Glycemic Abnormalities in Pancreatic Cystic Lesions—A Single-Center Retrospective Analysis

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Abstract: Background and Objectives: Glucose metabolism alterations are very common in solid pancreatic lesions, particularly in pancreatic cancer. Similarly, diabetes and especially new-onset diabetes (NOD) have been associated with the malignant transformation of pancreatic cysts. We aimed to assess the prevalence and relevant associations of glycemic abnormalities in pancreatic cystic lesions (PCLs) in a retrospective analysis. Materials and Methods: We retrospectively recruited all patients who underwent endoscopic ultrasound for a PCL over a period of 36 months (January 2018 to December 2021). Final diagnosis was set by means of tissue acquisition, surgery, follow-up, or board decision. Demographic and clinical data, laboratory workup, and imaging features were extracted from the patients’ charts according to a predefined protocol. We considered fasting blood glucose (FBG) and HbA1c values and stratified the patients as nondiabetic (FBG ≤ 99 mg/dL, HbA1c ≤ 5.6%, no history of glycemic abnormalities), prediabetic (FBG 100–125 mg/dL, HbA1c 5.7–6.4%), or diabetic (long-lasting diabetes or NOD). Results: Altogether, 81 patients were included, with a median age of 66 years, and 54.3% of them were male. The overall prevalence of fasting hyperglycemia was 54.3%, comprising 34.6% prediabetes and 22.2% diabetes, of which 16.7% had NOD. The mean FBG and HbA1c levels were higher in malignant and premalignant PCLs (intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), cystadenocarcinoma, and cystic neuroendocrine tumor) compared to the benign lesions (pseudocysts, walled-off necrosis, and serous cystadenoma): 117.0 mg/dL vs. 108.3 mg/dL and 6.1% vs. 5.5%, respectively. Conclusions: Hyperglycemia and diabetes are common in PCLs, with a high prevalence in premalignant and malignant cysts. Screening and follow-up for glycemic abnormalities should be routinely conducted for PCLs, as they can contribute to a tailored risk assessment of cysts.

Keywords: diabetes; new-onset diabetes; pancreatic cysts; cancer

1. Introduction

Glucose metabolism alterations have frequently been reported in pancreatic diseases, both in benign and in malignant pathologies [1,2]. Among them, the bidirectional relationship between pancreatic cancer and diabetes mellitus (DM) has been extensively studied—on the one hand, long-standing diabetes is regarded as a risk factor for the occurrence of pancreatic ductal adenocarcinoma (PDAC), and on the other hand, malignant pancreatic lesions induce or worsen preexisting DM by paraneoplastic phenomena to such an extent that new-onset or worsening diabetes has been proven to be a harbinger of pancreatic malignancy [3,4]. Moreover, further stratifying the population of individuals with new-onset diabetes (NOD) by additional risk factors has been proposed as a screening strategy for PDAC [5]. A high-risk profile for PDAC has been defined as NOD individuals over 50 years of age, with weight loss and poorly controlled diabetes, in contrast...
to non-PDAC-related DM, which is usually associated with weight gain in patients with metabolic syndrome and is not as severe at onset [6]. Another population at risk for PDAC is represented by patients with pancreatic cysts, in whom surveillance is recommended [7,8].

Based on the association between diabetes and solid pancreatic tumors, there has been growing interest in a potential similar link with pancreatic cystic lesions (PCLs). Several papers have reported a higher prevalence of PCLs among diabetics compared to the general population [9], and DM has been reported to be more prevalent in patients with PCLs [10]. Moreover, a systematic review concluded that the prevalence of DM in intraductal papillary mucinous neoplasms is high, and that diabetics have a more aggressive disease course [11]. Others have shown that patients with diabetes and pancreatic cysts have larger cyst sizes at diagnosis and a faster cyst growth rate than individuals without diabetes [12]. Due to its association with an increased risk of malignancy and progression of a PCL [13], and its impact on pancreatic surgery outcomes [14], the presence of diabetes should be checked systematically in these patients and included in the risk-stratification and decision-making process. Similarly to solid pancreatic neoplasia, NOD has been associated with malignant cysts and the progression of lower-risk cysts [15–18].

In the current study, we aimed to assess the association between DM and PCLs in a retrospective analysis at our center, with regard to the prevalence and severity of glucose abnormalities according to different cyst types.

