Gastroenterology 2018;155:490–500

Fasting Blood Glucose Levels Provide Estimate of Duration and Progression of Pancreatic Cancer Before Diagnosis

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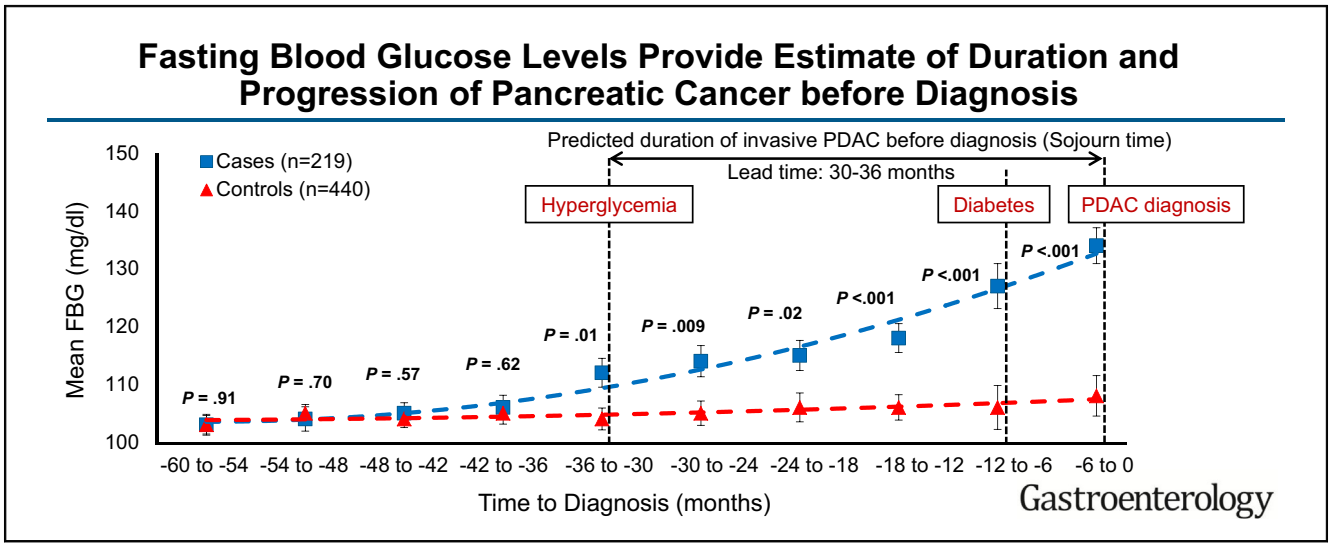


See editorial on page 265.

BACKGROUND & AIMS: It is unclear how long pancreatic ductal adenocarcinomas (PDACs) are present before diagnosis. Patients with PDAC usually develop hyperglycemia and diabetes before the tumor is identified. If early invasive PDACs are associated with hyperglycemia, the duration of hyperglycemia should associate with the time that they have had the tumor. **METHODS:** We collected data on patients with PDACs from medical databases in Olmsted County, Minnesota, from 2000 through 2015 and from the Mayo Clinic's tumor registry from January 1, 1976, through January 1, 2017. We compared glycemic profiles of patients with PDAC (cases) compared with patients without cancer, matched for age and sex (controls). We analyzed temporal fasting blood glucose (FBG) profiles collected for 60 months before patients received a PDAC diagnosis (index date) (n = 219) (cohort A), FBG profiles of patients with resected PDAC (n = 526) stratified by tumor volume and grade (cohort B), and temporal FBG profiles of patients with resected PDACs from whom long-term FBG data were available (n = 103) (cohort C). The primary outcome was to estimate duration of presence of invasive PDAC before its diagnosis based on hyperglycemia, defined as significantly higher ($P < .05$) FBG levels in cases compared with controls. **RESULTS:** In cohort A, the mean FBG did not differ significantly between cases and controls 36 months before the index date. Hyperglycemia was first noted 36 to 30 months before PDAC diagnosis in all cases, those with or without diabetes at baseline and those with or without resection at diagnosis. FBG level increased until diagnosis of PDAC. In cohort B, the mean FBG did not differ significantly in controls vs cases with PDACs below 1.0 mL. The smallest tumor volume associated with hyperglycemia was 1.1 to 2.0 mL; FBG level increased with tumor volume. FBG varied with tumor grade: well- or moderately differentiated tumors (5.8 mL) produced the same FBG levels as smaller, poorly differentiated tumors (1.5 mL) ($P < .001$). In cohort C, the duration of prediagnostic hyperglycemia for cases with large-, medium-, or small-volume PDACs was 36 to 24, 24 to 12, and 12 to 0 months, respectively. PDAC resection resolved hyperglycemia, regardless of tumor location. **CONCLUSIONS:** In a case–control study of patients with PDAC from 2 databases, we associated FBG level with time to PDAC diagnosis and tumor volume and grade. Patients are hyperglycemic for a mean period of 36 to 30 months before PDAC diagnosis; this information might be incorporated into strategies for early detection.

Keywords: Early Detection; Biomarker; Sojourn Time; Time Course Study.

Abbreviations used in this paper: **DM, diabetes mellitus; FBG, fasting blood glucose; PDAC, pancreatic ductal adenocarcinoma; T_{DX}, cancer diagnosis; T_{HG}, onset of hyperglycemia; V_{HG}, volume of hyperglycemia.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2018.04.025

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

It is unclear how long pancreatic cancer, a rapidly fatal disease, has been present before its diagnosis. Development of diabetes and hyperglycemia precede pancreatic cancer diagnosis.

NEW FINDINGS

Blood sugars in pancreatic cancer patients are elevated for up to 3 years prior to diagnosis and start rising when tumors are 1-2 mL in volume. Poorly differentiated tumors cause more hyperglycemia than well/moderately differentiated tumors.

LIMITATIONS

This a retrospective population-based case-control study.

IMPACT

There is a sufficient window of opportunity to make an earlier diagnosis of pancreatic cancer. Subjects with new-onset hyperglycemia may be screened for pancreatic cancer.

Pancreatic ductal adenocarcinoma (PDAC) carries a dismal prognosis. Currently the third leading cause of cancer death in the United States, by 2020 PDAC is expected to cause more deaths than breast, colon, and prostate cancers.[1] To address this issue, the US Congress passed the Recalcitrant Cancer Act and the National Institutes of Health (NIH) proposed priorities for PDAC research,[2] foremost among them being the study of the relationship between diabetes and PDAC and developing screening strategies for PDAC.[2] As 85% of PDACs are unresectable at diagnosis, early detection of resectable PDAC provides the best hope for prolonging survival.[3] New-onset diabetes is a harbinger of pancreatic cancer[4] and subjects with new-onset diabetes have an approximately 8-fold higher risk of having PDAC.[5]

In PDAC, which is rapidly fatal after diagnosis, it is important to know how long invasive cancer has been present before diagnosis. The progression of PDAC before its clinical diagnosis starts with first evidence of detectable cancer, progresses through an asymptomatic but potentially detectable phase (lead time), and terminates at clinical cancer diagnosis.[6] Knowing the duration of this prediagnostic stage of PDAC will help determine if early detection is even feasible.

For cancers with a clinical screening program, the duration of this prediagnostic stage has been estimated from time to development of interval cancer following a negative screening study, factoring in sensitivity of the screening test and the growth rate of cancer.[7–13] It is estimated that prostate cancer has a mean prediagnostic stage of 11 to 12 years,[14] breast cancer 3 to 4 years,[7,8] colon cancer 2 to 6 years,[9,10] and lung cancer 0.5 to 2.5 years.[11,12] As sporadic PDAC does not have an as-yet effective screening program, these approaches cannot be used to estimate its duration of prediagnostic stage.

