Course of acute pancreatitis
in diabetic patients

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INTRODUCTION: *In recent years, in many European countries, morbidity due to acute pancreatitis (AP) has shown a growing tendency. Some studies indicate an increased risk of contracting AP in the AIM: The objective of the presented study was evaluation of the clinical course of AP in patients with diabetes.*
METHODS: *The study covered all patients with the diagnosis of AP, treated in surgical wards. Into the group of diabetic patients were qualified those who during medical history taking confirmed the diagnosis of type 1 or type 2 diabetes prior to hospitalization due to AP.*
RESULTS: *Into the study were enrolled 963 patients hospitalized due to AP. In this group there were 87 (9%) patients with diabetes. In patients with diabetes, gallstones were the cause of the disease significantly more often (46% vs. 32%). In the majority of cases, the course of AP was mild; however, in 10.3% of patients with diabetes, the course of the disease was moderately severe, and in 12.7% – severe AP was observed. No differences were found in mortality due to AP between the groups. Systemic failure was more frequently observed in the group of patients with D.T.2. 5.4% and as many as 23.1% with D.T.1. vs. 5.1% of those without diabetes, the differences were statistically insignificant.*
CONCLUSIONS: *The frequency of occurrence of AP in patients with diabetes increases with age, and is most often related with gallstones. The clinical course of AP in this group of patients is more often severe, with systemic failure in patients with type 1 diabetes.*

KEY WORDS: Acute pancreatitis, Diabetes, Etiology

Introduction

In recent years, in many European countries, morbidity due to acute pancreatitis has shown a growing tendency. Such a trend has also been observed in Poland. In an epidemiological study conducted in 2011, the prevalence of AP was 99,96/100,000 inhabitants. The incidence of the first episode was 79.7/100,000 [1]. In the majority of cases, acute pancreatitis has a mild course;

however, in 12.3% of patients a moderately severe and in 7% severe course of the disease were observed [1]. Based on data published by the National Health Insurance concerning the period 2009-2012, a systematic increase may be noted in the number of hospitalizations due to AP in the whole Poland, especially an increase in the number of patients hospitalized with severe AP [2]. The causes of contracting the disease vary. In the majority of study results presented in literature, gallstone etiology is prevalent and concerns mainly females. Gallstones and alcohol are the causes of approximately 80% of the cases of AP [3,4]. It is also suggested that hyperlipidaemia may be a factor predisposing for AP, especially in combination with exposure to gallstones and alcohol [5,6]. Medicines used by patients, especially by those at an older age, still remain an underestimated predictive factor in the etiology of usually mild forms of AP [7-9]. Among more rare causes is endoscopic retrograde cholangiopan-

creatography (ERCP). Other rare causes of AP include: hyperparathyroidism, functional pancreatic sphincter of Oddi disorder, congenital defects, abdominal cavity injuries, postoperative, viruses, bacteria, parasites, diseases on an autoimmune background, and mucoviscidosis. Some studies indicate an increased risk of contracting AP in the group of patients with type 2 diabetes [10-12]. This may be related with common risk factors, such as obesity, cigarette smoking, and alcohol consumption [13]. Diabetes is a chronic metabolic disease affecting an increasingly larger number of the population. It is estimated that in Poland, approximately 2.6 million people suffer from diabetes, including 60% of cases of diagnosed and treated diabetes. For a long time, efforts have been undertaken to establish which drugs used in diabetes may increase the risk of pancreatitis. It was observed that among the biguanides, both phenformin and metformin (the latter in patients with renal insufficiency) have been cited in case reports as a potential cause of acute pancreatitis. Sulphonylureas, as both entire the class and single compound (glibenclamide) have also been found in cohort studies to increase its risk [14]. These drugs may cause damage to the pancreas irrespective of the occurrence of renal function disorders [15]. Usually, drug induced pancreatitis takes a mild course and is characterized by low mortality [15].

The objective of the presented study was evaluation of the clinical course of acute pancreatitis in patients with diabetes.

