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New-onset diabetes in pancreatic cancer: A study in the primary care setting

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Abstract

Background—Onset of diabetes mellitus (DM) is often first noted by primary care physicians. New-onset DM (duration <36 months before PaC diagnosis) can be a harbinger of pancreatic cancer (PaC). However, its clinical significance remains unclear.

Methods—To determine the prevalence, onset, and delay in diagnosis of DM in PaC patients in the primary care setting, we retrospectively reviewed the records of consecutive patients followed in Mayo Clinic's primary care clinics (at least one visit in the preceding 2 years) from 1995 to 2009 who were eventually diagnosed with PaC. Onset of DM was the first date the fasting blood glucose was ≥ 126 mg/dl.

Results—Of the 111 PaC patients (59 male, median age 74 years), 52 (47%) had DM of whom 30 (58%) had new-onset DM. Among the 30 with new-onset DM, 24 (80%) were asymptomatic (no cancer-specific symptoms), at DM onset. In these 24 patients, median duration of DM prior to PaC diagnosis was 6.5 (0.5–35) months, and median delay between onset and physician diagnosis of DM was 2.5 (0.25–14) months, which decreased from 8.8 (3.5–14) months in patients with DM onset between 1995 and 1999 to 0 (0–2) months, in patients with DM onset between 2004 and 2009. However, the proportion of patients with undiagnosed DM (~33%) remained unchanged.

Conclusions—Diabetes is very common (~50%) in PaC. In over a fifth of PaC, the onset of DM occurs when the cancer is asymptomatic, providing a potential window-of-opportunity to diagnose early PaC. However, nearly a third of new-onset DM in PaC remains undiagnosed.

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Conflict of interest/disclosure
None declared.

Keywords

Pancreatic cancer; Diabetes mellitus; Primary care

1. Background

The association between diabetes mellitus (DM) and pancreatic cancer (PaC) has been known for over a century. It is now well understood that while long-standing diabetes is an etiologic factor for pancreatic cancer, new-onset diabetes can be a manifestation of the cancer [1]. A recent meta-analysis of 17 case-control and 19 cohort (or nested case-control) studies published between 1966 and 2005 reported that the combined age- and sex-adjusted odds ratio (OR) for PaC associated with DM was 1.82 (95% confidence interval (95% CI) 1.66–1.89) [2]. This association was stronger in subjects with DM duration of ≥ 4 years compared to subjects with DM duration of < 4 years (OR 2.1 vs 1.5; $P = 0.005$) [2].

The association between PaC and DM reported in the epidemiologic studies noted above is very modest and similar to that reported between smoking and PaC [3]. This is contrary to observations by us and others that 45–65% of PaC patients have DM, the vast majority of which is new in onset [4]. Other investigators have screened for PaC among subjects with new-onset DM who have cancer-related symptoms such as jaundice, abdominal pain, weight loss and increased levels of Ca²⁺, and found a high prevalence of PaC (5.2–13.6%) [5,6].

While most epidemiologic studies do not suggest much clinical utility of newly identified diabetes as a marker for pancreatic cancer, a recent review concluded that patients with new-onset DM over age 50 do constitute a high-risk group for PaC [1]. The uncertainty over the clinical benefit of the recognition of new-onset DM as a harbinger of PaC is reflected in references to it in two major medical textbooks. While Cecil's Textbook of Medicine [7] emphatically states that pancreatic cancer should be considered in the differential diagnosis of the cause of new-onset diabetes in patients who are more than 50 years old, Harrison's Textbook of Medicine dismisses new-onset DM as one of the less common presenting features of PaC [8].

The reason for the discordance between epidemiologic and clinical studies appears to be the manner in which DM status was ascertained in these studies. DM status in most epidemiologic studies was self-reported, proxy-reported, or identified through chart review search for physician diagnosed DM. In contrast, clinical studies that reported a high prevalence of DM had prospectively screened PaC patients for DM using fasting blood glucose or glucose tolerance tests. In a recent retrospective epidemiologic study using fasting glucose values rather than physician diagnosed DM, the prevalence of DM in PaC was over 40% [9]. In another study using fasting glucose measurements to define DM, the relative risk of PaC in incident DM subjects over age 50 years was 8 times that of the general population [10].

