Diabetes and Weight Loss Are Associated With Malignancies in Patients With Intraductal Papillary Mucinous Neoplasms

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BACKGROUND & AIMS: **The role of diabetes in intraductal papillary mucinous neoplasms (IPMNs) is not known. We investigated the prevalence of diabetes among patients with resected IPMNs and the association between diabetes, clinical and morphological features, and high-grade dysplasia or invasive cancer.**

METHODS: **We collected clinical, pathology, laboratory, and demographic data from 134 patients who underwent pancreatic resection for IPMN from a referral center in Germany. We identified 50 patients with diabetes (37%).**

RESULTS: **Higher proportions of patients with diabetes were male and older, but did not have increased body mass index, compared to patients without diabetes. Diabetes was significantly associated with main-duct involvement (odds ratio [OR], 2.827; 95% CI, 1.059–7.546; $P = .038$) and high-grade dysplasia or invasive carcinoma (OR, 2.692; 95% CI, 1.283–5.651; $P = .009$). Risk of high-grade dysplasia or invasive cancer was even higher in patients with new-onset or worsening diabetes (OR, 4.615; 95% CI, 1.423–14.698; $P = .011$). Fifty-eight percent of patients (18/31) with weight loss at diagnosis had diabetes vs 32% of patients (31/97) without weight loss ($P = .009$). However, when the analysis was restricted to IPMNs with low-grade dysplasia, weight loss and diabetes were no longer associated (42% [5/12] vs 21% [9/44]; $P = .133$).**

CONCLUSIONS: **In patients with IPMNs, diabetes is associated with increased risk of main duct involvement and high-grade dysplasia or invasive carcinoma. Studies are needed to determine the relationship between diabetes and progression of IPMNs, which might lead to strategies for early detection and prevention of invasive cancer. Findings from this study should be considered in the guidelines for management of IPMN.**

Key Words: Metabolic Disorders; IPMN; Malignant Progression.

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing cystic tumors with variable extension in the pancreatic gland and variable malignant potential.[1,2] IPMN as precursor of pancreatic ductal adenocarcinoma (PDAC) offers a great opportunity for understanding the mechanisms behind the cancerization.[3] Determining risk factors involved in the progression to cancer is of paramount importance to achieve earlier diagnosis and prevention of pancreatic cancer.[3]

The European guidelines for the management of IPMN have recently introduced new-onset diabetes as a relative indication for surgery but with a low level of evidence.[4] Previous guidelines, such as American Gastroenterological Association and revised Fukuoka guidelines, do not mention diabetes mellitus (DM) and other metabolic factors in the management of IPMN.[1,5] In fact, scant attention has been paid in the past to DM and other metabolic disorders in IPMN and our current knowledge on this topic is limited. Previous studies examined mostly overweight as a potential risk factor for developing an IPMN and progression, and DM as long-

Abbreviations used in this paper: **BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; CI, confidence interval; DM, diabetes mellitus; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD-IPMN, main-duct/mixed intraductal papillary mucinous neoplasm; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma.**

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term complication depending on the extension of resection.[6–9] Only a few papers focused on the prevalence of preoperative DM among patients with IPMN and its potential role in the progression to high-grade dysplasia (HGD) and invasive cancer.[7,10–14] By contrast, DM has been much better investigated in PDAC, where it seems to play a double role: as risk factor for PDAC, but also as manifestation/consequence of pancreatic cancer.[15,16] Interestingly, several studies showed that DM induced by PDAC is paradoxically associated with weight loss (eg, as paraneoplastic phenomena preceding the onset of cancer-specific symptoms by several months).[15,17] We have questioned if these metabolic changes also occur in IPMN with HGD and may help for earlier diagnosis and prevention of invasive cancer.

Therefore, this study aimed to examine the prevalence of DM in a cohort of resected IPMNs in a referral center for pancreatic surgery and to evaluate the association of preoperative DM with other clinical-morphological features, with a focus on weight loss, and with the progression to HGD and invasive cancer.

What You Need to Know

Background

The association between diabetes mellitus in intraductal papillary mucinous neoplasm (IPMN) is not clear.

