

Risk factors for new-onset diabetes mellitus following acute pancreatitis: a prospective study

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Abstract. – OBJECTIVE: Acute pancreatitis (AP) is increasingly recognized as a major cause of diabetes, however, the frequency and risk factors associated with new-onset diabetes are not well established.

We aimed to assess the frequency and risk factors associated with new-onset diabetes, the time of diabetes occurrence, and the difference between early and late-onset diabetes following an AP episode.

PATIENTS AND METHODS: This prospective study included adult patients with AP admitted to a tertiary referral center, followed-up for one year to assess the occurrence of postpancreatitis diabetes. Diabetes was defined in accordance with World Health Organization criteria and the severity of AP was assessed based on the 2012 revised Atlanta classification.

RESULTS: Of 329 patients with AP, 29 (8.8%) were diagnosed with diabetes secondary to AP. Of these, 21 (6.37%) had early-onset diabetes (within one month after the acute episode) whereas 8 (2.42%) had late-onset diabetes (more than one month after the AP episode). Obesity and acute necrosis were more frequent in patients with new-onset diabetes compared to those without (55.2% vs. 33.4%, $p=0.040$ and 31% vs. 7.7%, $p<0.01$), and remained statistically significant in multivariate analysis. No statistically significant differences were found between these groups regarding sex, age, etiology and severity of AP. The patients with early-onset diabetes were older than those with late-onset (61 vs. 45 years old), in univariate and multivariate analysis ($p=0.018$ and $p=0.038$, $OR=0.87$).

CONCLUSIONS: Less than 10% of patients with AP developed diabetes within 1 year, particularly obese patients and those with acute pancreatic necrosis of more than 50%. Patients aged over 61 years old developed diabetes in the first month after the acute episode of AP.

Key Words:

Acute pancreatitis, New-onset diabetes, Endocrine pancreatic insufficiency, Risk factors, Severity, Necrosis.

Introduction

Acute pancreatitis (AP) is the most common pancreatic disease, having a worldwide incidence higher than the combined incidence of pancreatic cancer (PC) and chronic pancreatitis (CP)^{1,2}. Notably, severe and persistent epigastric pain associated with nausea and/or vomiting are typical pathognomonic symptoms. More rarely, abdominal symptoms may not be present, which could be a cause for misdiagnosis and delay the appropriate treatment³. Although the majority (75%-80%) of AP episodes are mild, self-limited^{4,5}, long term consequences are still present⁶. Pancreatic endocrine insufficiency after AP, as well as impaired glucose metabolism or diabetes mellitus (DM), have received increasing attention in recent years.

The World Health Organization (WHO) and the American Diabetes Association (ADA) have defined DM associated with pancreatic diseases as a specific type of diabetes of the exocrine pancreas („pancreatogenic diabetes”, previously classified as type 3c DM, which is outdated now)². However, the presence of exocrine pancreatic dysfunction is rather a significant risk factor, not a mandatory diagnostic criterion for this form of diabetes. Its prevalence is 5-10% in the Western diabetic population⁷⁻⁹, with CP responsible for 20% of cases and AP for 80% of cases¹⁰.

AP has been identified as an important cause of DM^{7,8} with a double risk of developing diabetes

after an attack of pancreatitis compared to general population¹⁰⁻¹². More importantly, the risk for pancreatic cancer mortality in such patients was shown to be higher than in those with type 2 DM^{13,14}, as well as the risk of mortality at younger age¹⁰.

Hyperglycemia typically occurs early in the evolution of AP^{15,16}, and is a common early feature that has been used in prognostic models¹⁷. This is usually a transient phenomenon that completely resolves after the resolution of the AP episode^{18,19}, and only persistent hyperglycemia should be considered as DM²⁰⁻²². The occurrence of DM after AP has been studied, but data are conflicting^{11,12,21-24}, ranging from rare cases to more than half of all patients developing DM.

