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Original Article

Diabetes mellitus as a risk factor for severity and mortality in acute pancreatitis

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Abstract

Diabetes mellitus is a lifestyle disease that is one of the most common co-morbidities among patients and can have a substantial impact on the course and case fatality rate of acute disease, including acute pancreatitis. Our primary aim in this study was to analyze the impact of diabetes mellitus type 2 on the severity of acute pancreatitis (AP) and on the hospital mortality of patients with AP. Our secondary aims were 1) to assess the impact of various types of chronic diabetes therapy on the morbidity and lethality of AP and 2) to assess the impacts of decompensation on admission in known diabetics and of acute stress hyperglycemia in non-diabetics on the morbidity and lethality of AP—prospective evaluation of observational data in 248 patients. The hospital mortality rate in patients with diabetes was 5 times higher (17.5% compared to 3.4%, p=0.0004), nd the incidence of persistent organ failure was 6 times higher (40% compared to 6.7%, p<0.0001). Patients without diabetes who had acute stress hyperglycemia >8 mmol/l on admission had a greater incidence of severe AP than those with normal glycemia levels (15.8% compared to 3.3%, p=0.0014). Diabetes mellitus type 2 is connected with a higher incidence of local complications, organ failure and overall hospital mortality rate in patients hospitalized with AP. In non-diabetic patients, acute stress hyperglycemia at the time of admission has a comparable negative impact on the course of AP.

Keywords: acute pancreatitis, diabetes mellitus type 2, organ failure, necrosis, hyperglycemia.

Introduction

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas with an annual incidence of between 5 and 80 cases per 100,000 population and varying severity (from a mild form to a severe, potentially fatal form with possible local or organ complications). In many countries, AP is one of the most frequent gastrointestinal causes of hospital admission. Gallstones and alcohol are the most common causes of AP worldwide; in 5–10% of cases, the etiology of the disease is idiopathic [1].

Population-based studies in recent years have revealed greater severity and mortality among diabetes patients with trauma, acute myocardial infarction, critical illness, cardiac surgery and sepsis worldwide [2].

Several studies have examined the impact of diabetes as a risk factor on outcomes (the severity and mortality of the disease) for patients with AP, but with discrepant results. Frey *et al*. published 2002 data from

84,713 patients with AP and reported an increased risk of multiorgan failure in AP patients with diabetes, but they did not detect a higher rate of early hospital mortality (i.e., within 14 days). Shen *et al*. compared 18,990 diabetic patients and 37,980 non-diabetic patients with AP from Taiwan's National Health Insurance Research Database and reported that diabetic patients had a 30% higher risk of local complications and a higher risk of ICU admission (16.2%, compared with 10.7% in non-diabetic patients). The risk of organ failure was similar in both groups, and surprisingly, hospital mortality was lower in the diabetes group: 3.5% (665/18990) compared with 4.1% (1557/37980) [2, 3]. Huh *et al*., on the other hand, published 2018 data from 201 patients that revealed a higher mortality rate of 16.7% (9/54) in diabetic patients compared to 3.4% (5/147) in non-diabetic patients and higher incidence of a severe form of AP in type 2 diabetes mellitus patients [4]; their findings are in line with those from a study by Kikuta *et al*., who use data from 1954 AP cases in Japan to confirm a higher mortality rate of 4% (10/250) in diabetic patients compared to 1.7% (29/1704) in non-diabetic patients, and a higher incidence of organ failure in patients with diabetes [5].

Finally, Miko *et al*. published a 2018 meta-analysis of 9 studies involving 354,880 patients. Diabetic patients had higher rates of admission to intensive care units, renal failure, and local complications, and their mean duration of hospitalization was also longer [6].

Several studies have also shown that acute and chronic hyperglycemia at the time of admission has impacts on AP patient outcomes. Mentula *et al*., Siegelaar *et al*. and Sun *et al*. have all reported an association between hyperglycemia and an increased mortality rate and risk of organ failure in non-diabetic patients, implying that acute and chronic hyperglycemia may have different consequences [7–9].

Patients with type 2 diabetes mellitus are at higher risk of developing AP. In a 2009 retrospective cohort study, Noel *et al*. reported a 2.83-fold higher risk of AP and a 1.91-fold higher risk of biliary disease in the type 2 diabetic population than in the non-diabetic population [10]. The AP incidence rate among type 2 diabetic patients was 30.1 per 100,000 person-years, compared with a rate of 54.0 per 100,000 person-years in the general population in a population-based cohort study published by Gonzalez-Perez *et al*. [11].

