Impaired glucose tolerance in acute pancreatitis

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Abstract

Acute pancreatitis (AP) is an acute inflammatory disease of the exocrine pancreas. In spite of the pivotal role of the endocrine pancreas in glucose metabolism, the impact of impaired glucose tolerance on AP has not been fully elucidated. A meta-analysis of seven observational studies showed that type 2 diabetes mellitus (DM) was associated with an increased risk of AP. The increased risk of AP shown in the meta-analysis was independent of hyperlipidemia, alcohol use and gallstones. Anti-diabetic drugs including incretins might increase the risk of AP, but no intervention trials have confirmed this. Although a controversial finding, DM seems to be associated with severe attacks and organ failure in AP. We analyzed the results of a nationwide epidemiological survey of AP in Japan. We studied the impact of pre-existing DM on the clinical course of AP in 1954 cases for which information on DM status was available at the onset of AP. The prevalence of DM in AP patients (12.8%) was higher than that in the general population in Japan (10.5%). AP patients with DM had higher morbidity of cardiovascular and renal failure than those without DM. About 35% of the idiopathic AP patients with DM had renal failure. The mortality of AP patients with DM (4.0%) was higher than that of AP patients without DM (1.7%). If stratified by etiology, idiopathic, but not alcoholic or biliary, AP patients with DM were predisposed to increased mortality (9.7%). In conclusion, impaired glucose tolerance might have an impact on the development and clinical outcome of AP. However, the impact might depend on the cause of hyperglycemia, the condition of DM including severity, duration and treatment, and the characteristics of the AP patients including age, etiology and comorbidity.

Key words: Alcohol; Diabetes mellitus; Epidemiology; Gallstone; Mortality; Organ failure

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Core tip: We analyzed the results of a nationwide epidemiological survey of acute pancreatitis (AP) in Japan to clarify the impact of pre-existing diabetes mellitus (DM) on the clinical course of AP. AP patients with DM had higher mortality and morbidity of cardiovascular and renal failure than those without DM. About 35% of the idiopathic AP patients with DM had renal failure. If stratified by etiology, idiopathic, but not alcoholic or biliary, AP patients with DM had higher mortality than those without DM. Impaired glucose tolerance might have an impact on the development and clinical outcome of AP.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas characterized by a sudden onset of upper abdominal pain, nausea, emesis, and an increase of pancreatic digestive enzymes in the serum and urine[1,2]. Most patients with AP have a mild disease that only affects the pancreas and resolves spontaneously. However, 10%-20% of the patients develop necrosis of the pancreas and multiple organ failure, which may eventually lead to death[1,2]. In Japan, the overall mortality of AP was found to be 2.6% and in severe AP, 10.1%[3]. Various factors such as gallstones, alcohol, comorbidity and age affect the development and the clinical condition of AP[1-4]. Diabetes mellitus (DM), a metabolic disease with a globally increasing prevalence, has an impact on various diseases including cardiovascular diseases[5], cancer[6] and sepsis[7]. In spite of the pivotal role of the endocrine pancreas in glucose metabolism, the impact of impaired glucose tolerance on AP remains to be fully elucidated. In this editorial, we review the association of DM with AP. In addition, we analyzed the results of a nationwide survey of AP in Japan to clarify the susceptibility of diabetic patients to AP and the impact of impaired glucose tolerance on the clinical outcome of AP.

PRE-EXISTING DM AND RISK OF DEVELOPING AP

Epidemiological evidence suggests that individuals with type 2 DM have an increased risk of AP. Noel et al[8] evaluated the risk of AP in patients with type 2 DM in a United States insurance claims database and found that the risk of AP was 2.83 times higher in the overall diabetic cohort than in the non-diabetic cohort, and five times higher in the youngest diabetic cohort (under the age of 45) than in the age-matched non-diabetic cohort. In the United Kingdom, patients with type 2 DM had a 1.49-fold higher risk of AP than those without diabetes[9]. In Taiwan, Lai et al[10] reported that patients with type 2 DM had 1.95-fold greater incidence of AP compared with non-diabetics (27.7 vs 14.2 per 10000 person-years). In agreement with the result of Noel et al[9], the age-specific risk was highest in type 2 DM subjects aged 20-39 years, followed by aged 40-64 years, and aged 65 years and older, compared with the non-diabetic age-matched group[10]. A meta-analysis of seven observational studies including these three studies[8-14] showed that type 2 DM was associated with an increased risk of AP [relative risk = 1.92; 95% confidence interval (CI): 1.50-2.47][15].

