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ORIGINAL ARTICLE

ASSESSMENT OF RISK OF ACUTE PANCREATITIS IN TYPE 2 DIABETES AND RISK REDUCTION ON ANTI-DIABETIC DRUGS: A COHORT STUDY

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ABSTRACT:
Background: Acute pancreatitis is an acute inflammatory disease of the Pancreas which is usually self-limited within few days but may turn out into severe and destructive, causing massive destruction followed by death. Several chronic diseases are associated with increased risk of development of acute pancreatitis. Whether Diabetes is associated with the risk of acute pancreatitis is unknown. Hence we assessed the risk of development of acute pancreatitis in type II diabetic patients. **Materials and Methods:** We conducted a population-based case control study in a cohort of 8000 type 2 diabetic patients and 2000 diabetes-free individuals from the general population as controls using data from community health care centres database. Follow-up of the subjects was done to ascertain incident cases of acute pancreatitis. **Results:** 55 cases of acute pancreatitis were identified 30 in the general population and 25 in the diabetes cohort. 30.9 And 53.9 per 100,000 person-years were the incident rate seen in the general population and the diabetes cohort, respectively. When compared with diabetes free individuals, patients with type 2 diabetes had a non significantly increased risk of acute pancreatitis. The risk of acute pancreatitis was observed to decrease among insulin treated diabetic patients. **Conclusion:** There might be slightly higher risk of acute pancreatitis associated with Type 2 diabetes. Insulin use in type 2 diabetes might also be associated with decreased risk.

Key Words: Acute pancreatitis, Diabetes, Risk

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INTRODUCTION

Acute inflammation of the pancreas is known as acute pancreatitis. Geographical variation is commonly seen regarding the incidence of acute pancreatitis in the general population Incidence rates reported in the literature range between 4 and up to 100 cases per 100,000 person-years in the western world.[1-3] Literature quotes an increase in acute pancreatitis's incidence over past few decades.[2]

Although the reason for this increase is unknown, a concurrent trend has been the rapid, worldwide increase in type 2 diabetes and obesity. Risk factors for acute pancreatitis also include type 2 diabetes and obesity. Therefore, it can be assumed type 2 diabetic patients might be at higher risk than general population for developing acute pancreatitis.[3] Literature quotes studies suggesting association of glucose-lowering therapies with increased or reduced risks of cancer. Although previous research studies have revealed the linkages between DM and colorectal, liver and pancreatic cancers, the associations between DM and other types of gastrointestinal (GI) cancers have not been well studied and the evidence is inconclusive.[4] Therefore we conducted this cohort study to evaluate the risk of acute pancreatitis in association with type 2 diabetic patients and antidiabetic treatment.

MATERIALS AND METHODS

We conducted this population-based cohort study with a nested case-control analysis which was based on information Community Health centre (CHC) in India. Information of patients with age between 25 to 75 years in CHC was included in the study. Only those patients were included in the study for which data information for 2 years or more was available. The period of study was between from January 2005 to December 2014. Individuals with history of any form of malignancy were excluded from the study. Two cohorts were identified within this population group: the type 2 diabetes cohort and the (diabetes-free) general population cohort. A total of 9000 patients were classified into type I diabetic and type II

