Published in final edited form as:

Pancreas. 2016 February ; 45(2): 228–233. doi:10.1097/MPA.0000000000000439.

Increased Serum Insulin Exposure Does Not Affect Age or Stage of Pancreatic Adenocarcinoma Diagnosis in Patients with Diabetes Mellitus

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Abstract

Objectives—In considering whether medications that increase insulin levels accelerate pancreatic adenocarcinoma (PC) development, we hypothesized that PC patients with diabetes mellitus (DM) who used exogenous insulin or insulin-stimulating medications should have an earlier age of diagnosis or present with more advanced disease.

Methods—Patients enrolled in our PC registry from 6/1/2003 to 5/31/2012 were stratified according to treatment solely with insulin, insulin-stimulating medications, or insulin-independent medications. Age of PC diagnosis, PC stage, and years between DM and PC diagnoses were analyzed among the cohorts.

Results—Of 122 DM patients (mean age: 67.4 ± 10.2 years), the mean age of PC diagnosis within the insulin-only ($n=40$), insulin-stimulating ($n=11$), insulin-independent ($n=71$), and non-DM ($n=321$) cohorts were 68.7 ± 10.5 years, 69.6 ± 10.8 years, 66.3 ± 9.7 years, and 65.5 ± 10.5

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Conflicts of Interest

For the remaining authors none were declared.

years, respectively. No significant difference among the age of PC diagnosis was observed based on duration or type of DM treatment. There was no correlation between PC stage and increased insulin exposure.

Conclusions—Anti-DM medications that increase exposure to insulin do not appear to accelerate PC development using outcomes of mean age of PC diagnosis, PC stage, or duration between DM and PC diagnoses.

Keywords

insulin; incretin mimetic; pancreatic cancer; diabetes mellitus; GLP-1 agonist; anti-diabetic medications

INTRODUCTION

Pancreatic adenocarcinoma (PC) is the fourth leading cause of cancer death for both men and women in the United States and is associated with a 5-year survival rate of 6%.^(1, 2) The low incidence of PC in the United States makes it unfeasible to screen the general population, but patients at high risk do warrant closer surveillance.⁽³⁾ Identifying factors that increase risk for developing PC would guide the development of appropriate surveillance and preventive measures for high-risk individuals. For example, obesity during early adulthood, heavy alcohol consumption, and cigarette smoking, are associated with an earlier age of PC diagnosis,^(4, 5) and setting an appropriate age to begin surveillance will require understanding how these and other risk factors influence the age of PC onset.

Individuals with diabetes mellitus (DM) have twice the lifetime risk of developing PC compared with those without,⁽⁶⁾ but whether DM predisposes patients to developing PC at an earlier age remains uncertain. Current evidence suggests that both the risk and course of pancreatic carcinogenesis could be modulated by anti-hyperglycemic medications such as insulin. Insulin has been shown to reduce insulin-like growth factor (IGF)-binding protein transcription^(7, 8) and increase IGF bioavailability, and overexpression of IGF proteins has been reported in human PC samples.⁽⁹⁾ While some anti-DM medications achieve glycemic control by increasing serum insulin levels through either exogenous administration or enhanced endogenous secretion (e.g., oral sulfonylureas, meglitinides, incretin mimetics),^(10–12) other classes of medications work independently of serum insulin levels and regulate hyperglycemia by enhancing insulin sensitivity (e.g., thiazolidinediones),⁽¹³⁾ decreasing gluconeogenesis (e.g., biguanides),⁽¹⁴⁾ or reducing gastrointestinal glucose absorption (e.g., alpha-glucosidase inhibitors).⁽¹⁵⁾