2. Materials and Methods

This study was conducted in a tertiary academic hospital in Bucharest, Romania. We retrospectively recruited all patients who underwent endoscopic ultrasound (EUS) for a PCL during a period of 36 months (January 2018 to December 2021). Final diagnosis was set by means of tissue acquisition, surgery, follow-up, or board decision. We excluded patients for whom a final diagnosis or at least 12 months of follow-up was not available. Moreover, solid lesions with cystic transformation or necrosis were not included in the analysis.

Demographic and clinical data, laboratory workup, and imaging features were extracted from the patients’ hospital electronic charts. Regarding the glycemic status, we considered the fasting blood glucose (FBG) and HbA1c values, and we stratified patients as nondiabetic (FBG \(\leq 99\) mg/dL, HbA1c \(\leq 5.6\)%, no history of glycemic abnormalities), prediabetic (FBG 100–125 mg/dL, HbA1c 5.7–6.4%), or diabetic (already diagnosed with DM, either long-lasting or new-onset DM), according to currently available guidelines [19]. In patients with divergent FBG and HbA1c levels, we considered the highest value of the two parameters when classifying patients as prediabetic or diabetic. We also checked the patient records for potential treatments that might affect glucose metabolism. We excluded patients for whom data regarding their glycemic status or the presence of DM were not available or were inconclusive. Endoscopic ultrasound was carried out by two experienced examiners, using a Hitachi ultrasound system and linear echoendoscope. All the included patients agreed through the hospital consent form to data collection (including the storage and use of medical images) for the purpose of medical research.

3. Results

Altogether, 81 patients were recruited for the purpose of this study, with a median age of 66 years, and 54.3% of them were male. Among the PCLs found, 50.6% were located in the head/uncinate process and 49.4% were located in the body/tail of the pancreas. We identified 27 inflammatory fluid collections (pseudocyst or walled-off necrosis); 35 intraductal papillary mucinous neoplasms (IPMNs), of which 9 were main duct (MD)-IPMN, 25 were side branch (SB)-IPMN, and 1 was mixed-type IPMN; 9 mucinous cystic neoplasms (MCNs); 4 cystadenocarcinomas; 5 serous cystadenomas (SCAs); and 1 cystic neuroendocrine tumor (NET). The patients’ characteristics and distribution according to the type of cystic lesion are summarized in Table 1.
Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>n = 81 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>44 (54.3)</td>
</tr>
<tr>
<td>Age (median, range)</td>
<td>66, 21–88 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of cystic lesion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>25 (30.9)</td>
</tr>
<tr>
<td>WON</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>IPMN (total)</td>
<td>35 (43.2)</td>
</tr>
<tr>
<td>MD-IPMN</td>
<td>9</td>
</tr>
<tr>
<td>SB-IPMN</td>
<td>25</td>
</tr>
<tr>
<td>Mixed-IPMN</td>
<td>1</td>
</tr>
<tr>
<td>MCN</td>
<td>9 (11.1)</td>
</tr>
<tr>
<td>Cystadenocarcinoma</td>
<td>4 (4.9)</td>
</tr>
<tr>
<td>SCA</td>
<td>5 (6.2)</td>
</tr>
<tr>
<td>NET</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

Abbreviations: WON—walled-off necrosis, IPMN—intraductal papillary mucinous neoplasms, MD—main duct, SB—side branch, MCN—mucinous cystic neoplasm, SCA—serous cystadenoma, NET—neuroendocrine tumor.

The overall prevalence of fasting hyperglycemia was 54.3%, comprising 34.6% prediabetes and 22.2% DM, of which 16.7% was new-onset. The glucose abnormalities in each PCL type are detailed in Table 2 and Figure 1a,b.

Table 2. Glucose abnormality classification according to the PCL type.

<table>
<thead>
<tr>
<th>Glycemic Abnormality Stratification</th>
<th>Non-DM (%)</th>
<th>IFG (%)</th>
<th>Long-Lasting DM (%)</th>
<th>NOD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WON</td>
<td>11 (40.7)</td>
<td>11 (40.7)</td>
<td>3 (11.1)</td>
<td>2 (7.4)</td>
</tr>
<tr>
<td>SCA</td>
<td>5 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPMN</td>
<td>16 (45.7)</td>
<td>11 (31.4)</td>
<td>7 (20)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>MD-IPMN</td>
<td>3 (33.3)</td>
<td>3 (33.3)</td>
<td>2 (22.2)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>SB-IPMN</td>
<td>12 (48)</td>
<td>8 (32)</td>
<td>5 (20)</td>
<td></td>
</tr>
<tr>
<td>Mixed-IPMN</td>
<td>1 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCN</td>
<td>2 (22.2)</td>
<td>3 (33.3)</td>
<td>3 (33.3)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>CystADK</td>
<td>1 (25)</td>
<td>2 (50)</td>
<td>1 (25)</td>
<td></td>
</tr>
<tr>
<td>NET</td>
<td>1 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: WON—walled-off necrosis, IPMN—intraductal papillary mucinous neoplasms, MD—main duct, SB—side branch, MCN—mucinous cystic neoplasm, SCA—serous cystadenoma, NET—neuroendocrine tumor, IFG—impaired fasting glucose, NOD—new-onset diabetes.

