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New-onset Diabetes Mellitus after EUS-guided Drainage with LAMS: A Pilot Study

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ABSTRACT

Background & Aims: Walled-off necrosis (WON) is a serious complication of severe pancreatitis, patients with necrotizing pancreatitis having an increased risk of developing diabetes mellitus (DM). The aim of this study was to assess the frequency of new-onset diabetes (NOD) in patients with symptomatic WON after endoscopic ultrasound (EUS)-guided drainage with lumen-apposing metal stents (LAMS).
Methods: We retrospectively analyzed a prospectively collected database of patients with symptomatic WON treated by EUS-guided drainage with LAMS in a tertiary referral center. The patients were followed-up for at least 12 months after stent removal. These patients were compared with age- and sex-matched asymptomatic WON controls without interventional treatment and healthy controls to assess the one-year occurrence of DM. Diabetes was defined according to the American Diabetes Association criteria.
Results: Of the 50 patients with symptomatic WON included in the study (male/female ratio, 33:17; median age, 60 years), 13 patients (26%) had pre-existing DM and were excluded. Ten of the remaining 37 patients (27%) without prior DM developed NOD within one year after stent removal, this frequency being higher than in asymptomatic WON controls (18.9%, p=0.581) and healthy controls (2%, p = 0.002). In the symptomatic WON group, NOD patients compared to non-DM patients were older (63.5 vs. 56 years old, p=0.042), had more frequent necrosis > 50% of the pancreatic parenchyma (p=0.002) and had a body-tail location of WON (p<0.001). On multivariate analysis, the number of direct endoscopic necrosectomy (DEN) sessions was the only significant factor for NOD occurrence (OR=7.05, p=0.010). NOD patients had poor glycemic control and required more DEN sessions to achieve WON resolution than patients with prior DM (p=0.017).
Conclusions: In patients with symptomatic WON treated by EUS-guided drainage, DM occurred in 27% of previously non-diabetic patients within one year of follow-up. Patients with extensive pancreatic necrosis were more likely to develop NOD, a high number of DEN sessions being a significant risk factor for NOD occurrence.

Key words: walled-off necrosis - lumen-apposing metal stent - endoscopic necrosectomy - diabetes mellitus - acute pancreatitis.

Abbreviations: ADA: American Diabetes Association; ANC: acute necrotic collection; ANP: acute necrotizing pancreatitis; AP: acute pancreatitis; BMI: body mass index; CP: chronic pancreatitis; CRP: C-reactive protein; CT: computed tomography; DEN: direct endoscopic necrosectomy; DM: diabetes mellitus; DPD: disconnected pancreatic duct; ERCP: endoscopic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; FPG: fasting plasma glucose level; HbA1c: glycosylated hemoglobin; LAMS: lumen-apposing metal stents; MRI: magnetic resonance imaging; mCTSI: modified CT severity index; MRCP: magnetic resonance cholangiopancreatography; NOD: new-onset diabetes; OR: odds-ratio; SD: standard deviation; WON: walled-off necrosis.

INTRODUCTION

Acute pancreatitis (AP) is one of the most common gastroenterological disorders requiring hospitalization [1, 2], having a wide spectrum of severity that ranges from mild, self-limiting disease to severe and fatal disease.

Up to 20% of AP patients will develop acute necrotizing pancreatitis (ANP) [3], which is defined as necrosis of the pancreatic parenchyma, peripancreatic tissue, or both. Acute necrotizing pancreatitis can be classified as either acute necrotic collection (ANC) or walled-off necrosis (WON), based on

complete encapsulation by a wall and collection age (4 weeks or >4 weeks) [1]. Patients with ANP have a mortality rate of 15%, which increases to 30-39% when a superimposed infection occurs, which is the case in approximately one-third of patients [4-6]. In half of WON patients, the fluid collection spontaneously regresses without an invasive procedure [7-9]. The other half of the patients develop symptoms related to fluid collection, which indicates the need for interventional treatment [7-9].

