

The early diagnosis of pancreatic cancer and diabetes: what's the relationship?

Changsong Zhang^{1*}, Guangshun Yang^{2*}, Yang Ling^{1*}, Guihua Chen³, Tianbao Zhou⁴

¹Clinical Oncology Laboratory, Changzhou Cancer Hospital of Soochow University, Changzhou 213002, China; ²The Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai 200433, China; ³The Hepatic Surgery Center, The Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510630, China; ⁴The Hepatobiliary Surgery Centre, The Ningbo No. 2 Hospital, Ningbo 315010, China

*These authors contributed equally to this work.

Correspondence to: Tianbao Zhou. The Hepatobiliary Surgery Centre, The Ningbo No. 2 Hospital, Ningbo 315010, China. Email: hbzcs@126.com.

Abstract: Pancreatic cancer (PC) has a dismal prognosis as cancer-specific symptoms occur only at an advanced stage. If the cancer is to be discovered early, it will have to be done in asymptomatic individuals. Since the incidence of PC is low, screening for asymptomatic cancer in the general population will not be feasible. Screening will have to be restricted to subjects at high risk for PC. The proportion of PC patients who also have hyperglycemia or diabetes has previously been under appreciated; new data show that up to 80% are either hyperglycemic or diabetic and this can be evident in the pre-symptomatic phase. Diabetes improves following PC resection suggesting that diabetes is caused by the cancer. Conversely, older subjects with new-onset diabetes have an approximately eight fold higher risk of having PC compared to the general population. Recognition of new-onset diabetes as an early manifestation of PC could lead to diagnosis of asymptomatic, early stage PC. However, primary type 2 diabetes is common and PC is relatively uncommon in the general population and the two forms of diabetes are clinically indistinguishable. The success of the strategy to use new-onset hyperglycemia and diabetes as a screening tool to identify subjects with a high likelihood of having asymptomatic PC will depend largely on our ability to differentiate PC-associated diabetes from the more common type 2 diabetes using a (serologic) biomarker.

Keywords: Pancreatic cancer (PC); diabetes; screening

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Introduction

A screening strategy for sporadic pancreatic cancer (PC) has not been established; given that cancer-specific symptoms occur late, early detection will require screening of asymptomatic individuals. PC is a markedly diabetogenic state and there is increasing evidence that diabetes is prevalent even in early stage, asymptomatic PC. The objective of this review is to present our current understanding of PC-associated diabetes and offer a perspective on the prospects and problems of using this strategy for early detection of PC.

Need for early detection of PC

The overall incidence of PC has increased over the past few decades such that over 265,000 people worldwide are diagnosed annually, which is the fourth leading cause of cancer death in the United States and is projected that PC will become the leading cause of cancer-related deaths in the USA by 2050 (1-4).

It has a dismal five-year survival of 5%, primarily related to the fact that disease-specific symptoms occur late in the course of the disease; at the time of diagnosis, 50% have distant metastases, 29% have local and/or regional spread,

and only 3% have tumors confined to the pancreas (19% remain unstaged/unknown) (5,6). By the time of diagnosis <15% of patients have surgically resectable disease. The median survival of unresectable PC is 4-6 months. While the overall five-year survival of resected PCs (median size 32 mm) is 10-20%, it is 30-60% after resection of small PC (tumor size ≤ 20 mm) and it exceeds 75% when minute PCs (≤ 10 mm in size) are resected (7-10). While future treatment advances may improve survival, the above noted statistics imply that, in order to substantially impact long-term survival, we will need to detect PC earlier.

Opportunity to detect resectable PC

Invasive PC develops from precancerous non-invasive precursor lesions called pancreatic intraepithelial neoplasia (PanIN) which progress from PanIN1 through PanIN3 (carcinoma in situ) (11). The timeline of progression of PC is not well established. In a case series, Brat *et al.* reported the presence of PanINs 17 months to 10 years prior to the clinical diagnosis of cancer (12). To understand the timeline of progression of PC better, we retrospectively reviewed 114 CT scans in 45 patients performed at or prior to cancer diagnosis and found that PC was either undetectable or resectable on scans performed >6 months prior to clinical diagnosis (13,14). In these studies the onset of symptoms coincided with appearance of radiologic features of unresectability. These studies suggest that PC is resectable as little as 6 months prior to clinical diagnosis when it is still asymptomatic and would not normally come to clinical attention.