Most epidemiologic studies have been conducted in tertiary centers using referred PaC patients. Since DM is generally first identified by primary care physicians, the goal of our study was to determine the true prevalence of DM in 111 consecutive PaC subjects in the

primary care setting. To further understand the clinical utility of new-onset DM as a marker of PaC, we also investigated the average interval between onset of DM (defined by glycemic criteria) and physician diagnosis of DM, onset of cancer-related symptoms and clinical diagnosis of PaC. Based on these data we determined the average delay in recognition of DM in PaC.

To overcome the problems noted earlier, we reviewed the hospital and ambulatory medical records (including all laboratory fasting blood glucose [FBG] values) before and at clinical diagnosis of PaC. Using this approach, we were able to identify not only subjects with a prior clinical diagnosis and/or treatment for DM, but also those who met glycemic criteria for DM but were undiagnosed. In addition, the date of onset of DM was based on the date subjects met glycemic criteria for DM rather than the date the clinical diagnosis of DM was assigned. Although we used a retrospective study design, the frequent determination of blood sugar in these subjects and the excellent medical records maintained on Mayo Clinic patients allowed us to satisfactorily study the questions.

2. Methods

This study was approved by the Mayo Foundation Institutional Review Board.

2.1. Patient selection

From our database of 155 patients living in Olmsted County diagnosed with PaC between May 1995 and December 2009, we identified 111 consecutive patients who had at least one visit to the Mayo Clinic's primary care clinics (Primary Care Internal Medicine, General Internal Medicine or Family Medicine) within the 2 years preceding the PaC diagnosis. The cohort selection was done with the intent of simulating a primary care practice where consecutive PaC patients were seen, and retrospectively assessing the applicability of new-onset DM as a screening criterion for PaC in this cohort. The 44 patients that were excluded fell into two groups. The first group consisted of patients who were not followed in Mayo clinic's primary care clinics ($n = 43$). These patients were excluded because we did not have access to their previous blood glucose measurements and medical records. The second group were patients who had not been seen in Mayo Clinic's primary care clinic within the 2 years preceding the PaC diagnosis ($n = 1$). For these patients blood glucose monitoring in the 2 years preceding the diagnosis of PaC was not available, which is when a majority of patients with PaC develop DM. Even if new-onset DM were to be used as a screening criterion for PaC, these patients would not be captured and were therefore, excluded.

2.2. Data collection

The medical records of these 111 patients were reviewed to abstract demographic information and clinical data, including age, gender, smoking history, family history of DM (grandparents, parents, siblings, children), height, serial weights, serial blood glucose, DM status, duration of DM, treatment for DM, onset and duration of cancer-specific symptoms (abdominal pain, back pain, weight loss and jaundice), and stage of pancreatic cancer. The most recent weight at least 6 months prior to the diagnosis of DM was used as the baseline.

Height and weight were used to calculate body mass index (BMI, calculated by weight (kg)/height [2] (m^2)) at baseline, the onset of DM, and the diagnosis of PaC.

2.3. Definitions

Subjects were defined as having DM using the 1997 American Diabetes Association (ADA) criteria (i.e., a fasting blood glucose (FBG) ≥ 126 mg/dL, random blood glucose (RBG) >200 mg/dL, or Hemoglobin A1c $\geq 6.5\%$) [11]. In keeping with the ADA guidelines, a repeat test was necessary to confirm the diagnosis of DM unless two different tests (FBG, RBG or A1c) were concordant for the diagnosis of DM [11]. Patients who were on anti-diabetic medications were classified as having DM as well. Onset of DM was defined by the date of the first of 2 consecutive tests that met the ADA criteria for DM diagnosis.

The interval to physician diagnosis of DM was calculated from the date the patient met criteria for DM to the first time the diagnosis of DM appeared in the medical record or the patient was initiated on anti-diabetic therapy. Since the ADA criteria came into effect in July of 1997, the 1979 World Health Organization (WHO) criteria (i.e. a fasting blood glucose ≥ 140 mg/dL) were used for patients diagnosed with DM before this date [11]. Duration of DM was defined as the time period between the onset of DM and the diagnosis of PaC. DM was considered to be new-onset if the onset preceded the PaC diagnosis by ≤ 36 months.

2.4. Statistical analysis

The proportion of PaC patients with new-onset DM and the median duration of DM prior to the onset of cancer-specific symptoms were calculated.

All statistical analyses were carried out using the SAS JMP 8 statistical software (Cary, NC). Statistical comparison of continuous variables was performed using the Wilcoxon rank-sum test. Comparison of categorical variables was done using the 2-tailed Fisher's exact test. A p -value <0.05 was considered statistically significant.

