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

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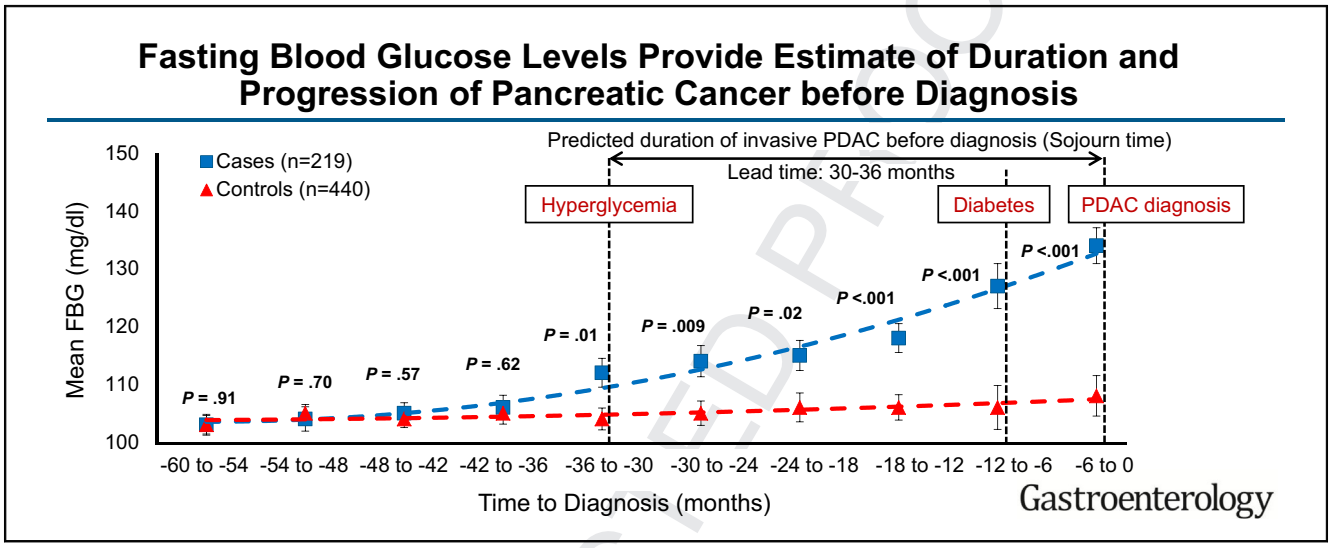

BACKGROUND & AIMS: It is unclear how long pancreatic ductal adenocarcinomas (PDACs) are present before diagnosis. Patients with PDAC usually develop hyperglycemia and diabetes before the tumor is identified. If early invasive PDACs are associated with hyperglycemia, the duration of hyperglycemia should 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.

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

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

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

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NEW FINDINGS

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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 cases 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.