The direct pathogenetic mechanism via which diabetes mellitus causes AP is unclear. The fact that diabetic patients have an increased rate of obesity, a higher risk of gallstones and take antidiabetic drugs may play a substantial role. The release rate of proinflammatory adipokine from peri-pancreatic fat may be higher in obese and diabetic patients with AP. The available data indicate that hyperglycemia coupled with factors influencing insulin resistance may cause an increase in reactive oxygen species generation in acinar cells [12–14].

Based on these data, we conducted a prospective study to analyze the impact of diabetes mellitus on AP patients' distinct clinical outcome characteristics.

The aims of our study were:

1. To assess the severity of the disease according to the modified Atlanta scale (local complications and organ failure) and the mortality of the disease;
2. To define what impact diabetes mellitus or acute hyperglycemia in non-diabetic patients has on the course of the disease;
3. To compare the course of AP in diabetes patients undergoing various types of diabetes treatment (diet, oral antidiabetics, insulin therapy).

Material and methods

Patients with AP admitted to the Department of Internal Medicine at the 1st Faculty of Medicine, Charles University and Military University Hospital in Prague between 01.01.2013 and 31.12.2020 were divided into a group of patients with type 2 diabetes (group A) and a group of patients without diabetes (group B). We subdivided group A into three sub-groups according to the type of diabetes treatment they were undergoing at the time of admission to the hospital with AP. We also subdivided groups A and B into subgroups of patients with hyperglycemia>8 mmol/l at the time of admission to the hospital and patients without hyperglycemia.

- A1 diabetics with hyperglycaemia >8 mmol/l (n=24);
- A2 diabetics without hyperglycemia (n=16);
- B1 non-diabetics with hyperglycaemia >8 mmol/l (n=57);
- B2 non-diabetics without hyperglycemia (n=151).

Diagnostic and therapeutic procedures were conducted in accordance with the valid professional recommendations of the American Gastroenterological Society [15]. For every participant in the study, a medical history was recorded at the time of their admission to the hospital. Observation of each patient was terminated at the time of their transfer or discharge from the hospital. We describe the disease course in each

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Table 1: Atlanta classification of acute pancreatitis, revision 2012.

Atlanta 2012	Mild form	Moderate form	Severe form
Organ failure	no	no or reversible <48 hours	yes, persistent >48 hours
Local Complications	no	yes	

patient as mild, moderate or severe according to the revised Atlanta scale, based on the presence or absence of local complications and organ failure, as shown in Table 1 [16].

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Each patient in the study provided writteninformed consent (approved by the Institutional Ethics Committee)

Statistical analysis

Comparisons of continuous variables were made using t-tests or Mann-Whitney tests as appropriate. Comparisons of categorical variables were performed using chi-square tests or Fischer tests as appropriate. In all cases, a p-value of less than 0.05 was considered significant. All computations were performed using STATISTICA 13.5 software.

Results

At the Department of Internal Medicine, 1st Faculty of Medicine, Charles University and Military University Hospital Prague, 248 patients (142 men and 106 women) with AP were hospitalized between 01.01.2013 and 31.12.2020. Forty of those patients had a history of diabetes mellitus type 2 (group A). Two hundred eight patients were non-diabetic (group B). Descriptive statistics of the sample are provided in Table 2.

Acute hyperglycemia>11 mmol/l was detected on admission in 6 of the 208 patients in group B. New onset of type 2 diabetes was diagnosed in all of these patients during their hospitalization.

Table 3 presents further patient outcome statistics.

In group B (208 patients), 76.4% (159/208) had a mild form of AP, 16.8% (35/208) had a moderate form and 6.7% (14/208) had a severe form. In group A (40 patients),

Table 2: Characteristics of patient groups and their AP courses.

	Total n (%)	Median age	Men	Women	Mild form n (%)	Moderate form n (%)	Severe form n (%)	Mortality n (%)	Duration of hospitalization in days
Group A DM type 2	40 (16.1)	66	26	14	16 (40)	8 (20)	16 (40)	7 (17.5)	16.7
Group B Non-DM patients	208 (83.8)	58	116	92	159 (76.4)	35 (16.8)	14 (6.7)	7 (3.4)	10.7

Table 3: Statistical analysis DM and Non-DM patients.