3. Results

3.1. Patient demographics (Table 1)

The cohort of 111 PaC patients (59 males, 52 females) had a median age of 74 years (range 38–100 years). A prior or current history of smoking was noted in 61% of patients. Having at least one family member with DM was noted for 42% of patients. The subgroup of patients with DM ($n = 52$) comprised 23 females and 29 males with a median age of 74.5 years (range 39–90 years); in addition, there was a history of smoking in 64% and a positive family history of DM in 46%.

3.2. Cancer-specific symptoms (Table 2)

Cancer-specific symptoms were present in 101 patients at the time of diagnosis. Abdominal pain was the most common symptom (60%), followed by weight loss (26%), jaundice (24%), and back pain (17%). Data on duration of symptoms was available on all but two patients. The median duration of cancer-specific symptoms in these patients was 1 month (range 1 day–7 months).

Ten patients had no cancer-specific symptoms at the time of diagnosis. The PaC was found incidentally during imaging (CT chest in 1, CT abdomen in 6, and abdominal ultrasound in 2) for unrelated indications including motor vehicle accident, hematuria, chronic diarrhea, small bowel obstruction, and follow-ups of a pulmonary nodule, colorectal cancer, non-alcoholic fatty liver disease and abdominal aortic aneurysm. In one patient, hepatomegaly noted during a routine physical examination led to the diagnosis of PaC.

3.3. Prevalence of diabetes mellitus

The prevalence of DM in this cohort was 47% (52/111). The median duration of DM was 20 months (range 0–195 months). (Data on duration of DM was available in all but one DM patient.) Nearly two-thirds (30/52) of PaC patients with DM had onset of DM in the 36 months prior to PaC diagnosis (i.e. new-onset); median duration of DM was 5.5 months (range 0–35 months) (Fig. 1).

3.4. Frequency of blood glucose monitoring

In patients with new-onset DM, blood glucose was monitored a median of 4 times (range 0–7 times) over the 5 years preceding the onset of DM. The median number of outpatient blood glucose measurements in patients without DM in the 5 years preceding the diagnosis of PaC (4, range 0–11 times) was not different ($p = 0.78$).

3.5. Characteristics of diabetes mellitus in PaC

When patients with new-onset DM were compared to those with long-standing DM, there were no statistically significant differences in age, family history of DM, smoking history, or BMI between the 2 groups. There were more males ($p = 0.02$) in the long-standing DM group (76%) as compared to the new-onset DM group (40%). Data on change in weight at the onset of DM was unavailable in 13 patients (2 new-onset, 10 long-standing and 1 unknown duration). For the remaining subjects, patients with new-onset DM had a median weight loss of 2.2 kg [range (–36)–7.4 kg] compared to those with long-standing DM who had a median weight gain of 2.5 kg [range (–2)–16 kg] at DM onset ($p = 0.001$).

3.6. Asymptomatic PaC at onset of DM

In 24/30 (80%) patients with new-onset DM, there were no cancer-specific symptoms at the time they met criteria for DM. The median duration of DM before the onset of cancer-specific symptoms in this sub-group was 6 months (range 0.5–34.5 months).

Based on the American Joint Committee on Cancer's (AJCC) staging system [12] for PaC, 3 (13%) patients were Stage Ib, 1 (4%) Stage IIa, 6 (25%) Stage IIb, 4 (17%) Stage III, and 10 (42%) Stage IV, at the time of PaC diagnosis.

3.7. Physician diagnosis of diabetes mellitus

Of the 52 patients that met the American Diabetes Association criteria for DM, the diagnosis of DM was made at its onset in only 13 patients. The diagnosis of DM was never made in 11 (21%) patients. The median delay in the diagnosis of DM in the remaining 21/28 for whom data was available was 5 months (range 0.25–63 months).

In the sub-group of 30 patients with new-onset DM, the diagnosis of DM was made at its onset in only 6 patients (20%). The diagnosis of DM was never made in more than one third of the patients ($n = 11$). The median delay in the diagnosis of DM in the remaining 12/13 patients for whom data was available was 2.5 months (range 0.25–14 months).

Among the 24 patients with new-onset DM who did not have cancer-specific symptoms at the onset of DM, the diagnosis of DM was made at its onset in only 5 (21%) patients. The diagnosis of DM was never made in 6 (25%) patients. The median delay in diagnosis of DM in the remaining 12/13 patients for whom data was available was 2.5 months (range 0.25–14 months).