Recently, the safety of incretin mimetics has come under intense scrutiny following reports of PC cases during post-marketing surveillance by the United States Food and Drug Administration (FDA) and German regulatory agencies.^(16–18) Studies recognizing the presence of glucagon-like peptide (GLP)-1 receptors on PC tissue samples⁽¹⁹⁾ led to further speculation that lax oversight and improper regulatory monitoring have obscured the relationship between incretin mimetics and PC.⁽²⁰⁾ Conversely, however, the FDA and European Medicines Agency recently agreed “that present assertions concerning a casual

association between incretin-based drugs and pancreatitis or pancreatic cancer...are inconsistent with the current data.”(21)

We hypothesized that if medications that enhance serum insulin levels do accelerate the development of PC, patients who take such medications should show: 1) earlier age of PC diagnosis, 2) more advanced stage of PC presentation at time of diagnosis, and/or 3) shorter duration between DM and PC diagnosis compared with those who do not. We tested this hypothesis by examining PC patients with DM enrolled in our institutional PC registry.

MATERIALS and METHODS

Study Design and Patient Population

We reviewed data for 531 consecutive patients with a histologically proven adenocarcinoma of the pancreas who provided informed consent to participate in our Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) study over a 9-year period from 6/1/2003 to 5/31/2012. At the time of enrollment, patients completed a self-reported medical history questionnaire created for the PAGER study.

Data Abstraction and Collection

Information abstracted from the PAGER database included demographic history (sex, ethnicity, birth date), PC history (age at diagnosis, biopsy date, clinical stage at diagnosis), smoking history (frequency and duration of cigarette use), alcohol history (frequency, type, and duration of use), body mass index (BMI) at PC diagnosis, family history of PC (first-degree relatives), and DM history (date of diagnosis, age at diagnosis, DM subtype, treatment regimen). Careful review of individual electronic medical records was performed to validate the self-reported information in the PAGER database.

Two primary cohorts were defined based on the presence or absence of co-morbid DM. Patients with DM were further allocated to three subgroups according to their use of exogenous insulin (“insulin only”), medications that stimulate endogenous insulin secretion (“insulin-stimulating” e.g., oral sulfonylureas, incretin mimetics, meglitinides), or medications that do not enhance insulin exposure (“insulin-independent”, e.g., biguanides, thiazolidinediones). Treatment-naïve (i.e., diet-controlled) DM patients were grouped with the insulin-independent DM patients, while patients exposed to multiple classes of anti-DM medications were excluded from analysis. A flow chart describing patient cohort formation is described in Figure 1.

Statistical Analysis

We first compared the age of PC diagnosis for varying duration (in years) between diagnosis of DM and diagnosis of PC. We looked for these differences within each of three treatment groups: insulin only, insulin-stimulating only, and insulin-independent only. We also combined the insulin only and insulin-stimulating groups to create an “insulin-exposed” group. We performed a one-way analysis of variance (ANOVA) to test for differences in the mean age of PC diagnosis both across duration categories for each treatment cohort and across treatment cohorts for each duration period. Duration periods were categorized into

three groups: < 1 year, 1–5 years, and > 6 years between DM and PC diagnoses. Linear regression was used to adjust for smoking, BMI, and alcohol status (Table 1) and to relate within each duration category the mean age of PC diagnosis across treatment groups. We then compared the mean age of PC diagnosis across duration within each treatment group.

To evaluate associations between stage of PC and DM treatment, we used chi-square tests of association (and Fisher's exact test where appropriate). We stratified PC stage into two groups: non-metastatic disease (stage 1–3) or metastatic disease (stage 4). We compared each treatment cohort with the non-DM group. Statistical analyses were performed using Stata software version 10.1 (StataCorp LP, College Station, TX), with statistical significance set at $p < 0.05$.

RESULTS

Demographics

We identified 531 patients with a histologically confirmed diagnosis of adenocarcinoma of the pancreas, including 199 (37.5%) with a history of DM (type 1: 7.2%; type 2: 92.8%) over the study period. This comprised 34% of all pancreatic cancer patients seen at our recruiting hospitals over the same time period. Fifty-five percent of all patients seen at our participating hospitals were stages 1–3 as compared to 72% in our registry population. The mean age of PC diagnosis for all patients was 66.3 ± 10.4 years. We excluded DM patients who reported using multiple DM medications ($n=77$); a separate analysis showed that they were demographically similar to the rest of the DM cohort (Table 1).