We aimed to assess the frequency of new-onset DM and the time of DM occurrence following an AP attack, as well as the risk factors associated with new-onset DM. We also sought to evaluate the differences between early and late-onset DM after an AP episode.

Patients and Methods

Study Population

This prospective, cohort study included consecutive adult patients (> 18 years old) with a diagnosis of AP admitted to a tertiary referral center between January 2018 and February 2019. Eligible patients were subsequently followed-up for 1 year in order to assess the occurrence of diabetes secondary to AP. Invitations to participate were made either face-to-face during hospitalization, or by telephone following discharge from the hospital. All included patients had previously signed an informed written consent for participation in the study.

The diagnosis of AP was established according to the 2012 revised Atlanta classification criteria²⁵, by meeting at least two of the following: (a) abdominal pain, (b) level of serum lipase or amylase at least three times greater than the upper limit of normal, and (c) findings on cross-sectional abdominal imaging consistent with AP.

The etiology of AP in patients with common bile duct stones, sludge or microlithiasis in the bile duct, confirmed by abdominal ultrasound (US), contrast-enhanced computed tomography (CT) scan, endoscopic ultrasound (EUS), abdominal magnetic resonance imaging (MRI), was classified as “biliary”. Patients with hypertriglyceridemia (triglyceride > 1000 mg/dL) were classified as having “metabolic” AP. “Alcoholic” AP

was diagnosed in patients with high-volume alcohol consumption and no biliary or metabolic pancreatitis. Idiopathic AP was established where the etiology of AP remained unknown.

The severity of acute pancreatitis was assessed according to the 2012 revised Atlanta classification²⁵.

Acute pancreatic necrosis was assessed by abdominal contrast-enhanced CT scan, and its extent was categorised according to Balthazar’s classification²⁶.

Local complications, such as pancreatic or peripancreatic necrotic collections after one month following the AP onset were assessed based on CT scan imaging.

The following were considered systemic complications following the AP episode: organ failure (such as respiratory, cardiovascular and renal) and exacerbation of underlying comorbidities (coronary artery disease, chronic lung disease)

Patients fulfilling one or more of the following criteria were excluded from participation in this study: history of DM (type 1, type 2) or prediabetes prior to the AP episode; history of impaired glucose tolerance; chronic pancreatitis; pancreatic cancer; pancreatic resections; death during hospitalization or lost to follow-up; refusal to participate in this study.

Primary Endpoint

The endocrine pancreatic function after AP onset was assessed by measuring the fasting blood glucose level (FPG), oral glucose tolerance test (OGTT) and/or glycosylated hemoglobin (HbA1c) at the following timepoints: at admission, during hospitalization, prior to hospital discharge and during follow-up at 1 month, 3 months, and 1 year. The diagnosis of DM was established in accordance with the WHO criteria²⁷, which include the typical symptoms along with any of the following:

- Fasting plasma glucose (FPG) ≥ 7.0 mmol/L (≥ 126 mg/dL) or
- Glucose at any time of the day ≥ 11.1 mmol/L (200 mg/dL) in the presence of symptoms or
- Fasting plasma glucose < 7.0 mmol/L (≤ 126 mg/dL) and 2-hour plasma glucose (2h-PG) after 75 g oral glucose tolerance test (OGTT) > 11.1 mmol/L (200 mg/dL) or
- Impaired glucose tolerance was diagnosed if: FPG < 7.0 mmol/L (< 126 mg/dL) and 2h-PG between 7.0 mmol/L (126 mg/dL) and 11.1 mmol/L (200 mg/dL)

Transient hyperglycemia during hospitalization was not considered diabetes.

Early onset diabetes was considered when DM occurred within one month after the acute episode of pancreatitis (0-1 month), whereas late-onset diabetes occurred after more than one month following the AP episode (≥ 1 month).