We took a novel approach to estimate the duration of prediagnostic stage of sporadic PDAC by following the trail of hyperglycemia that precedes its clinical diagnosis. At PDAC diagnosis, approximately 85% of subjects have hyperglycemia and 50% have diabetes, suggesting that elevation of glucose is a near universal phenomenon in PDAC.[13] This makes it a suitable marker to study the duration of prediagnostic stage, assuming that cancer is detectable at the onset of hyperglycemia, currently an unproven but hopeful premise. For this study, we constructed a temporal glycemic profile of PDAC and matched general population controls to determine the duration of prediagnostic hyperglycemia.

The challenge with this approach is to show that the earliest glycemic signal is produced by invasive cancer. We postulated that the fading hyperglycemic signal with time observed in the temporal glycemic profile was caused by decreasing tumor volume. We determined if a threshold of tumor volume is required to cause hyperglycemia. To test this hypothesis, we constructed a cross-sectional glycemic profile in a large cohort of resected PDAC and compared mean fasting blood glucose (FBG) at each doubling of tumor volume with that of matched controls. We validated some of our key findings in a cohort of patients with resected PDAC who also had longitudinal FBG data. Based on our studies, we conclude that the mean hyperglycemia-defined duration of prediagnostic stage of PDAC is 30 yo 36 months, providing a sufficient window of opportunity for early detection of PDAC.

Patients and Methods

This study was approved by the Mayo Clinic Foundation Institutional Review Board and Olmsted Medical Center Institutional Review Board.

Cohorts Assembled

We compared glycemic profiles of patients with PDAC vs age- and gender-matched controls in 3 cohorts: a temporal FBG profile for 60 months before PDAC diagnosis (index date) (cohort A); a cross-sectional FBG profile of resected PDAC stratified by tumor volume and grade (cohort B); and a temporal FBG profile in resected PDAC with longitudinal FBG data (cohort C). Supplementary Figure 1 is a flowchart describing identification of patients with PDAC in the various cohorts.

Cohort A: Population-based temporal glycemic profile of all PDAC. Population-based epidemiologic studies can be conducted in Olmsted County, Minnesota, because medical care is effectively restricted to 2 major health care providers serving almost the entire population.[15] Their health records are linked by the Rochester Epidemiology Project (REP), funded by the NIH since 1966.[16] We used diagnostic index codes to identify all PDAC subjects in Olmsted County between 2000 and 2015 (n = 400), and manually reviewed their medical charts to include only those (n = 219) with a definite (confirmed by histopathology, n = 190) or probable diagnosis of PDAC (pancreatic mass with elevated CA19–9 or obstructive jaundice, n = 29). For each patient with PDAC we selected 2 age- (same birth year) and gender-matched Olmsted County residents as controls who were seen at the Mayo Clinic in the same calendar month as the matched patient's date of PDAC diagnosis (index date) (n = 440). Control selection was blinded to glycemic status. To construct the temporal glycemic profile, we electronically retrieved all outpatient FBG values at and up to 60 months

before the index date for cases and controls, grouped into 6-month time periods.

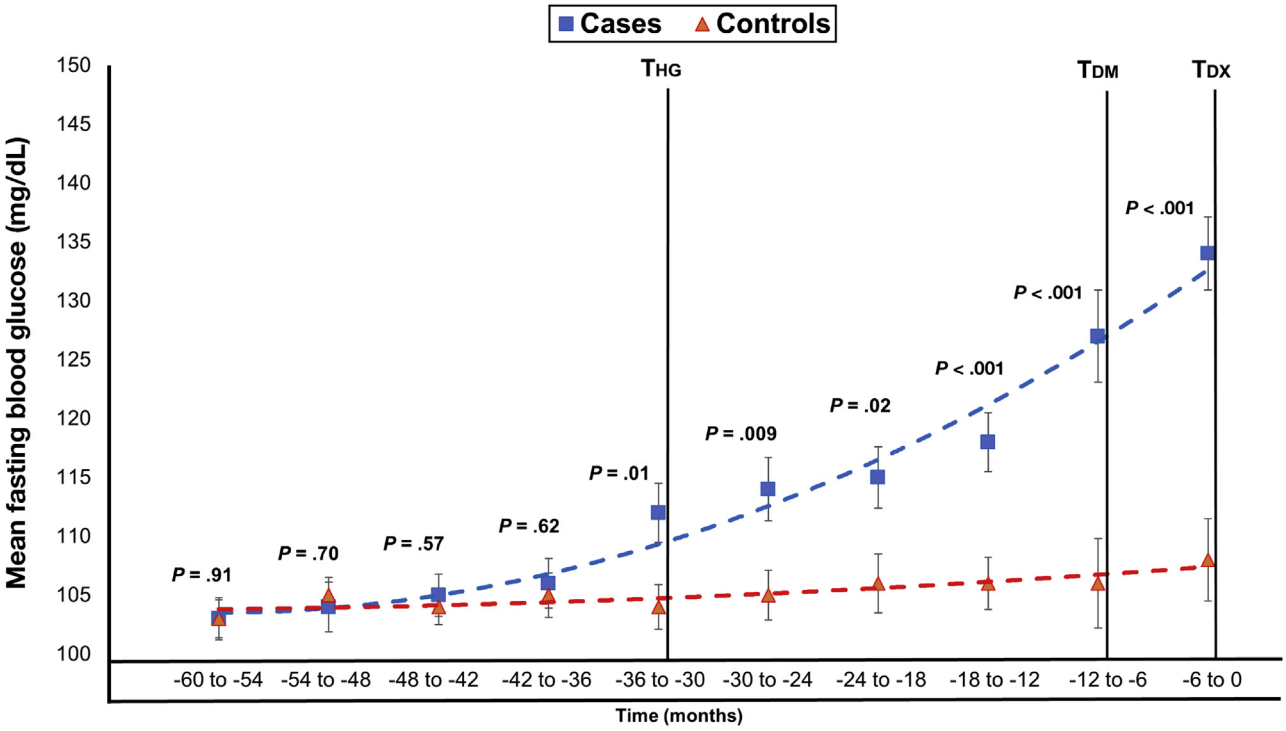
Cohort B: Cross-sectional glycemic profile of resected PDAC. To correlate tumor volume with FBG, we constructed the glycemic profile of a cohort of resected PDAC. From the Mayo Clinic's prospective tumor registry, we identified all resected PDACs between January 1, 1976, and January 1, 2017. We included all tumors with a diameter of <30 mm (n = 386) and sub-sampled a representative cohort of 190 patients from among the rest (n = 874); we then excluded patients without reported tumor size or those who had received neoadjuvant chemotherapy/radiotherapy (n = 50). All histopathological reports were manually reviewed to verify PDAC diagnosis, tumor size, grade, and lymph node positivity. The tumor slides were re-reviewed in 10% of resected PDACs by an expert pancreatic pathologist (T.C.S) to validate the reported pathologic grade (concordance 85%). Tumors were grouped by doubling tumor volumes starting at <0.5 mL (V1) through V7 (>16.0 mL). We abstracted all outpatient FBG values at the time of PDAC diagnosis and between 4 and 6 weeks after surgical resection. In addition, data on CA 19–9 (IU/L) levels at cancer diagnosis were noted. Vital status was noted from tumor registry and medical records.

For each case, we randomly identified 3 controls blinded to glycemic status and matched for gender and birth year who were seen in the clinic in the same month as the index date (n = 1650). Of these, 1023 subjects (62%) had an outpatient FBG value and were included in the study; on average there were 2 controls with FBG per case at each tumor volume.