Endoscopic ultrasound (EUS)-guided transluminal drainage, followed by direct endoscopic necrosectomy (DEN), if required, has evolved to become the treatment of choice for symptomatic WON situated in the upper abdomen [10], given its higher efficacy and fewer adverse events compared with surgery and percutaneous drainage [11-14]. The recent introduction of lumen-apposing metal stents (LAMS) has simplified the endoscopic drainage of WON and facilitated DEN [15]. Drainage with LAMS showed better clinical success than plastic stents, with similar side effects [16]. Electrocautery-tipped LAMS (EC-LAMS), a transmural stent that allows one-step EUS-guided drainage of pancreatic fluid collections, has demonstrated a high technical and clinical success rate for various therapeutic EUS procedures, including endoscopic transmural drainage of pancreatic and peripancreatic fluid collections [17].

Although several studies have shown that the endoscopic approach to the treatment of WON improves short-term outcomes [11, 13, 14], knowledge of the effects of endoscopic treatment on pancreatic endocrine function is limited.

It has been reported that AP can lead to diabetes mellitus (DM) [18-21], with an incidence ranging from a few cases to more than half of all patients [20, 22-26]. Acute necrotizing pancreatitis has also been linked to an increased risk of subsequent endocrine insufficiency and DM when compared to patients without necrosis [20, 26, 27].

Some studies [26, 27] have confirmed the effects of surgical necrosectomy on pancreatic endocrine function, whereas the effects of the endoscopic treatment of pancreatic necrosis on pancreatic endocrine function have been reported in only a few studies.

In this study, the primary aim was to assess the frequency of new-onset diabetes (NOD) in symptomatic WON patients after EUS-guided drainage with LAMS compared to asymptomatic WON patients and healthy patients. The secondary aim was to assess the predictors associated with the occurrence of NOD.

METHODS

This retrospective observational study included prospectively collected patients with WON treated by EUS-guided drainage with LAMS at a tertiary medical center between October 2016 and January 2022. Only patients followed-up for 12 months after the endoscopic removal of the stent were included in the study.

Patients with symptomatic WON who underwent EUS-guided drainage with LAMS at least four weeks after the initial episode of AP were enrolled in the study. Infected WON and/or refractory abdominal pain, gastric outlet or biliary obstruction, early satiety or weight loss were indications for drainage. Chronic pancreatitis (CP), previous pancreatic surgery, a previous diagnosis of endocrine pancreatic insufficiency, less than 12 months of follow-up, pseudocysts, absence of necrotic content, and drainage with plastic stents only were excluded.

The occurrence of NOD was assessed in group A (symptomatic WON patients without previous DM who underwent EUS-guided drainage by LAMS with or without necrosectomy), control group B [asymptomatic WON patients with no history of DM, CP and no interventional treatment (percutaneous, endoscopic, or surgical) during hospitalization or follow-up], and control group C (healthy patients with no history of DM, pancreatic, and/or chronic diseases).

The two control groups were retrospectively identified from our hospital database and followed similarly to the study group.

The study complied with the ethical standards of the responsible institutional committee and the revised (2000) Helsinki Declaration, and it was approved by the Institutional Review Board.

Data Collection

We collected: a) clinical and demographic data such as age, sex, body mass index (BMI), history of DM, date of AP onset, etiology of AP, current smoking status, laboratory tests (fasting plasma glucose level (FPG) and/or glycosylated hemoglobin (HbA1c), cholesterol, triglycerides) and diabetes treatment data (insulin or oral hypoglycemic agents); b) imaging data (computed tomography (CT) scan or magnetic resonance imaging (MRI)) during hospitalization, such as the extent of pancreatic necrosis (≤30%, 30%- 50%, > 50%), modified CT severity index (mCTSI) [28], location of WON (head, body, tail), presence of gas, presence of disconnected pancreatic duct (DPD) and imaging data during follow-up; c) procedural data: indication for endoscopic drainage, time from LAMS placement to removal, patients undergoing DEN-indication, number of sessions, clinical success (defined as symptom resolution and remnant WON < 3 cm in diameter) and WON recurrence.

