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Original Article

Chronic osteomyelitis correlates with increased risk of acute pancreatitis in a case–control study in Taiwan

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ABSTRACT

Objectives: The objective of this study was to examine the relationship between chronic osteomyelitis and acute pancreatitis in Taiwan.
Methods: This was a population-based case–control study utilizing the database of the Taiwan National Health Insurance Program. We identified 7678 cases aged 20–84 with newly diagnosed acute pancreatitis during the period of 1998 to 2011. From the same database, 30,712 subjects without diagnosis of acute pancreatitis were selected as controls. The cases and controls were matched with sex, age and index year of diagnosing acute pancreatitis. The odds ratio with 95% confidence interval of acute pancreatitis associated with chronic osteomyelitis was examined by the multivariable unconditional logistic regression analysis.
Results: After adjustment for multiple confounders, the multivariable analysis showed that the adjusted odds ratio of acute pancreatitis was 1.93 for subjects with chronic osteomyelitis (95% confidence interval 1.01, 3.69), when compared with subjects without chronic osteomyelitis.
Conclusions: Chronic osteomyelitis correlates with increased risk of acute pancreatitis. Patients with chronic osteomyelitis should be carefully monitored about the risk of acute pancreatitis.

1. Introduction

Acute pancreatitis is an acute inflammatory condition of the pancreas with variable clinical course that may range from mild, self-limiting to severe and life-threatening [1]. Extensive evidence has revealed that many etiologic factors, including alcoholism, biliary stone, cardiovascular disease, diabetes mellitus, viral hepatitis and hypertriglyceridemia, are associated with acute pancreatitis [2–6], but chronic osteomyelitis is not yet studied.

Chronic osteomyelitis is a chronically recurrent inflammatory condition of the bone which is mainly caused by bacteria [7,8]. Chronic osteomyelitis is extremely difficult to treat because it has a high rate of relapse or therapeutic failure even after long-term antibiotic therapy and surgical debridement [8,9]. Its long-term recurrence rate is about 20% to 30% [8,10]. In addition to impact on the bone and bone marrow, there is growing body of evidence that chronic osteomyelitis is associated with other diseases, including diabetes mellitus, deep-vein thrombosis, coronary heart disease, epilepsy, depression and dementia [11–16], but acute pancreatitis is not yet studied.

Given that chronic osteomyelitis and acute pancreatitis are both inflammatory conditions, we make a rational hypothesis that bacterial surface antigens not only attack the bone, but also might attack the pancreas. Acute pancreatitis then develops. Therefore, we think that there could be an association between chronic osteomyelitis and acute pancreatitis. From a view of clinical and public health implications, if an association substantially exists, patients with chronic osteomyelitis can be carefully monitored about the risk of acute pancreatitis. Since there is a lack of formal epidemiological study about this issue, we

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therefore examine the relationship between chronic osteomyelitis and acute pancreatitis in a case–control study utilizing the database of the Taiwan National Health Insurance Program.

2. Methods

2.1. Study design and study population

This was a population-based case–control study using the database of the Taiwan National Health Insurance Program. In a brief, this insurance program began in March 1, 1995, which has included about 99% of 23 million citizens living in Taiwan [17]. The details of the program have been well recorded in previous high-quality studies [18,19]. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMU-REC-101-012).

2.2. Participant selection

Based on diagnostic codes of the International Classification of Diseases (ICD) 9th Revision, we selected subjects with newly diagnosed acute pancreatitis as cases during the period of 1998 to 2011 (ICD-9 code 577.0), who were aged 20–84 years at the date of diagnosing acute pancreatitis. The index date for each case was defined as the date of diagnosing acute pancreatitis. For each acute pancreatitis case, we randomly selected 4 subjects without acute pancreatitis as controls from the same database, frequency matched with sex, age (per 5 years) and the index year of diagnosing acute pancreatitis. Subjects with prior history of acute osteomyelitis (ICD-9 code 730.0), chronic pancreatitis (ICD-9 code 577.1) or pancreatic cancer (ICD-9 code 157) before the date of diagnosing acute pancreatitis were excluded from this study.