Although DM may play a causative role in AP, the underlying mechanisms remain largely unknown. Solanki et al[16] conducted a systematic search of the scientific literature for the years 1965-2011 exploring the mechanisms of pathogenesis of AP in patients with DM. They found that no clinical studies could be identified which directly provide pathogenetic mechanisms of DM in the causation of AP. The available data on DM and its associated metabolic changes and therapy indicate that hyperglycemia coupled with the factors influencing insulin resistance (tumor necrosis-α, nuclear factor-κB, and amylin) cause an increase in the generation of reactive oxygen species in pancreatic acinar cells[16]. On the other hand, the susceptibility of DM to AP might result from confounding factors because the risk factors for AP such as alcohol consumption, gallstones, obesity, hypertriglyceridemia and chronic pancreatitis are also complications and risk factors for DM[17-19]. A history of DM might represent both an underlying pathogenetic mechanism and a potential confounding factor for the development of AP. However, the increased risk of AP shown in the meta-analysis was independent of hyperlipidemia, alcohol use and gallstones[13].

ANTI-DIABETIC DRUGS AND RISK OF AP

It has been of debate whether anti-diabetic drugs increase the risk of AP. Among the biguanides, both phenformin and metformin, the latter in patients with renal insufficiency, have been reported in case reports as a potential cause of AP[20,21]. Sulphonylureas have also been found in cohort studies to increase the AP risk. Gonzalez-Perez[14] reported that past use of sulphonylureas was associated with an increased risk of AP compared with that of non-users (OR = 2.58, 95%CI: 1.34-4.96). Conversely, Lai et al[10] reported that patients taking anti-diabetic drugs had a reduced risk of AP. The hazard ratios (HRs) of developing AP ranged from 0.44 to 0.63 (all P < 0.05) for subjects taking α-glucosidase inhibitors, metformin, sulfonylureas, or thiazolidinediones, after controlling for sex, age and comorbidities. The beneficial effect of insulin was likely,
but not statistically significant (HR = 0.81, 95%CI: 0.64-1.02). Interestingly, the beneficial effects were increased as the number of drugs taken increased. From an adjusted HR of 0.7 for patients who had used two medications, the adjusted HR was reduced to 0.31 (95%CI: 0.18-0.56) in patients taking five anti-diabetic drugs. There was a significant dose-response effect of the duration of taking anti-diabetic drugs on reducing the risk of AP\(^{[10]}\). The HR decreased to 0.14 among patients taking metformin, and to 0.13 among those taking sulfonylureas, when the treatment was longer than 3 years. The beneficial effect was also observed among those using insulin for more than a year.

Several case reports and the United States Food and Drug Administration pharmacovigilance database indicate an association between AP and incretin-based agents: dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists (reviewed in\(^{[23]}\)). In the drug development program and clinical trials of both incretin classes, the incidence of AP was similar to placebo-treated cohorts, and a meta-analysis confirmed this result\(^{[23]}\). In addition, none of the intervention trials investigating these compounds, including two large randomized controlled trials with cardiovascular endpoints, confirmed the increased risk of AP with incretin use. In the EXAMINE trial, the incidence of AP was 0.4% in the alogliptin group and 0.3% in the placebo group\(^{[24]}\). In the SAVOR-TIMI53 trial, cases of definite AP were confirmed in 17 (0.2%) vs 9 (0.1%) (HR = 1.88, 95%CI: 0.86-4.41, \(P = 0.17\)) and definite plus possible pancreatitis in 22 vs 16 (HR = 1.36, 95%CI: 0.72-2.64, \(P = 0.42\)) in the saxagliptin and placebo arms, respectively\(^{[25]}\). No differences in time to event onset, concomitant risk factors for pancreatitis, investigator-reported causality from study medication or disease severity, and outcome were found between treatment arms. Further understanding of the association between anti-diabetic drugs and AP may provide clues to developing preventive strategies in patients with DM.