Material and Methods

The study covered all patients with the diagnosis of acute pancreatitis, treated in surgical wards in the Kielce Region. The observation time of hospitalization of patients with AP was 12 months. The criterion for enrolment into the study, according to the modified Atlanta classification, was the satisfaction of 2 of the following 3 elements: severe abdominal pain consistent with acute pancreatitis, amylase or lipase activity at least 3 times greater than the upper limit of normal, characteristic findings of AP in ultrasound examination (USG) or computed tomography (CT). The documentation of the course of diagnostics and treatment of a patient consisted in carrying out an interview, physical examination of the patient, and analysis of the course of treatment and results of examinations performed. The severity of the course of acute pancreatitis was assessed using the following scales: Balthazar, Ranson, and APACHE II. For this purpose, the results of biochemical and imaging examinations (USG, CT) were used. The examinations performed in each patient with acute pancreatitis resulted from the status and clinical indications. According to the new Atlanta classification, 3 degrees of the severity of AP were distinguished: mild, moderate and severe. Patients were classified based on the presence or absence

of persistent organ failure, as well as local and systemic complications. Into the group of diabetic patients were qualified those who during medical history taking confirmed the diagnosis of type 1 or type 2 diabetes prior to hospitalization due to AP.

Consent for the study was obtained from the Bioethics Commission at the Jan Kochanowski University in Kielce.

Statistical analysis

The associations between the diabetes illness and the occurrence of a particular event of interest (the specific etiology of AP or severity of the course) were analysed by using Fisher's exact test with the data sets displayed in the form of 2x2 contingency tables. Odds ratio (OR) were used as a measure that compares the odds of the specific event occurrence (for example, an alcohol as the etiology of AP) in the diabetes group vs. the control group of non-diabetes patients. 95 % confidence intervals for ORs were also reported.

Results

During the period of one year analyzed, 1,044 hospitalizations due to acute pancreatitis were registered. According to the adopted assumption, 963 patients (368 females and 595 males) were qualified for further analysis who were hospitalized due to AP only once within the observed period of one year. In this group there were 87 (9%) patients with diabetes; 13 (1.3%) patients (6 females and 7 males) with type 1 diabetes (D.T.1.); type 2 diabetes (D.T.2.) diagnosed prior to hospitlization due to AP was reported by 74 (7.7%) patients (36 females and 38 males). The mean age of patients with AP and with type 2 diabetes was 66.2 which was significantly higher compared to the group of patients without diabetes – 53.5. Females with D.T.2. were older than males: 72.3 (min. 43; max. 92) vs. 60.4 (min. 33; max. 86) p<0.05. Relapses of AP in this group concerned 20 (27%) patients with diabetes, and occurred with a frequency comparable to that noted in the group without diabetes 189 (21.6%). 13 patients were treated with insulin and oral rugs, whereas the remainder received only oral drugs.

In patients with diabetes D.T.2, gallstones were the cause of the disease significantly more often than among non-diabetic patients (47.3% vs. 32%), and alcohol dominated in AP etiology in patients without diabetes (26.9% vs. 7.7% D.T.1 and 8.1% D.T.2.). In the majority of cases, the course of AP was mild; however, in 15.4% of patients with D.T.1, and 9.5% of those with D.T.2, the course of the disease was moderately severe, and in 30.8% D.T.1, and in 9.5% D.T.2 – severe AP was observed. No differences were found in mortality due to AP between the groups of patients with and without diabetes.