	Total n (%)	Mild form n (%)	Moderate form n (%)	Severe form n (%)	Mortality n (%)	Local complications n (%)	Organ failure <48 h n (%)	Organ failure >48 h n (%)
Group A DM type 2	40 (16.1)	16 (40)	8 (20)	16 (40)	7 (17.5)	14 (35)	5 (12.5)	16 (40)
Group B Non-DM	208 (83.9)	159 (76.4)	35 (16.8)	14 (6.73)	7 (3.4)	35 (16.8)	11 (5.3)	14 (6.7)
Groups A+B (whole sample)	248	175 (70.6)	43 (17.3)	30 (12.1)	14 (5.65)	49 (19.8)	16 (6.5)	30 (12.1)

40% (16/40) had a mild form of AP, 20% (8/40) had a moderate form, and 40% (16/40) had a severe form. While 76% of patients in group B had a mild form of the disease, the same was true for only 40% of those in group A (p<0.0001). The severe form of AP was much more prevalent in group A (40%, compared to 6.73% in group B, p<0.0001).

The overall mortality rate among all 248 AP patients was 5.7% (14/248). In group B, the mortality rate was 3.4% (7/208), while in group A, it was 17.5% (7/40). This difference is highly statistically significant (p=0.0004).

We registered local complications (necrosis or acute fluid collection) in 16.8% (35/208) of group B patients and 35% (14/40) of group A patients. This difference in the incidence of local complications is also statistically significant (p=0.0082).

In group B, 88% (183/208) of patients were without organ failure, 5.3% (11/208) with reversible organ failure and 6.7% (14/208) with organ failure persistent for more than 48 hours. In group A, 47.5% (19/40) of patients were without organ failure, 12.5% (5/40) with reversible organ failure and 40% (16/40) with persistent organ failure. In other words, the incidence of persistent (>48 hours) organ failure was 6 times higher in group A (40%, compared to 6.7% in group B, p<0.0001). The mean duration of hospitalization was 16.7 days in group A and 10.7 days in group B (p=0.0220).

Varying types of therapy for diabetes

In group A, consisting of patients with AP who had already been diagnosed with type 2 diabetes, we compared the type of therapy (diet, oral antidiabetics or insulin) the patients were undergoing for diabetes with their AP outcomes. The comparative statistics are presented in Table 4.

Of 16 diabetic patients on therapeutic diets, 7 (43.8%) had a mild form of AP, while 4 (25%) had a moderate form and 5 (31.3%) had a severe form. The mortality rate among these 16 patients was 12.5% (2/16).

Among the 19 patients on oral antidiabetics (PAD), 7 (36.8%) had a mild form of AP, 3 (15.8%) had a moderate form, and 9 (47.4%) had a severe form; the mortality rate in this group was 21% (4/19).

Only 5 of our patients with diabetes and AP were on insulin therapy. Of these, 3 (60%) had a mild form of AP, 1 (20%) had a moderate form, and 1 (20%) had a severe form. The mortality rate in this group was 20% (1/5).

These results from the group of patients with diabetes revealed a higher mortality rate and a higher incidence of severe AP in patients using oral antidiabetics than in patients whose diabetes was treated exclusively via their diet.

Glycemia level on admission in diabetic patients

We further distinguished patients in group A (with diabetes) according to their glycemia level on admission, observing potential correlations with the course of their AP disease. Patients with glycemia >8 mmol/l on admission form group A1, while those with glycemia<8 mmol/l on admission form group A2. The comparative statistics are presented in Table 5.

50% (8/16) of patients in group A2 had a mild form of AP, while 12.5% (2/16) had a moderate form, and 37.5% (6/16) had a severe form.

In group A1, 33.3% (8/24) of patients had a mild form of AP, 25% (6/24) had a moderate form, and 41.7% (10/24) had a severe form. The patients in group A2 (diabetic patients with normal glycemia on admission) had a higher incidence of mild AP than the patients in group A1 (p=0.2918), and the patients in group A1 (diabetic patients with hyperglycemia on admission) had a higher incidence of severe AP than the patients in group A2 (p=0.7921). The mortality rate was similar in both groups: 18.75% (3/16) in group A2 and 16.7% (4/24) in group A1.

Acute hyperglycemia on admission in non-diabetic patients

Similarly, we also distinguished between patients in group B (with no prior diabetes diagnosis) according to their glycemia level on admission, observing potential

Table 4: DM patients' AP outcomes by type of DM therapy.