Cohort C: Population-based temporal glycemic profile of all resected PDACs. We constructed a population-based cohort of resected PDACs from a 27-county region of the recently expanded REP catchment area who also had longitudinal FBG data before PDAC diagnosis (n = 103). Of these, 48 were from Olmsted County and were also included in cohort A. We used the Olmsted County population-based controls for comparison. Cohort C served as a validation cohort for key findings from cohorts A and B. Pre- and postoperative FBGs were recorded in all subjects and compared with FBG of controls. Subset analyses were performed based on tumor location (head and body/tail) as well as by type of surgery (Whipple [pancreatico-duodenectomy] vs distal pancreatectomy).

Calculating Tumor Volume

The most common method of reporting tumor size is by its largest diameter. This assumes that the tumor is spherical in shape and that growth occurs uniformly in all directions. We, however, observed that very few tumors (<10%) were spherical and most had 3 different reported dimensions. Therefore, we calculated tumor volume as for a scalene ellipsoid (4/3Π r1 × r2 × r3) factoring in all 3 tumor dimensions. For each



Time	-60 to -54	-54 to -48	-48 to -42	-42 to -36	-36 to -30	-30 to -24	-24 to -18	-18 to -12	-12 to -6	-6 to 0
Cases	81	72	60	61	68	71	69	90	88	159
Controls	106	122	99	125	116	128	86	123	106	123

Cases: $y = 0.36x^2 - 0.68x + 103.83$; $R^2 = 0.97$ controls: $y = 0.03x^2 + 0.03x + 103.75$; $R^2 = 0.79$

For additional details see supplementary table 3

Figure 1. Cohort A: Temporal glycemic profile of population-based controls and pancreatic cancer up to 60 months before index date (see also Supplementary Table 3). T_{DM}, onset of diabetes.

Table 1. Cohort B: Profile of Patients With Resected Pancreatic Cancer

Characteristics	V1, n = 37	V2, n = 67	V3, n = 108	V4, n = 136	V5, n = 88	V6, n = 90
Volume groupings, *mL*	<1.0	1.1 to 2.0	2.1 to 4.0	4.1 to 8.0	8.1 to 16.0	>16.0
Longest dimension, *mm*, Median (IQR)	14 (12–16)	18 (15–20)	22 (20–25)	26 (25–28)	34 (30–39)	48 (42–59)
Clinical characteristics						
Age, *y*, mean ± SD	62 ± 12.3	64 ± 10.9	67 ± 10.4	65 ± 11.8	65 ± 10.5	67 ± 11.2
Gender, male (%)	19 (51)	30 (45)	58 (54)	58 (43)	51 (58)	51 (57)
Mean BMI, kg/m^2	26.3	26.9	26.9	26.2	26.1	26.2
Mean weight, *kg*	76	86	85	101	86	80
Tumor differentiation (%)						
Well/Moderate	11 (32)	26 (42)	34 (32)	38 (28)	24 (27)	19 (21)
Poor	16 (47)	31 (50)	64 (60)	78 (58)	53 (60)	58 (64)
Undifferentiated	7 (21)	5 (8)	8 (8)	19 (14)	11 (13)	13 (14)
Lymph nodes+ (%)	11/34 (32)	28/63 (44)	56/106 (53)	83/135 (61)	57/88 (65)	64/88 (73)
CA19–9>50 IU/L (%)	3/11 (27)	9/34 (37)	12/34 (35)	27/48 (56)	12/16 (75)	25/32 (78)
Diabetes						
Overall, %	15	31	35	36	46	48
Mean FBG, *mg/dL*	105	118	124	128	132	137
Survival						
Median, *mo*	29	27	24	21	19	15
Range, *mo*	4–316	1.7–276	0.5–215	0.8–281	0.5–170	2–158
Tumor location (%)						
Head/neck	32 (86)	56 (84)	96 (89)	116 (85)	73 (83)	60 (67)
Body	1 (3)	3 (4)	7 (6)	8 (6)	5 (6)	11 (12)
Tail	1 (3)	2 (3)	3 (3)	8 (6)	7 (8)	19 (21)
Unknown	3 (8)	6 (9)	2 (2)	4 (3)	3 (3)	0
Resection type (%)						
Whipple	3 (8)	7 (10)	10 (9)	10 (7)	16 (18)	30 (33)
Distal	18 (48)	46 (69)	73 (68)	86 (63)	63 (72)	44 (49)
Total	4 (11)	1 (2)	9 (8)	18 (13)	6 (7)	7 (8)
Extended	1 (3)	0	5 (5)	6 (4)	2 (2)	3 (3)
Unknown	11 (30)	13 (19)	11 (10)	11 (8)	1 (1)	6 (7)
Symptoms (%)						
Abdominal pain	12 (32)	31 (46)	46 (43)	75 (55)	53 (60)	52 (58)
Back pain	3 (8)	5 (7)	7 (6)	15 (11)	11 (12)	8 (9)
Jaundice	28 (76)	48 (72)	77 (71)	87 (64)	61 (69)	47 (52)
Anorexia	2 (5)	7 (10)	12 (11)	49 (36)	42 (48)	44 (49)
Appetite loss	4 (11)	5 (7)	18 (17)	39 (29)	38 (43)	23 (26)
Weight loss	17 (46)	34 (51)	63 (58)	79 (58)	56 (64)	57 (63)

BMI, body mass index; IQR, interquartile range; V, volume.

category of an ellipsoid volume, there was a wide range of the largest tumor diameter (Supplementary Table 1).

Sensitivity Analysis

Exclusion of subjects with diabetes at baseline. We compared the temporal glycemic profile of cases and controls after excluding subjects with a diagnosis of diabetes or with FBG of >126 mg/dL at baseline (60 to 54 months) in cohort A and reevaluated the temporal glycemic progression between cases and controls.

Resected vs unresected PDAC. We compared the temporal glycemic profile of Olmsted County population-based controls with that of all resected PDAC subjects in cohort C and all un-resected PDAC subjects in cohort A. We further compared the temporal glycemic profile of Olmsted County population-based controls with that of subjects with PDAC with large resected tumors (>16.0 mL), intermediate and small resected tumors (<16.0 mL) in cohort C and all subjects with unresected PDAC in cohort A.

Statistical Analyses

Statistical analyses were carried out using commercial software (JMP, version 10.0, SAS Institute Inc., Cary, NC). All the results are expressed as mean (standard deviation [SD]) or median (interquartile range) as appropriate. The Pearson's χ^2 test was used to compare categorical variables. The 2-tailed *t* test was used to compare continuous variables. Polynomial regression analyses were used to model the observed mean FBG (± standard error of mean) in each time interval/volume category between cases and controls. A *P* value of ≤.05 indicated statistical significance.

Results

Cohort A: Temporal Glycemic Profile of Population-based PDAC

In cohort A, the baseline demographic and clinical profiles of patients and controls were comparable

(Supplementary Table 2) with 159 (73%) of 219 patients with PDAC having FBG at diagnosis and an average of 3.5 (±2) measurements in previous 60 months. The mean FBG was similar in patients and controls in the 60 to 54, 54 to 48, 48 to 42, and 42 to 36-month intervals before the index date (Supplementary Table 3). Relative hyperglycemia (mean FBG in patients higher than mean FBG in controls, $P \leq .05$) was seen starting 36 to 30 months before the index date (T_{HG}) and progressively worsened in the subsequent time intervals until diagnosis (T_{DX}). FBG in the PDAC cohort peaked above diabetes level (≥126 mg/dL) (onset of diabetes) 6 months before T_{DX} (Figure 1).