Challenges to screening for asymptomatic PC

Detecting early PC will require screening asymptomatic subjects for the disease. Two major obstacles limit our ability to screen for PC: lack of a high risk group and lack of sensitive and specific marker(s) of early PC. However, even if a biomarker with very high sensitivity and specificity is identified, screening the general population for asymptomatic PC is unlikely to be cost effective or practical. The age-adjusted incidence of PC in subjects ≥ 50 years of age is 38/100,000 (6). Thus screening for asymptomatic PC will likely require at least two "sieves" to enrich the population to allow cost-effective screening (15). The first sieve could be a high-risk group, i.e., a population of subjects at higher than average risk of PC and the

second sieve could be a unique clinical phenotype, one or more biomarker(s) of early PC, or non-invasive imaging. Currently, among genetic syndromes with a high incidence of PC (first sieve), those with ≥ 2 first degree relatives with PC (second sieve) are being screened using endoscopic ultrasonography (EUS) (16,17). EUS-guided fine-needle aspiration (EUS-FNA), combined with analysis of the KRAS mutation, improves the diagnosis of PC. Sensitivity, specificity, positive and negative predictive values, and overall accuracy of cytopathology alone to diagnose adenocarcinoma were 73%, 100%, 100%, 75%, and 85%, respectively. When KRAS mutation analysis was combined with pathology, these values reached 88%, 99%, 99%, 89%, and 93%, respectively (18). However, such patients account for <5% of all PC. An entirely different approach will be needed to screen for sporadic PC.

Diabetes and PC: what's the relationship?

A review of studies examining the association between diabetes and PC suggests that while long-standing diabetes is an etiologic factor for PC, new-onset diabetes is its manifestation (19-21).

Long-standing diabetes increases the risk of PC by 40% to 100%, and recent-onset diabetes is associated with a 4- to 7-fold increase in risk, such that 1% to 2% of patients with recent-onset diabetes will develop PC within 3 years. Type 2 and type 1 diabetes mellitus (DM) increase the risk of PC with a latency period of more than 5 years. Type 3 DM is an effect, and therefore a harbinger, of PC in at least 30% of patients (22). A recent meta-analysis of 17 case-control and 19 cohort (or nested case-control) studies published between 1966 and 2005 found that the combined age- and sex-adjusted odds ratio (OR) for PC associated with diabetes was 1.8 (95% CI, 1.7-1.9) and it was still lower (OR =1.5) in subjects with diabetes duration of ≥ 5 years (23). The etiology of PC is complex and poorly understood. Risk factors for PC include family history, smoking, obesity, chronic pancreatitis (CP), and DM. The recent increase in the prevalence of type 2 DM (T2DM) is thought to have contributed to a parallel rise in the incidence of PC. Diabetes and PC have a complex relationship that requires more clinical attention. The risk of developing PC can be reduced by aggressive prevention and treatment of T2DM and obesity and the prompt diagnosis of T3cDM may allow detection of a tumor at a potentially curable stage (24).

PC causes diabetes

PC often has new-onset diabetes which resolves with cancer resection as was observed in the case study presented. Diabetes or impaired glucose tolerance is present in more than 2/3rd of PC patients. Epidemiological studies have consistently shown a modest increase in the risk of PC in type 2 diabetes, with an inverse relationship to duration of disease. Subjects >50 years of age with new onset diabetes are at higher risk of having PC. However, to screen new-onset diabetes for PC, additional markers are needed that can distinguish PC-associated diabetes from type 2 diabetes (25).

PC is a markedly diabetogenic state

Using fasting blood glucose values and the diagnostic criteria for diabetes suggested by the American Diabetes Association (ADA), Pannala, Chari *et al.* collectively studied 642 newly diagnosed PC patients in two studies and noted that 303/642 (47%) met criteria for diabetes (26,27). Of the 512 PC patients in one of the studies, 197 (38%) had impaired fasting glucose and only 72/512 patients (14%) had a normal fasting glucose (28). The incidence of PC was higher in patients with diabetic duration less than 2 years, as compared to the non-diabetic group. Patients with concurrent DM and CP had an appreciably elevated risk of developing PC. Long-standing diabetes was not found to be a risk factor for PC in Taiwan's patients (29).