Of the 122 eligible patients with DM, 40 (32.8%) were treated only with exogenous insulin, 11 (9.0%) were exposed only to medications that stimulated endogenous insulin secretion, and 71 (58.2%) were either naïve to anti-DM medications or only exposed to insulin-independent anti-DM medications. A significantly higher proportion of DM patients was obese compared with non-DM patients ($n=321$), but otherwise, DM and non-DM patients were demographically similar with regard to sex, smoking history, alcohol use, and family history of PC in first-degree relatives (Table 1).

Mean age of PC diagnosis and PC stage by cohort

The mean age of PC diagnosis was 65.5 ± 10.5 years for patients without DM and 67.4 ± 10.2 years for patients with DM; the 1.9 year difference demonstrated a trend toward statistical significance ($p=0.065$). Of the 122 eligible PC patients from Figure 1, 73 had complete covariate data for smoking, alcohol, and BMI. No significant difference was observed in the mean age of PC diagnosis among the three cohorts of DM patients after adjusting for these covariates ($p=0.15$).

We attempted subgroup analysis based on number of years between DM and PC diagnoses, but the cohorts were too small to perform a reliable analysis. Even then, patients treated with exogenous insulin or insulin-stimulating DM medications were diagnosed with PC at a comparable, if not older, age compared with non-DM patients (Table 2).

We further analyzed PC stage at time of diagnosis for each group. PC stage at diagnosis was similar for patients without DM (31% Stage 4) and insulin-exposed DM patients (32% Stage 4) but was different ($p<0.01$) for insulin-independent DM patients (8.5% Stage 4). These results are reported in Table 3.

DISCUSSION

Results from our retrospective study demonstrate that patients who use exogenous insulin or insulin-stimulating medications do not exhibit outcomes consistent with an accelerated course of pancreatic carcinogenesis. Patients exposed to increased insulin are unlikely to be diagnosed with PC at an earlier age or a later stage compared with patients whose DM treatment does not directly increase serum insulin levels or with patients who do not have DM. Patients treated with exogenous insulin also exhibited a longer duration between DM and PC diagnoses compared with patients on insulin-independent glycemic control strategies. Even when assessing the subset of patients diagnosed with PC one to five years following DM diagnosis, no consistent trend of an expedited carcinogenesis was observed in those treated with insulin or insulin-stimulating drugs. We did observe that patients taking metformin had a significantly lower incidence of being diagnosed with metastatic PC (9.5%). Previous studies have reported that metformin may protect against the development of PC,(22–24) although to our knowledge, no other studies have commented whether metformin may protect against the spread of PC. However, metformin has been previously suggested to inhibit the metastases of ovarian cancer.(25)

We performed this study to address the potential association between PC and incretin mimetics, which prolong an innate transient hyperinsulinemic state (26) and have been previously associated with pancreatic enzyme elevations,(27) acute pancreatitis,(28, 29) and pancreatic ductal proliferation.(30–32) A recent report noted increased pancreatic cellular proliferation, dysplasia, and PanIN lesions in pancreatic tissue samples from deceased patients exposed to at least one year of incretin therapy compared with the pancreases of non-exposed individuals;(33) however, the validity of these findings has since been disputed following re-examination of the data by Harja *et al.*, who reported the incretin-exposed cohort was not appropriately matched by age and sex.(34) Because only 1 patient in our registry was treated solely with incretin mimetics, we combined data for patients using exogenous insulin and anti-DM medications known to stimulate insulin production, such as sulfonylureas (11) and meglitinides,(10) to help identify any clinically relevant relationship between increased insulin exposure and PC presentation.