Findings

In 134 patients who underwent pancreatic resection for an IPMN, the overall prevalence of preoperative diabetes was 37%. Diabetes was significantly associated with weight loss, main-duct involvement, and progression to high-grade dysplasia or invasive carcinoma.

Implications for patient care

Diabetes, in patients with IPMNs, appears to be associated with a more aggressive course of neoplasia and should be considered in management of IPMNs.

Materials and Methods

Study Population

A cohort of consecutive patients who underwent pancreatic resection for histologically confirmed IPMN between July 2007 and December 2018 at the Klinikum Rechts der Isar, Technical University of Munich, Germany, were retrospectively reviewed. Patients' demographic and clinicopathologic features were obtained from medical records. Variables included sex, age at initial diagnosis and surgery, personal medical history, preoperative daily medications, symptoms at the time of diagnosis, serum tumor markers (carcinoembryonic antigen, normal value <5 ng/mL; and CA 19.9, normal value 0–37 U/mL), cyst morphology, main pancreatic duct (MPD) features, indication for surgery, date and type of surgery, postoperative course, and final pathological findings. Patients with IPMN associated with pancreatic or duodenal neuroendocrine tumors at pathology were excluded. As well, patients with distinct concomitant PDAC were not considered in the analysis. The study was approved by the Ethics Committee of the Technical University of Munich (approval nr. 118/19s). All authors had access to the study data and reviewed and approved the final paper.

Preoperative DM

The prevalence of preoperative DM, the association of DM with other clinical-morphological features and with the progression to HGD and invasive cancer were the main endpoints of this study. A diabetic status was determined based on the medical reports of the preoperative surgical consultation in case of self-reported history of DM and intake of hypoglycemic medications or insulin. Patients were further categorized as diabetic in case of fasting plasma glucose $\geq$126 mg/dl at the preoperative workup, according to the current American Diabetes Association guidelines.[18] Patients with type I diabetes were excluded from the study.

DM was defined as new onset when diagnosed within 2 years from the diagnosis of IPMN or in conjunction with the preoperative laboratory tests. The presence of worsening DM at the moment of IPMN diagnosis was also collected. In the remaining cases, DM was considered as long-standing.

Clinical-Morphological Features of IPMNs

Patients were defined as asymptomatic when the diagnosis was made in absence of the following symptoms: jaundice, upper abdominal pain, acute pancreatitis, worsening or new-onset DM, unjustified weight loss, or steatorrhea. Weight loss was quantified by the patient at the time of the preoperative visit and was considered as positive when reported as significant ($\geq$5%), unjustified and occurred in the last 6 months/1 year. The diagnosis was achieved by computed tomography, magnetic resonance imaging/magnetic resonance cholangiopancreatography, or endoscopic ultrasonography or endoscopic retrograde cholangiopancreatography. Endoscopic ultrasonography with or without fine needle aspiration was performed at the discretion of the physician; when performed, cytological characteristics and fluid carcinoembryonic antigen levels were collected. The following IPMN characteristics were recorded: predominant location, MPD diameter, cyst size, communication of the cyst with the MPD, presence in the cyst of septations, wall thickening, and solid component with or without enhancement. When patients underwent

primary surveillance for a certain time before surgery, we collected the largest size and the worse features developed by the cyst and the MPD during this time. The presence of associated chronic pancreatitis, clinically or radiologically recognized, was also recorded. IPMN was preoperatively considered as branch-duct IPMN (BD-IPMN) in presence of cysts >5 mm in communication with the MPD but in absence of MPD dilation. IPMNs with MPD dilation ≥5 mm with or without associated side-branch cystic lesions were classified as main-duct/mixed IPMN (MD-IPMN).

Moreover, all patients were retrospectively reviewed for worrisome features and high-risk stigmata according to the revised International Consensus Guidelines.[1] Briefly, worrisome features were acute pancreatitis, cyst size ≥3 cm, thickened or enhancing cyst walls, nonenhancing mural nodules, MPD size of 5–9 mm, abrupt change in caliber of the MPD, lymphadenopathy, and an elevated serum level of CA 19.9. High-risk stigmata were defined by the presence of obstructive jaundice in case of a cystic lesion of the head of the pancreas, MPD ≥10 mm, enhancing solid mass or mural nodule, or cytology positive for HGD or adenocarcinoma.