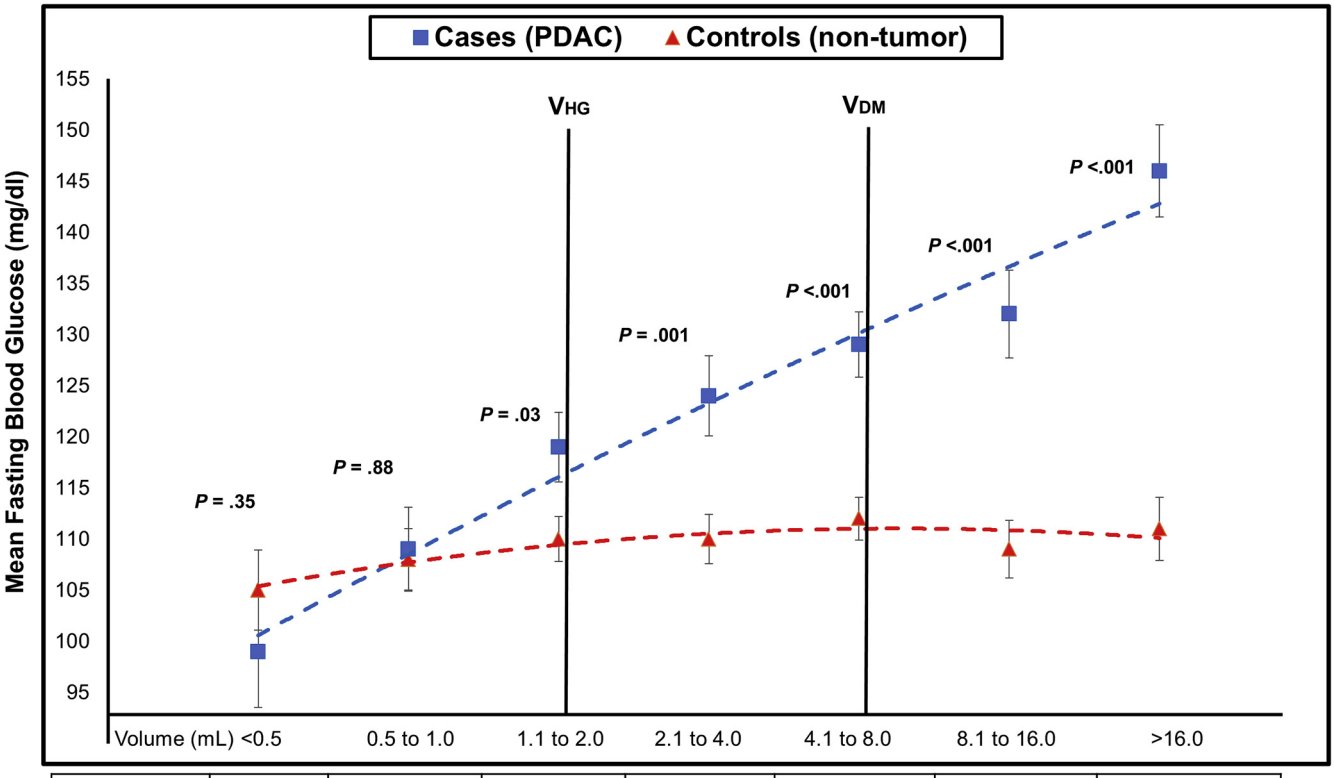
Cohort B: Cross-sectional Glycemic Profile of Resected PDAC

The details of demographic, clinical, and pathologic features of resected PDAC in cohort B are in Table 1. Of patients with PDAC in cohort B, 466 (90%) of 526 had FBG values at T_{DX}. The mean FBG was similar in cases and controls for volume 1 (V1) (<0.5 mL) and V2 (0.5–1.0 mL) tumor volumes. Relative hyperglycemia was first noted at V3 (1.1–2.0 mL) (V_{HG}) and progressively worsened with subsequent tumor volume doublings (Figure 2 and Supplementary Table 4). The cohort mean FBG peaked above diabetes level (≥126 mg/dL) at V5 (4.1 to 8.0 mL) tumor volume (Figure 2).

When compared with tumor volume not associated with hyperglycemia (V1; ≤1.0 mL), these features were first noted at the following tumor volumes: relative hyperglycemia at V2 (1.1–2.0 mL) (105 vs 118; $P = .02$), CA19–9 (>50 IU/L) at V5 (8.1–16.0 mL) (27% vs 75%; $P = .002$) and lymph node involvement at V3 (2.1–4.0 mL) (31% vs 53%; $P = .03$) (Figure 3).

Cohort C: Temporal Glycemic Profile of Population-based Resected PDAC

Subjects with PDAC in cohort C had a mean age (years) of 67 (±11.8), 50% were women and had a median tumor volume of 11.5 mL (interquartile range, 5.4 to 17.5). Of patients with PDAC in cohort C, 91 (88%) of 103 had FBG values at diagnosis with 83 (81%) having ≥3 measurements in previous years (mean 3.5 [±1.2]/subject). For patients with PDAC with large tumor volume (>16.1 mL), mean FBG (mg/dL) similar to controls was noted at 48- to 36-month interval before index date with progressively worsening relative hyperglycemia in the 36 to 24, 24 to 12, and 12 to