PC-associated diabetes is predominantly new-onset

The onset of diabetes is temporally associated with diagnosis of PC. Gullo *et al.* reported that diabetes in PC was diagnosed either concomitantly with the cancer (in 40%), or within two years before the diagnosis of cancer (16%) (30). In other studies, diabetes was new-onset, i.e., <24 months in duration, in 74-88% of PC patients (27,28). In a recent population-based case-control study, Chari *et al.* abstracted fasting blood glucose values from medical records for five years preceding cancer diagnosis in 736 PC patients and 1,875 age- and sex-matched controls (31). Among the 736 PC cases, 296 cases (40.2%) had diabetes compared to 360/1,875 (19.2%) controls; 50% of diabetes among cases was new-onset. In this study the proportion of diabetic cases and controls were similar >36 months before cancer diagnosis; however, a greater proportion of cases than controls met criteria for diabetes in the 36 to 24 (P=0.04), 24 to 12 (P<0.001) and 12 to 0 (P<0.001) month time periods

before cancer diagnosis. Collectively these studies indicate that the majority of PC-associated diabetes is of recent onset, beginning up to two years preceding the diagnosis of cancer.

PC resection ameliorates diabetes

PC-associated diabetes improves following resection of tumor despite surgical removal of variable amounts of pancreas. In a study of 7 PC patients, Permert *et al.* observed that after sub-total pancreatectomy, diabetic status and glucose tolerance improved in all 7 patients, 6 of whom had diabetes pre-operatively (32). Fogar *et al.* also reported improvement in oral glucose tolerance in 8/9 (89%) patients who underwent radical resection for PC (33). In a study of 41 diabetic PC patients who underwent pancreaticoduodenectomy, Pannala *et al.* found that the diabetes resolved postoperatively in 57% of those with new-onset diabetes (n=30); none of the patients with long-standing diabetes (n=11) experienced any improvement in glycemic status (28). These studies provide further evidence that PC induces glucose intolerance.

Experimental data that PC induces diabetes

PC cell line conditioned media are metabolically active. They impair glucose metabolism in human myoblasts and isolated and perfused rat hepatocytes (34,35). Insulin release is reduced when isolated rat pancreatic islets are incubated with conditioned media of Panc-1 and HPAF cell lines or co-cultured with Panc-1 and HPAF cells (36,37). In a study by Basso *et al.*, daily intraperitoneal injection of supernatant from PC cell line (MIA PaCa2) into immunodeficient mice led to significant increase in blood glucose levels and significantly reduced glucose tolerance compared to control mice injected with saline. These studies suggest that PC cell lines produce soluble factor(s) that can impair glucose metabolism *in vitro* and cause hyperglycemia *in vivo* (38).

In summary, the very high prevalence of new-onset diabetes, which appears to improve after tumor resection coupled with the above experimental evidence, suggests that PC causes diabetes and this may have a unique pathogenic mechanism.

New-onset diabetes: a potential first sieve for PC screening

Patients with new-onset diabetes have a higher probability of subsequently being diagnosed with PC (6). In a population based cohort of 2,122 diabetic individuals in

Olmsted County, it's determined that 18 (0.8%) new-onset diabetic individuals aged 50 or older were diagnosed with PC within 3 years of meeting criteria for diabetes and the observed-to-expected ratio of PC in this cohort of newly diagnosed diabetes subjects was 7.9 (95% CI: 4.7-12.5) (39).

For diabetes to be useful as a screening tool, it should be an early phenomenon that offers a window of opportunity to detect early stage PC in asymptomatic individuals. As noted previously, there is a marked and continuous increase in prevalence of diabetes from 24 to 36 months preceding the diagnosis of PC and leading up to the time of diagnosis (31). In a recent retrospective study, Pelaez-Luna *et al.* noted that the mean interval between onset of diabetes and diagnosis of PC was 10 months (range, 5-29 months) (14). In addition, several studies have noted that diabetes is prevalent even in early stage PC (10,27,40-42).

In a recent large study, Pannala *et al.* found that 115/232 (50%) patients with stage I and II PCs had diabetes (28). Small (≤ 20 mm) and minute PCs (< 10 mm) are often resectable. Tsuchiya *et al.* reported that 61% of patients with small PC (≤ 2 cm) had an abnormal glucose tolerance test and a study of minute PCs (< 10 mm) found 33% prevalence of diabetes (9,10). Thus nearly half the patients with early stage, resectable tumors have diabetes.

In summary, new-onset diabetes not only defines a high-risk group for PC but is also a marker of early, asymptomatic cancer. Its occurrence in nearly half the patients with PC makes it an attractive screening target for early PC.

Proposed screening strategy based on new-onset diabetes

We propose that asymptomatic subjects be screened for diabetes and those with new-onset diabetes undergo "secondary sieving" to further enrich the group for PC. This cohort would then undergo noninvasive imaging or EUS to identify and confirm the diagnosis of PC.