Risk Factors Assessment

Demographic data (age, sex, body mass index (BMI), etiology, alcohol intake), history of comorbidities associated with an increased risk of DM (obesity, hypertriglyceridemia), laboratory test results and imaging reports (abdominal US, contrast-enhanced CT scan, MRI and EUS) were extracted.

Contrast-enhanced CT scan was performed three days following the AP onset in all patients, one month later in patients with local complications, such as pancreatic necrosis, during follow-up based on the patient's clinical status, or when invasive intervention was required.

MRI was performed in patients with altered liver function tests, suspected common bile duct obstruction, abnormal or disconnected pancreatic duct and in patients with iodine allergy.

EUS was performed in case of suspected acute biliary pancreatitis for detection of microlithiasis or choledocholithiasis, in acute idiopathic (recurrent) pancreatitis and when invasive endoscopic intervention was considered.

Endoscopic transmural drainage and endoscopic transmural necrosectomy were the most common methods of debridement or necrosectomy. Surgical necrosectomy was performed when endoscopic techniques were not feasible or failed.

The study was approved by the Ethics Committee of the 'Iuliu Hațieganu' University of Medicine and Pharmacy (approval No. 491 from November 21, 2019) and by the Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania (approval No. 16264 from November 29, 2019).

Statistical Analysis

We used medians (with ranges) or frequencies (with percentages) to describe data. We studied the differences between patients with new-onset DM and without DM following AP and also between patients with early and late-onset DM. In both cases, the following tests were performed: Mann-Whitney (MW), *t*-test, odds ratio (OR, with 95% confidence intervals) followed by Fisher's exact test or Cramér's V and the chi-square test. Two multivariate logistic models were also applied. For the comparison between patients with and without DM, we included variables de-

tected as statistically significant plus demographics (age and sex). For the comparison between late vs. early-onset patients, we included all variables in a stepwise selection to reduce the variable set. $p < 0.05$ was considered statistically significant. We performed all analyses in R version 3.5.1 (<https://www.R-project.org/>).

Results

Baseline Characteristics Of The Study Participants

355 patients met the initial inclusion criteria for enrolment in this study; of these, 26 (7.3%) patients were excluded, 7 (2% in all patients) due to death during hospitalization or following hospital discharge, whereas 19 (5.3%) have failed to engage with the follow-up protocol.

Finally, 329 patients were included in the study, of which 177 (53.8%) were male and 152 (46.2%) female, with a median age of 59 years old (18-90) and median body mass index (BMI) of 27.5 (15.46-44.6). 115 patients (35.4%) met the BMI criteria for obesity. The most common AP etiology was biliary (217 patients, 66.7%) followed by alcoholic (87 patients, 26.4%) and metabolic (20 patients, 6.1%). 265 patients (80.5%) had a singular episode of AP. For the severity, 117 patients (35.6%) were classified as mild AP, 167 patients (50.8%) as moderate AP and 45 patients (13.7%) met the criteria for severe AP. Balthazar E score at admission was found in 137 patients (41.6%). The 72-hours CT scan revealed less than 30% pancreatic/peripancreatic necrosis in 35 patients (10.6%), 30%-50% necrosis in 32 patients (9.7%) and more than 50% necrosis in 32 patients (9.7%). 56 patients (43.6%) had necrotic collections at the one-month CT scan assessment.

There were 47 patients (14.3%) with infected pancreatic fluid collections that required either necrosectomy (42 patients, 12.8%) or conservative treatment. Systemic complications were encountered in 45 patients (13.7%).

New-Onset DM Following An Episode Of AP

Of the 329 patients included in the study, 29 (8.8%) were diagnosed with DM secondary to AP (Table I); 21 (6.37%) had early-onset DM, whereas 8 (2.42%) were diagnosed with late-onset DM (Table II).

The patients had a median age of 53 years (34-86), the male: female ratio was 15:14 and the

Table I. Comparison between patients with new-onset DM and without DM following AP.