Surgical Indications

Surgery was performed in patients with signs of malignancy and for patients' decision. The type of resection was planned according to the dimension and the site of the tumor. The final extension of the resection was determined based on the intraoperative findings and the results of the frozen section analysis of the resection margin.

Pathology

At pathology, IPMN were defined as BD-IPMN in presence of cysts >5 mm without the involvement of the MPD. IPMN with MPD involvement with/without associated cystic lesions were classified as MD-IPMN.[1] According to the Baltimore Consensus, IPMNs were classified as (1) IPMNs with low-grade dysplasia (LGD-IPMN), (2) IPMNs with high-grade dysplasia (HGD-IPMN), and (3) invasive ductal carcinoma arising from IPMN (invasive-IPMN).[19] This last was defined as invasive carcinoma originated within the area with the known pancreatic cyst and extended contiguously to the IPMN; by contrast, pancreatic cancer arising away and separately from the IPMN was considered a concomitant or distinct pancreatic ductal carcinoma and these patients were excluded from our analysis.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as median and range. Comparisons of categorical variables were conducted using the chi-square or Fisher exact tests depending on the number of observations. Odds ratio (ORs) and 95% confidence intervals (CIs) were calculated using an unadjusted and multivariable-adjusted binomial logistic regression. Continuous variables were compared by Mann-Whitney U test or Kruskal-Wallis test, as appropriate. All hypothesis tests were 2-sided; statistical significance was set at $P < .05$. Statistical analyses were performed using SPSS Statistics 22 (IBM Corporation, Armonk, NY). This study was designed according to the REMARK (REporting recommendations for tumor MARKer prognostic studies) and STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines.[20,21] All authors had access to the study data and reviewed and approved the final paper.

Results

Of the 148 patients who underwent pancreatic resection for IPMN during the study period, 134 met the selection criteria and were included in the analysis (Figure 1).

Patient characteristics and surgical and pathological data regarding the entire cohort are presented in Tables 1 and 2. Invasive pancreatic cancer arising from IPMN was recognized in 58 (43%) patients, while HGD was present in an additional 16 (12%) patients. The global prevalence of preoperative DM consisted of 37% (n = 50 of 134). In 20 (15%) of them, DM was defined as new-onset or worsening DM: 10 patients showed positive preoperative laboratory tests within 1 month before surgery, while in the remaining 10 cases new or worsening DM led to the diagnosis of IPMN. Overall, 38 (28%) patients were followed for >6 months before surgery. A total of 51% of patients underwent resection because of high-risk stigmata, while only 6 (4.5%) patients without worrisome features or high-risk stigmata at diagnosis or during follow-up were resected for other reasons. In 25 patients of our cohort, new worrisome features or high-risk stigmata or a worsening of them were detected during follow-up. Thirty-five (26%) patients

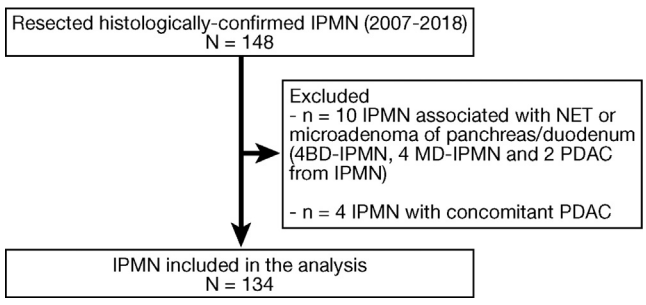

Figure 1. Patient Selection. BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; IPMN, intraductal papillary mucinous neoplasm; MD-IPMN, main-duct/mixed intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; PDAC, pancreatic ductal adenocarcinoma.