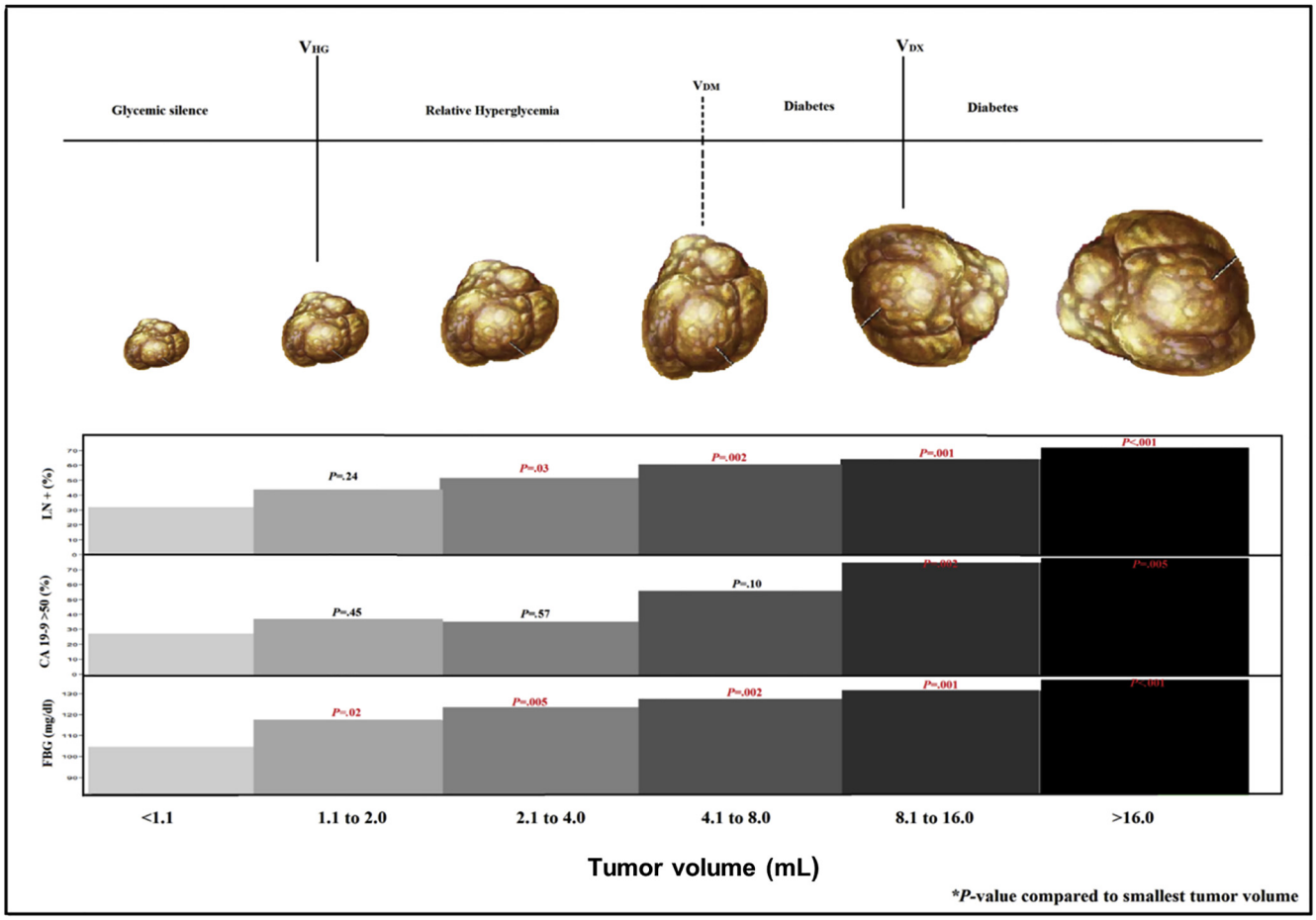


Volume (mL)	<0.5	0.5 to 1.0	1.1 to 2.0	2.1 to 4.0	4.1 to 8.0	8.1 to 16.0	>16.0
Cases	12	25	57	94	124	75	80
Controls	24	51	137	232	305	109	165

cases: $y = -0.18x^2 + 8.46x + 92.29$; $R^2 = 0.97$ controls: $y = -0.31x^2 + 3.26x + 102.43$; $R^2 = 0.81$

For additional details see supplementary table 4

Figure 2. Cohort B: Cross-sectional glycemic profile of controls (non-tumor bearing) and subjects with resected pancreatic cancer stratified by tumor volume (see also Supplementary Table 4). V_{DM}, volume associated with diabetes; V_{DX}, median volume at diagnosis.



Parameter	<1.1	1.1 to 2.0	2.1 to 4.0	4.1 to 8.0	8.1 to 16.0	>16.0
Lymph node +	11/36	28/63	56/105	83/135	57/88	64/88
CA19-9>50 IU/L	3/11	10/25	12/33	26/48	16/21	25/32
FBG (mg/dl)	34	58	97	122	75	80

Figure 3. FBG, CA19–9, and lymph node involvement with increasing tumor volume of pancreatic cancer. V_{DM}, volume associated with diabetes; V_{DX}, median volume at diagnosis.

0-month intervals before the index date. For patients with PDAC with medium tumor volumes (8.1 to 16.0 mL) mean FBG (mg/dL) similar to controls was noted in the 48 to 36 and 36 to 24-month intervals before the index date with progressively worsening relative hyperglycemia in 24 to 12 and 12 to 0-month intervals before the index date. For patients with PDAC with small tumor volumes (<8.1 mL) mean FBG (mg/dL) similar to controls was noted in 48 to 36, 36 to 24, and 24 to 12-month intervals before the index date with relative hyperglycemia seen only in the 12 to 0-month interval before the index date (Figure 4 and Supplementary Table 5). In subjects with PDAC, resolution of hyperglycemia was noted post-resection and was independent of tumor location or type of surgery (Figure 5, Supplementary Table 6).

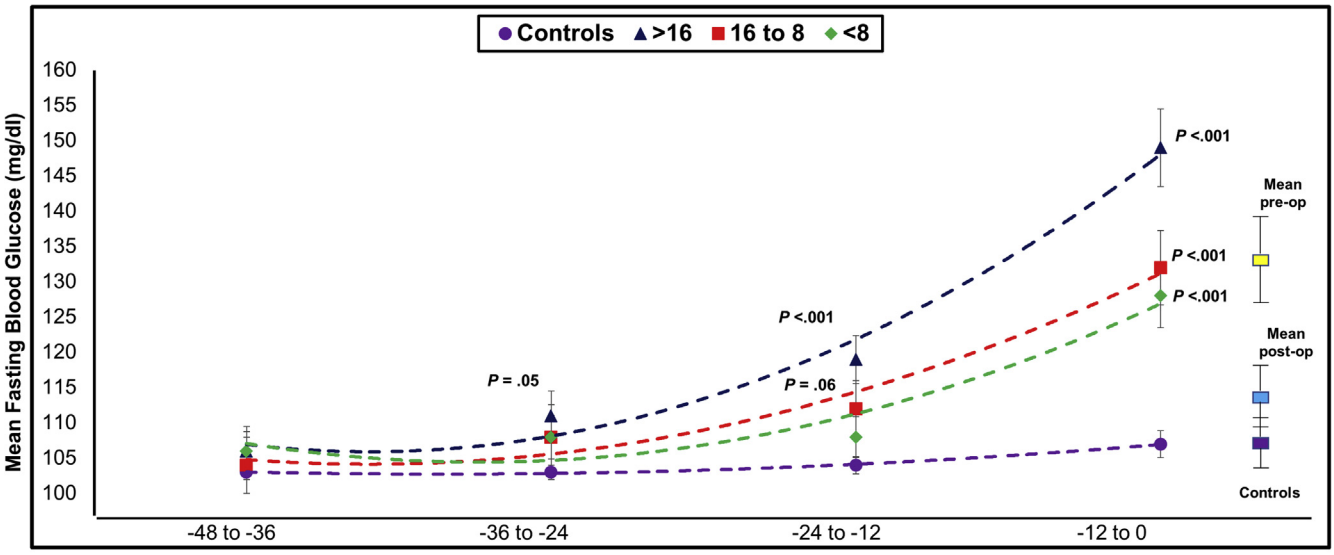
Cross-sectional Glycemic Profile of Resected PDACs by Tumor Grade

Of the resected PDACs 300 (57%) of 526 were poorly differentiated, 152 (29%) were well/moderately differentiated, and 63 (12%) were undifferentiated; 11 (2%) were of undetermined grade. The mean FBG of well to moderately differentiated tumors was lower than that of poorly differentiated tumors (118 vs 134; $P = .01$). There was no significant difference in the average tumor volume (mL) of the well/moderate vs poorly differentiated tumors (8.3 vs 10.6; $P = .09$). The V_{HG} of poorly differentiated tumors occurred at smaller tumor volumes (1.1 to 2.0 mL; mean 1.5 [±0.3]) in comparison to moderately differentiated tumors (4.1 to 8.0 mL; mean 5.8 [±1.1]).

Sensitivity Analysis

Subjects with diabetes at baseline. The T_{HG} of the cohort A, after excluding subjects with baseline (60 to 54 months) FBG of ≥126 mg/dL or a diagnosis of diabetes, was similar to that of the entire cohort A, that is, 36 to 30 months (Figure 6*A*, Supplementary Table 7).

Resected vs unresected. Compared with controls, the T_{HG} of subjects with resected PDAC was similar to that of subjects with unresected PDAC (Supplementary Figure 2).



Time	-48 to -36	-36 to -24	-24 to -12	-12 to 0
V3 (>16.0 mL)	15	15	16	20
V2 (8 to 16 mL)	11	11	18	31
V1 (<8.0 mL)	26	27	34	40
Controls	214	235	202	214

For additional details see supplementary table 5

Figure 4. Cohort C: Temporal glycemic profile of population-based controls and subjects with resected pancreatic cancer stratified by tumor volume up to 48 months before index date (see also Supplementary Table 5).