Insulin has been suggested to accelerate pancreatic carcinogenesis through IGF-gene axis pathways. Elevated serum insulin levels increase hepatic expression of IGF-1 and reduce expression of IGF-binding proteins, resulting in an overall increased bioavailability of serum IGF. Circulating levels of IGF have previously been associated with cancer risk, (35–37) while IGF-receptor overexpression is reported to promote the survival, development, and proliferation of PC cell lines.(38–41) Increased expression of IGF receptors has been observed on PC tumors and in the sera of PC patients (42–45) and is associated with a higher tumor grade.(46) Prior studies have concluded patients on insulin-based DM

management strategies have a relatively increased risk of carcinogenesis and cancer mortality.(47)

However, the relationship between insulin use and risk of PC remains poorly understood and not fully characterized. Prior studies have suggested different forms of insulin and insulin analogues vary in their potential carcinogenicity.(48) The risk of PC among insulin users may also be confounded by clinical (e.g., obesity) and subclinical factors, including IGF axis gene polymorphisms (49) and epidermal growth factor receptors.(40, 44)

Our finding of a 37.5% incidence of DM in our PC registry is comparable with data reported for patients seen at a community-based referral care center.(50) We noted a trend toward heavy alcohol consumption among our non-DM patients (Table 1), but no significant variability was observed between DM and non-DM PC patients with respect to smoking history, family history, or frequency of alcohol use.

With an average BMI of 28.9 kg/m², our patient population was generally overweight, with a significantly higher proportion of overweight or obesity noted among DM PC patients compared with non-DM PC patients (49.1% vs. 26.7%). This was expected, given the established relationship between obesity and insulin resistance. Further analysis of the three DM treatment cohorts revealed that patients managed with insulin-independent strategies had the highest average BMI (31.3 kg/m²), which may reflect the preferential selection of metformin in patients where further weight gain is undesirable.

A recent workshop sponsored by the National Institute of Diabetes and Digestive Kidney Diseases and National Cancer Institute brought together experts to discuss the relationship between DM, chronic pancreatitis, and PC.(51) While long-standing DM is a recognized risk factor for the development of PC, the concept of “reverse causality” suggests new-onset DM may develop from underlying PC.(52) Pancreaticogenic diabetes is classified by the American Diabetes Association as type 3c DM and is defined by diabetes which develops from diseases of the exocrine pancreas including pancreatitis, trauma, neoplasia, cystic fibrosis, and hemochromatosis.(53) The most common etiology of type 3c DM is chronic pancreatitis, which accounts for nearly 80% of patients with type 3c DM.(54) Review of our current database demonstrated less than 3% of the patients had chronic pancreatitis (data not shown). Although one would suspect a higher proportion of type 3c DM in our database of PC patients, analysis of our patients who developed PC less than 1 year and between 1 and 5 years after developing DM did not yield any significant difference in the mean age of PC diagnosis between patients in the insulin-exposed cohort and those in the insulin-independent cohort (Table 2).

We acknowledge several limitations with the current study. The small number of patients limited our ability to evaluate alcohol use, smoking, family history of PC, and BMI when analyzing the age or stage of PC diagnosis and duration between DM and PC diagnoses. In addition, we could not review the EMR or validate the DM treatment for 49 patients with DM and 141 patients without DM because we could not access their records from providers outside our healthcare system.

Another limitation of this study may be the generalizability of our findings. Since our data were collected at an academic medical center, our patient population may differ demographically and may be biased toward higher resectable stages compared with the general population. Indeed, metastatic PC was observed in 28% of our patient population, compared with the 53% reported nationally.(55) However, our conclusions regarding the effect of serum insulin on PC should not differ, as both our non-diabetic control and diabetic groups are derived from the same patient population.