Disconnected pancreatic duct was defined as disruption of the main pancreatic duct with a loss of continuity between the pancreatic duct and the gastrointestinal tract caused by ductal necrosis after severe acute necrotizing pancreatitis, seen on imaging such as magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), or EUS [29].

Procedure

All patients included signed an informed consent form before the endoscopic procedure and/or each admission.

Endoscopic ultrasound-guided drainage was performed with the patient under general anesthesia and on broad-spectrum antibiotic prophylaxis. A therapeutic linear array echoendoscope, Olympus UCT 180, was used in combination with an Aloka F75/Arietta 850 ultrasound device. All endosonographers (A.S., C.P., O.M.) were experienced in EUS-guided drainage of pancreatic collection and DEN. WON was assessed by CT scan, and EUS-guided drainage was indicated in symptomatic patients with WON > 4 weeks from AP onset, if located in the upper part of the abdomen, close to the gastroduodenal wall. LAMS (15 mm diameter, AXIOS; Boston Scientific, Europe) was deployed and an additional plastic stent

was used in case of necrotic content > 50% for avoiding the early obstruction of LAMS. A transpapillary stent was placed when imaging raised suspicion of a disconnected pancreatic duct. Direct endoscopic necrosectomy was performed after the index procedure, at the discretion of the endoscopist, when necessary, if obstruction by necrotic tissue or inflammation (fever, leukocytosis, high C-reactive protein) occurred. Solid, non-adherent necrotic debris was removed using rat-tooth forceps, a small snare, or a Dormia basket through a gastroscope inserted into the WON.

Patients were discharged after the clinical resolution of symptoms (pain, jaundice, emesis, or fever) and normalization of leukocyte counts and CRP levels. They were readmitted if fever or abdominal pain occurred. Complications were managed in a multidisciplinary manner.

Lumen-apposing metal stents were removed when CT showed a residual cavity of less than 3 cm with no solid content. This was usually around 30 days after the index procedure, but earlier if collateral circulation was present, or later if the nutritional status was poor.

Clinical examination and transabdominal ultrasound were carried out at one month and every four to six months afterwards. A control CT scan was performed in the first year of follow-up to assess recurrence, or whenever it was considered necessary.

Assessment of Endocrine Pancreatic Function

In the study group A, the endocrine pancreatic function was assessed by FPG and/or HbA1c, when available, at the following timepoints: on admission, before endoscopic placement of LAMS, during hospitalization, at discharge and during follow-up: at 1 month and 1 year after LAMS removal. In the control groups B and C, endocrine function was evaluated at admission, during hospitalization, at discharge, at 1 month and at 1 year during the follow-up period. Patients were diagnosed as having diabetes based on the American Diabetes Association (ADA) criteria [30], or if they required insulin or an oral hypoglycemic agent. Glycemic control was considered poor if HbA1c was ≥7% or FPG ≥130 mg/dl, when HbA1c was not available [30].

Endpoints

The endpoint data analyzed included the frequency of NOD in the study and control groups, diabetes treatment, glycemic control, number of DEN, presence of DPD, clinical resolution, and clinical recurrence of WON. The clinical resolution was defined as a WON diameter at follow-up < 3 cm and no related symptoms. Clinical recurrence was defined as WON diameter > 3 cm at follow-up imaging.

Statistical Analysis

We used mean ±standard deviation (SD) [95% confidence interval (CI)], as well as extreme and median values to describe the quantitative data. We calculated absolute and percentual frequencies for the qualitative data. To study the relationships between variables, we used the T or Mann-Whitney (MW) or Kruskal-Wallis (KW) tests, as appropriate. We presented the p values generated by these tests, as well as the mean ±SD of the groups, and the difference between the means with associated 95% CI. To describe the relationships between the qualitative variables, we used the Chi^2 or Fisher's test and the Cramer phi or V and Odds-Ratio (OR) indicators with 95% CI. Multivariate logistic regression was used to assess potential predictors of new-onset diabetes. The variables in the model were selected based on the results of the univariate analysis and the clinical characteristics. We used Microsoft Excel for database management. We used R 4.1.1 for all statistical analyses and subsequent graphs. We considered that $p < 0.05$ was statistically significant while $p < 0.10$ showed only a tendency towards statistical significance.