TABLE I - *Characteristics of patients with AP with and without diabetes.*

N=963	Patients with diabetes N= 87	Patients without diabetes N=876	P value	OR (95% CI)	Patients with diabetes T.1. n=13	P value	OR (95% CI)	Patients with diabetes T. 2. N=74	P value	OR (95% CI)
Etiology										
Alcohol	7 (8%)	236 (26,9%)	0.00004	0,24 (0,1-0,52)	1 (7,7%)	0.203	0,22 (0,01- 1,54)	6 (8,1%)	0.00014	0,24 (0,08-0,56)
Biliary	40 (46%)	280 (32%)	0.012	1.81 (1,12- 2,89)	5 (38,5%)	0.765	1,32 (0,34- 4,66)	35 (47,3%)	0.0097	1,91 (1,15 - 3,17
Other	-	38 (4,3%)	0.042	-	-	1	-	-	0.066	-
Unexplained cause	40 (46%)	322 (36,8%)	0.104	1,46 (0,91- 2,33)	7 (53,8%)	0.250	2,01 (0,57 - 7,290)	33 (44,6%)	0.211	1,38 (0,83- 2,29)
Course of disease										
Mild	67 (77%)	683 (77,9%)	0.892	0,95 (0,55- 1,69)	7 (53,8%)	0.049	0,33 (0,09- 1,20)	60 (81%)	0.660	1,21 (0,65 - 2,40)
Moderate	9 (10,3%)	131 (15%)	0.337	0,66 (0,28- 1,35)	2 (15,4%)	1	1,03 (0,11- 4,81)	7 (9,5%)	0.232	0,59 (0,23- 1,33)
Severe	11 (12,7%)	62 (7,1%)	0.085	1,90 (0,86- 3,83)	4 (30,8%)	0.012	5,81 (1,27- 21,56)	7 (9,5%)	0.480	1,37 (0,51-3,1608)
Death	5 (5,7%)	33 (3,8%)	0.380	1,56 (0,46- 4,17)	2 (15,4%)	0.090*	4,63 (0,48- 22,52)	3 (4,1%)	0.755	1,08 (0,21- 3,58)

*Pearson's Chi-squared test p-value = 0.03

TABLE II - *Effect of diabetes on the risk of severe attack in patients with AP.*

Severity criteria	Non-diabetic patients N= 876	Diabetic patients N=87	P value	OR (95% CI)	Diabetic T.1. N=13	Diabetic T.2. N=74
Organ failure	45 (5,1%)	7 (8%)	0.314	1.61 (0.59- 3.77)	3 (23,1%)	4 (5,4%)
SIRS >48 hours	11(1,3%)	-	0.612	-	-	-
SIRS<48 hours	18(2,1%)	1	1	0.55 (0.01 - 3.60)	1	-
Gastrointestinal bleeding	3 (0,3%)	2 (2,3%)	0.067*	6.82 (0.56 60.43)	-	2 (2,7%)
Local complications	116 (13,2%)	10 (11,5%)	0.741	0.85 (0.38-1.71)	2 (%)	8(10,8%)

*Pearson's Chi-squared test, p-value = 0.015

Various criteria for the severity of AP were examined in the groups of patients with and without diabetes. Systemic failure was more frequently observed in the group of patients with diabetes D.T.2. 5.4% and as many as 23.1% with D.T.1. vs. 5.1% of those without diabetes; however, in the whole group, the differences were statistically insignificant. Gastrointestinal bleeding was the complication which was noted in 2 patients with diabetes and 3 patients without diabetes. The frequency of occurrence of local complications was analyzed, such as peri-pancreatic fluid collections, pancreatic pseudocysts, necrotic collections, and walled-off pancreatic necrosis. No significant differences between the groups examined were found according to the frequency of occurrence of local complications.

Discussion

The conducted study allowed the presumption that a considerable percentage of patients with acute pancreatitis from the Kielce Region were patients with previously diagnosed diabetes. The concomitance of diabetes in patients with acute pancreatitis has been poorly documented. Meta-analysis of 7 observation studies conducted on a large group of patients showed a significant relationship between diabetes and an increased risk of development of pancreatitis (relative risk = 1.84, confidence interval 95%). At the same time, the authors of the presented study indicate a high variation according to the geographic region, gender and study project [16]. In a comprehensive study conducted in Taiwan, the relative risk