Table 1. Clinical-Morphological Features Based on Diabetes Mellitus

	Entire cohort (N = 134)	Nondiabetic patients	Diabetic patients	*P* value
Male	67 (50)	36 (43)	31 (62)	.032[a]
Age at diagnosis, *y*	68 (34–86)	66.0 (34–85)	70.5 (35–86)	.002[a]
Age at surgery, *y*	69 (35–86)	67.5 (36–85)	71 (35–86)	.009[a]
BMI, kg/m^2	24.6 (16.4–41.0), n = 133	24.5 (18–41)	25,3 (16–41)	.115
Comorbidities				
Prostate hypertrophy	7 (5)	2 (2)	5 (10)	.055
Hypertension	72 (54)	40 (48)	32 (64)	.066
Hypercholesterolemia	25 (19)	12 (14)	13 (26)	.092
Cardiovascular disease	18 (13)	11 (13)	7 (14)	.882
Hepatopathy	13 (10)	7 (8)	6 (12)	.488
Dysthyroidism	39 (29)	28 (33)	11 (22)	.162
Autoimmune disease	6 (5)	3 (4)	3 (6)	.511
History of transplantation	3 (2)	3 (2)	0 (0)	.177
Previous cancers	28 (21)	18 (21)	10 (20)	.844
Chronic pancreatitis	29 (22)	18 (21)	11 (22)	.938
Clinical presentation				
Symptoms at diagnosis				
No	45 (35)	30 (38)	15 (30)	.355
Yes	84 (65)	49 (62)	35 (70)	
Abdominal pain				
No	80 (62)	45 (57)	35 (70)	.137
Yes	49 (38)	34 (43)	15 (30)	
Jaundice				
No	111 (85)	71 (89)	40 (80)	.169
Yes	19 (15)	9 (11)	10 (20)	
Weight loss				
No	97 (76)	66 (84)	31 (63)	.009[a]
Yes	31 (24)	13 (16)	18 (37)	
History of acute pancreatitis				
No	102 (80)	60 (76)	42 (86)	.182
Yes	26 (20)	19 (24)	7 (14)	
Steatorrhea				
No	118 (91)	75 (94)	43 (89)	.237
Yes	11 (9)	5 (6)	6 (11)	
Nausea				
No	116 (91)	71 (90)	45 (92)	.711
Yes	12 (9)	8 (10)	4 (8)	
Preoperative CA 19.9, *ng/mL*	22.5 (0–8667), n = 82	13.5 (0–2370)	35 (1–8667)	.042[a]
Preoperative CEA, *ng/mL*	2.3 (0.5–621.0), n = 66	2.3 (0.5–10.2)	2.4 (0.8–621)	.146
Morphological features				
Multifocal localization	57 (43)	28 (33)	29 (58)	.005[a]
Localization				.001[a]
Head	59 (44)	35 (42)	24 (48)	
Body/tail	36 (27)	31 (37)	5 (10)	
Diffuse	39 (29)	18 (21)	21 (42)	
Cyst size max, *mm*	30 (0–100), n = 120	30 (0–100)	32 (11–80)	.064
Main duct size max, *mm*	7 (2–30), n = 130	6 (2–30)	8 (2–22)	.006[a]
MPD 5–9 *mm*				
No	76 (57)	44 (52)	32 (65)	.146
Yes	57 (43)	40 (48)	17 (35)	
History of acute pancreatitis				
No	102 (80)	60 (76)	42 (86)	.182
Yes	26 (20)	19 (24)	7 (14)	
Abrupt change of caliber				
No	120 (90)	75 (89)	45 (92)	.663
Yes	13 (10)	9 (11)	4 (8)	
Cyst size $\geq$3 *cm*				
No	65 (49)	43 (51)	22 (45)	.484
Yes	68 (51)	41 (49)	27 (55)	
Wall Thickening				
No	120 (91)	80 (96)	40 (82)	.004[a]
Yes	12 (9)	3 (4)	9 (18)	

Table 1. Continued

	Entire cohort (N = 134)	Nondiabetic patients	Diabetic patients	*P* value
Nodule/solid component				
No	72 (54)	53 (64)	19 (39)	.005[a]
Yes	60 (46)	30 (36)	30 (61)	
Lymphadenopathy				
No	106 (80)	69 (83)	37 (75)	.287
Yes	26 (20)	14 (17)	12 (25)	
Obstructive jaundice				
No	111 (85)	71 (89)	40 (80)	.169
Yes	19 (15)	9 (11)	10 (20)	
Enhanced solid component				
No	96 (72)	69 (82)	27 (55)	.001[a]
Yes	37 (28)	15 (18)	22 (45)	
MPD ≥10 mm				
No	93 (70)	67 (80)	26 (53)	.001[a]
Yes	40 (30)	17 (20)	23 (47)	
Positive cytology				
No	126 (95)	79 (94)	47 (96)	.641
Yes	7 (5)	5 (6)	2 (4)	