Approximately half the patients with sporadic PC have diabetes. In nearly 50% of diabetic PC patients, the diabetes is diagnosed concomitant with or shortly before cancer diagnosis (27,30). Hence, a strategy that relies only on physician diagnosed new-onset diabetes may capture at the most 25% of cancers. While this in itself would be a significant advance, it can certainly be improved upon. It is very likely that onset of diabetes precedes its symptomatic presentation by many months and sometimes a few years. Recent temporal association studies indicate that there is a substantial window of opportunity between the date subjects

meet biochemical criteria for diabetes and diagnosis of cancer (31). Therefore, to fully utilize the potential of recent hyperglycemia as a clue to early diagnosis of PC one would have to screen individuals for asymptomatic incident diabetes (for example, during annual physical examinations) rather than wait till symptomatic diabetes is diagnosed. The case study presented illustrates this point. Presently the ADA recommends measurement of fasting blood glucose every three years beginning at age 45 in all individuals (43). If a marker that can distinguish PC-associated diabetes from type 2 diabetes is identified, consideration could be given to shortening the interval of fasting blood glucose measurements to every year in individuals over the age of 50 years.

Whether subjects with new-onset diabetes should be directly screened for PC using CT and/or EUS or undergo "secondary sieving" to further enrich the population for PC is debatable. The specific performance characteristics of CT and EUS in the setting of new-onset diabetes should be investigated in a clinical trial before advocating this approach clinically. While in the case study presented CT scan revealed a resectable cancer at onset of diabetes, Pelaez-Luna *et al.* believe that non-invasive imaging techniques, such as abdominal CT scans, are unlikely to consistently detect PC in asymptomatic individuals. This is based on retrospective reviews of CT scans done prior to PC diagnosis, which noted that PC was often undetectable > 6 months prior to its diagnosis (13,14). Therefore, confirmation of the presence of PC in the screening population (i.e., in asymptomatic subjects) may require invasive tests such as EUS. Screening all new-onset diabetics for PC using invasive tests is unlikely to be cost-effective as the prevalence of PC in this population is $< 1\%$. More importantly, it is becoming increasingly clear that abnormalities on EUS are seen even in the absence of clinical disease, especially in older subjects, smokers and alcohol users (44). This "background noise" is likely to create doubt about the presence or absence of cancer possibly leading to unnecessary pancreatic resection. This indeed has been the experience of centers screening familial PC kindreds (16). There are presently no studies that have screened asymptomatic new-onset diabetics for PC.

New-onset diabetes based screening strategy: search for the second sieve

The secondary sieve could be symptoms, clinical phenotype, or a unique biomarker of PC. Two studies have prospectively screened for PC in new-onset diabetes using

symptoms and CA 19-9 elevation as secondary sieves (45,46). Though the prevalence of PC in the screened population was high (4.7% and 13%), most cancers identified were unresectable, again reiterating that screening for PC will have to be done in asymptomatic subjects.

Previous authors have suggested that new-onset diabetes in a lean patient or a patient without a family history of diabetes should raise suspicion for PC (47). In a study of 240 PC patients with diabetes and 62 with type 2 diabetes, Chari *et al.* noted that most patients with PC were overweight or obese prior to onset of symptoms (27). Indeed, obesity is a recognized risk factor for the development of PC (48). Therefore, a purely clinical distinction between PC-associated diabetes and type 2 diabetes is likely to be difficult.

In the absence of clinical features that distinguish PC-associated diabetes from type 2 diabetes, we will require a serologic or molecular biomarker to identify PC among patients with new-onset diabetes. This biomarker does not necessarily have to be metabolically active or even be the mediator of diabetes. For example, a marker in stool that detects early PC could serve as the secondary sieve. However, as new-onset glucose intolerance is a very frequent and characteristic feature of PC, it is reasonable to presume that the mediator(s) of diabetes will also be useful biomarker(s) of PC.

Previous candidate biomarkers of PC-associated diabetes have either failed in validation studies or remain to be validated. Though fasting levels of diabetogenic islet hormones, glucagon, somatostatin, and islet amyloid polypeptide (IAPP) are elevated in diabetic PC patients, they have not proven to be useful discriminators between PC-associated diabetes and type 2 diabetes (49). Though initial reports of plasma islet amyloid peptide (IAPP) were promising, this peptide has poor sensitivity for PC-associated diabetes or resectable PC (27,50). Basso *et al.* reported PC derived S100A8 N-terminal peptide in tumors from diabetics but not from non-diabetic PC or non-neoplastic tissues and this peptide had effects on glucose catabolism in myoblasts *in vitro* (51). Recently Pfeffer *et al.* reported that connexin26, a gap junction protein, is over-expressed in islets of PC and there is a correlation between connexin26 mRNA abundance and glucose level in glucose tolerance tests (52). However, these preliminary findings remain to be confirmed.

