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CBG, RP, GC and RG had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For the study period examined, 1003 cases of acute pancreatitis and 4012 controls with type 2 diabetes met the inclusion criteria (figure). Compared with controls, prevalence of known risk factors for acute pancreatitis was increased in cases, although other baseline characteristics did not differ (table 1). Prevalence of cardiovascular disease was higher in cases than controls, but prevalence of diabetic retinopathy did not differ between groups. Types of incretin used did not differ between cases and controls (71% were on sitagliptin), whereas use of metformin and glibenclamide was more frequently used by cases (table 1).

In a retrospective power calculation, with a one-sided test and α level of 5%, the smallest risk (ie, OR >1) that could be detected with 80% power was an OR of 1·73. After adjustment for available confounders, use of incretins up to 6 months before hospital admission was not associated with the risk of acute pancreatitis (OR 0·98, 95% CI 0·69–1·38; p=0·8958). A history of gallstones or of previous chronic pancreatitis was associated with risk of acute pancreatitis (table 2). In the first sensitivity analysis, in which the time window was extended to include incretin use at any time before hospital admission, the ORs were substantially unchanged (0·99, 0·72–1·35; p=0·9267). In the second sensitivity analysis, in which only patients with incident acute pancreatitis were considered, we included 921 cases and 3684 matched controls. Again, the conditional logistic model confirmed the absence of an association between incretins exposure and the occurrence of acute pancreatitis (0·98, 0·68–1·40; p=0·9031). A history of gallstones (3·92, 3·30–4·66; p<0·0001) and chronic pancreatitis (2·23, 1·01–5·00; p=0·0489) were confirmed in both sensitivity analyses as significant predictors of acute pancreatitis.

	Cases (n=1003)	Controls (n=4012)	p value
Age at recruitment, years	72·2 (11·1)	72·2 (11·1)	..
Sex, male	550 (55%)	2200 (55%)	..
Incretin use*	17 (2%)	78 (2%)	0·6045
Previous disorders or treatments (in the past 5 years)			
Gallstones	500 (50%)	86 (2%)	<0·0001
Pancreatic or billiary cancer	25 (2%)	17 (<1%)	<0·0001
History of any pancreatitis before index date	88 (9%)	19 (<1%)	<0·0001
Alcohol misuse	18 (2%)	12 (<1%)	<0·0001
Hypertriglyceridaemia	64 (6%)	145 (4%)	<0·0001
Obesity	75 (7%)	85 (2%)	<0·0001
Retinopathy	12 (1%)	35 (1%)	0·3408
Cardiovascular disease	304 (30%)	656 (16%)	<0·0001
Other antidiabetic drugs use			
Metformin use	494 (49%)	1654 (41%)	<0·0001
Glibenclamide use	161 (16%)	489 (12%)	0·0011

Data are mean (SD) or n (%), unless otherwise stated. *One case and one control received more than one incretin.

Table 1: **Baseline characteristics**

	Unadjusted odds ratio (95% CI; p value)	Adjusted odds ratio (95% CI; p value)
Incretin use*	0·97 (0·69–1·36); p=0·8644	0·98 (0·69–1·38); p=0·8958
Previous disorders or treatments (in the past 5 years)		
Gallstones	4·18 (3·55–4·92); p<0·0001	3·87 (3·27–4·59); p<0·0001
Pancreatic or billiary cancer	1·99 (1·16–3·43); p=0·0132	1·23 (0·69–2·12); p=0·4874
Chronic or acute pancreatitis	3·56 (2·49–5·09); p<0·0001	1·83 (1·24–2·71); p=0·0024
Alcohol misuse	2·01 (1·06–3·82); p=0·0338	1·57 (0·81–3·06); p=0·184
Hypertriglyceridaemia	1·17 (0·93–1·48); p=0·1806	1·06 (0·82–1·35); p=0·6733
Obesity	1·55 (1·18–2·04); p=0·0017	1·32 (0·99–1·75); p=0·0553
Cardiovascular disease	1·23 (1·09–1·39); p=0·0006	1·12 (0·99–1·27); p=0·0745
Other antidiabetic drug use		
Metformin use	1·08 (0·98–1·18); p=0·1242	1·09 (0·98–1·21); p=0·1283
Glibenclamide use	1·08 (0·94–1·24); p=0·2707	1·01 (0·87–1·18); p=0·8941

*One case and one control received more than one incretin.

Table 2: **Matched odds ratio of acute pancreatitis associated with exposure to incretins in the 6 months before index date**

Discussion

Whether incretin therapies cause acute pancreatitis has raised concern among practitioners.[12–14] In our analysis of a large unselected population of treated individuals with type 2 diabetes, no association was noted between incretin use and incidence of acute pancreatitis, irrespective of causality.