Values are n (%) or median (range).
BMI, body mass index; CEA, carcinoembryonic antigen; MPD, main pancreatic duct.
[a]Significant *P* value (< .05)

underwent total pancreatectomy; however, pancreaticoduodenectomy was the most frequent procedure (44%). At pathology, 94 (75%) patients presented MD-IPMN, while 31 (25%) IPMNs were described as BD. In 9 patients, the type of IPMN was undetermined or unknown.

DM and Clinical-Morphological Features

Comparison results between diabetic and nondiabetic patients are shown in Tables 1 and 2. Patients with DM were more frequently male and older, with no differences regarding other comorbidities. Surprisingly, median body mass index did not correlate with the presence of a diabetic status (median body mass index: 25.3 kg/m^2 in diabetic patients vs 24.5 kg/m^2 in nondiabetic patients; $P = .115$), neither with progression to malignancy. By contrast, at the time of diagnosis, diabetic patients reported more frequently weight loss as a reason for medical consultation and diagnosis of IPMN (37% in diabetic patients vs 16% in nondiabetic patients; $P = .009$). Seven of the 10 patients in whom new-onset or worsening DM was determined for the diagnosis of the IPMN also presented weight loss at diagnosis, but none of them had jaundice. Jaundice showed no association with DM or new-onset DM. In addition, history of acute and chronic exocrine dysfunction of the pancreatic gland did not correlate with the simultaneous presence of endocrine dysfunction. Interestingly, median CA 19.9 was significantly higher in patients with DM (35 mg/dL in diabetic patients vs 13.5 mg/dL in nondiabetic patients; $P = .042$). Of note, in our series higher CA 19.9 was significantly associated with HGD or invasive cancer (12 mg/dl in LGD vs 39.5 mg/dL HGD or invasive cancer; $P = .023$).

Regarding the morphological features of IPMN, the presence of multifocal disease (58% in diabetic patients vs 33% in nondiabetic patients; $P = .005$) and diffuse location in the pancreatic gland (42% in diabetic patients vs 21% in nondiabetic patients; $P = .001$) was significantly associated with DM, but no differences in median cyst size were found (32 mm in diabetic patients vs 30 mm in nondiabetic patients; $P = .064$). However, 63% of patients with a cyst ≥4 cm had DM ($P = .003$). By contrast, MPD diameter was significantly bigger in diabetic patients (8 mm in diabetic patients vs 6 mm in nondiabetic patients; $P = .006$).

DM and Worrisome Features or High-Risk Stigmata

Within the worrisome features and high-risk stigmata of the updated Fukuoka guidelines, a diabetic status was significantly associated with a MPD ≥10 mm and the presence of a nodule or solid component. Diabetic patients had more frequently a high-risk stigmata than nondiabetic patients (74% in diabetic patients vs 38% in nondiabetic patients; $P < .001$).

DM and Surgical Outcomes

Patients underwent surgery after a median of 2 (range, 0–123) months after diagnosis. In diabetic patients a total pancreatectomy was more frequently carried out (42% in diabetic patients vs 17% in nondiabetic patients; $P = .002$). As well, vascular resections were more frequently performed in patients with DM (30% in diabetic patients vs 12% in nondiabetic patients; $P = .009$). No differences in the complication and mortality