Variable	New-onset DM (n=29)	Without new-onset DM (n=300)	p-value	OR value [95%CI] Or Cramer V
Age (years), median (range)	53 (34:86)	60 (18:90)	0.794	
Sex, n (%)	Female	14 (48.3)	0.847	OR=1.10 [0.51, 2.35]
	Male	15 (51.7)		
BMI (kg/m ²), median (range)	31.64 (21.46-41.13)	27.35 (15.4-44.6)	0.037	
Overweight & Obesity, n (%)	BMI<25	9 (31.0)	0.040	V=0.14
	BMI: 25-29.9	4 (13.8)		
	BMI≥30	16 (55.2)		
Etiology, n (%)	biliary	16 (55.2)	0.213	OR=0.58 [0.27, 1.25]
	alcoholic+metabolic	13 (44.8)		
Severity of AP, n (%)	mild	5 (17.2)	0.079	V=0.12
	moderate	20 (69.0)		
	severe	4 (13.8)		
Number of episodes of AP, n (%)	1	25 (86.2)	0.742	V = 0.08
	2	2 (6.9)		
	3	2 (6.9)		
	>3	0 (0.0)		
Balthazar score at admission, n (%)	A	2 (6.9)	0.010	V=0.20
	B	2 (6.9)		
	C	2 (6.9)		
	D	2 (6.9)		
	E	21 (72.4)		
Acute necrosis (CT at 72h), n (%)	0%	13 (44.8)	<0.001	V=0.23
	<30%	4 (13.8)		
	30-50%	3 (10.3)		
	>50%	9 (31.0)		
Pancreatic necrosis (CT at 1 month), n (%)	8 (27.6)	48 (16.0)	0.123	OR=2.00 [0.84, 4.78]
Infection of pancreatic fluid collections, n (%)	7 (24.1)	40 (13.3)	0.158	OR=2.07 [0.83, 5.16]
Necrosectomy, n (%)	7 (24.1)	35 (11.7)	0.075	OR=2.41 [0.96, 6.05]
Systemic complications, n (%)	4 (13.8)	41 (13.7)	0.999	OR=1.01 [0.33, 3.05]

DM, diabetes mellitus; AP, acute pancreatitis; BMI, body mass index; CT, computed tomography; OR/RR, odds-ratio/risk-ratio; CI, confidence interval; V, Cramér V.

median BMI was 31.64 (21.46-41.13). According to BMI criteria, 16 (55.2%) patients were obese, and 4 (13.8%) patients were overweight. The most commonly encountered AP etiology was biliary (16 patients, 55.2%), followed by alcoholic (8 patients, 27.6%) and metabolic (5 patients, 17.2%). Twenty-five patients (86.2%) had a singular episode of AP, whereas 4 patients (13.8%) had recurrent episodes. Twenty patients (69%) had moderate AP, 4 patients (13.8%) had severe AP and 5 (17.2%) had mild AP. The 72-hours CT scan showed no or less than 30% necrosis in 17 patients (58.6%) whereas 9 patients (31.0%) had more than 50% necrosis. Of these, 8 patients (27.6%) had necrotic collections at the one-month CT scan. None of these patients met the imaging criteria

for chronic pancreatitis at the one-year follow-up (Table I).

Seven patients (24.1%) underwent pancreatic necrosectomy, for either infected necrotic collections (5 patients, 17.2%) or adjacent structures compression due to necrotic collections (2 patients, 6.9%). Four patients (13.8%) had systemic complications (Table I).

Comparison Between Patients With New-Onset DM And Without DM Following AP

Patients with new-onset DM had a significantly higher rate of obesity and Balthazar E score at admission compared to patients without DM ($p=0.040$ and 0.010 , respectively). There were

no statistically significant differences between groups regarding sex, age, AP etiology, number of AP attacks and severity of AP (Table I). However, the acute necrosis more than 50% of the parenchyma, but not the necrosis at the one-month CT scan assessment, was more frequent in patients with new-onset DM compared to those without DM (31% vs. 7.7%, $p < 0.001$) (Table I).

