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Diabetes mellitus as a result of pancreatic cancer

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1. Introduction

The interaction between diabetes mellitus (DM) and pancreatic ductal adenocarcinoma (PDAC) is complex. Although long-standing diabetes is a modest risk factor for PDAC, DM is often induced by PDAC (16). In addition, recent studies suggest that anti-diabetic medications can modify risk of PDAC in subjects with DM (24, 38). Lastly, both PDAC and DM share common risk factors such as obesity. DM secondary to an underlying disease of the exocrine pancreas is currently classified as type 3c DM by the American Diabetic Association. Recent onset DM (within 36 months) in relation to PDAC may represent a separate entity from other pancreatic diseases such as chronic pancreatitis, and will be referred to as pancreatic cancer-associated diabetes mellitus (PaCDM). The terminology of PaCDM does not technically involve DM secondary to pancreatic resection, however this is discussed in the present chapter as it relates to treatment of PDAC and provides supportive evidence for the theory that PaCDM may actually be induced by cancer.

2. Characteristics of PaCDM

Estimates of the prevalence of DM in PDAC differ depending on whether or not subjects are screened for diabetes (using fasting glucose or glucose tolerance test) or data on DM is retrospectively obtained through chart review or patient self-reporting. When evaluated by glucose tolerance testing or fasting glucose measurements, hyperglycemia occurs in up to 80% of PDAC patients at the time of diagnosis, while approximately 45-65% of PDAC patients have DM (28, 31). In a large prospective study of PDAC patients with a recent fasting blood glucose level, DM was present in 47% of patients (243/512), impaired fasting glucose in 38%, and normoglycemia in 14% (**Figure 1**) (28). Of those with DM, the duration of DM was <2 years for 74% (177/243), which represented 34% of the entire study population.

The clinical profile of PaCDM is not significantly different compared with those having type 2 diabetes mellitus (T2DM). The comparison of PaCDM with non-cancer controls with DM revealed similar age, gender distribution, adult body mass index, and frequency of family history of DM (28). Although the body mass index is similar at the time of DM onset, one study demonstrated most patients with T2DM are gaining weight at the time of DM onset, while many with PaCDM develop DM despite preceding weight loss (17).

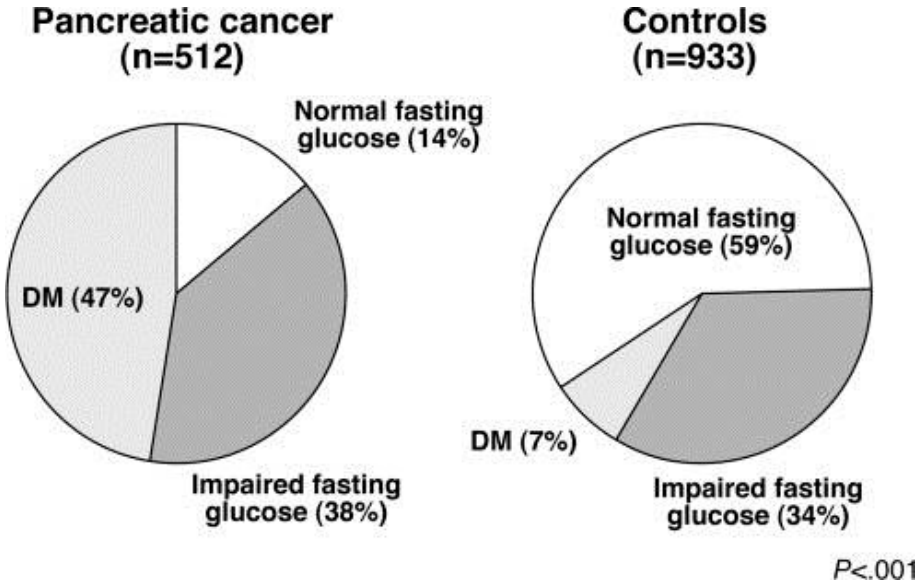

Figure 1. Distribution of fasting blood glucose among pancreatic cancer cases and controls. Normal fasting glucose, ≤99 mg/dL; Impaired fasting glucose, 100-125 mg/dL; DM ≥126 mg/dL. Adapted with permission from Pannala *et al* (28).

3. Potential Mechanisms of PaCDM

Several explanations for PaCDM have been considered including it simply being an incidental finding, or mechanistically as the result of cancer cachexia or secondary parenchymal destruction. Additionally, there are emerging data supporting the hypothesis PaCDM may be tumor-induced, representing a paraneoplastic phenomenon.

Is DM in PDAC is Simply T2DM Ddentified Due to Intensive Testing at the Time of Diagnosis?

One explanation for PACDM is that those with PaC are more likely to have DM due to the presence of canonical risk factors for T2DM, including obesity and family history of DM. Since PDAC patients undergo extensive testing immediately preceding diagnosis, it is possible that PaCDM is simply T2DM. However, DM is not increased in prevalence in other cancers where similar testing would be undertaken, such as lung, breast, colon, and prostate cancer (**Figure 2**) (1). Thus, the high (50-70%) prevalence of DM at the time of PDAC diagnosis cannot be explained by incidental discovery of preexisting T2DM.

