3 Pancreatic Cancer and Diabetes Mellitus

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Background

In the United States (US), pancreatic cancer is the tenth most common cancer diagnosis; however, it is the third most common cause of cancer death [1]. Recent estimates suggest that in less than a decade, pancreatic cancer will be the second most common cause of cancer death in the US. The 5-year survival rate in all patients with pancreatic cancer is only ~9% and has only marginally improved over the past five decades [2]. Therefore, extensive efforts are underway for early detection of PDAC. The United States Prevention and Screening Task Force recommends against screening for pancreatic cancer in asymptomatic adults. The focus of early detection efforts is on identifying a high-risk group (HRG) that will benefit from regular surveillance. A HRG for sporadic PDAC has been identified in patients at least 50 years of age with new-onset diabetes (NOD).

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Multidirectional Interaction Between DM and PDAC (Fig. 3.1)

Though the relationship between diabetes mellitus (DM) and pancreatic cancer has been known for over 125 years [3], it is incompletely understood. Multiple clinical, epidemiological, laboratory, and experimental studies have examined the complex relationship between the two diseases.

The prevalence of type 2 DM in patients with PDAC ranges from 4% to 65%, depending on how diabetes is diagnosed [4–6]. Epidemiologic studies suggest that long-standing type 2 DM is a modest risk factor for the development of sporadic PDAC. Meta-analysis of multiple cohort and case-control studies shows that the risk of PDAC in patients with type 2 DM for greater than 5 years is 1.5 to 2.0-fold higher than the general population [7, 8]. This is not fully explained by shared risk factors between the two diseases such as obesity and insulin resistance. However, this risk is not sufficient to cost-effectively screen all patients with type 2 DM for PDAC. PDAC also causes established type 2 DM and impaired glucose tolerance to worsen and for DM to become difficult to control. Some studies have suggested that sudden worsening of long-standing DM may be a clue to underlying PDAC [9–11]. Importantly, among patients with PDAC and DM, majority (~75%) of diabetes is new-onset diabetes (NOD), i.e., less than 3 years in duration [12, 13] suggesting that NOD may be caused by pancreatic cancer.

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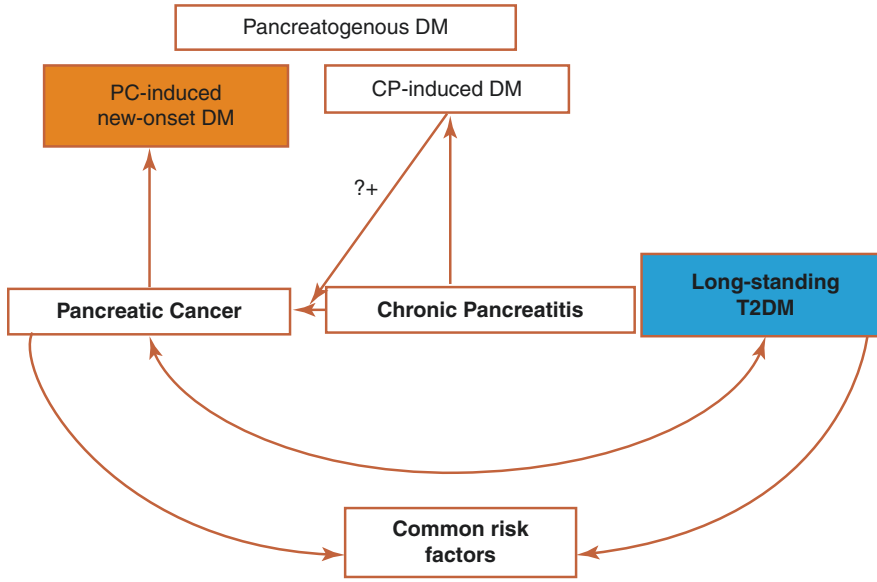

Fig. 3.1 Complex inter-relationship between pancreatic cancer and diabetes

Pathogenesis of Glycemic Disturbance due to PDAC

There are many hypotheses for pathogenesis of diabetes associated with pancreatic cancer [14].

1. Is PC-DM an unmasking of preexisting type 2 diabetes mellitus? Despite the presence of shared risk factors between type 2 DM (e.g., older age, obesity, and family history of DM) and PC-DM, they appear to be distinct clinical entities. The prevalence of NOD and hyperglycemia in 85% of patients with PDAC suggests a cancer related stressor that consistently and profoundly decompensates glucose homeostasis. Also, unlike patients with type 2 DM, glucose control worsens in patients with PDAC in the setting of ongoing, often profound, weight loss.
2. Is PC-DM a consequence of profound cachexia associated with PDAC? Although cancer related cachexia is associated with insulin resistance and disruption of glucose homeostasis, especially in the elderly, it is unlikely to lead to insulin resistance in PDAC [15]. This is because cachexia in PDAC patients is a late finding and has been observed 6 months prior to PDAC diagnosis compared to NOD which occurs 2–3 years prior to the PDAC diagnosis.
3. Is PC-DM due to pancreatic duct obstruction and consequent pancreatic atrophy? PDAC is frequently associated with obstructive pancreatitis and distal atrophy. However, onset of PC-DM occurs before visible appearance of a mass on imaging studies rendering this hypothesis unlikely. Further, insulin levels would be low in patients with DM due to destruction of islet cell mass, while insulin levels are relatively high in PC-DM, reflecting a state of insulin resistance.
4. The pathogenesis of DM in PC is likely related to a paraneoplastic phenomenon caused by tumor secreted products. This is supported by clinical and epidemiological studies and laboratory data that supernatant from pancreatic cancer cell lines inhibits insulin secretion.