**IMPACT OF IMPAIRED GLUCOSE TOLERANCE ON THE CLINICAL COURSE OF AP**

Some studies have shown that AP patients with diabetes had a lower risk of hospital mortality, but with conflicting results. The University HealthSystem Consortium database and the prospective Mayo Clinic database showed that diabetic patients discharged with a diagnosis of AP experienced a significantly decreased mortality (Table 1)\(^{[26]}\). A retrospective cohort study in Taiwan also showed that AP patients with DM had a lower risk of hospital mortality (adjusted OR = 0.77, 95%CI: 0.65-0.91)\(^{[27]}\). It is not clear why diabetes may have such an intriguingly protective effect on the mortality in AP patients. A survival advantage of DM has been reported in patients with other critical illnesses\(^{[28]}\) such as pneumonia, congestive heart failure\(^{[26]}\), and sepsis\(^{[29]}\). The proposed biological mechanisms that favor diabetes during critical illnesses include the anti-inflammatory effect of some antidiabetic agents such as insulin\(^{[29]}\) and thiazolidinediones\(^{[31]}\), and the preventive effects against acute lung injury\(^{[29,32]}\). Furthermore, nonbiological mechanisms such as an improvement of lifestyle before the onset of AP and vigilant treatments after admission for patients with DM could explain, at least in part, the finding of decreased mortality in patients with DM.

In contrast, several studies have shown that AP patients with DM might have more severe courses and poor outcomes. Frey et al\(^{[4]}\) reported that DM increased the risk of multi-organ failure (≥ 2 systems) (OR = 1.6, 95%CI: 1.4-1.8). AP patients with a previous history of DM or with glycosylated hemoglobin A1c higher than 6.5% had a higher mortality than those without DM\(^{[33]}\). Shen et al\(^{[27]}\) retrospectively compared 18990 first-attack AP patients with DM to 37980 matched control subjects from Taiwan’s National Health Insurance Research Database between 2000 and 2009. They showed that AP patients with DM had a higher risk of severe attack than their non-diabetic counterparts (adjusted OR = 1.21, 95%CI: 1.16-1.26). When severity criteria, defined by the modified Atlanta classification, were individually analyzed, diabetic AP patients had a 58% higher risk of intensive care unit admittance and more life-supporting treatments, especially hemodialysis and mechanical ventilation, than non-diabetic AP patients\(^{[27]}\). Diabetic AP patients had a 30% higher risk of local complications than AP patients without diabetes. Zhao et al\(^{[33]}\) reported that AP patients with DM had a longer length of hospitalization than those without DM (18.3 ± 4.6 d vs

| Ref.          | Country       | Diagnosis of DM          | Prevalence of DM | Mortality of AP with DM | Mortality of AP without DM | Mortality of AP with DM compared to AP without DM |
|--------------|--------------|--------------------------|------------------|-------------------------|---------------------------|-----------------------------------------------|
| Graham et al\(^{[24]}\), (2010) | United States | Two patients databases   | Undescribed      | Undescribed             | 4.5%                       | Lower                                         |
| Shen et al\(^{[33]}\), (2012)    | Taiwan       | The Taiwan National Insurance Research Database | Case-control study | 15.0%                   | 4.1%                       | Lower                                         |
| Zhao et al\(^{[20]}\), (2012)    | China        | History or HbA1c         | 12.6% (40/318)   | 4.0%                    | 1.7%                       | Higher                                        |
| Kikuta et al, (present study)    | Japan        | Questionnaire            | 12.8% (250/1954) | Lower                   | Lower                      |                                               |