The mean FBG and HbA1c levels were higher in the malignant and premalignant PCLs (IPMNs + MCN + CystADK + NET) compared to the benign lesions (pseudocyst + WON + SCA), with values of 117.0 mg/dL vs. 108.3 mg/dL and 6.1% vs. 5.5%, respectively. Regarding the distribution of cysts, patients with tail-located lesions had higher FBG and HbA1c values (141.3 mg/dL and 6%, respectively), compared to those with body (108.2 mg/dL and 5.9%, respectively) and head-located cysts (102.2 mg/dL and 5.8%, respectively).

The prevalence of diabetes was high in patients with cystadenocarcinoma, MCN, and MD-IPMN. Fasting glycemia was also high in pseudocysts and walled-off necrosis (112.3 mg/dL), reflecting the altered glucose metabolism in the setting of pancreatitis. Notably, 4/16 patients with post-pancreatitis inflammatory fluid collections showed complete remission of glucose regulation abnormalities at the 3-month follow-up, after drainage of the collections.

When looking at the cyst size, after excluding the pseudocysts and WON, we found that patients with DM and prediabetes had larger cysts (mean values of 3.4 cm and 3.8 cm, respectively), as compared to nondiabetics (2.8 cm).
4. Discussion

Considering its dismal prognosis, sustained efforts have been made by the academic community to facilitate the early detection of PDAC, in order to improve outcomes. In this setting, NOD has been regarded as a risk factor for PDAC occurrence, and NOD cohorts are being prospectively analyzed in order to better define the PDAC risk [20]. The Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model was recently developed and validated in order to identify new-onset diabetics at high risk for PDAC [21,22], taking into consideration three variables with specific score ranges—change in blood glucose from one year before diagnosis (A), weight change (B), and age at NOD diagnosis (C). A total score (A + B + C) of at least 3 was found to successfully identify patients who developed PC within three years of the NOD diagnosis with 80% sensitivity and specificity. Of clinical importance is the fact that pancreatic cancer patients suffered from weight loss...
before the diagnosis, while the controls gained weight after NOD diagnosis. Regarding the serum HbA1c level, there was a significant annual increase in the study group, compared with the control group (1.3% vs. 0.82%, \( p = 0.02 \)) [22]. Moreover, several biomarkers are being assessed for the differential diagnosis of conventional DM and PDAC-associated DM [23,24].

Diabetes in PDAC is recognized as being a paraneoplastic phenomenon since factors other than the simple mass effect of the tumor seem to contribute to its development in malignant pancreatic lesions (Figure 2). Current knowledge on these paracrine mechanisms focuses on the \( \beta \) cell dysfunction driven by the tumor-secreted products: exosomes are released from pancreatic neoplastic cells, which, in turn, deliver adrenomedullin to \( \beta \) cells and induce oxidative stress and cell death [25,26]. Another molecule of interest is represented by osteoprotegerin (OPG), a member of the TNF receptor super-family that has been shown to affect glucose homeostasis; while OPG levels are increased in patients with both type 1 and type 2 diabetes, compared to controls [27], Shi et al. showed that OPG levels are increased in patients with NOD associated with PDAC as compared to patients suffering from type 2 DM, suggesting the potential benefit of this peptide as a biomarker for diagnosing NOD related to pancreatic cancer [28]. Moreover, the paracrine mechanism of DM in PDAC is also supported by surgical series: there is evidence that glycemic control can improve after subtotal pancreatectomy for pancreatic cancer, despite a reduction in insulin secretion, as revealed by Permert et al. [29]. Pannala et al. also reported that following pancreaticoduodenectomy, more than half of the patients who were previously diagnosed with NOD no longer met the criteria for diabetes after surgery [30].