Our findings are in line with previous reports of US administrative databases[6–9] that suggested no link between the use of incretins and pancreatic events in patients with type 2 diabetes. Conversely, in a cohort study,[8] Dore and colleagues reported a significant increase in pancreatitis in a subgroup of patients who had used exanatide (but not sitagliptin) beyond 62 days after drug was stopped, but this finding was not confirmed in a case-control revision. The study was criticised for failing to adjust for confounders (especially obesity, which is an indication for exenatide use and a known risk factor for acute pancreatitis)[6] and for its low statistical power and short exposure windows.[10]

Singh and colleagues[10] reported a significantly increased risk of hospital admission for acute pancreatitis associated with the use of sitagliptin and exenatide in adults with type 2 diabetes, with an OR of more than

twice that which we reported. One possible, although speculative, explanation for this discrepancy is difference in the average age between the cohorts (72 years in our cohort *vs* 52 years in Singh and colleagues' cohort). In view of reports of a higher incidence of acute pancreatitis in young patients either with[2] or without[1] diabetes, the hypothesis for a different pattern or risk of the incidence of acute pancreatitis in relation to age cannot be ruled out. The hypothetical confounding role of increased prevalence of biliary disease and of polypharmacy in elderly people should also be better defined. Moreover, when we controlled for a history of pancreatitis before enrolment, we noted that this confounder has a significantly increased OR. An additional difference is that Singh's case-control study[10] addressed only the effects of two incretins (exenatide and sitagliptin) and in a selected population of insured individuals. Finally, the well-known gastrointestinal side-effects of incretins (nausea and vomiting) have been consistently reported as less frequent in Europe than the USA (almost half the rate reported), pointing to a different pattern of incidence of untoward effects associated with these drugs, perhaps due to dietary habits or ethnic disparities.[15]

Our study design allowed us to eliminate recall bias and minimise selection bias. We used data retrieved from a population-based database that contained data for the real type 2 diabetes population in Europe, without any selection based on insurance claims, and without an upper age cutoff, which distinguish it from other published studies using administrative data.

We included all five incretin drugs that are presently available in Europe at the time of analysis in July, 2013, and because incretins are dispensed and reimbursed only by prescription, we are confident that we included all dispensations. However, our study also had limitations. Our sample size was not sufficient to exclude small increases in ORs. Thus, a weaker association between incretins use and acute pancreatitis cannot be ruled out; however, if such an association did exist, it would not be as strong as previously reported.[14,16,17] We also recognise that because the information about alcohol misuse, hypertriglyceridaemia, and obesity was drawn from a hospital discharge database, this information could have been recorded more accurately for cases than controls. Another weakness was the missing data on metabolic control and other clinical variables such as bodyweight and duration of disease. Nonetheless, we do not believe data for these variables would have favoured the control group and thus masked an association. As a proxy of diabetes severity, we adjusted for cardiovascular disease. We did not consider drug dose or adherence to therapy, and, in view of the low prevalence of exposed individuals, we were unable to factor in the effect of the two classes of incretins separately. In addition, the use of a database of dispensed drugs rather than data for actual use might have overestimated the use of incretins; however, this difference would probably not have affected cases and controls differently. Finally, only severe cases of pancreatitis resulting in hospital admission were included, leaving open the question as to whether mild inflammation of the pancreas, which would only be detectable by laboratory tests, such as amylase, might progressively damage the organ.[18]

Continued basic and epidemiological research on the untoward effects of incretins is desirable, ideally including in-depth analysis of administrative databases. Our findings suggest the need for larger studies to clarify whether age or type of incretin or both could increase the risk of acute pancreatitis in type 2 diabetes patients receiving such therapy.

Panel: Research in context

Systematic review

We searched PubMed for studies published in any language before July 31, 2013, with the search terms "sitagliptin" or "vildagliptin" or "saxagliptin" or "linagliptin" or "exenatide" or "liraglutide" or "incretins" and "pancreatitis" in the title or abstract. Ten of 79 references retrieved were pathophysiological studies on animals, 16 were case reports, six were observational studies (three case-control studies and three small cohort studies), and one focused on a US Food and Drug Administration database of reported adverse events. The other 46 publications included three meta-analyses, three pooled analyses, 28 reviews, and 12 opinion or position papers. We searched the reference lists in these publications and selected citations that we regarded as relevant. All observational studies were based on US insurance claims for exenatide or sitagliptin use, with limiting age cutoffs. We noted no previous studies based on data for unselected populations or populations outside the USA.

Interpretation

No clear-cut association between incretin treatment and the occurrence of acute pancreatitis has been shown, despite claims for a relative risk increase of up to 30-times with use of these drugs. The link between the two is unclear because of numerous confounding factors. For example, the prevalence of risk factors for acute pancreatitis and the incidence of the disorder itself are higher in patients with type 2 diabetes than they are in the non-diabetic population, irrespective of treatment. Furthermore, several drugs commonly used in type 2 diabetes therapy have been reported to increase the risk of acute pancreatitis. In our study, we suggest that after adjustment for available confounders in an unselected population of patients with type 2 diabetes, hospital admission for pancreatitis was associated with gallstones and a history of previous pancreatitis but not with incretin use. Because acute pancreatitis is a relatively rare event, the power of our study allowed us to rule out associations with an odds ratio of greater than 1·73, although weaker associations cannot be excluded completely. To better define the possible association between incretins and acute pancreatitis, salient information on all types of available incretins needs to be gleaned from observational studies encompassing whole populations of other geographical areas outside the USA. Such studies are not only useful for future integrated analysis but could provide the practitioner with elements to weigh benefits versus risk when considering incretin therapy. Because the use of incretins and acute pancreatitis are both relatively rare, more research is needed, especially large cohort studies, which might prove to be demanding.

Contributors

CBG and RG designed the study and did the literature search, data collection, data interpretation, and writing. RP did the data collection and data analysis. EN and BT did the literature search and provided writing assistance. LM did the literature search, study design, and data interpretation. GC did the data interpretation and writing. All authors approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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