2.3. Potential confounders

Comorbidities before the date of diagnosing acute pancreatitis were included as follows: chronic osteomyelitis (ICD-9 code 730.1), alcohol-related disease (ICD-9 codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3 and V11.3), biliary stone (ICD-9 code 574), cardiovascular disease including coronary artery disease, heart failure, cerebrovascular disease and peripheral atherosclerosis (ICD-9 codes 410–414, 428, 430–438 and 440–448), chronic kidney disease (ICD-9 codes 585–586 and 588.8–588.9), chronic obstructive pulmonary disease (ICD-9 codes 491, 492, 493 and 496), diabetes mellitus (ICD-9 code 250), hepatitis B (ICD-9 codes V02.61, 070.20, 070.22, 070.30 and 070.32), hepatitis C (ICD-9 codes V02.62, 070.41, 070.44, 070.51 and 070.54), hyperparathyroidism (ICD-9 code 252.0) and hypertriglyceridemia (ICD-9 codes 272.1, 272.2 and 272.4). According to ICD-9 codes, the diagnosis accuracy of these comorbidities has been recorded in previous studies [4,19,20].

2.4. Statistical analysis

We used the Chi-square test and the *t* test to compare the differences for distribution of demographic information and comorbidities between the case group and the control group. Only factors found to be significant in the univariable unconditional logistic regression model were further included in the multivariable unconditional logistic regression model to estimate the odds ratio (OR) and 95% confidence interval (CI) for acute pancreatitis associated with chronic osteomyelitis and other comorbidities. The probability value < 0.05 was considered statistically significant (SAS software version 9.1, SAS Institute Inc., Cary, North Carolina, USA).

Table 1
Descriptive characteristics of cases with acute pancreatitis and controls.

	Controls N = 30,712		Cases N = 7678		
Variable	n	(%)	n	(%)	*P* value*
Sex					0.99
Female	10,236	33.3	2559	33.3	
Male	20,476	66.7	5119	66.7	
Age group (years)					0.99
20–39	9418	30.7	2354	30.7	
40–64	14,590	47.5	3648	47.5	
65–84	6704	21.8	1676	21.8	
Age (year), mean (SD) †	50.0	16.0	50.4	15.8	0.05
Comorbidities before index date					
Chronic osteomyelitis	28	0.09	22	0.29	<0.001
Alcohol-related disease	95	0.31	340	4.43	<0.001
Biliary stone	584	1.90	1587	20.7	<0.001
Cardiovascular disease	5058	16.5	1949	25.4	<0.001
Chronic kidney disease	499	1.62	338	4.40	<0.001
Chronic obstructive pulmonary disease	3665	11.9	1219	15.9	<0.001
Diabetes mellitus	2897	9.43	1541	20.1	<0.001
Hepatitis B	550	1.79	318	4.14	<0.001
Hepatitis C	278	0.91	192	2.50	<0.001
Hyperparathyroidism	18	(0.06)	19	(0.25)	<0.001
Hypertriglyceridemia	1304	(4.25)	735	(9.57)	<0.001

Data are presented as the number of subjects in each group, with percentages given in parentheses.
*Chi-square test, and †*t* test comparing subjects with and without acute pancreatitis.

3. Results

3.1. Characteristics of the study population

There were 7678 subjects with acute pancreatitis as cases and 30,712 subjects without acute pancreatitis as controls. Cases and controls had similar distributions of sex and age. Table 1 shows that the case group had higher proportions of chronic osteomyelitis, alcohol-related disease, biliary stone, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hepatitis B, hepatitis C, hyperparathyroidism and hypertriglyceridemia than the control group ($P < 0.001$ for Chi-square test).

3.2. Association between acute pancreatitis and comorbidities

After adjustment for multiple confounders that were found to be significant in the univariable analysis, the multivariable analysis showed that the adjusted odds ratio of acute pancreatitis was 1.93 for subjects with chronic osteomyelitis (95% confidence interval 1.01, 3.69), when compared with subjects without chronic osteomyelitis (Table 2). In addition, alcohol-related disease, biliary stone, cardiovascular disease, chronic kidney disease, diabetes mellitus, hepatitis B, hepatitis C, hyperparathyroidism and hypertriglyceridemia were other factors significantly related to acute pancreatitis.

4. Discussion

In this population-based case–control study, we observed that patients with chronic osteomyelitis were associated with increased odds of acute pancreatitis, as compared with patients without chronic osteomyelitis (adjusted OR 1.93). In addition, alcohol-related disease and biliary stone seem to be significantly associated with acute pancreatitis (Table 2). In order to test whether the confounding effect of alcohol-related disease or biliary stone exists, we made a further analysis. When compared with patients without chronic osteomyelitis and without alcohol-related disease and biliary stone, the adjusted odds ratio of acute pancreatitis was 2.44 among those with chronic osteomyelitis and without alcohol-related disease and biliary stone (95% confidence interval 1.26, 4.73, table not shown). This indicates that the increased risk of acute pancreatitis associated with chronic