Figure 2. Paracrine and mass effect of pancreatic tumors on diabetes occurrence.

Along with NOD individuals, patients with PCLs are also at risk of developing PDAC, and considering the association of PCLs with DM, a three-way relationship (NOD–DM–PCL) arises, which might further contribute to the earlier detection of cancer. PCLs are regarded as a disease of technology, as they are commonly encountered in routine practice due to the widespread use of high-resolution imaging for nonpancreatic-related indications [31]. The challenge facing a PCL is securing a definite diagnosis and deciding on surveillance or surgery. The difficulty lies in the fact that very few PCLs are clinically relevant regarding progression to malignancy, and the pitfalls can be both missing a cancerous lesion and performing unnecessary surgery [32]. There is significant variation in the malignancy risk of different PCLs, from completely benign lesions to those at risk of progression to malignancy and pre-malignant cysts. Malignancy risk is low in SCA and branch-duct IPMN but increases significantly for MCN and main-duct IPMN. In clinical practice, however, it is sometimes challenging to establish a definite preoperative diagnosis for a specific type of cyst, and this can lead to erroneous decisions. In this setting, over the last two decades, several guidelines have been proposed in order to aid clinicians in the decision-making process [33–37], but the analysis of the management decisions based on the current tools is far from optimal [32,38,39]. Also, improvements in imaging and EUS techniques in particular, such as contrast enhancement, confocal laser endomicroscopy, or through-the-needle microbiopsy forceps, have contributed to a more precise diagnosis and
change in management in a significant proportion of cysts [40,41]. In addition, surgical outcomes have improved significantly through advances in surgical techniques and better assessment of patient risk.

In recent years, an extrapolation of the strong link between PDAC and DM has been theorized for pancreatic cysts as well, although with some limitations: the spectrum of PCLs is very heterogenous compared to that of PDAC, and the paracrine mechanisms of PDAC-associated DM do not apply for benign PCLs. Despite these drawbacks, owing to the implications for decision making regarding a cystic lesion, as well as the consequences on pancreatic surgery outcomes, the bidirectional link between DM and PCLs has been increasingly studied. In this setting, while most guidelines focus on the morphological features of a cystic lesion and cyst fluid analysis for the management of PCLs [42,43], DM and NOD in particular have been incorporated into indications for surgical resection in the recent literature [44]. In addition, the trophic effect of some antidiabetic agents such as GLP (glucagon-like peptide)-1 analogues, DPP-IV (dipeptidyl peptidase IV) inhibitors, or insulin has been considered as a risk factor for pancreatic malignancy [45,46] (Figure 3). In addition to the markers of glucose metabolism (fasting blood glucose, glycated hemoglobin (HbA1c)), other biomarkers can be useful in assessing the malignancy risk of PCL and progression during surveillance, such as the serum CA 19-9 value in IPMN, which, similar to NOD, is considered a relative indication for surgery according to the European guideline on cystic pancreatic tumors [44].

Several studies have reported an increased frequency of PCLs among patients with DM, 3.5 times higher among diabetics than among nondiabetics; the associated risk factors reported in the studies were male sex, obesity, cardiovascular comorbidities, and a history of smoking [9,47]. Moreover, the presence of DM is reported as a risk factor for a larger cyst size (2.42 cm vs. 1.62 cm) and a faster growth rate (0.15 vs. 0.11 cm/year), when
compared to nondiabetics [12]. In our study, we obtained similar findings regarding cyst size and the presence of diabetes: in diabetics, the mean cyst size was 3.4 cm, compared to 2.8 cm in nondiabetics. Interestingly, we found a slightly larger cyst size in patients with prediabetes—3.8 cm—which again emphasizes the need for close follow-up of these patients with respect to both the cyst growth rate and the deterioration of glycemic control.

In our study, there was a high prevalence of abnormal fasting glucose and diabetes among patients with PCLs (54.3%, with 22.2% DM), similar to the results reported by other authors but lower than those seen in pancreatic cancer [30] (Table 3). According to the research results summarized in Table 3, patients with different types of PCLs, some of which are known precursors of pancreatic cancer, have a variable prevalence of DM. Among them, IPMNs were the most studied with regard to the prevalence of long-standing DM and NOD, along with MCN and, to a lesser extent, pseudocysts and serous cystic neoplasms.

In addition, an association between HbA1c in the prediabetic range or higher and the presence of a cyst has also been reported in the high-risk populations proposed for pancreatic surveillance [48].