Compared with controls, the glycemic profile of unresected tumors and large (>16.0 mL) resected tumors was similar, with both groups having T_{HG} at 36 to 24 months before the index date compared with intermediate and small (<16.0 mL) resected tumors, T_{HG} occurred at 24 to 12 months before the index date (Figure 6*B*, Supplementary Table 8).

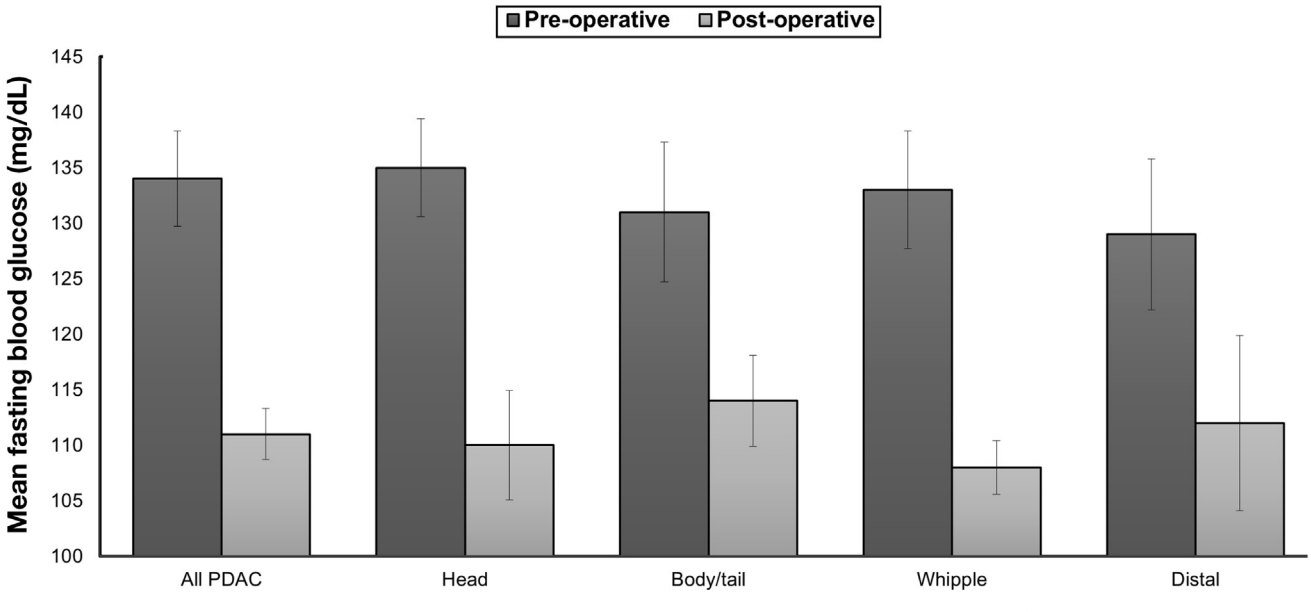
Discussion

The goal of our study was to estimate the mean duration of prediagnostic progression of sporadic PDAC, an important but unknown parameter that is key to developing early detection strategies for PDAC. For this, we took advantage of the fact that the cancer causes hyperglycemia that predates its diagnosis. By constructing glycemic profiles of multiple large longitudinal and cross-sectional PDAC cohorts, both population- and clinic-based, and matched controls, we have made multiple novel observations in addition to confirming many previous observations. We show that the hyperglycemic signal in PDAC is strongest at diagnosis and fades over the preceding 30 to 36 months, is associated with tumor volume threshold of >1.1 mL, and is caused by invasive cancer. Based on these data, we estimate the mean hyperglycemia-defined duration of prediagnostic progression of PDAC to be 30 to 36 months.

Previous studies, by others and us, have shown that new-onset diabetes is a harbinger of PDAC.[17] To study this phenomenon further, we constructed the first population-based glycemic profile of PDAC, a 60-month temporal FBG profile of all PDAC diagnosed in Olmsted County over a 16-year period and matched controls. There were mean of 3.5 FBG measurements for each subject in the 5-year study period. This density of FBG data allowed us to analyze it by 6-month intervals. The temporal glycemic profile shows that hyperglycemia first occurs 36 to 30 months before PDAC diagnosis, rapidly progresses with decreasing lead time, and crosses the diabetes threshold 12 to 6 months before cancer diagnosis.

To determine if there is tumor volume threshold (V_{HG}) associated with relative hyperglycemia, we constructed a cross-sectional glycemic profile in a cohort of patients with resected PDAC and matched controls. This large cohort had strong representation of tumors in every volume category, from very small (<1 mL) to very large (>16 mL). We observed that the hyperglycemic signal was strongest in larger tumors and faded with decreasing tumor volume. Importantly, we noted mean FBG (mg/dL) similar to age- and gender-matched controls in invasive PDAC <1 mL in volume and after PDAC resection, confirming that invasive PDAC with a certain volume threshold is the cause of hyperglycemia. Interestingly, we did not note a difference between the pre- and post-resected mean FBG levels based on location of tumor or type of surgical resection (Figure 5).

PDAC cohort C allowed us to study the temporal glycemic profile of tumors of known volume at diagnosis. In this cohort, we could show that larger resected tumors have longer hyperglycemia-defined sojourn time compared with smaller tumors, as was seen in cross-sectional profile of



N	All PDAC	Head	Body/tail	Whipple	Distal
Pre-operative	91	65	22	54	18
Post-operative	68	52	13	44	11
P-value	< .001	< .001	.04	< .001	.04

Figure 5. Pre- and postoperative FBG in patients with resected pancreatic cancer by location of tumor and type of surgical resection (see also Supplementary Table 6).

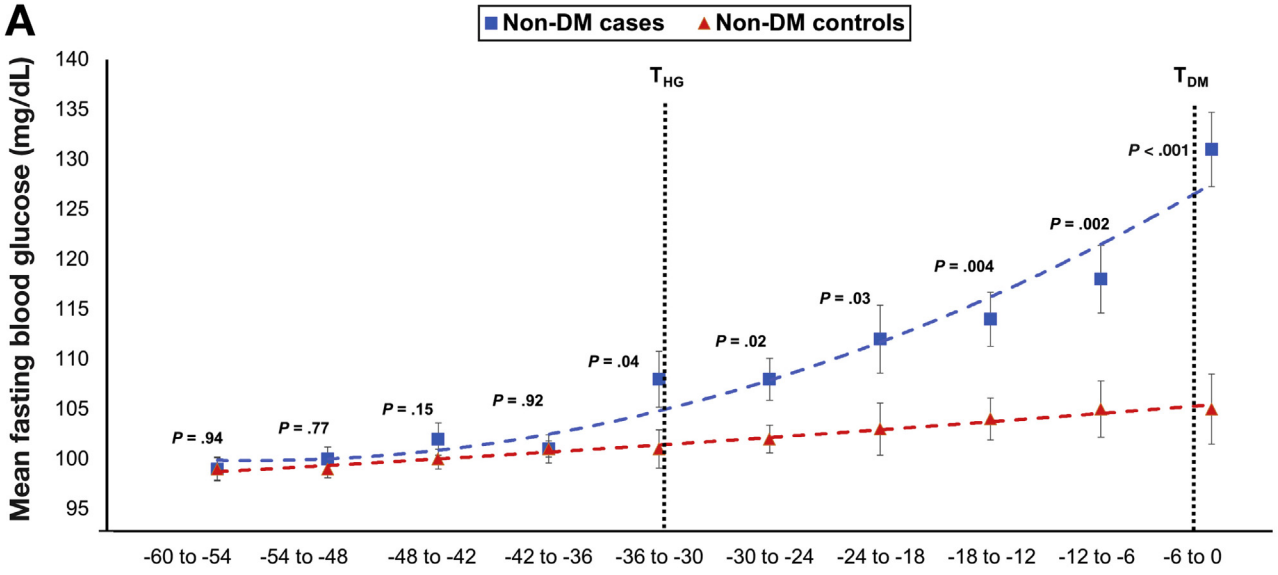
resected PDAC. Both temporal and cross-sectional glycemic profiles showed an average of 3 years between T/V_{HG} and an average volume of PDAC at diagnosis (~11.5 mL). Thus, both temporal and cross-sectional glycemic profiles suggest a 3-year hyperglycemia-defined duration of prediagnostic stage.