Table 2. Surgical and Pathological Outcomes Based on Diabetes Mellitus

	Entire cohort (N = 134)	Nondiabetic patients	Diabetic patients	*P* value
Surgery				
Type of resection				.002[a]
Duodenopancreatectomy	59 (44)	37 (44)	22 (44)	
Distal pancreatectomy	33 (25)	28 (33)	5 (10)	
Total pancreatectomy	35 (26)	14 (17)	21 (42)	
Enucleation	3 (2)	2 (2)	1 (2)	
Middle pancreatectomy	2 (1.5)	2 (2)	0 (0)	
other	2 (1.5)	1 (1)	1 (2)	
Vascular resection	25 (19)	10 (12)	15 (30)	.009[a]
Complications	77 (58)	49 (58)	28 (56)	.792
Pancreatic fistula	18 (13)	15 (18)	3 (6)	.052
Biliary fistula	4 (3)	3 (4)	1 (2)	.605
Enteric fistula	3 (2)	2 (2)	1 (2)	.885
Abdominal fluid collection	18 (13)	15 (18)	3 (6)	.052
Bleeding	3 (2)	2 (2)	1 (2)	.885
Delayed gastric emptying	16 (12)	8 (10)	8 (16)	.264
Ileus	7 (5)	4 (5)	3 (6)	.755
Wound infection	14 (10)	10 (12)	4 (8)	.475
Systemic complications	42 (31)	25 (30)	17 (34)	.609
Readmission	8 (7)	5 (7)	3 (8)	.765
Pathology				
Type of IPMN				.033[a]
MD-IPMN	94 (75)	56 (69)	38 (86)	
BD-IPMN	31 (25)	25 (31)	6 (14)	
Grade of dysplasia				.018[a]
LGD	60 (45)	45 (54)	15 (30)	
HGD	16 (12)	10 (12)	6 (12)	
Invasive cancer from IPMN	58 (43)	29 (35)	29 (58)	
Malignant IPMN (HGD/invasive)				.008[a]
No	60 (45)	45 (54)	15 (30)	
Yes	74 (55)	39 (46)	35 (70)	
Pathological cyst size, *mm*	30 (4–90), n = 118	29 (4–70)	35 (7–90)	.120
Pathological duct size, *mm*	10 (2–40), n = 56	9.5 (2–40)	10 (2–24)	.554
Epithelial type				
Intestinal	42 (38)	27 (38)	15 (38)	.138
Gastric	54 (49)	38 (53)	16 (41)	
Pancreatobiliary	13 (12)	5 (7)	8 (21)	
Oncocytic	2 (2)	2 (3)	0 (0)	
Presence of chronic pancreatitis				.100
No	47 (36)	34 (42)	13 (27)	
Yes	83 (64)	48 (58)	35 (73)	

Values are n (%) or median (range).
BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD-IPMN, main-duct/mixed intraductal papillary mucinous neoplasm ; PDAC, pancreatic ductal adenocarcinoma.
[a]Significant *P* value (< .05)

rate between diabetic and nondiabetic patients were recognized.

DM and Type of IPMN, Epithelial Subtypes, and Grade of Dysplasia

At pathology, 40% of patients with MD-IPMN vs 19% of patients with BD-IPMN were diabetic ($P = .033$). DM was significantly associated with a higher risk of MPD involvement. (OR, 2.827; 95% CI, 1.059–7.546; $P = .038$). In our cohort, DM did not show an association with specific epithelial subtypes. Gastric and intestinal subtypes were predominant, with no significant differences between diabetic and nondiabetic patients. Of note, in 23 patients, the epithelial type was unknown or undetermined.

Overall, 50% of patients with invasive cancer were diabetic vs 38% and 25% of those with HGD and LGD, respectively ($P = .018$). DM was associated with a higher risk of HGD or invasive cancer in unadjusted analysis (OR, 2.692; 95% CI, 1.283–5.651; $P = .009$). This association remained after adjusting for worrisome features (OR, 2.380; 95% CI, 1.021–5.550; $P = .045$) but was not found after adjusting for high-risk stigmata (OR, 1.546; 95% CI, 0.605–3.948; $P = .363$) (Table 3).

Regarding patients with new-onset or worsening DM, 80% of them harbored a malignant lesion vs 63% and

Table 3. ORs for High-Grade Dysplasia and Invasive Carcinoma by Diabetes Mellitus

	High-Grade Dysplasia/Invasive Cancer From IPMN		
Diabetes	Patients	OR (95% CI)	*P* Value
Yes	50	1.00 (reference)	
No	84		
Unadjusted		2.692 (1.283–5.651)	.009
Adjusted for worrisome features		2.380 (1.021–5.550)	.045
Adjusted for high-risk stigmata		1.546 (0.605–3.948)	.363

Worrisome features: history of acute pancreatitis, cyst size ≥3 cm, thickened cyst wall, nodule/solid component, abrupt change in caliber of main pancreatic duct, lymphadenopathy, and main pancreatic duct diameter 5–9 mm. High-risk stigmata: jaundice, enhancing solid component, and main pancreatic duct diameter ≥10 mm.
CI, confidential interval; IPMN, intraductal papillary mucinous neoplasm; OR, odds ratio.