**Table 3.** The prevalence of diabetes in PCL series, compared to controls and pancreatic cancer patients [10,12,16–18,30,49–54].

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence DM (%)</th>
<th>LSDM (%)</th>
<th>NODM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pannala et al., 2008 [30]</td>
<td>7.2%</td>
<td>47%</td>
<td>53%</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>47.4%</td>
<td>26%</td>
<td>74%</td>
</tr>
<tr>
<td>Lubetzky et al., 2009 [51]</td>
<td>IPMN</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Leal et al., 2015 [49]</td>
<td>IPMN</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Nguyen et al., 2014 [50]</td>
<td>IPMN</td>
<td>24.20%</td>
<td>NS</td>
</tr>
<tr>
<td>Morales-Oyarvide et al., 2017 [16]</td>
<td>IPMN</td>
<td>34%</td>
<td>NS</td>
</tr>
<tr>
<td>Perez-Cuadro-Robles et al., 2018 [53]</td>
<td>IPMN</td>
<td>15%</td>
<td>NS</td>
</tr>
<tr>
<td>Del Chiaro et al., 2020 [54]</td>
<td>IPMN</td>
<td>21%</td>
<td>NS</td>
</tr>
<tr>
<td>Schweber et al., 2020 [18]</td>
<td>MCN/IPMN</td>
<td>27.60%</td>
<td>NS</td>
</tr>
<tr>
<td>Deng et al., 2022 [17]</td>
<td>IPMN, MCN, SCN</td>
<td>24.1%</td>
<td>9.37%</td>
</tr>
<tr>
<td>Mizuno et al., 2017 [10]</td>
<td>NS</td>
<td>18.4%</td>
<td>NS</td>
</tr>
<tr>
<td>Yoshioka et al., 2020 [50]</td>
<td>IPMN</td>
<td>19%</td>
<td>NS</td>
</tr>
<tr>
<td>Kadosh et al., 2021 [12]</td>
<td>PC</td>
<td>34.8%</td>
<td>NS</td>
</tr>
</tbody>
</table>

IPMN, intraductal papillary mucinous neoplasm; PC, pseudocyst; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; PCN, pancreatic cystic neoplasm; PC, pancreatic cyst; NS, not specified.

In our study, the highest HbA1c values were observed in MCN (7.1%) and cystadenocarcinoma (6.4%), followed by MD-IPMN (6%) (Figure 4). Considering that IPMNs represent the majority of PCLs and that the guidelines emphasize the absolute/relative indications for surgery, referring to worrisome features (WF) or high-risk stigmata (HRS), several authors have shown that the consideration of DM is important, as DM is associated with a higher risk of high-grade dysplasia or invasive carcinoma. Moreover, the risk of invasive cancer is highest in NOD patients [16]. This has fueled researchers to recommend aggressive surveillance for patients with IPMN who are diagnosed with DM [16]. One of the pitfalls of the current guidelines is the so-called Sendai-negative or Fukuoka-negative IPMNs, which harbor a nonnegligible malignancy risk according to some surgical series [55,56], and DM might be the additional feature in tipping the scale towards resection [57]. In the French experience reported by Duconsell et al., diabetic males with Fukuoka-negative branch-duct IPMN had a malignancy rate of 67% [57]. On the other hand, there is the risk of excessive surgery, with a study from two referral centers in Europe reporting that 40% of patients resected according to European guidelines had only low-grade dysplasia [58]. These results concerning presumptive malignant IPMNs which are not confirmed in the surgical specimen challenge current decision making and raise
questions about potentially excessive resections. Of note, Marchegiani et al. [14] reported
that complications after surgery did not spare resected patients in whom malignancy was
not confirmed in the surgical specimen; also, considering the impact of DM on the surgical
outcome, the authors concluded that in diabetic patients with uncertain malignant cysts
proposed for distal pancreatectomy, close surveillance might be a safer option.

Figure 4. Diabetes risk according to PCL subtype. Abbreviations: SCA—serous cystadenoma, PFC—
pancreatic fluid collection, IPMN—intraductal papillary mucinous neoplasms, MCN—mucinous
cystic neoplasm, CystADK—cystadenocarcinoma.