Our data show that glycemic profile of unresected tumors is similar to that of large (≥16 mL) resected tumors, with both groups having similar T_{HG} at 36 to 24 months before cancer diagnosis (Figure 6*B*). The profile of unresected tumors is intermediate between that of large resected (≥16 mL) and medium-sized (8–16 mL) resected tumors, which have a T_{HG} at 24 to 12 months (Figure 6*B*). Unresected tumors, like resected ones, are likely a mixture of tumors of different volumes, but collectively have a profile similar to that of the largest resected tumors. It is unclear if and how much metastases contribute to rising FBG in PDAC. It is also unclear if increasing hyperglycemia causes increasing tumor volume and so a self-perpetuating cycle is established. However, whether hyperglycemia is the cause or effect of increasing tumor volume is difficult to prove, at least in humans.

Clinico-pathological,[18] transcriptomic,[19,20] and molecular[21] data show tumor heterogeneity. We see this in the hyperglycemic profiles as well, with poorly differentiated tumors having smaller V_{HG} and higher FBG at diagnosis compared with moderate/well-differentiated tumors. This novel observation likely reflects metabolic reprogramming in poorly differentiated tumors to cope with a harsh microenvironment.[22,23] The mechanism(s) of PDAC-induced hyperglycemia still remains unknown, although others[24,25] and us[17,26] have postulated possible mediators of the paraneoplastic diabetes mellitus (DM) in PDAC. The current efforts to find potential mediator(s) of PDAC-induced diabetes have been focused on PDAC cells. However, the fact that increasing volume of a predominantly desmoplastic tumor causes increasing hyperglycemia raises the possibility that the mediators of hyperglycemia may be produced by the stroma or cancer-associated fibroblasts.

From an early detection standpoint, it is clear from our data that distinguishing PDAC-induced hyperglycemia from prediabetes of type 2 DM could lead to early detection of PDAC. However, this will require enrichment of the prediabetes cohort for PDAC, as nearly half the population at the age of 60 has elevated FBG.[27] Efforts are under way to identify blood-based biomarkers of PDAC.[28,29] Efforts to develop algorithms that can distinguish new-onset DM due to PDAC from new-onset type 2 DM[30] are also ongoing. If these algorithms could be extended to subjects with new-onset rapidly worsening prediabetes, it could potentially detect PDAC even earlier. This is supported by our findings that tumor volume (mL) at V_{HG} (1.1 to 2.0) was markedly lower than at volume associated with diabetes (4.1 to 8.0).

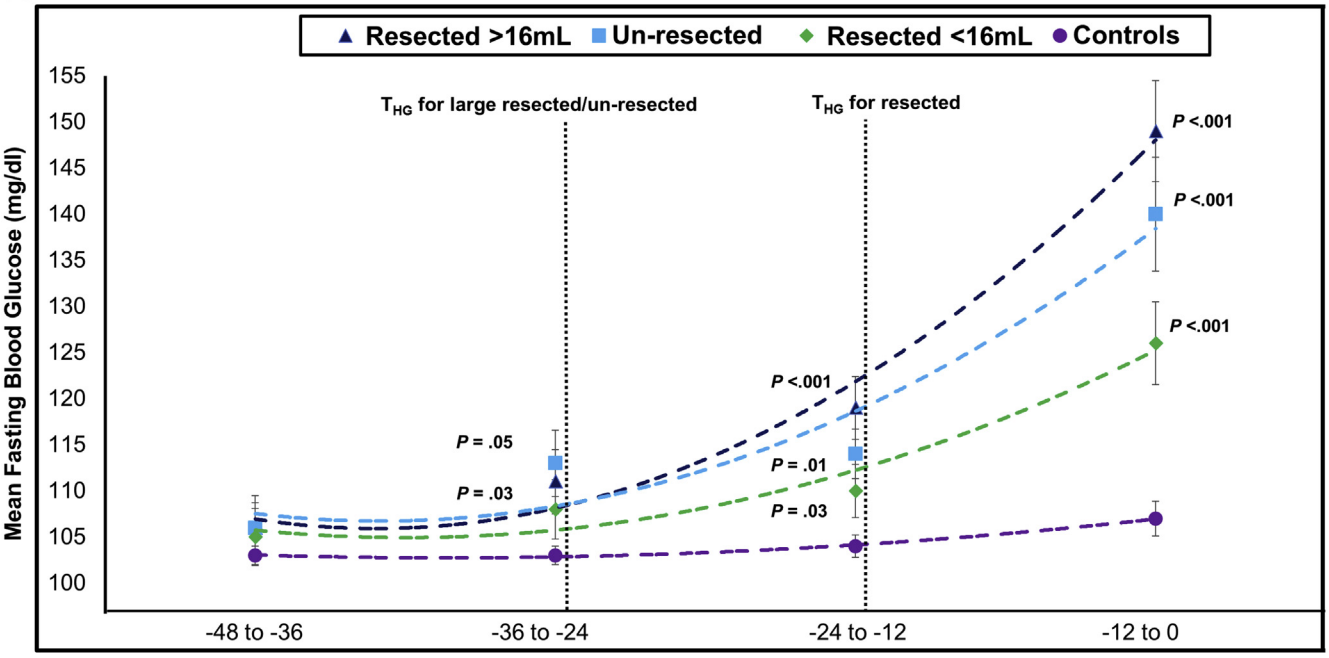
An important finding of our study is the estimate of smallest tumor volume that is associated with hyperglycemia and with diabetes. At these volumes, the range of largest tumor diameter of these irregularly shaped tumors is quite



Time	-60 to -54	-54 to -48	-48 to -42	-42 to -36	-36 to -30	-30 to -24	-24 to -18	-18 to -12	-12 to -6	-6 to 0
Cases	71	62	38	38	49	47	45	67	58	103
Controls	93	103	87	107	104	110	75	112	86	111

Cases: $y = 0.37x^2 - 0.97x + 100.48$; $R^2 = 0.95$ controls: $y = 0.02x^2 + 0.58x + 98.13$; $R^2 = 0.98$

For additional details see supplementary table 7



Time	-48 to -36	-36 to -24	-24 to -12	-12 to 0
Resected >16 mL	15	15	16	20
Un-resected	75	81	84	98
Resected <16mL	40	41	48	65
Controls	214	235	202	214

Figure 6. (*A*) Cohort A: Temporal glycemic profile of population-based controls and pancreatic cancer after excluding subjects with diabetes at baseline (60 to 54 months) (see also Supplementary Table 7). (*B*) Temporal glycemic profile of population-based controls and large resected (>16.0 mL), intermediate and small resected (<16.0 mL), and subjects with unresected pancreatic cancer up to 48 months before index date (see also Supplementary Table 8). T_{DM}, onset of diabetes.

broad (Supplementary Table 1), but provides hope that such tumors can be detected by endoscopic ultrasound or a novel imaging modality. Between the volume of smallest tumor associated with hyperglycemia and typical volume of cancer at diagnosis, we estimate that the tumor doubles in volume 4 to 5 times. This provides ample opportunity for early diagnosis of PDAC.