New insights on the pathogenesis of metabolic alterations in PDAC have recently emerged. Adrenomedullin, which is over-expressed in pan-

creatic cancer, was identified as a potential mediator of beta-cell dysfunction in PC-DM. Adrenomedullin is a hormone with homology semblance to amylin. Adrenomedullin receptors are found on beta cells and it is expressed in the F cells of the islets [16, 17]. Inhibition of insulin secretion in beta cells induced by supernatant from pancreatic cancer cell lines was replicated by external addition of adrenomedullin and absent by its genetic knockdown [18, 19]. Similar results were seen in orthotopic and subcutaneous in vivo tumor models using pancreatic cell lines expressing adrenomedullin [20]. Further, plasma adrenomedullin levels were higher in pancreatic cancer compared to controls and even higher levels were seen in PC-DM [20]. Overexpression of adrenomedullin was found in surgically resected specimens of pancreatic cancer [20]. These data strongly support the role of adrenomedullin for mediating diabetes in pancreatic cancer.

New-Onset Diabetes as a Harbinger of PDAC

Among the most compelling needs for PDAC research today is to develop a rational, evidence-based strategy to detect cancer at a resectable and early stage using a "DEF-C" approach: Define a high-risk group (HRG) with sixfold to eightfold higher risk of getting PDAC compared to general population; Enrich this HRG to identify a very-high risk group having 25–50 fold higher risk; and Find the lesion using an imaging modality and Confirm PDAC diagnosis with a biopsy of the lesion.

Define HRG for Sporadic PDAC: Since PDAC is relatively uncommon and often presents at an advanced stage, screening can only be effective in asymptomatic HRGs. Currently, the cohort of subjects with new-onset diabetes (NOD) over age 50 years (The NOD Cohort) is the only "actionable" HRG for PDAC. About 25% of patients with pancreatic cancer are diagnosed with DM 6 months to 36 months before the diagnosis of the cancer [12]. Conversely, subjects with NOD over age of 50 years have an eightfold higher risk for having pancreatic cancer [21]. Thus NOD may be a clue to the early detection of pancreatic cancer. However, the success of the strategy to use NOD as a marker of pancreatic cancer will depend on our ability to distinguish pancreatic cancer-associated diabetes from the more common type 2 diabetes.

Enrich HRG for Sporadic PDAC: To further enrich new-onset diabetes for PDAC, Sharma and colleagues developed the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) model based on changes in weight, blood glucose, and age at onset of diabetes. The weighted scores for these 3 most discriminatory factors identify NOD subjects at high, intermediate, and very low risk of having PDAC. A score >3 in the ENDPAC model had sensitivity and specificity of 80% for PDAC. In the validation sample a model score of >3 identified 7/9 PDAC (78%) with specificity 85% while enriching PDAC prevalence 4.4-fold (3.6%). Most importantly, an ENDPAC score of <0 designated 49% of NOD as having extremely low risk for PDAC. An ENDPAC score of >3 identified 75% of PC-NOD >6 months before PDAC diagnosis [21].

Find PDAC in NOD: Using a cohort of subjects who had high-resolution scans in the pre-diagnostic phase of PDAC, Singh and colleagues determined the sensitivity of CT for pre-diagnostic PDAC and developed a PDAC CT Gram that defines the CT stages (CTs) of pre-diagnostic PDAC. CTs were abnormal in 16% and 85% at 24–36 and 3–6 months, respectively, before PDAC diagnosis. On PDAC CT Gram, an abrupt pancreatic duct cut-off/duct dilatation was seen at a median of −12.8 months; a low-density mass confined to pancreas at 9.5 months, peri-pancreatic infiltration at 5.8 months, and distant metastases only at diagnosis [22].

Efforts to Use NOD for Early Detection of PDAC

Almost all (~85%) PDAC patients have an abnormal fasting glucose and nearly half have DM, which is frequently new-onset, i.e., of <36 months duration. In a retrospectively assembled NOD

Cohort of 2122 subjects, 18 (0.85%) developed PDAC within 3 years of onset of DM, a sixfold to eightfold higher probability of being diagnosed with PDAC compared to the general population [23, 24]. In prospective screening studies in subsets of NOD, 3–14% had PDAC. Biomarker work for early detection of PDAC is currently severely limited by lack of samples from asymptomatic subjects with early stage PDAC. To address these serious impediments to early detection of PDAC, efforts are underway to assemble a prospective NOD Cohort with the goals of determining the risk of PDAC in NOD and collect biosamples from presymptomatic PDAC (Clinicaltrials.gov NCT03731637) [25]. In an ancillary study within the NOD cohort, called the Early Detection Initiative (ClinicalTrials.gov NCT04662879), subjects with NOD with an ENDPAC score >0 will be imaged with high-resolution CT scan to screen for PDAC. These studies will pave the way for utilizing a near-universal phenomenon in PDAC, glycemic disturbance, to identify the cancer early [26].

Summary

Early detection of pancreatic cancer can improve long-term survival. Strategies for early detection include identification of a high-risk group for PDAC, enrichment of the high-risk group further, and finding the lesion in the highly enriched cohort. A high-risk group has been identified in patients at least 50 years of age with new-onset diabetes. Approximately half of patients with PDAC have NOD and emerging evidence suggests that diabetes is caused by cancer. Compared to the general population, patients with NOD have sixfold to eightfold higher risk of being diagnosed with PDAC within 3 years which offers a unique opportunity for early detection. Further enrichment of the NOD group with risk prediction models could identify a very-high risk group for PDAC. Future studies should focus on understanding the pathogenesis of pancreatic cancer-associated diabetes and identifying and validating novel biomarkers and clinical risk scores that can distinguish it from type 2 diabetes.

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