3.8. Trends in interval to physician diagnosis of new-onset DM (Fig. 2)

The delay in the physician diagnosis of new-onset DM in patients with PaC decreased from a median of 8.8 months (range 3.5–14 months) in patients with DM onset between 1995 and 1999 to 0 months (range 0–2 months) in patients with DM onset between 2004 and 2009 ($p = 0.03$). In 1/3 (33%) patients in the 1995–1999 group and 4/10 (40%) patients in the 2004–2009 group, DM was never diagnosed ($p = 1.0$).

4. Discussion

In this retrospective study of 111 consecutive PaC patients followed in the Mayo Clinic primary care clinics, we show that the prevalence of DM is high (47%). The majority (58%) of DM in PaC is new-onset (<36 months in duration). Among 30 PaC subjects with new-onset DM, 24 (80%) had no symptoms of PaC when they first met criteria for DM. The diagnosis of DM was made at its onset in only 5/24 (21%) patients with DM and asymptomatic PaC. In fact, in nearly one-fourth (6/24) of patients, the diagnosis of DM was never made. For the remaining patients, there was a delay in diagnosis that ranged from months to greater than one year (median 2.5 months). When all DM patients were considered, this delay in diagnosis ranged from weeks to over 5 years.

The observations in our study not only confirm the potential clinical utility of new-onset DM as a harbinger of PaC, but also explain why epidemiologic studies using chart reviews to identify physician-diagnosed DM have consistently underestimated the association between DM and PaC. Despite the high prevalence of new-onset DM in patients with PaC based on glycemic criteria, the diagnosis of DM was made at its onset in only 20% of patients who meet glycemic criteria for new-onset DM.

Analysis of the trends in physician delay in diagnosis of (new-onset) DM, showed a decrease in this delay from 1995–1999 to 2005–2009. We also noted that there was a relatively small number of patients ($n = 3$) with new-onset DM from 1995 to 1999 as compared to 2000–2004 ($n = 16$), and 2005–2009 ($n = 10$). One possible explanation is that patients diagnosed between 1995 and 1999 underwent less frequent blood glucose monitoring causing some new-onset DM patients to remain undiagnosed. Since most new-onset DM patients are diagnosed in the 1 year preceding the diagnosis of the PaC and the diagnosis of DM can have an impact upon the frequency of blood glucose monitoring, we analyzed the trends in blood glucose monitoring in the 1 year preceding the PaC diagnosis in

patients without DM. From 1995 to 1999, only 9/15 (60%) had a blood glucose measurement in the 1 year preceding the PaC diagnosis as compared to 18/21 (86%) patients without DM diagnosed with PaC from 2005 to 2009 (Fig. 2). These observations support a reduction in physician delays in the diagnosis of DM, possibly related to an increase in the frequency of blood glucose monitoring from 1995 to 2009. Yet, the proportion of patients that were not diagnosed with DM has remained unchanged (~30%) over this time.

Previous studies in type 2 DM have demonstrated that the delay in DM diagnosis can span several years [13,14]. An extensive body of literature also shows that patients often develop end-organ damage during this delay [15]. The prevention of these morbid and often fatal complications is the argument to close the gap between onset and diagnosis of DM. A parallel argument can be made if PaC were to be considered a temporal sequela of DM, at least in some patients. This argument is even more compelling if one considers the high mortality associated with PaC [16]. In comparison to other complications caused by DM that take years to develop, the shorter window of time to the development of PaC emphasizes the need for timely diagnosis of DM.

The obvious next question becomes: If we identify new-onset DM subjects over 50 years in a timely manner, how would we screen them for asymptomatic, presumably early stage PaC? Two prior studies that retrospectively reviewed CT scans done prior to PaC diagnosis found that PaC was often undetectable >6 months prior to its diagnosis, making it unlikely that PaC in asymptomatic patients could be detected with noninvasive imaging [17,18]. Experience from screening patients at risk of inherited PaC would suggest that screening asymptomatic subjects for PaC will require invasive tests such as endoscopic ultrasonography (EUS) [19–21]. Since the prevalence of PaC in the population is low (0.85%), screening all patients with new-onset DM for PaC using invasive tests will neither be cost-effective nor safe given the risk of false positives [22].