Our study has some limitations. It is a retrospective study based on review of medical records; however, such a study would be very difficult to perform prospectively. The glycemic profiles constructed are that of the cohort; individual glycemic profiles vary. Hyperglycemia-defined duration of prediagnostic progression is applicable only to tumors that develop hyperglycemia; however, only 10% of the subjects with sporadic PDAC have normal FBG at diagnosis.[13] Thus, this estimated duration of prediagnostic progression is relevant to most of the sporadic PDAC patients.

In summary, our study shows that hyperglycemia is a marker of invasive PDAC and allows estimation of its preclinical dwell time. Hyperglycemia-defined duration of prediagnostic stage of 36 to 30 months is long enough to allow opportunity for early diagnosis of PDAC at earlier stages.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.04.025.

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Received November 13, 2017. Accepted April 25, 2018.

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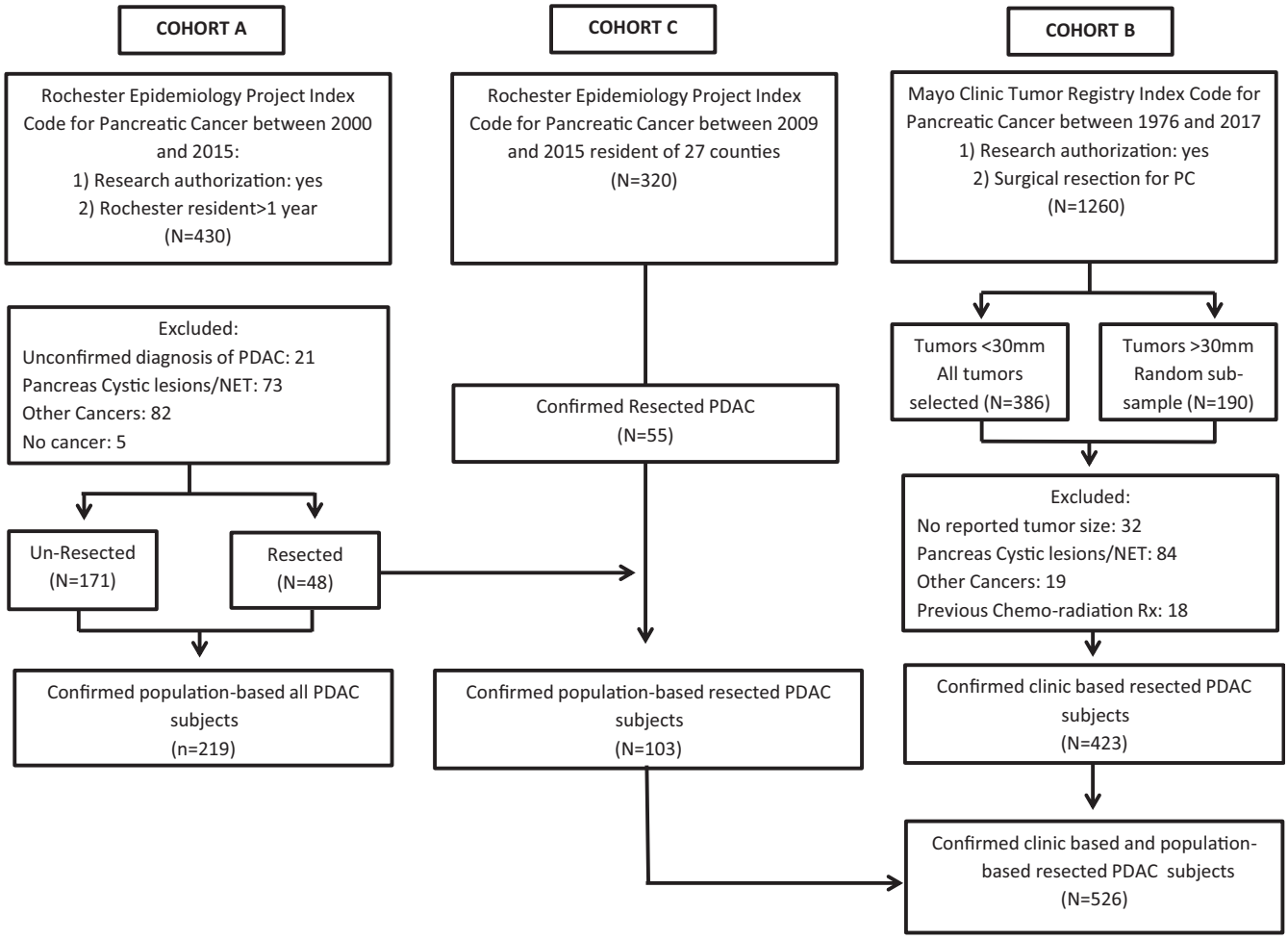
Acknowledgments
We gratefully acknowledge the critical review of the manuscript by Dr David Ahlquist, Mayo Clinic Rochester, and Dr Rahul Suresh, University of Texas Medical Branch.

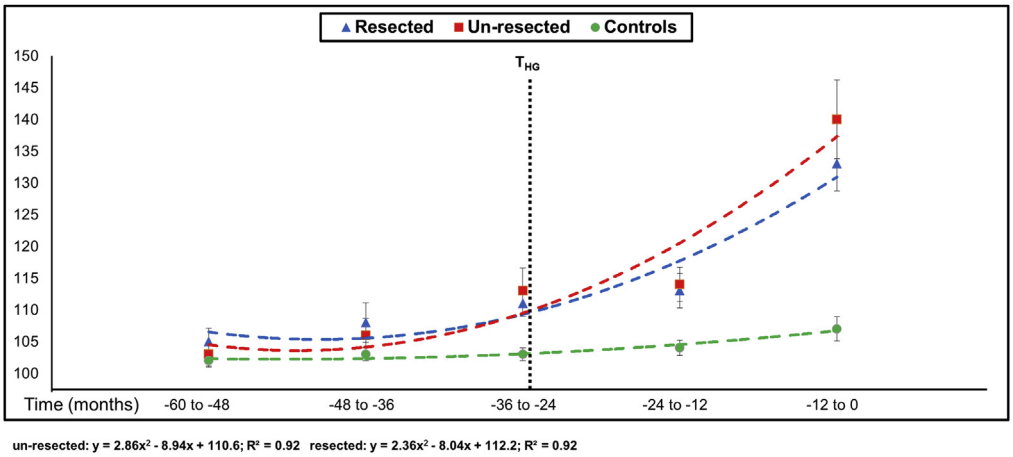
Author contributions: Study concept and design: Suresh T. Chari and Ayush Sharma; acquisition of data: Ayush Sharma; analysis and interpretation of data: Ayush Sharma and Suresh T. Chari; drafting of the manuscript: all authors; and critical revision of the manuscript for important intellectual content: all authors.

Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by the National Institutes of Health U01 Consortium for Study of Chronic Pancreatitis, Diabetes and Pancreatic Cancer (CPDPC) (Suresh T. Chari and Mark A. Topazian), Pancreatic Cancer Action Network (Suresh T. Chari), Kenner Family Research Fund (Suresh T. Chari), and Prokopanko Gift to Mayo Foundation (Ayush Sharma and Suresh T. Chari). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or any other funding source.



Supplementary Figure 1. Flowchart describing identification of pancreatic cancer patients in: cohort A (population-based all PDAC); cohort B (clinic based resected PDAC); and cohort C (population-based resected PDAC).



Supplementary Figure 2. Temporal glycemic profile of population-based controls and subjects with resected and un-resected pancreatic cancer up to 60 months prior to index date.