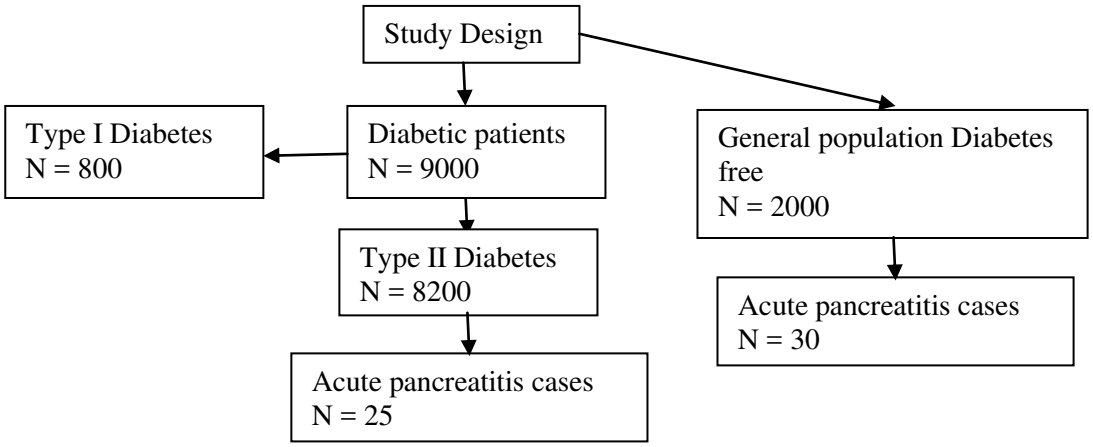
diabetic bases on type specific READ codes (i.e., those that denote explicitly the type of diabetes), the age at diagnosis, and the lifetime history of antidiabetic pharmacological treatment. 8200 patients were type II diabetic and 800 patients were type I diabetic. The earlier one comprised the type 2 diabetes cohort (Figure 1). 2000 individuals were selected randomly as control to the diabetic cohort. The same eligibility criteria as for the diabetes cohort were applied with the additional condition that patients had to be free of a recorded diagnosis of diabetes. Potentially pancreatitis candidates were identified by reviewing the computerized patient profiles with free text comments of all individuals. Manual reviewing of all the potential cases was done and cases which were not confirmed were excluded from the study. Classification of the person-time at the risk in each cohort study was done according to age, sex, and calendar year. Age and sex-specific incidence rates of acute pancreatitis were calculated using the corresponding person-time at risk in each cohort as denominator. Crude and adjusted incidence rate ratios (IRRs) with 95% CIs associated with diabetes were computed using a Poisson regression model with age, sex, and calendar year included in the model. Nested case-control analysis was performed additionally to evaluate in more detail the role of diabetes and of antidiabetic drugs on the risk of acute pancreatitis. For the study, it was ascertained exposure to antidiabetic drugs using separate exposure variables for insulin, metformin, sulfonylureas, thiazolidinediones, and other antidiabetic drugs (i.e., acarbose, repaglinide, and nateglinide) and other common drugs or drug classes including antibiotics, antidepressants, corticosteroids, acid-suppressing drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), antihypertensive agents, lipid-lowering drugs, and hormone replacement therapy. Individuals were classified as current user and past users depending upon the current status of taking drug. Remaining was classified as non users. Everyone else was classified as nonuser. We also tried to evaluate the drug duration effect on the risk of acute pancreatitis. We also explored the effect of drug duration (<1 year, 1-3 years and > 3 years) on the risk of acute pancreatitis. Unconditional regression analyses were used to assess odds ratios (ORs) together with 95% CIs. The fully adjusted model included the matching variables age and sex and the following predictors of acute pancreatitis: smoking status, alcohol intake, ischemic heart disease, previous gastrointestinal disease, exposure to antidiabetic drugs, antibiotics, acid suppressing drugs, NSAIDs and antihypertensive drugs, BMI, and Townsend deprivation index. All the data were analysed by SPSS software.

RESULTS

Cohort analysis

We included 8200 patients with type 2 diabetes for the cohort analyses along with the 2000 frequency-matched general population of individuals. 1840 person-years was the total amount of follow- up time in the type 2 diabetes and 808 person-years in the general population cohort. 55 potential cases of acute pancreatitis, 30 in the general population and 25 in the diabetes cohort were identified in this cohort study. Because of the non-confirmation of information of 2 individuals, confirmation rate of 95.5% in the validation study.

Figure 1: Study cohorts and acute pancreatitis assessment



The corresponding crude incidence rate of acute pancreatitis was 30.9 per 100,000 person- years in the general population and 53.9 per 100,000 person-years in the diabetes cohort. Incidence rates stratified by age and sex for the diabetic and the general population cohort are presented in Table 1. In the overall cohort study, increasing age was associated with a higher risk of acute pancreatitis. Compared with those aged < 40 years, the risk of acute pancreatitis was increased in those aged 40–59, 60–69, and ≥70 years by 17, 20, and 50%, respectively (P_{trend} = 0.02). While exploring the potential effect f the association between diabetes and acute pancreatitis by age, we found significant trend toward regressing association between diabetes and acute pancreatitis with increasing age.

Nested case-control analysis

When compared with diabetes free individuals, patients with type 2 diabetes had a nonsignificantly increased risk of acute pancreatitis. While separately analyzing the risk associated with incident diabetes and prevalent diabetes, the adjusted ORs were virtually the same. Furthermore, to explore the possibility of an increased risk of acute pancreatitis around the time of the first diagnosis of diabetes, we further divided our cohort of incident diabetic patients according to the time elapsed since the first diagnosis of diabetes. During the 1st year after the diagnosis of diabetes, the risk was somewhat higher than thereafter. The difference was statistically non-significant. Among the patients who were on diabetic therapy, insulin users were at a decreased risk of acute pancreatitis compared with nonusers. Antidiabetic drugs were not found to be associated with the risk of acute pancreatitis (Table 2). Metformin and sulfonylureas, were associated with decreased and increased risks, respectively, but only among long-term users of these drugs.

Table 1: Incidence rate of acute pancreatitis by age and sex in the general population without diabetes and in type 2 diabetic patients (cohort analysis)

Variable	Age strata	Person-years	Cases	Incidence rate per 100000 person-years (95%)
General population (n=2000)				
Women	**20-39 years**	25	1	18.6
	40-59 years	120	4	21.8
	60-69 years	110	4	24.4
	70-79 years	118	3	33.2
	Overall	363	12	25.8
Men	**20-39 years**	25	2	19.2
	40-59 years	150	5	28.2
	60-69 years	140	5	27.6
	70-79 years	130	6	44.5
	Overall	445	18	31.5
	TOTAL	808	30	30.9
Type II Diabetes (n=8200)				
Women	**20-39 years**	50	1	76.2
	40-59 years	400	3	50.6
	60-69 years	450	3	58.4
	70-79 years	510	3	42.8
	Overall	1860	10	51.5
Men	**20-39 years**	40	2	42.8
	40-59 years	600	4	58.2
	60-69 years	650	4	50.6
	70-79 years	550	5	58.2
	Overall	1840	15	54.7
Total		3700	25	53.9