	Total n (%)	Mild form n (%)	Moderate form n (%)	Severe form n (%)	Mortality n (%)
Diet	16 (40)	7 (43.8)	4 (25)	5 (31.3)	2 (12.5)
PAD	19 (47.5)	7 (36.8)	3 (15.8)	9 (47.4)	4 (21)
Insulin	5 (12.5)	3 (60)	1 (20)	1 (20)	1 (20)

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Table 5: DM patients' AP outcomes by glycemia level on admission.

	Total n (%)	Mild form n (%)	Moderate form n (%)	Severe form n (%)	Mortality n (%)
Group A1 Glc >8	24 (60)	8 (33.3)	6 (25)	10 (41.7)	4 (16.7)
Group A2 Glc <8	16 (40)	8 (50)	2 (12.5)	6 (37.5)	3 (18.8)
Groups A1+A2	40	16 (40)	8 (20)	16 (40)	7 (17.5)

correlations with the course of their AP disease. Out of the 208 patients in group B (non-diabetic patients), 151 patients had glycemia <8 mmol/l on admission (group B2), while 57 patients had glycemia >8 mmol/l on admission (group B1). The comparative statistics are presented in Table 6.

In group B2 (non-diabetic patients with normal glycemia), 81.5% (123/151) of patients had a mild form of AP, 15.2% (23/151) had a moderate form, and 3.3% (5/151) had a severe form.

In group B1 (non-diabetic patients with hyperglycemia on admission), 63.2% (36/57) of patients had a mild form of AP, 21.1% (12/57) had a moderate form, and 15.8% (9/57) had a severe form. In other words, based on our sample, The incidence of severe AP was 5 times higher for group B1 (15.8%, compared to 3.3% in group B2, p=0.0014). The mortality rate was also much higher in Group B1 (8.8% compared to 1.3% in Group B2 p=0.0079).

Local complications (necrosis or acute fluid collection) were identified in 12.6% (19/151) of the group B2 patients and 28.1% (16/57) of the group B1 patients (p=0.0077). Reversible organ failure occurred in 4.6% (7/151) of group B2 patients compared to 7% (4/57) of group B1 patients; persistent organ failure occurred in 3.3% (5/151) of group B2 patients, while the incidence was higher in group B1 at 15.8% (9/57, p=0.0039).

Discussion

Our study of 248 patients confirms that diabetes mellitus type 2 is a co-morbidity that increases the risk of complications in patients with AP of various etiologies, extends their hospitalization and increases their hospital mortality.

According to the study by Shen *et al.*, the incidence of complications is 30% higher among people with diabetes than non-diabetics. Huh *et al.* also demonstrated that the incidence of local complications is twice as high among people with diabetes than non-diabetics: 13% compared with 6.1%. In our sample, we similarly find that the incidence of complications is twice as high among people with diabetes than non-diabetics (35% compared with 16.8%, p=0.0082). The size of our sample (n=248) is comparable with that studied by Huh *et al.* (n=201). The difference between their findings and ours, including the higher overall incidence of local complications in our sample, may be due to the fact that—unlike the aforementioned studies—we considered there to have been local complications not only in cases with proven necrosis but also in cases with acute fluid collection around the pancreas, visible via ultrasound or CT scan, even where this did not require intervention (*e.g.*, transgastric drainage).

Huh *et al.* describe organ failure requiring admission to ICU in 31.5% of patients with diabetes and 18.4%

Table 6: Non-diabetic patients' AP outcomes by glycemia level on admission.

	Total n (%)	Mild form n (%)	Moderate form n (%)	Severe form n (%)	Mortality n (%)	Local complications n (%)	Organ failure <48 h n (%)	Organ failure >48 h n (%)
Group B1 Glc >8	57 (27.4)	36 (63.2)	12 (21.1)	9 (15.8)	5 (8.8)	16 (28.1)	4 (7)	9 (15.8)
Group B2 Glc <8	151 (72.6)	123 (81.5)	23 (15.2)	5 (3.3)	2 (1.3)	19 (12.6)	7 (4.6)	5 (3.3)
Groups B1+B2	208	159 (76.4)	35 (16.8)	14 (6.7)	7 (3.4)	35 (16.8)	11 (5.3)	14 (6.7)

of patients without diabetes. Shen *et al.* report organ failure requiring admission to ICU in 16.2% of patients with diabetes and 10.7% of patients without diabetes; however, from the original study, it is not possible to tell precisely in what percentage of cases failure of specific organs was the reason for ICU admission. The meta-analysis by Mikó *et al.* confirms a higher risk of organ failure requiring admission to ICU in the diabetic group: 16.5% compared with 10.9% among non-diabetic patients.