RESULTS

Characteristics of the Study Participants

The study group included 50 patients with symptomatic WON treated by EUS-guided drainage with LAMS, and DEN in 33 of them (66%). Thirteen patients (26%) had DM before AP onset and were excluded (Supplementary Table I). Group A included patients with symptomatic WON without previous DM (37 patients, (74%). The control group B included 37 patients with asymptomatic WON, and the control group C included 50 healthy individuals. The two control groups were matched for age (53 vs. 58, respectively, 61 vs. 58 years) and gender (67.6% vs. 73%, respectively, 66% vs. 73% men) with the study group A and had similar followed-up periods (Table I).

In group A, the patients had more necrosis of the pancreatic parenchyma ($p<0.001$) and a significantly higher mCTSI score than in group B (9.41 ±0.927 vs. 8.00 ±1.33, $p<0.001$). There were no differences between the two groups in terms of BMI, smoking status, etiology, or location of WON (Supplementary Table II).

Endocrine Pancreatic Function

In group A, from 37 patients without DM before the AP episode, NOD developed in 10 of them (27%), in two patients immediately after EUS-guided drainage, and in eight patients during follow-up (Table I), with half of the NOD patients requiring insulin treatment (Table II). None of the patients had any evidence of CP at the one-year follow-up.

The group A patients with NOD were predominantly male (60%), with a median age of 63.5 years and a mean BMI of 26.86 ±4.39. The most common AP etiology was biliary in eight patients (80%) (Table II). The body and tail of the pancreas were affected in all patients, and eight patients (80%) had more than 50% necrosis of the pancreatic tissue. DEN was performed in nine of these patients (90%), with four DEN sessions per patient. DPD was found in three patients (30%) with NOD and WON recurrence in two (20%) (Table II). All the cases with recurrent WON had DPD.

The frequency of NOD in group A was higher than in group B (27% vs. 18.9%); however, these differences did not reach statistical significance ($p=0.581$) (Table I). The characteristics of NOD, the need for insulin therapy, and glycemic control were similar in these two groups (Supplementary Table III).

Also, the frequency of NOD in group A was higher than in group C (27.0% vs. 2%, $p<001$) (Table I).

Table I. Occurrence of diabetes in group A (symptomatic WON), control group B (asymptomatic WON) and control group C (healthy patients)

Parameters	Group A (n=37)	Group B (n=37)	Group C (n=50)	Group A vs. Group B	Group A vs. Group C
				p	p
Age (years), M(min:max)	58 (33:81)	53 (38:79)	61 (47:78)	0.219	0.409
Gender, n (%)					
Female	10 (27.0)	12 (32.4)	17 (34.0)	0.800	0.640
Male	27 (73.0)	25 (67.6)	33 (66.0)		
Follow-up time, (months), M(min:max)	12 (12:17)	12 (12:15)	12 (12:16)	0.795	0.072
DM at 1 year, n (%)	10 (27.0)	7 (18.9)	1 (2.0)	0.581	<0.001
Onset of DM, n (%)					
until discharge	2 (20.0)	1 (14.3)	0	0.761	0.621
1st months after discharge	0	0	0		
1st month until 1 year after discharge	8 (80.0)	6 (85.7)	1 (100)		

WON: walled off necrosis; DM: diabetes mellitus; μ ±SD: mean ± standard deviation; M (min:max): median (min:max); MW: Mann-Whitney test; OR: odds-ratio [95% CI] and p value from Fisher's test; V, Cramér V (p value from Chi^2 test).