Systemic complications were similar between the two groups (13.8% vs. 13.7%, $p = 0.999$, OR=1.01) and the need for necrosectomy was more frequent in patients with new-onset DM (7 patients (24%), OR=2.41, $p = 0.075$) (Table I).

The multivariate logistic regression analysis showed that BMI and acute necrosis remained important risk factors for the occurrence of

new-onset DM ($p = 0.039$, OR=1.08 and $p = 0.013$, OR=1.64) (Table III).

Comparison Between Patients With Late And Early-Onset DM

The patients with early-onset DM were significantly older than those with late-onset DM at the univariate and multivariate analysis ($p = 0.018$ and $p = 0.038$, OR=0.87, respectively) (Table II, Table IV). The etiology, time from AP occurrence to DM onset, BMI, severity of AP or necrosis volume as measured on the CT scan were not significantly different between the two groups. The need for necrosectomy was associated with a higher risk of developing late-onset DM, although the difference was not statistically significant ($p = 0.357$, OR=2.55) (Table II).

Table II. Comparison between late and early-onset DM after AP.

Variable	Late-onset DM (n=8)	Early-onset DM (n=21)	p-value	OR value [95%CI] Or Cramer V
Age (years) median (range)	45.5 (40:65)	61 (34:86)	0.018	
Sex, n (%)	Female	11 (52.4)	0.682	OR=0.55 [0.10, 2.89]
	Male	5 (62.5)		
BMI (kg/m ²), median (range)	27.46 (22.62:39.01)	31.75 (21.46-41.13)	0.272	
Overweight & Obesity, n (%)	BMI <25	6 (28.6)	0.675	OR=1.50 [0.27, 8.34]
	BMI ≥25	15 (71.4)		
Obesity, n (%)	BMI <30	8 (38.1)	0.406	OR=2.71 [0.50, 14.54]
	BMI ≥30	13 (61.9)		
Etiology, n (%)	alcoholic+ metabolic	8 (38.1)	0.406	OR=2.71 [0.50, 14.54]
	biliary	13 (61.9)		
Severity of AP, n (%)	mild	5 (23.8)	0.227	V=0.32
	moderate	14 (66.7)		
	severe	2 (9.5)		
	severe	2 (9.5)		
Number of AP episodes, n (%)	1	19 (90.4)	0.253	V=0.37
	2	1 (4.8)		
	3	1 (4.8)		
Balthazar score at admission, n (%)	E	14 (66.7%)	0.381	OR=3.50 [0.36, 34.33]
	A-D	7 (33.3%)		
Acute necrosis (CT at 72h), n (%)	0%	10 (47.6)	0.251	V=0.38
	<30%	4 (19.0)		
	30-50%	1 (4.8)		
	>50%	6 (28.6)		
Pancreatic necrosis (CT at 1 month), n (%)	3 (37.5)	5 (23.8)	0.646	OR=1.92 [0.334, 11.03]
Infection of pancreatic fluid collections, n (%)	2 (25.0)	5 (23.8)	1.000	OR=1.07 [0.16, 7.06]
Necrosectomy, n (%)	3 (37.5)	4 (19.0)	0.357	OR=2.55 [0.42, 15.41]
Systemic complications, n (%)	2 (25.0)	2 (9.5)	0.567	OR=3.17 [0.36, 27.57]

DM, diabetes mellitus; AP, acute pancreatitis; BMI, body mass index; CT, computed tomography; OR/RR, odds-ratio/risk-ratio; CI, confidence interval; V, Cramér V.

Table III. Multivariate logistic regression analysis for new-onset DM after AP.