In summary, we did not observe any significant difference in the presentation of PC among patients who used insulin or insulin-stimulating agents based on mean age of PC diagnosis, stage of PC diagnosis, and duration between PC and DM diagnoses. We did, however, observe that our insulin-independent cohort presented with a lower proportion of metastatic PC, suggesting the anti-DM therapies used in this cohort may limit the spread of PC. The proposed mechanism of increased insulin exposure by incretin mimetics to pancreatic carcinogenesis is not supported by our findings. Further studies in larger cohorts are warranted to clarify any potential association between pancreatic disease and the long-term use of incretin mimetics.

Acknowledgments

Source of Funding: Nilesch Shah was supported by National Institutes of Health grant T32DK063922 and the Shirley Hobbs Martin Memorial Fund (Brand).

We would also like to acknowledge Michelle Kienholz for her critical review of our manuscript draft.

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PC: Pancreatic Cancer; DM: Diabetes Mellitus; TDZ: Thiazolidinediones

* Includes patients treated with incretin mimetics, oral sulfonylureas, or meglitinides

** Includes treatment-naïve patients and patients treated with biguanides, thiazolidinediones, or alpha-glucosidase inhibitors

Figure 1.

The patient flow chart details distribution of patient cohort formation.

PC: Pancreatic Cancer; DM: Diabetes Mellitus; TDZ: Thiazolidinediones

* Includes patients treated with incretin mimetics, oral sulfonylureas, or meglitinides

** Includes treatment-naïve patients and patients treated with biguanides, thiazolidinediones, or alpha-glucosidase inhibitors

Table 1

Demographic Characteristics of DM and non-DM Patients with PC

Variable	Overall [†] (N=531)	Excluded (multiple medications) (N=77)	Insulin Only (N=40)	Insulin Stimulating (N=11)	Insulin Independent (N=71)	Non-diabetics (N=321)	p-value [*]
Age of pancreatic cancer diagnosis (y, mean $\pm$ SD)	66.3 $\pm$ 10.4	66.8 $\pm$ 9.9	68.7 $\pm$ 10.5	69.6 $\pm$ 10.8	66.3 $\pm$ 9.7	65.5 $\pm$ 10.5	0.20
Sex [N (%)]							0.26
Male	280 (52.7)	42 (54.6)	21 (52.5)	6 (54.6)	30 (42.3)	175 (54.5)	
Female	251 (47.3)	35 (45.4)	19 (47.5)	5 (45.4)	41 (57.7)	146 (45.5)	
Smoking status [N (%)] ^{**}							0.47
Active Smoker	61 (15.6)	6 (10.7)	6 (20.7)	3 (37.5)	11 (21.6)	36 (14.6)	
Quit 1–10 years prior dx	49 (12.5)	13 (23.2)	4 (13.8)	0 (0.0)	2 (3.9)	31 (12.6)	
Quit >10 years prior dx	129 (33.0)	17 (30.4)	8 (27.6)	3 (37.5)	17 (33.3)	85 (34.6)	
Non-smoker	152 (38.9)	20 (35.7)	11 (37.9)	2 (25.0)	21 (41.2)	94 (38.2)	
Alcohol status [N (%)] ^{**}							0.07
Heavy (>3 drinks/day)	91 (20.4)	13 (19.7)	3 (7.7)	1 (9.1)	10 (16.4)	64 (23.5)	
Light (≤ 3 drinks/day)	356 (79.6)	53 (80.3)	36 (92.3)	10 (90.9)	51 (83.6)	208 (76.5)	
Family history of PC [N (%)]	39 (8.4)	7 (10.5)	4 (10.0)	1 (9.1)	4 (6.1)	23 (8.4)	0.79
BMI (kg/m ² , mean $\pm$ SD)	28.9 $\pm$ 5.7	32.2 $\pm$ 5.7	29.4 $\pm$ 5.7	29.1 $\pm$ 4.0	31.3 $\pm$ 7.6	27.7 $\pm$ 4.9	<0.01
BMI category [N (%)] ^{**}							<0.01
< 18.5 kg/m ²	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	
18.5–24.9 kg/m ²	113 (23.9)	4 (6.2)	9 (24.3)	2 (18.2)	9 (13.6)	86 (29.9)	
25.0–29.9 kg/m ²	184 (38.9)	19 (29.2)	14 (37.8)	4 (36.4)	20 (30.3)	123 (42.7)	
30.0–34.9 kg/m ²	119 (25.2)	27 (41.5)	7 (18.9)	4 (36.4)	27 (40.9)	55 (19.1)	
35 + kg/m ²	54 (11.4)	15 (23.1)	7 (18.9)	1 (9.1)	10 (15.2)	22 (7.6)	
Stage [N (%)] ^{**}							0.01
1	44 (8.4)	4 (5.2)	2 (5.0)	1 (9.1)	9 (12.7)	28 (8.7)	
2	242 (46.2)	35 (45.5)	20 (50.0)	4 (36.4)	39 (54.9)	146 (45.5)	
3	92 (17.6)	15 (19.5)	5 (12.5)	3 (27.3)	17 (23.9)	48 (15.0)	
4	146 (27.9)	23 (29.9)	13 (32.5)	3 (27.3)	6 (8.5)	99 (30.8)	