Patients with NOD vs. Patients without DM in Group A

In univariate analysis, NOD patients were significantly older than non-DM patients (63.5 vs. 56 years, p=0.042), they had more frequent necrosis > 50% of the pancreatic parenchyma (80% vs. 22.2%, p=0.002), and had a body-tail location of WON (100% vs. 18.5%, p<0.001). In addition, the mean mCTSI was higher in NOD patients (p=0.019) while DEN was also performed in more patients (90% vs. 59.3%), with a higher median number of DEN sessions (4 vs. 1, p<0.001). The presence of DPD and WON recurrence were more common in NOD patients (30% vs. 18.5%, p=0.655, respectively, 20% vs. 11.1%, p=0.597) (Table II).

Table II. Predictors of NOD in patients with symptomatic WON treated with EUS-drainage ± necrosectomy in univariate analysis

Parameters	Group A NOD (n=10)	Group A Non-DM (n=27)	Previous DM, excluded from group A (n=13)	a		b	
				p	OR [95% CI) or Cramer V	p	OR [95% CI) or Cramer V
Age(year), M(min:max)	63.5 (54:78)	56 (33:81)	67 (44:75)	0.042		>0.999	
Gender, n (%)							
Female	4 (40.0)	6 (22.2)	7 (53.8)	0.407	OR=2.33 [0.49, 11.07]	0.680	OR=0.57 [0.11, 3.04]
Male	6 (60.0)	21 (77.8)	6 (46.2)				
BMI(kg/m^2), μ ±SD	26.86 ±4.39	27.64 ±3.77	29.97 ±4.07	0.515		0.050	
Weight status, n (%)							
normal weight	4 (40.0)	10 (37.0)	2 (15.4)	0.426	V=0.21	0.017	V=0.59
overweight	5 (50.0)	9 (33.3)	2 (15.4)				
obese	1 (10.0)	8 (29.6)	9 (69.2)				
Current smoking, n(%)	4 (40.0)	11 (40.7)	3 (23.1)	>0.999	OR=0.97 [0.22, 4.26]	0.650	OR=2.22 [0.36, 13.54]
Etiology, n (%)							
alcoholic	1 (10.0)	12 (44.4)	0	0.147	V=0.32	0.178	V=0.46
biliary	8 (80.0)	13 (48.1)	10 (76.9)				
idiopathic	1 (10.0)	2 (7.4)	0				
others	0	0	3 (23.1)				
DM treatment, n (%)							
oral antidiabetic drugs	5 (50.0)		8 (61.5)	0.999	OR=1.00 [0.02, 59.99]	0.685	OR=0.62 [0.12, 3.32]
insulin	5 (50.0)		5 (38.5)				
Glycemic control at 1 year, n (%)							
good control	3 (30.0)		10 (76.9)			0.040	OR=0.13 [0.02, 0.83]
poor control	7 (70.0)		3 (23.1)				

Table II (continued)

Main locations of WON, n (%)							
head	0	4 (14.8)	4 (30.8)	<0.001	V=0.76	0.002	V=0.79
body	0	18 (66.7)	5 (38.5)				
body+tail	10 (100.0)	5 (18.5)	4 (30.8)				
Extent of pancreatic necrosis before drainage, n (%)							
≤ 30%	0	0	0	0.002	OR=0.07 [0.01, 0.43]	0.379	OR=0.29 [0.04, 1.94]
30%-50%	2 (20.0)	21 (77.8)	6 (46.2)				
>50%	8 (80.0)	6 (22.2)	7 (53.8)				
mCTSI score before drainage, μ ±SD	10.00 ±0.0	9.19 ±1.0	9.69 ±0.751	0.019		0.228	
Infected WON, n (%)	8 (80.0)	14 (51.9)	6 (46.2)	0.153	OR=3.71 [0.66, 20.82]	0.197	OR=4.67 [0.70, 31.04]
DEN, n (%)	9 (90.0)	16 (59.3)	8 (61.5)	0.119	OR=6.19 [0.68, 56.07]	0.179	OR=5.62 [0.54, 58.91]
DEN number, n (%)							
1	0	9 (56.2)	4 (50.0)	<0.001	V=0.81	0.098	V=0.61
2	1 (11.1)	4 (25.0)	1 (12.5)				
3	2 (22.2)	3 (18.8)	1 (12.5)				
>4	6 (66.7)	0	2 (25.0)				
DEN, M (min:max)	4 (0:5)	1 (0:3)	1 (0:5)	<0.001		0.017	
Additional plastic stent, n (%)	2 (20.0)	8 (29.6)	1 (7.7)	0.694	OR=1.68 [0.29, 9.75]	0.560	OR=0.33 [0.03, 4.32]
Median days from stent placement to removal	36	30	30	0.347		0.575	
DPD, n (%)	3 (30.0)	5 (18.5)	2 (15.4)	0.655	OR=1.89 [0.36, 9.97]	0.618	OR=2.36 [0.31, 17.85]
WON recurrence, n (%)	2 (20.0)	3 (11.1)	1 (7.7)	0.597	OR=2.00 [0.28, 14.20]	0.560	OR=3.00 [0.23, 38.87]
Cholesterole (mg/dL), μ±SD	145.60 ±44.6	182.19 ±57.0	225.15 ±75.6	0.090		0.007	
Triglycerides (mg/dL), μ±SD	139.20 ±52.2	147.70 ±71.6	153.75 ±39.9	0.959		0.621	