An interesting correlation was observed in post-pancreatitis inflammatory fluid collec-
tions, which were part of our PCL cohort. Among them, 4 out of 16 patients with diabetes or
prediabetes showed complete remission of glycemic abnormalities at three months after the
drainage of the collection and post-pancreatitis recovery, suggesting transient abnormalities
in glucose metabolism. In the setting of acute pancreatitis (AP), glycemic abnormalities are
regarded as a consequence of direct pancreatic injury. Given the fact that improvement of
glycemic control is anticipated after drainage of peripancreatic fluid collections, follow-up
for the reversibility of impaired glucose regulation is warranted. On the contrary, patients
with persistently elevated HbA1c levels or those who develop type 3c DM may be at risk of
pancreatic malignancy, and in particular clinical settings, such as the presence of associated
risk factors, they should be recommended for follow-up. To further define the magnitude
of this risk, in patients with persistent glucose impairment after drainage of pancreatic fluid
collections, prospective cohort studies with systematic follow-up are needed. Irrespective
of the presence of post-pancreatitis DM, AP is a recognized risk factor for pancreatic neo-
plasia, with the risk being highest in the first years after the pancreatitis flare and gradually
decreasing over time, a time-pattern similar to that of the relationship between PDAC and
DM [59,60]. In addition, we should keep in mind that the first presentation of a PCL can
be as a bout of AP, and differential diagnosis with fluid collection is needed at the first
observation of a pancreatic cyst in this setting.
Regarding the anatomical distribution of PCLs, a high prevalence of glucose abnormalities was seen in patients with pancreatic tail lesions compared to those with head or body cysts. This is supported by studies showing that the metabolic consequences of pancreatectomy are more pronounced in tail lesions with consecutive distal resections, and the fact that islet density and distribution are higher in the tail than in the head and body of the pancreas [61,62]. However, this might be influenced by the particular distribution of different PCLs—MCNs, which are considered high-risk for PDAC and are frequently associated with glucose metabolism impairment, are more commonly located in the body and tail of the pancreas.

In summary, a high prevalence of glycemic abnormalities was observed in our cohort of PCLs, ranging from elevated fasting glucose to new-onset diabetes. The assessment of the glycemic profile of patients with PCL is being increasingly recognized as an important tool for decision making, along with already validated criteria. While most PCLs are low-risk, we should keep in mind that up to 15% of PDAC arises from the progression of a cystic lesion, and the outcomes are different for conventional PDAC compared to PCL-associated carcinoma, with individual prognosis according to the lesion subtype [63–68]. Incorporating DM into the decision making might aid in further risk stratification of the cystic lesions. Models based on NOD, similar to those that have been developed and validated for PDAC, should also be analyzed for PCLs [21,22,69,70]. Extrapolating the temporal relationship reported for PDAC, that glucose abnormalities precede the diagnosis of neoplasia by up to three years, offers a wide window of opportunity for follow-up of at-risk PCLs, with monitoring of HbA1c and the body mass index, in order to select individuals who may progress to malignancy [71,72].

The current investigation has certain limitations. On one hand, it is a retrospective study, which limits us in collecting relevant data regarding metabolic risk and family history of pancreatic neoplasia. On the other hand, there was no control group in our study, but we included patients with pseudocysts as a pseudo-control group to compare the glycemic abnormalities of pancreatic cystic neoplasms with those of inflammatory cystic lesions. We also reported on a selected patient population, including patients who underwent EUS at the decision of the treating physician. However, considering the literature-based added value of DM on top of the currently used EUS criteria for PCL decision making, we might consider our study cohort a real-life PCL population in whom EUS was indicated according to available guidelines and in whom glycemic abnormalities might have impacted treatment decisions. Another limitation was that our lot of cysts did not include the full spectrum of PCLs; however, considering that some of them are rare encounters, the lesions included are relevant for clinical practice.

5. Conclusions

Hyperglycemia and diabetes are common in PCLs, with a high prevalence in cystadenocarcinoma, MD-IPMN, and MCN. Screening and follow-up for glycemic abnormalities should be routinely conducted for PCLs. Routine assessment of glucose metabolism can provide a tailored risk assessment of PCLs, with an emphasis on IFG/NOD or sudden deterioration of glycemic control in patients with previous DM. In order to better define the association between PCL and diabetes, future studies should focus on understanding the molecular mechanisms of pancreatic-cyst-associated diabetes, particularly identifying potential paracrine mechanisms or biomarkers that can distinguish it from other types of diabetes.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Institutional Review Board (Approval no. 345/25 July 2019).

Informed Consent Statement: Informed consent to use data for research purposes was given by patients during admission, in a specific paragraph on the standard hospital consent form.

Data Availability Statement: The dataset is available from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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