Variable	Overall† (N=531)	Excluded (multiple medications) (N=77)	Insulin Only (N=40)	Insulin Stimulating (N=11)	Insulin Independent (N=71)	Non-diabetics (N=321)	p-value*
Duration between DM and PC (years, mean ± SD)	6.4 ± 8.8	8.0 ± 9.2	11.8 ± 11.6	6.4 ± 6.9	1.9 ± 3.0		<0.01

† Overall group consists of all patients with PC, including 11 who were excluded for missing DM status.

* p-values test for differences among insulin only, insulin stimulating, insulin independent and non-DM groups.

** Numbers may not add up to column total due to missing covariate data.

PC: Pancreatic Cancer; DM: Diabetes Mellitus; BMI: Body Mass Index

Table 2Mean Age of PC Diagnosis by Type of Anti-DM Treatment and Duration of DM Prior to PC Diagnosis[†]

Treatment Cohort	Overall Mean Age of PC Diagnosis	Duration between DM and PC		
		< 1 year	1–5 years	6+ years
Insulin-exposed (n=33)	70.0 ± 9.9	67.4 (n=7)	68.0 (n=6)	71.5 (n=20)
Insulin Only (n=25)	69.1 ± 10.2	66.5 (n=4)	65.0 (n=4)	70.6 (n=17)
Insulin-Stimulating* (n=8)	72.3 ± 8.6	68.7 (n=3)	74.0 (n=2)	76.3 (n=3)
Insulin-Independent** (n=40)	67.6 ± 8.8	67.8 (n=18)	67.2 (n=18)	68.5 (n=4)

PC: Pancreatic Cancer; DM: Diabetes Mellitus

[†] Comparisons of age of PC diagnosis by duration are not statistically significant for each treatment cohort. Analysis is adjusted for smoking, alcohol, and body mass index.

* Includes patients treated with incretin mimetics, oral sulfonylureas, or meglitinides

** Includes treatment-naïve patients and patients treated with biguanides, thiazolidinediones, or alpha-glucosidase inhibitors

Table 3Stage of PC Diagnosis[†]

	Stage 1–3	Stage 4	<i>p</i> -value
Non-DM	69.0% (n=220)	31.0% (n=99)	Ref
Insulin-exposed	68.0% (n=34)	32.0% (n=16)	0.89
Exogenous Insulin	66.7% (n=26)	33.3% (n=13)	0.77
Insulin-Stimulating	72.7% (n=8)	27.3% (n=3)	0.79
Insulin-Independent	91.5% (n=65)	8.5% (n=6)	<0.01
Metformin	90.5% (n=19)	9.5% (n=2)	0.04

PC: Pancreatic Cancer; DM: Diabetes Mellitus

[†] Analysis is not adjusted for smoking, alcohol, or body mass index