46% of patients with long-standing DM and without DM, respectively. On the one hand, patients with new-onset or worsening DM showed a significantly higher risk of HGD or invasive cancer in contrast to patients without DM in an unadjusted analysis (OR, 4.615; 95% CI, 1.423–14.698; $P = .011$), and even higher after adjusting for worrisome features (OR, 8.165; 95% CI, 1.967–33.886; $P = .004$) (Table 4). On the other hand, long-standing DM was not associated with an increased risk of HGD or invasive cancer compared with patients without DM (OR, 1.993; 95% CI, 0.845–4.698; $P = .115$) and with new-onset or worsening-DM (OR, 0.432; 95% CI, 0.115–1.622; $P = .214$).

Table 4. Odds Ratios for High-Grade Dysplasia and Invasive Carcinoma by New-Onset/Worsening Diabetes Compared With Nondiabetic Patients

	High-Grade Dysplasia/Invasive Cancer From IPMN		
New-onset/worsening diabetes	Patients	OR (95% CI)	*P* value
Yes	20	1.00 (reference)	
No	84		
Unadjusted		4.615 (1.423–14.698)	.011
Adjusted for worrisome features		8.165,1.967–33.886)	.004
Adjusted for high-risk stigmata		3.853 (0.886–16.747)	.072

Worrisome features: history of acute pancreatitis, cyst size ≥3 cm, thickened cyst wall, nodule/solid component, abrupt change in caliber of main pancreatic duct, lymphadenopathy, and main pancreatic duct diameter 5–9 mm. High-risk stigmata: jaundice, enhancing solid component, and main pancreatic duct diameter ≥10 mm.
CI, confidential interval; IPMN, intraductal papillary mucinous neoplasm; OR, odds ratio.

DM and Weight Loss

In our study, DM but not weight loss was associated with HGD or invasive carcinoma. However, we noticed that 58% (n = 18 of 31) of patients who presented at diagnosis with weight loss had a DM status vs 32% (n = 31 of 97) of those without weight loss ($P = .009$). Importantly, a consistently higher percentage of patients with weight loss showed new-onset or worsening DM in comparison with patients with constant weight (26% [n = 8 of 31] vs 11% [n = 11 of 97]; $P = .026$). Overall, patients with DM had an increased risk of showing associated weight loss at diagnosis (OR, 2.948; 95% CI, 1.284–6.769; $P = .011$). This association persisted even when the analysis was conducted excluding patients with invasive carcinoma and limited to IPMN with LGD and HGD. In this case, 50% (n = 8 of 16) of patients with weight loss at diagnosis were diabetic vs 21% (n = 12 of 66) of patients who maintained the usual weight ($P = .024$). By contrast, when the analysis was restricted only to patients with LGD, DM and weight loss were no longer associated [42% [n = 5 of 12] vs 21% [n = 9 of 44]; $P = .133$).

Discussion

In our retrospective cohort, the prevalence of DM was pretty high, and patients with a previous history of DM revealed a more aggressive disease. Thirty-seven percent of our study population was diabetic at diagnosis, in line with previous studies (15%–43%),[8–11,14,22,23] reaching 50% in patients with invasive carcinoma arising from IPMN, similar to the prevalence reported in patients with PDAC.[17] As a possible explanation of this high prevalence, a case-control by Capurso et al[24] showed that a previous history of DM represents a risk factor for the development of IPMN (OR, 1.79; 95% CI, 1.08–2.98; $P = .025$), even more for MD-IPMNs. In our cohort, DM was significantly associated with the involvement of the MPD, and diabetic patients showed a 2.7-fold higher risk of harboring a malignant IPMN (HGD or invasive cancer). These results are in line with other series investigating predictors of malignant progression in IPMN.[10,11,14,25] However, the possible mechanisms behind this association are still unknown. In fact, in the present literature, only a few papers specifically focus on the role of DM in IPMN,[7,14,24] and it is important to underline a gap of knowledge on this topic.