AP: Acute pancreatitis; DM: Diabetes mellitus.
of the Pancreas, targeting AP patients treated in 2007 in Japan. The details of the survey were published elsewhere[38]. Briefly, a first survey was performed by sending a questionnaire to randomly selected 3027 departments to determine the number of hospitalized patients with AP during 2007. A second survey was conducted by sending a questionnaire to 693 departments in which hospitalized patients with AP were treated based on the first questionnaire. This study was approved by the Ethics Committee of Tohoku University School of Medicine (article No. 2008-327, 2014-220). We studied the impact of DM on the clinical outcome of AP using 1954 cases for which information on DM status was available at the onset of AP. DM was diagnosed by respondents to the questionnaire, based on clinical information such as history, hemoglobin A1c and blood sugar level. The clinico-epidemiological information on individual patients including patient profile, etiology, symptoms, blood biochemical findings, computed tomography (CT) findings, and prognosis was collected from medical records of patients. The characteristics of the study population are shown in Table 2.

Respiratory failure was defined as necessity of ventilatory support. Cardiovascular failure was defined as systolic blood pressure ≤ 80 mmHg or symptoms of shock. Renal failure was defined as blood urea nitrogen ≥ 40 mg/dL or serum creatinine ≥ 2.0 mg/dL. Three organ failures were evaluated daily until 72 h after AP onset.

CT findings within 48 h of onset were graded based on the severity scoring system of AP proposed by the Japanese Ministry of Health, Labour and Welfare[39]. Extrapancreatic inflammation was graded into four categories: none, anterior pararenal space, root of mesocolon, and beyond lower pole of kidney. The pancreas was conveniently divided into three segments (head, body, and tail), and hypoenhanced lesion of the pancreas by contrast-enhanced CT was also graded into four categories: none, localized in each segment, extends to 2 segments, and occupies 2

Table 2  Characteristics of the study population n (%)  

|               | Total AP patients | AP patients with DM | AP patients without DM | P value |
|---------------|-------------------|---------------------|------------------------|---------|
| Patients, n   | 1954              | 250                 | 1704                   |         |
| Sex           |                   |                     |                        |         |
| Male          | 1289 (66.0)       | 185 (74.0)          | 1104 (64.8)            | 0.004   |
| Female        | 665 (34.0)        | 65 (26.0)           | 600 (35.2)             |         |
| Age, yr, mean ± SD | 59.3 ± 18.0     | 60.3 ± 16.6        | 59.1 ± 18.2            | 0.319   |
| Etiology      |                   |                     |                        |         |
| Alcoholic     | 621 (31.8)        | 97 (38.8)           | 524 (30.8)             | 0.107   |
| Biliary       | 482 (24.7)        | 52 (20.8)           | 430 (25.2)             |         |
| Idiopathic    | 319 (16.3)        | 34 (13.6)           | 285 (16.7)             |         |
| Miscellaneous | 482 (24.7)        | 60 (24.0)           | 422 (24.8)             |         |
| Undescribed   | 50 (2.6)          | 7 (2.8)             | 43 (2.5)               |         |
| BMI, mean ± SD| 22.5 ± 4.0        | 23.5 ± 4.2          | 22.3 ± 4.0             | < 0.001 |
| Triglyceride, mg/dL, median (1, 3rd quartile) | 97 (64, 170.5)  | 137 (79.5, 526)   | 94 (60, 157.75)        | 0.004   |

AP: Acute pancreatitis; DM: Diabetes mellitus.

13.2 ± 5.1 d).