One strategy to address these concerns is to enrich the population of new-onset DM patients with those more likely to have PaC. This will largely depend on our ability to differentiate PaC-associated DM from the more common type 2 DM. While canonical risk factors for DM (age, BMI, and family history of PaC) do not appear to differ between these two groups [9], trends in weight at DM onset might be useful to make this distinction. This and other studies [6] have noted that while patients with long-standing DM gain weight (median, 2.5 kg [range, (–2)–16]) at DM onset, PaC-associated DM patients lose weight (median, 2.2 kg [range, (–36)–7.4]). Alternatively, a biomarker such as CA 19-9 (median sensitivity of 79% and specificity of 82%) could be used to enrich the population of subjects with new-onset diabetes for PaC [23]. Based on these data, our proposed screening strategy is summarized in Fig. 3. Prospective screening studies in the research setting to validate this algorithm are needed before this strategy can be recommended for PaC screening.

Patients with new-onset DM are a population of high risk, asymptomatic (no cancer-specific symptoms) individuals who could be targeted for PaC screening at a time when the cancer is resectable. While we await the validation of a screening strategy, significant delays from onset to the physician's diagnosis of DM are a major hurdle to successful implementation of any screening strategy that is applied to new-onset DM patients. Overestimation of care

provided by physicians, use of “soft” reasons such as the physician's perception that the blood sugar is improving, and lack of training are cited as reasons for failure of physicians to diagnose DM in a timely manner [24]. Increasing physician awareness, institution of quality improvement measures by providing clinicians timely feedback, and measures to build practice systems (e.g., electronic flowcharts) where patients receive the necessary care are proposed solutions to improve the diagnosis of DM by physicians [15]. The magnitude of this problem and the likely delays in the impact of any intervention to circumvent it warrant the institution of the existing measures and the development of newer measures urgently. Only then will successful application of screening become a reality for our patients.

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Abbreviations

PaC	pancreatic cancer
BMI	body mass index
DM	diabetes mellitus
EUS	endoscopic ultrasound
FBG	fasting blood glucose
RBG	random blood glucose
CT	computed tomography

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DM: Diabetes Mellitus, PaC: Pancreatic cancer, MD: Doctor of Medicine

Fig. 1.
Prevalence of DM prior to diagnosis of PaC.

Fig. 2.
Trends to delay in DM diagnosis in PaC patients.

RBG: Random Blood Glucose, FBG: Fasting Blood Glucose, CT: Computed Tomography, DM: Diabetes Mellitus

Fig 3.
Proposed screening strategy for patients with new-onset DM.

Table 1

Case Demographics.

Characteristic	All patients N (%)	Total DM N (%)	New-onset DM N (%)	Long-standing DM N (%)
N	111	52	30	22
Age at PaC diagnosis (years) (median, range)	74 (38–100)	74.5 (39–90)	76 (39–90)	73 (44–88)
Males	59 (53)	29 (56)	12 (40)	16(76)
Ever smokers	68 (61)	33 (64)	16(53)	17(81)
Positive family history of DM	47 (42)	24 (46)	12 (40)	11 (52)
BMI at DM onset (kg/m ²) (median, range)	–	29.6 (22–46.6)	29.4 (22–46.6)	30.3 (24.7–36.4)
Weight change at DM diagnosis (kg) (median, range) ^a	–	–1[(–36)–16]	–2.2[(–36)–7.4]	2.5 [(–2)–16]

^aNegative values represent weight loss; positive values represent weight gain.

Table 2

Presenting symptoms at diagnosis of PaC.

Symptom	N (%)
Patients with symptoms	101 (91)
- Abdominal pain	61 (60)
- Weight loss	26 (26)
- Jaundice	24 (24)
- Back pain	17 (17)
- Diarrhea	4 (4)
- Steatorrhea	2 (2)
- Nausea	1 (1)
- Colonic obstruction	1 (1)
- Pulmonary metastases	2 (2)
Asymptomatic patients/Incidental findings	10 (9)
- CT Chest (Pulmonary nodule)	1 (10)
- CT Abdomen (AAA, SBO, CRC, MVA, diarrhea, hematuria)	6 (60)
- USG (AAA, NAFLD)	2 (20)
- Physical exam (Hepatomegaly)	1 (10)

CT: Computed Tomography, AAA: Abdominal aortic aneurysm, SBO: Small bowel obstruction, CRC: Colorectal cancer followup, USG: Ultrasonogram, MVA: Motor vehicle accident, NAFLD: Non-alcoholic fatty liver disease.