In this study,we do not report organ failure requiring admission to Ithe CU but rather organ failure that was reversible within 48 hours and persistent organ failure longer than 48 hours. We do so because we routinely use the criteria of the Atlanta Classification and its distinction between mild, moderate and severe forms of AP (Table 1) [16].

In cases of mild organ failure without the need for vasopressor or ventilatory support, patients were hospitalized in standard wards with non-invasive monitoring of their vital functions. We recorded reversible organ failure in 12.5% of patients in Group A and 5.3% of patients in Group B; we recorded persistent organ failure in 40% of patients in Group A and 6.7% of patients in Group B. The difference in the incidence of organ failure between diabetics and non-diabetics is greater in our sample than in the previous studies; this is likely due to the number of patients studied (greater differences are evident in studies with smaller numbers of patients).

The hospital mortality in both groups of patients with AP varies widely between studies. Published studies on smaller patient samples indicate a decidedly higher mortality among people with diabetes: Huh *et al.* find 16.7% mortality in the diabetic group *versus* 3.4% in the non-diabetic group. In their Japanese study, Kikuta *et al.* found 4% mortality among diabetic patients and 1.7% mortality among non-diabetics. However, studies on large population samples and meta-analyses have found minimal differences in mortality between the two groups. Indeed, Shen *et al.* even reported lower mortality among diabetic patients – 3.5% compared to 4.1% among non-diabetic patients. In their meta-analysis, Mikó *et al.* find that mortality is the same across both groups at 4.4%. Our study works with a sample of comparable size to that studied by Huh *et al.* and finds similar results. Mortality was significantly higher among our group of diabetic patients at 17.5% (7/40) than among non-diabetic patients, where mortality was 3.4% (7/208, p=0.0004). Early mortality within 14 days of hospital admission was similarly higher in our sample: 7.5% among diabetic patients and 1.9% among non-diabetic patients.

Acute stress hyperglycemia among non-diabetics at the time of hospital admission increases the risk of developing moderate or severe AP. Sun *et al.* report average glycemia levels at admission to be 8.1±3.2 mmol/l for mild AP, 12.14±3.55 mmol/l for moderate AP and 14.32±3.15 mmol/l for severe AP. The results we obtained from our sample confirm the importance of hyperglycemia in non-diabetic patients: acute stress hyperglycemia >8 mmol/l at the time of hospital admission without a previous history of diabetes increases the risk of local complications (28.1% compared to 12.6% p=0.0077), organ failure (22.8% compared to 8%, p=0.0039) and hospital mortality (8.8% compared to 1.3%, p=0.0079). On the other hand, our study reveals a rather insignificant difference in the severity of AP between patients with well-compensated (glycemia <8 mmol/l on admission) and decompensated (hyperglycemia >8 mmol/l on admission) known type 2 diabetes. However, it is important to recall that our evaluation so far included only 40 patients with type 2 diabetes. No similar sample distinguishing between compensated and decompensated diabetes concerning the severity of AP, with which we could compare our findings, has yet been described in the foreign literature.

We further examined whether certain types of therapy for type 2 diabetes affect the course or mortality of AP. Our data reveal that people with diabetes treated via a diet had a lower chance of severe AP than patients undergoing PAD treatment (31.3% compared to 47.4%) and also lower mortality (12.5% compared to 21%). However, to draw any clear conclusions from this, it would be necessary to assess a larger sample of diabetic patients with AP because there are only 40 patients in our sample with diabetes mellitus type 2, and only 5 of them were undergoing insulin therapy. Our findings in relation to the different types of diabetes therapy are thus necessarily affected by sampling error. No similar analysis with stratification by treatment type has yet been described in the foreign literature.

Conclusion

Diabetes mellitus type 2 has a serious impact on the course of many acute diseases, including acute pancreatitis. Our study confirms that the incidence of local complications and organ failure during acute pancreatitis is higher in patients with diabetes mellitus than in non-diabetic patients and that AP patients with diabetes mellitus have higher early and overall hospital mortality. We also found that acute stress hyperglycemia

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on hospital admission in non-diabetic patients has a very similar impact on the course of acute pancreatitis and associated mortality.

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Conflict of interest

The authors declare no conflict of interest.

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