Variable		Adjusted <i>p</i> -value	Adjusted OR [95%CI]
Age		0.982	1.00 [0.97-1.03]
Sex	Female	0.825	0.91
	Male		[0.39-2.08]
BMI (kg/m ²), median (range)		0.039	1.08 [1.00-1.16]
Balthazar score at admission	A	0.593	0.82
	B		[0.40-1.78]
	C		
	D		
	E		
Acute necrosis	0%	0.013	1.64
	<30%		[1.11-2.45]
	30-50%		
	>50%		

DM, diabetes mellitus; AP, acute pancreatitis; BMI, body mass index; CT, computed tomography; OR, odds-ratio; CI, confidence

Table IV. Multivariate logistic regression analysis for late vs. early-onset DM after AP.

Variable		Adjusted <i>p</i> -value	Adjusted OR [95%CI]
Age		0.038	0.87 [0.75 - 0.97]
Severity of AP	mild	0.167	5.83
	moderate		[0.65 - 134.37]
	severe		

DM, diabetes mellitus; AP, acute pancreatitis; OR, odds-ratio; CI, confidence interval.

Discussion

This prospective, cohort study showed the occurrence of new-onset DM in 8.8% of patients after one year following an AP attack, especially in patients with obesity and acute pancreatic necrosis of more than 50% of the parenchyma. The occurrence of early-onset DM was more frequent in older patients.

AP has been reported to cause DM in several studies^{21,22}, although the new-onset DM has often been misclassified as type 2 DM. A meta-analysis of 24 studies, including 1102 patients following a first AP episode, reported a 15% one-year prevalence of new-onset DM, and the risk increased significantly at 5 years (relative risk, RR=2.7)²¹. These findings show a higher prevalence compared to our study (8.8% at one year). Another meta-analysis²⁸ including 31 relevant studies in 13894 subjects, reported a 20% prevalence at 5 years. It has also been previously demonstrated^{11,12} that the risk of

developing new-onset DM doubles in individuals following an episode of AP compared to control group. The transient hyperglycemia patients should be excluded, otherwise the frequency of new-onset DM after AP would rise to 45-60.2%^{22,29}.

Regarding the latency period between an AP attack and DM onset, we found that 6.37% of patients developed early-onset DM within one month following the AP episode, whereas 2.42% developed late-onset DM, up to one year after the first episode of pancreatitis. Other studies^{12,21} have reported higher rates of DM: 15% during the first year following an AP attack, and 23% at 5 years, whereas the risk of developing DM was twice as high at 10 years following the acute episode. A controlled study of 2966 first attack of AP patients, reported a 3 month new-onset DM incidence of 6% person-year and 2.25% after 3 months¹². Also, another study³⁰ showed a cumulative incidence of new-onset DM after AP of 3.3% at 6 months and 7.2% at 12 months. Similarly to

previous reports^{11,12,21}, no influence of severity AP was found in developing the timing of DM onset (Table II).

The risk of developing new-onset DM after AP as well as the timing of DM onset was independent of sex, etiology, number of attacks or AP severity. These findings are in keeping with other studies^{11,21}.

Previous studies^{22,24,31} have suggested that the occurrence of newly diagnosed DM secondary to AP with loss of pancreatic cells was related to the severity of AP, involving pancreatic necrosis of more than 50% of the parenchyma and insulin resistance as independent risk factors³¹. However, different data has highlighted the rather controversial relationship between DM after AP and necrosis of <30%^{11,21,32}, suggesting that other mechanisms than mechanical beta cell destruction may be involved, such as: genetic susceptibility, autoimmune factors, metabolic factors or low-grade inflammation^{21,33}. Our results showed that patients with acute pancreatic necrosis of > 50% of the parenchyma had a higher probability of developing new-onset DM (31% vs. 7.7%, $p < 0.001$), but the necrosis extent at 1 month-CT scan had no implications. Similarly, necrosectomy, previously linked to critical decline of β -cell (up to 28.5%)³⁴ was not associated with new-onset DM (OR=2.41, $p=0.075$, Table I); also, the probability of developing late-onset DM or early-onset DM after AP (Table II) was similar. However, this results should be interpreted with caution because of the small number of patients with necrosectomy included.