TRANSIENT HYPERGLYCEMIA IN THE EARLY COURSE OF AP

Hyperglycemia is the common early feature of AP and is used in prognostic models[34,35]. The association between hyperglycemia and poor clinical outcomes in critically ill patients has been demonstrated in a number of observational studies[28,36], but the adverse effect of hyperglycemia may be complicated by pre-existing diabetes. Egi et al[28] showed that hyperglycemia while staying in an intensive care unit was strongly associated with the outcome in patients without pre-existing DM but showed no significant association with the outcome in patients with pre-existing DM. This finding suggests that acute and chronic impaired glucose tolerance may be distinct pathophysiological entities and may have different clinical consequences. Hence, hyperglycemia in the early phase of AP seems to be complicated and may arise from mechanisms such as uncontrolled pre-existing DM, damage to the endocrine pancreas due to severe attack of AP, and metabolic stress associated with critical illness[37].

THE IMPACT OF DM ON CLINICAL COURSE OF AP BASED ON THE NATIONWIDE SURVEY IN JAPAN

As described above, the impact of impaired glucose tolerance in AP seems to be complicated. To clarify this issue, we examined the impact of DM on the clinical course of AP using the results of the nationwide epidemiological survey of AP in Japan.

Methods

A nationwide epidemiological survey was conducted by the Research Committee of Intractable Diseases of the Pancreas, targeting AP patients treated in 2007 in Japan. The details of the survey were published elsewhere[38]. Briefly, a first survey was performed by sending a questionnaire to randomly selected 3027 departments to determine the number of hospitalized patients with AP during 2007. A second survey was conducted by sending a questionnaire to 693 departments in which hospitalized patients with AP were treated based on the first questionnaire. This study was approved by the Ethics Committee of Tohoku University School of Medicine (article No. 2008-327, 2014-220). We studied the impact of DM on the clinical outcome of AP using 1954 cases for which information on DM status was available at the onset of AP. DM was diagnosed by respondents to the questionnaire, based on clinical information such as history, hemoglobin A1c and blood sugar level. The clinico-epidemiological information on individual patients including patient profile, etiology, symptoms, blood biochemical findings, computed tomography (CT) findings, and prognosis was collected from medical records of patients. The characteristics of the study population are shown in Table 2.

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whole segments or more.

The number and percentage of patients were calculated and compared between groups by the chi-square test or a two-tailed Fisher's exact test (when at least one expected cell value in 2 × 2 table was less than 5). Risk factors for mortality of AP were assessed using logistic regression analysis. Stepwise logistic regression analysis with a variable entry criterion of P < 0.10, and a variable retention criterion of P < 0.05 was used to identify multivariable risk factors. Logistic regression results were summarized as the OR, 95%CI for OR, and P value. Data were analyzed using JMP7 software (SAS Institute, Inc., Cary, NC). All statistical tests were 2-sided and P < 0.05 was used to indicate statistical significance.

Prevalence of DM at the onset of AP

The prevalence of DM in AP patients (12.8%) was significantly higher than that in the general population in Japan (10.5%) (Table 3). If stratified by etiology, patients with alcoholic AP (15.6%) had a significantly higher prevalence of DM than the Japanese general population. The prevalence of DM in patients with biliary or idiopathic AP was not different from that in the Japanese general population. Of note, the prevalence of DM in AP patients under 60 years old was significantly higher than in the Japanese general population of the same generation.

Organ failure

The morbidity of organ failures diagnosed within 72 h of AP onset is summarized in Figure 1. In AP patients without pre-existing DM, the morbidity of cardiovascular, respiratory and renal failures was around 1%, 2% and 5%, respectively. AP patients with DM had higher morbidity of cardiovascular and renal failure than those without DM, although the morbidity of respiratory failure was not different between the patients with DM and those without DM. Interestingly, the morbidity of organ failure varied among etiologies in DM patients, but not in non-DM patients. About 35% of the idiopathic AP patients with DM had renal failure.

CT findings

CT findings within 48 h of AP onset are shown in Figure 2. CT findings did not differ between the patients with DM and those without DM. Even if stratified by etiology, pre-existing DM did not have an impact on CT findings (data not shown).