NOD: new-onset diabetes; a: Group A NOD patients vs. Group A non-DM patients; b: Group A NOD patients vs. previous DM patients excluded from group A; BMI: body mass index; mCTSI: modified computed tomography severity index; DEN: direct endoscopic necrosectomy; DPD: disconnected pancreatic duct syndrome; μ ±SD: mean ± standard deviation; M (min:max): median (min:max); OR: odds-ratio [95% CI] and p value from Fisher's test; V: Cramér V (p value from Chi^2 test).

In multivariate analysis, only the number of DEN sessions was found to be a significant factor for NOD occurrence (OR=7.05, 95% CI: 2.38- 58.54, p=0.010), whereas age lost its significant effect (p=0.057) (Table III).

Table III. Multivariate analysis of NOD predictors in patients with symptomatic WON

Predictors	OR	95% CI	p value
Age (10 years)	7.64	1.43 – 131.18	0.057
Current smoker	13.58	0.53 – 1772.93	0.166
BMI (5 kg/m2)	6.88	0.78 – 277.77	0.161
Extent of pancreatic necrosis >50%	0.45	0.00 – 62.15	0.729
DEN number	7.05	2.38 – 58.54	0.010

NOD: new-onset diabetes; WON: walled off necrosis; BMI: body mass index; DEN: direct endoscopic necrosectomy; OR: odds-ratio; CI: confidence interval.

Patients with NOD (Group A) vs Patients with Previous DM (Excluded from Group A)

In univariate analysis, compared to patients with previous DM, NOD patients were more frequently non-obese (90% vs. 30.8%, p=0.017) and had normal serum cholesterol levels (145.60 ±44.6 vs. 225.15 ±75.6, p=0.007). Their WON involved the body and tail of the pancreas (100.0% vs. 30.8%, p=0.002) and required a higher number of DEN sessions (4 vs. 1, p=0.017). There was no difference in the need for insulin therapy between patients with NOD and those with previous DM (Table II). At the one-year follow-up, a significantly higher number of patients with NOD had poor glycemic control compared to patients with previous DM (70% vs. 23.1%, p=0.040) (Table II).

In multivariate analysis, the associations found in the univariate analysis did not retain their statistical significance (Table IV).

Table IV. Multivariate analysis for NOD vs. previous DM in patients with symptomatic WON

Predictors	OR	95% CI	p value
Age (10 years)	0.54	0.06 – 5.70	0.573
Gender (Female)	2.71	0.06 – 205.56	0.599
BMI	0.72	0.07 – 7.98	0.775
Cholesterol	0.76	0.47 – 1.01	0.127
DEN number	1.64	0.79 – 4.03	0.211

NOD: new-onset diabetes; DM: diabetes mellitus; BMI: body mass index; DEN: direct endoscopic necrosectomy; OR: odds-ratio; CI: confidence interval.