In summary, we currently do not have a reliable marker of early PC or a marker specific for PC-associated diabetes. Understanding the pathogenesis of PC-associated diabetes

and identifying unique defects in glucose turnover is likely to give important insights into its possible mediators.

Pathogenesis of PC-associated diabetes

Diabetes is caused by a relative or absolute impairment in insulin secretion (β -cell dysfunction) along with varying degrees of peripheral resistance to insulin action (insulin resistance) (53,54). Though insulin resistance is frequently observed in a number of physiologic and pathologic states including puberty, pregnancy, ageing, and obesity, most insulin-resistant individuals do not develop hyperglycemia as normal pancreatic islet cells compensate for impaired insulin action by augmenting insulin release. In type 2 diabetes defective insulin secretion (β -cell failure) in the face of persistently impaired insulin action (insulin resistance), impaired glucose effectiveness (ability of glucose to stimulate its own uptake and suppress its own release in the absence of a dynamic insulin response), and defective suppression of glucagon secretion contribute to hyperglycemia.

The pathogenesis of PC-associated diabetes and its biochemical mediators are not known. This is unlikely to be simply due to destruction of the gland by the tumor or due to obstructive CP induced by the tumor. The high prevalence of diabetes and glucose intolerance in small PC (tumors <2 cm) and early stage tumors and the onset of diabetes nearly two years before diagnosis and prior to radiologically detectable tumor tends to favor a humoral process rather than a local tumor effect (10,14,28,31). Additionally, insulin and C-peptide levels in PC, especially in those with diabetes have been reported to be higher than in healthy controls (49,50). If pancreatic destruction and resultant decrease in beta cell mass was the cause of diabetes in PC, one would have expected low levels of C-peptide and insulin, as are seen in diabetes associated with CP (55,56).

Whole body physiology studies

Whole body physiology studies in humans with PC have used hyperglycemic or hyperinsulinemic glucose clamp techniques to measure insulin action (40,57). In a series of studies Permert *et al.* reported increased insulin resistance in PC subjects, more so in diabetic than in non-diabetic subjects (32,40,49,57). As noted earlier, these authors also demonstrated that insulin resistance improves after PC resection (32). β -cell response, i.e., increase in insulin and C-peptide levels to oral glucose load, hyperglycemic

clamp, or glucagon stimulation is also impaired in PC (58–60). Permert *et al.* found that while insulin-requiring PC patients did not elevate C-peptide levels in response to hyperglycemia or glucagon, non-insulin requiring diabetic PC patients raised C-peptide levels in response to glucagon but not hyperglycemia (49). Following sub-total pancreatectomy for tumor resection there was an expected marked decline in β -cell response to both stimuli (49). Using Homeostasis Model Assessment (HOMA), Chari *et al.* observed that β -cell function was markedly diminished in PC with impaired fasting glucose while insulin resistance was only modestly increased (61).

Also, the development of diabetes in PC is likely a result of interaction between host (age BMI, and family history of diabetes) and tumor factors. Among patients who meet criteria for diabetes within 2 years, those who are elderly, have lower premorbid BMI, weight loss, no family history of DM, need screening of PC (62). Subjects with predisposition to diabetes (older age, positive family history of diabetes or obesity) may decompensate and develop diabetes more often than those without risk factors for diabetes. How this interaction affects the development and progression of diabetes is unclear. Better understanding of the pathogenesis of PC-associated diabetes may shed light on this issue.

Conclusions

Early detection of PC appears to hold the greatest promise with regards to improving long-term survival. New-onset diabetes is present in nearly half of all PC and various lines of evidence suggest that diabetes is caused by the cancer. Importantly, diabetes appears to be associated with early stage PC. However, further enrichment of the population of new-onset diabetics will be needed before screening becomes cost-effective. The pathogenesis of PC-associated diabetes remains to be elucidated. Future studies should focus on understanding the pathogenesis of PC-associated diabetes and identifying biomarkers that can distinguish it from type 2 diabetes. In addition it would be important to investigate the prevalence, clinical profile, and temporal association between diabetes and PC in other patient populations.

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