Table 2: Risk of acute pancreatitis and duration of current use of antidiabetic drugs (nested case-control analysis)

Drug	Variable	Case subjects (n=45)	Control subjects (n=500)	OR (95% CI)
Insulin				
	Non-use	37	460	1 (Referent)
	Short duration (< 1 year)	3	10	.39
	Mid duration (< 1 year)	2	10	.33
	Long duration (< 1 year)	3	20	.30
Metformin				
	Non-use	32	430	1 (Referent)
	Short duration (< 1 year)	8	20	.80
	Mid duration (< 1 year)	3	25	.95
	Long duration (< 1 year)	2	25	.52
Sulfonylureas				
	Non-use	30	435	1 (Referent)
	Short duration (< 1 year)	7	25	.79
	Mid duration (< 1 year)	5	20	.88
	Long duration (< 1 year)	3	20	.45
Thiazolidinediones				
	Non-use	39	480	1 (Referent)
	Short duration (< 1 year)	1	8	1.25
	Mid duration (< 1 year)	4	8	1.10
	Long duration (< 1 year)	1	4	1.35
Other antidiabetic drugs				
	Non-use	41	475	1 (Referent)
	Short duration (< 1 year)	3	15	1.35
	Mid duration (< 1 year)	3	8	1.01
	Long duration (< 1 year)	3	2	1.69

DISCUSSION

Acute pancreatitis (AP) refers to acute inflammation of the pancreas associated with a high morbidity and even the risk of mortality. No specific treatment exists for this disease till date. Since past 7 years, the association between AP and diabetes mellitus (DM) has been very well known.[5, 6] Since then, there have been a large number of studies linking DM with AP, either as a factor associated with poor outcome in patients with AP, or as an outcome of severe or repeated attacks of AP. Recently, however, four large epidemiological studies have shown a higher incidence of AP amongst patients with DM as compared to patients without DM. The mechanisms underlying have not been completely elucidated. Given the increased risk of morbidity and even mortality due to the co-existence of DM and AP, it is important to clarify the role played by DM in the development and/or progression of AP.[7, 8] This may potentially provide clues to developing preventative strategies in this group of patients. Patients with DM often have co-morbid factors such as obesity, hypertension, and hypertriglyceridaemia which are frequently treated with medications. Interestingly, obesity, hypertriglyceridemia, as well as, anti-hypertensives have also been reported to be associated

with AP. All these hypothesis and results directs the knowledge towards the question that whether having DM actually poses an additional independent risk of developing AP.[9] Therefore, we analysed the risk factor for acute pancreatitis in patients with type II DM. We observed a higher risk of acute pancreatitis in type II DM patients when compared to normal control group (Table 1). Our results were in correlation with the results of Lai et al who found elevated risk of acute pancreatitis in patients with type 2 DM. They concluded that patients with type 2 DM are at an elevated risk of subsequent acute pancreatitis, and the risk is relatively greater among young patients. They hypothesized that patients infected with hepatitis C and those who suffer from alcoholism may be at an additional risk. Assessing the results, they also concluded that use of anti-diabetic drugs has been found to be effective in reducing the risk of acute pancreatitis among type 2 DM patients, particularly those taking metformin, sulfonylureas, thiazolidinediones, or alpha-glucosidase inhibitors.[10] Same results are also observed in previous studies highlighting the excessive risk of acute pancreatitis associated with type 2 diabetes.[11, 12] We observed an increased risk of acute pancreatitis and type 2 diabetes seems more pronounced at younger ages and has already been seen in a recent retrospective cohort analysis based on information from a U.S, health claims database.[13] on analysing the effect of anti-diabetic therapy, we observed that the use of insulin and long-term use of metformin were associated with a decreased risk of pancreatitis, as opposed to long-term use of sulfonylureas, which seems to increase the risk (Table 2). Our results were in correlation with the results of Blomgren et al who observed that the sulfonylureas increases the risk of acute pancreatitis.[11] Some of the studies in the past highlight development of acute pancreatitis in patients using metformin after an episode of acute renal failure.[14] Chiu et al analysed population of Taiwan to explore the relationship between DM and cancer of the digestive organs. They conducted a study cohort consisting of 39,515 patients with newly diagnosed diabetes without a previous diagnosis of gastrointestinal (GI) cancer from the National Health Insurance Research Database in Taiwan and concluded that Patients with DM have an increased risk of GI malignancy that may be affected by the use of different categories of glucose-lowering therapies.[15] While interpreting the results of such population based cohort studies, one should avoid assessing the subanalyses that do not belong to the main purpose of the study.

CONCLUSION

Under the light of above results, we conclude that type II diabetes is associated with increased of developing acute pancreatitis. Also, use of insulin might be associated with a reduced risk. Further research is recommended with higher study group and more parameters to evaluate the association of systemic diseases with acute inflammatory conditions of digestive track.

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