DISCUSSION

This study showed that DM after EUS-guided drainage followed by DEN, if required, occurred in 27% of the patients with symptomatic WON, compared to 18.9% in the asymptomatic WON group without any minimally invasive therapy and 2% in the healthy control group, half of them requiring insulin for glycemic control. Only the number of DEN sessions influenced the occurrence of NOD in symptomatic WON patients, but not the CT severity index, or the location of WON. NOD occurred especially in non-obese patients and had poorer glycemic control than patients with previous DM.

Acute pancreatitis is increasingly recognized as a major cause of diabetes. However, data on the incidence of diabetes following AP are inconsistent, ranging from rare cases to more than half of patients developing diabetes [20, 22-26]. A meta-analysis of 24 studies found a 15% one-year prevalence of NOD, with the risk significantly increasing at five years [25]. A 2019 meta-analysis found a similar incidence of 20% within five years and of 37% after five years [31]. In contrast, a study using a large population-based database from Taiwan reported a three-month NOD incidence of 6% per person-year and of 2.25% after three months [32].

In surgical series, the minimally invasive treatment of pancreatic necrosis compared to open surgery was associated with lower rates of endocrine insufficiency (40% vs. 64%) or exocrine insufficiency (29% vs. 56%) after a mean of 86 months of follow-up [33], thus highlighting the advantage of the minimally invasive procedure. For this reason, EUS-guided treatment is preferred in symptomatic WON located in the upper abdomen [10], because of its comparable efficacy and lower morbidity and mortality compared with minimal surgery [11-14, 20]. However, the effect of treatment for symptomatic pancreatic necrosis on the endocrine pancreatic function has been reported in fewer patients [34-36], data being consistent with our results. A six-month follow-up study on 22 patients with infected pancreatic necrosis, who underwent endoscopic transluminal drainage with or without necrosectomy, found a 27.3% incidence of NOD, with no difference compared to the surgical group [34]. In a 27-month follow-up study on 60 patients, the incidence of NOD in WON patients who underwent endoscopic drainage and necrosectomy was 20% [37]. Two studies on 65 and 17 patients, respectively, found that 27.7% and 24% of WON patients treated endoscopically developed NOD during one year of follow-up [36, 38].

The strength of our study lies in the comparison with the control groups. In our study, diabetes occurred more frequently in WON patients treated with EUS drainage with LAMS than in asymptomatic WON controls treated conservatively, at the one-year follow-up (27% vs. 18.9%). These findings are consistent with those of previous studies [20, 39]. A study found a higher incidence of endocrine insufficiency at 46 months of follow-up in patients who underwent necrosis intervention compared to those who recovered with medical therapy (38% vs. 19%) [39], similar to our results. Another study [20] found a 66.3% prevalence of NOD in the debridement group compared with 29.1% in the non-debridement group. These findings may highlight the significance of necrosis intervention in the development of diabetes in patients with acute necrotizing pancreatitis.

New onset diabetes was also found more common in patients with WON and EUS drainage with LAMS when compared to healthy controls, with no history of diabetes, pancreatic or chronic disease (27% vs. 2%, p=0.002). This is consistent with another study that found a two-fold increased risk of developing diabetes after an AP episode compared with the general population [32].

The association between NOD occurrence and the severity of pancreatitis is conflicting in the literature: no association in some studies [18, 25, 32], whereas others have found a strong correlation [20, 21, 26, 40]. Our results showed that the severity of necrosis according to the CT severity index was higher in patients who developed NOD than in those without DM only in univariate analysis, while this influence was not maintained in multivariate analysis. Pancreatic necrosis has been associated with an increased risk of endocrine pancreatic insufficiency and diabetes in many studies [20, 26, 27], the extent of the necrosis being a determining factor [20, 41-43]. The incidence of NOD in infected WON patients was higher in cases of extended necrosis (57.7% in patients with more than 50% necrosis compared to 19.4% in patients with less than 30% necrosis), as well as when the necrosis was located in the tail of the pancreas, according to one study [20], perhaps because the tail of the pancreas contains more islets that are impaired by pancreatic necrosis [44-46]. These findings are consistent with those of our study, which showed that pancreatic necrosis extended to > 50% of the pancreatic parenchyma, as well as WON located in the body and tail of the pancreas, was significantly more frequent in NOD patients than in those without DM ($p = 0.002$, $p<0.001$), although this was not a significant independent factor when the number of DEN sessions were considered. Even if in surgical series necrosectomy was related to the occurrence of DM [26, 27, 47, 48], we found a seven-fold risk of NOD when four or more DEN sessions were performed.