Obesity is known to be an important risk factor for the occurrence of hyperglycemia and insulin resistance³⁵. Obesity and hypertriglyceridemia were found to be independent risk factors for AP and secondary DM^{36,37}. Similarly, our findings have shown that two thirds of the patients with new-onset DM were overweight or obese ($p=0.040$) compared to those without DM, making obesity an important risk factor for the occurrence of new-onset DM, even when adjusted for other covariates. This could be due to lipolyse in the adipose tissue³⁸, partly explained by TNF alpha or IL-6 driven inflammation³⁹.

It has previously been reported¹² that the risk of DM was higher in younger patients (<45 years); however, our findings showed that older age (61 years) was associated with early DM occurrence compared to late DM occurrence (45 years). This could be explained by the geographical differences of the population included in this study and by the increasing DM incidence in people over

45 years old^{40,41}. Another potential explanation could be conveyed by the effect of aging on β cell function and the increased insulin resistance associated with visceral adiposity²¹. This is the most important aspect to be considered by further follow-up strategies, as higher mortality rate was reported in young and middle aged patients with DM secondary to AP¹³.

Despite the more frequent biliary etiology, no significant association between AP etiology, biliary or alcoholic, and development of secondary DM was found in our study, similarly to previous reports^{21,42}. However several studies^{23,43} found that alcohol-related AP was associated with an increased risk of DM.

The pathogenesis of DM secondary to AP is not fully understood. It has been observed that both impaired insulin and insulin resistance function seem to be crucial for the development of DM secondary to AP^{7,15,44}. Although it is known that endocrine pancreatic insufficiency is common after an episode of AP^{7,8}, this is not routinely evaluated. Previous studies^{18,32} suggest that hyperglycemia is a transient phenomenon, endocrine pancreatic function recovering completely after AP regardless of severity.

Limitations

This study has several limitations. Firstly, the short follow-up period after an AP episode (1 year), might have led to missing those patients who had potentially developed DM beyond this timepoint. The risk of developing DM secondary to AP was shown to double at five²¹ or ten years¹². Moreover, the effect of recurrent AP attacks on the occurrence of DM could not be evaluated within the 1 year follow-up. Secondly, our local infrastructure did not support the dosage of the auto antibodies associated with type 1 diabetes, which may have influenced patients inclusion and interpretation of the results. Finally, there was no controlled arm with general healthy population for comparison of new-onset DM.

Conclusions

DM is common after AP; the frequency of DM was slightly higher in our study when compared to the general population. The risk of developing DM after AP was independent of sex, etiology, or severity of AP; however, obese patients and those with important pancreatic necrosis were at an increased risk of developing new-onset DM after AP. In addition, patients with early-onset DM were sig-

nificantly older than those who developed late-onset DM. These findings are important for setting up adequate follow-up strategies after AP, in order to diagnose alteration of glucose tolerance or DM.

Conflicts of Interest

The authors declare that they have no conflict of interest to declare.

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Authors' Contributions

Teodora Man – conception and study design, acquisition, analysis and interpretation of data, drafting the manuscript, critical revision of the manuscript, validation. Radu Seicean – conception and study design, analysis and interpretation of data, critical revision of the manuscript, validation. Laura Lucaciu-analysis and interpretation of data, critical revision of the manuscript, validation. Alexandru Istrate – statistical analysis. Andrada Seicean – conception and study design, critical revision of the manuscript, validation, supervision. All authors approved the final draft of the manuscript.

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Data Availability Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the 'Iuliu Hațieganu' University of Medicine and Pharmacy (No. 491) and also by the hospital (No. 16264) and the reporting followed the STROBE criteria. Written informed consent was obtained from all subjects involved in the study.

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