DM has been more extensively investigated in PDAC. Several authors support the existence of a bidirectional association between DM and PDAC: (1) DM represents a risk factor for the development of PDAC; (2) DM can be induced by pancreatic cancer and be paradoxically associated with weight loss.[15,16] Interestingly, PDAC-induced diabetes, which by definition is new-onset DM, and weight loss precede the onset of other cancer-specific symptoms by several months.[15,26] Indeed, a

reduction of weight seems to begin as early as 3 years before the diagnosis of cancer. Despite this reduction, the glycemic control worsened over time in these patients, in contrast to patients with type 2 diabetes, in whom glycemia improves with weight loss.[26,27] IPMN represents a different entity than PDAC and the association between weight loss and DM has not been investigated yet. In our study, we found that a higher percentage of patients with weight loss at diagnosis were also diabetic in comparison with patients with constant weight (58% vs 32%; $P = .009$). Moreover, these patients who lost weight had more frequently a new-onset or worsening DM. When we excluded patients with invasive cancer, in whose DM and weight loss were expected to be associated, we saw that this association was still present. In other words, this association was already existing in presence of HGD, whereas it was absent among patients with LGD-IPMNs (42% in diabetic patients vs 21% in nondiabetic patients; $P = .151$).

In our series, we also showed that DM remained associated with progression to HGD or invasive cancer even after adjusting for worrisome features (OR, 2.380; 95% CI, 1.021–5.550; $P = .045$) but not after adjusting for high-risk stigmata ($P = .363$). On the same line, Morales-Oyarvide et al[14] found that in patients with MPD <10 mm, DM significantly correlates with a higher risk of HGD but not of invasive cancer. A previous publication focused specifically on low-risk IPMNs (asymptomatic IPMNs without worrisome features) showed that DM, male sex, and recent weight loss are associated with a higher risk of developing HGD and invasive cancer.[12] In addition, in another series, 67% of male patients with Fukuoka-negative BD-IPMN and recent DM (<1 year) harbored a malignant lesion.[13]

Overall, these results suggest that DM appears to be helpful for early prediction of progression, notably in association with weight loss and in low-risk IPMNs. In this setting, further investigations are certainly worthwhile for understanding the pathogenesis of these disorders in IPMN and for including diabetes as worrisome feature in the guidelines for the management of IPMN. Identifying factors predictive for HGD is crucial in the management of IPMN to achieve early diagnosis and prevention of pancreatic cancer and to offer an excellent prognosis to these patients.

Particular emphasis should be placed on new-onset DM. Although included in the European guidelines as relative indication for surgery, the role of new-onset DM in IPMN is considered controversial. In our study, patients with new-onset or worsening DM showed a significantly higher risk of HGD or invasive cancer compared with patients without DM, even after adjusting for worrisome features. By contrast, other series demonstrated that recent-onset DM (diagnosed within 12 months) was not associated with an increased risk of IPMN[24] and of progression to HGD or invasive cancer.[10] It is also necessary to note that in the current literature there is no clear definition of new-onset or recent DM. The onset timing of new-onset DM is often not defined or greatly varies from 1 to 5 years before diagnosis of IPMN.[10,13,14,24] Thus, a consensus on the definition of new-onset DM is needed, and its role should be further investigated.

Limitations of this study include its retrospective nature and the limited sample size that increases the risk of selection and data collection bias and limits the possibility of making definite conclusions. In addition, we are conscious that most of our study population underwent surgery because of worrisome features or high-risk stigmata selecting cases with more aggressive disease. However, even though the management of patients changed over time, patients' selection and surgical treatment were carried out in the same institution by an established multidisciplinary team.

In conclusion, we advise surgeons to give greater importance to DM in IPMN and to be aware that diabetic patients may harbor a more aggressive disease requiring surgery. Further investigations focused on the role of DM and weight loss in larger series of patients are needed to include DM in the guidelines for the management of IPMN.

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Conflicts of interest
The authors disclose no conflicts.