was estimated to be 1.53, confidence interval 95%). The frequency of occurrence of AP was 2.98/1,000 person-years in patients with diabetes, and 1.68/1,000 person-years in non-diabetic patients. The highest rate was noted among patients aged <45 [17]. In American studies, the morbidity risk of was 3 times higher [12]. The precise pathogenetic mechanism leading to the development of AP in diabetic patients has not been precisely recognized. It was found that insulin-resistance and hyperglycaemia may be of great importance [18]. An increased risk of the development of the disease did not depend on alcohol consumption, gallstones, or hyperlipidaemia [19]. In the presented study, a significantly more frequent occurrence of gallstones as the recognized cause of AP was noted in patients with type 2 diabetes, compared to the remaining group of patients (47.3% vs. 32%). Also, in the study by Noel et al. [12], gallstones were responsible for approximately 50% of cases of AP. Alcoholism and hepatitis C increase the risk of development of AP in the group of patients with D.T.2. [20]. In the presented group of patients with diabetes, alcohol was considerably more rarely the recognized cause of the disease, compared to the group of patients without diabetes (8% vs. 26.9%). In a large group of patients with D.T.2, the cause of the disease was not ultimately explained (44.6% and 53.8% in D.T.1.), which may indicate other epidemiological factors apart from those most often considered. The mean age of patients in the presented study with diabetes was significantly higher than those without diabetes (66.2 vs. 53.5). These results are consistent with the results obtained by American researchers, who found that in patients with diabetes the incidence was the highest not only in the youngest (18-30), but also in the oldest (>65) age groups [12], and with Japanese studies (mean age of patients with diabetes 65.6, and those without diabetes – 54.9) [21].

It was observed that diabetes predisposes to a more severe clinical course of pancreatitis in patients with D.T.2: 9.5% and as many as 30.8% of patients with D.T.1 (p<0.05). Such a relationship was also confirmed in studies by Shen HN et al. (hazard ratio of severe acute pancreatitis was 1.46) [17,22]. While analyzing various criteria of the severe form of AP separately, it was noted that the risk of admission of patients to the intensive care unit was by 58% higher, and the risk of local complications was by 30% higher; while the risk of gastrointestinal bleeding was by 16% lower [22]. In this study, it was an interesting fact [22] that the risk of death in the course of AP among patients with diabetes was lower, compared to the group of patients without diabetes. In the presented study, no statistically significant differences were confirmed between the presence of diabetes and mortality due to AP; however, in the group of patients with D.T.1 as many as 2/13 patients died (15.4%). Also, bleeding from gastrointestinal tract occurred more frequently among patients with type 2 diabetes; however, it was statistically insignificant.

The interpretation of the results obtained may have its limitations related with a small group of patients with diabetes enrolled into the presented study, compared to the current results. However, it should be emphasized that the analysis covered all the patients who were treated due to AP in the Kielce Region. The limitation in the interpretation of the results of this study may also be the lack of consideration of the time which had elapsed from the diagnosis of diabetes and the development of AP.

Conclusions

The frequency of occurrence of acute pancreatitis in patients with diabetes increases with age, and is most often related with gallstones; however it is necessary to examine the pathogenetic mechanisms leading to the development of AP in diabetic patients. The clinical course of acute pancreatitis in this group of patients is more often severe, with systemic failure in patients with type 1 diabetes.

Riassunto

Negli anni recenti in molti paesi europei si è dimostrata una crescente incidenza della pancreatite acuta (AP), ed alcuni studi indicano un aumento di rischio di AP nei pazienti diabetici. Questo studio è pertanto finalizzato a valutare il decorso clinico della AP nei pazienti diabetici.

Sono stati studiati tutti i pazienti curati in reparto chirurgico per una diagnosi di AP identificando come pazienti diabetici quelli che all'anamnesi hanno confermato essere affetti da diabete di tipo 1 o di tipo 2 prima di essere ricoverati per AP.

I pazienti ricoverati per AP, ed arruolati nello studio sono stati 963, e tra essi vi erano 87 (9%) diabetici. Tra questi ultimi erano più numerosi quelli portatori di calcolosi biliare quale causa della pancreatite (46% vs 32%). Nella maggioranza dei casi il decorso della AP è stato di gravità moderata, ma comunque nel 10,3% dei pazienti con diabete il decorso della malattia è stato moderatamente grave, e nel 12,7% decisamente grave.

Non sono state osservate differenze nella mortalità da AP in entrambi i gruppi. Insufficienza sistemica è stata osservata più frequentemente nel gruppo dei diabetici di tipo 2 (5,4%) e 23,1% in quelli di tipo 2, a fronte del 5,1% dei pazienti non diabetici, con differenze statisticamente non significative.

In conclusione l'incidenza della AP nei pazienti diabetici aumenta con l'età, ed è più spesso correlata con la calcolosi biliare. In questo gruppo di pazienti in decorso clinico è èiù frequentemente grave, con insufficienza sistemica nei diabetici di tipo 1.

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