Several studies have found that DPD has a significant effect on the occurrence of NOD [49, 50]. Despite the higher frequency of DPD in NOD patients compared to non-DM patients, we found that DPD was not related to the occurrence of DM in our study. However, the incidence of recurrent WON was low in our study, findings that are consistent with those of previous studies [50, 51].

Despite the more common biliary etiology, our study found no significant association between the biliary or

alcoholic etiology of AP and the development of NOD, which is consistent with previous findings [20, 25]. However, some studies [31, 52] have found a higher risk of developing diabetes in alcohol-related AP.

Moreover, associations between NOD and middle-aged adult patients were established [32, 53, 54], with men under the age of 45 having the highest age-specific risk, followed by men aged between 45 and 64 years [32]. However, these findings have not been confirmed by other studies [43, 55]. In our study, NOD patients were older compared to patients without diabetes, but, according to multivariate analyses, age had only a minimal effect on the occurrence of NOD (OR=7.64, p=0.057). A possible explanation for this trend could be the exponential increase in the prevalence of diabetes after 45 years of age [46, 56], as well as the effect of aging on β-cell function and the increased insulin resistance related to visceral adiposity [25].

Post-pancreatitis DM is associated with poor glycemic control, a lower BMI at diagnosis, a higher risk of developing cancer, death at a younger age, and a significantly higher risk of mortality than type 2 DM [57-59]. These findings are consistent with our study, which showed that NOD patients were more likely to be normal or overweight compared to patients with prior DM (90% vs. 30.8%, p=0.017), while also having lower cholesterol levels and a higher median number of DEN sessions. In addition, at the one-year follow-up, a higher percentage of patients with NOD after AP had poor glycemic control compared to patients with prior DM (70% vs. 23.1%, p=0.040), half of them already being on insulin treatment.

Our study has several limitations. First, it was a retrospective analysis of prospectively collected data on a small number of patients. Second, we defined NOD based on FPG and/or HbA1c, when available. This has the risk of underestimating the number of patients with NOD, whereas measurement of HbA1c in all patients or of C-peptide could have led to a more accurate estimate. Third, the short follow-up period after treatment (one year) may have resulted in the omission of patients who could have developed DM after this period.

CONCLUSIONS

New onset diabetes occurred in 27% of previously non-diabetic patients with symptomatic WON treated with EUS-guided drainage during a one-year follow-up, which was higher than the 18.9% recorded in asymptomatic WON patients and 2% recorded in healthy controls. Patients with extensive pancreatic necrosis were more likely to develop NOD, a high number of DEN sessions being a significant risk factor for NOD occurrence. In addition, compared to patients with prior DM, NOD patients were more likely to be normal or overweight, they had poor glycemic control and required a higher number of DEN sessions to achieve WON resolution.

Considering the small group of patients, further multicenter prospective studies are needed to predict the risk of developing DM after EUS-guided drainage of WON with LAMS.

Conflicts of interest: None to declare.

Authors' contribution: T.M., A.S. conceived and designed the manuscript. A.S.S., L.N., V.R. collected and analyzed the data. T.M. analyzed and interpreted the data and drafted the manuscript. A.I. performed the statistical analysis. M.M.M., C.P., R.S. revised the manuscript. A.S. critically revised and analyzed the final version of the manuscript. All authors approved the final version to be published, and agreed to be accountable for all aspects of the work.

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