Mortality

Mortality was assessed excluding the patients whose outcome was unspecified and who died due to other causes than AP. The mortality of AP patients with DM (4.0%) was higher than that of AP patients without DM (1.7%) (Tables 1 and 4). In particular, AP patients with DM aged 70 or older manifested an increased mortality (9.5%). If stratified by etiology, idiopathic AP patients with DM were predisposed to increased mortality (9.7%). On the other hand, DM did not affect the mortality of alcoholic AP patients. In addition, sex, body mass index (BMI) and triglyceride level, in which there was a significant difference between the patients with DM and those without DM (Table 2), did not affect the mortality of the study population. The mortality of male and female AP patients was 1.8% (22/1197) and 2.3% (14/616) (P = 0.59), and that of AP patients with BMI ≥ 30 and < 30 was 0% (0/62) and 1.8% (25/1390) (P = 0.62), respectively. Stepwise

| Table 3  Prevalence of diabetes mellitus in patients with acute pancreatitis stratified by age |
| Age       | General population (MHLW 2007) | All AP patients | Alcoholic AP | Biliary AP | Idiopathic AP |
|-----------|-------------------------------|-----------------|--------------|------------|---------------|
| Total     | 10.5% (420/4003)              | 12.8% (250/1954) | 15.6% (97/621) | 10.8% (52/482) | 10.7% (34/319) |
| < 19      | Not available                 | 5.3% (1/19)     | 0% (0/1)     |             |               |
| 20-29     | 0.5% (1/204)                 | 9.3% (9/97)     | 11.9% (5/42) | 0% (0/4)    | 3.4% (1/29)   |
| 30-39     | 1.4% (8/589)                 | 12.0% (25/208)  | 13.0% (15/115) | 0% (0/18) | 13.8% (1/29)  |
| 40-49     | 4.7% (26/557)                | 12.8% (34/265)  | (21/164)     | (4/28)      | (4/24)        |
| 50-59     | 8.0% (57/711)                | 12.2% (41/336)  | (21/161)     | (5/64)      | (5/32)        |
| 60-69     | 17.7% (165/934)              | 14.8% (50/338)  | (19/84)      | (13/100)    | (7/52)        |
| > 70      | 16.2% (163/1008)             | 13.3% (87/652)  | 22.6% (16/75) | 11.2% (29/259) | 8.5% (12/141) |
| Uncertain age | No patients                 | 7.7% (3/39)     | 0% (0/9)     | 11.1% (1/9) | 0% (0/6)      |

The prevalence of DM in the Japanese general population in 2007 was cited from a report by the Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/bunya/kenkou/eiyou09/dl/01-kekka-01.pdf). *P < 0.05, *P < 0.01, *P < 0.005, *P < 0.001 vs the prevalence of DM in Japanese general population. AP: Acute pancreatitis; DM: Diabetes mellitus.
Figure 1  Morbidity of organ failure. The morbidity of cardiovascular failure (A), respiratory failure (B) and renal failure (C) was compared between the AP patients with or without DM (a $P < 0.05$, b $P < 0.01$ vs non-DM; Fisher’s exact test). AP: Acute pancreatitis; DM: Diabetes mellitus.

Figure 2  Comparison of the computed tomography findings between the acute pancreatitis patients with or without diabetes mellitus. A: Extra-pancreatic inflammation; B: Hypo-enhanced lesion of the pancreas. There were no significant differences in the distribution of the extra-pancreatic inflammation and hypo-enhanced lesions between non-DM and DM patients ($\chi^2$ test). DM: Diabetes mellitus.
logistic regression revealed that age and DM were independently associated with mortality of AP (Table 5). Of note, the impact of DM on the mortality of AP varies according to the etiology. Alcoholic AP with DM patients might have a concomitant disorder of the exocrine pancreas, which might result in lower mortality than idiopathic AP with DM. The impact of DM on the mortality of AP might depend on the characteristics of patients, which might partially account for the discrepancies in the impact of DM among previous reports.

It was of interest to see whether the type of anti-diabetic medicine, number of drugs and poor glycemic control status are associated with the course of AP. However, because such items were not included in the questionnaire of this nationwide survey, we could not analyze the data from these points of view. Further studies are required to clarify the effects of these factors on AP.

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