Does Insulin Resistance Due to Cancer Cachexia Precipitates PaCDM?

Both PDAC and cachexia have been associated with insulin resistance (33). It has therefore been proposed that cachexia-induced insulin resistance may unmask DM in subjects with PDAC, analogous to steroid-induced or gestational DM. However, the prevalence of DM is not increased in other cancers associated with cachexia, and the onset of PaCDM precedes onset of cachexia by many months (1, 17). Therefore, cachexia alone appears insufficient to cause DM, although it may contribute to worsening of preexisting DM.

Is DM in PDAC is Secondary to Parenchymal Destruction?

As in chronic pancreatitis, it is certainly the case that patients with large tumors can develop DM as a consequence of destruction of the islet-containing pancreatic parenchyma. Additionally, many pancreatic tumors cause pancreatic duct obstruction and atrophy of the pancreas upstream from the obstruction. Thus, obstructive chronic pancreatitis could be a potential cause of PaCDM.

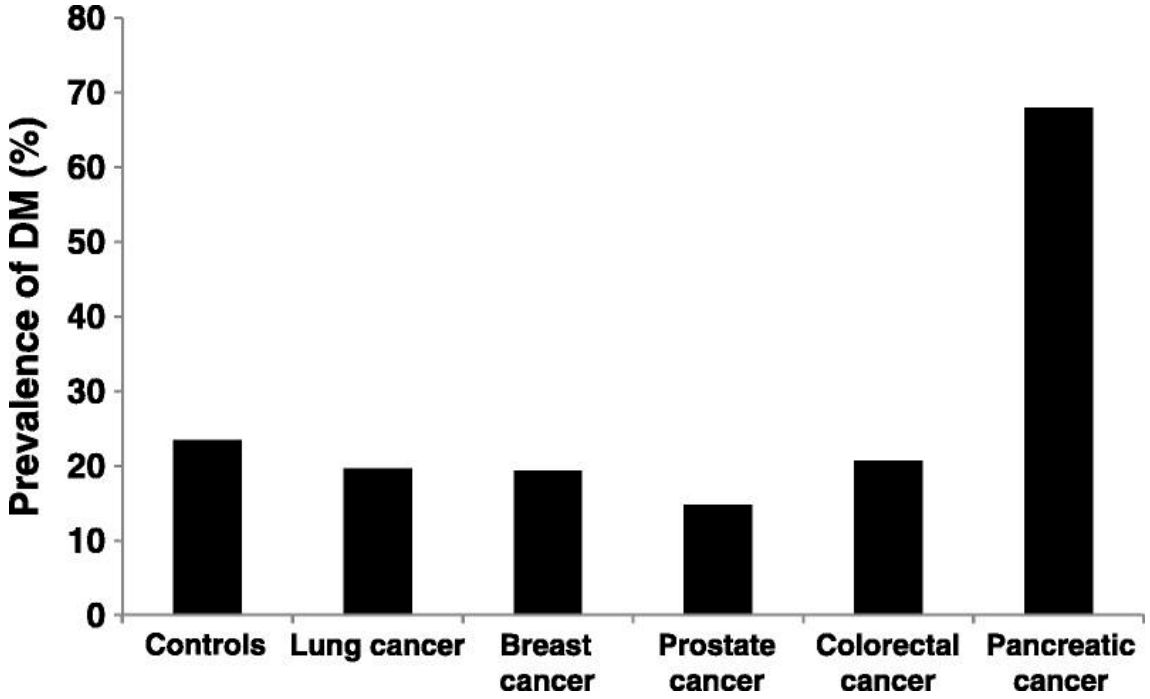

Figure 2. Prevalence of DM in PDAC compared to common cancers and non-cancer controls. Adapted with permission from Aggarwal *et al* (1).

However, this is not a predominant factor in most cases, considering the observation that the onset of DM typically occurs 12 months prior to clinical diagnosis. Additionally, at the time of DM onset there is frequently no radiographically detectable mass or pancreatic atrophy (12, 29). Lastly, islet cell loss results in low insulin levels and decreased peripheral insulin resistance, however PDAC is associated with high insulin levels and marked insulin resistance (4, 6, 36).

Is Pancreatic Cancer-Induced DM a Paraneoplastic Event?

There are growing epidemiological data to support the hypothesis that PaCDM can be the result of a paraneoplastic process. Although long-standing DM is considered a modest risk factor for development of PDAC, there is an even greater risk in those with the onset of DM within 3-5 years of cancer diagnosis (9, 20). A population based study of more than 2,000 patients with new-onset DM reported an incidence of PaC of 0.85% (1 in 125), which was 8 times the risk of the general population (8). These results were confirmed in later studies involving patients identified through the SEER and Veterans' Health Administration National Patient Care databases (14, 41). The markedly increased risk of PDAC in patients with new-onset DM compared to long-standing DM suggests that PDAC itself may cause DM, representing an early disease manifestation rather than a predisposing risk factor. The development of DM at an early stage in PDAC suggests new-onset DM could be used to enrich a higher risk population to target for screening of sporadic PDAC (27). However, additional tests to discriminate DM secondary to PDAC from the much more prevalent T2DM for this strategy to be effective.

Additional evidence suggesting PaCDM is a paraneoplastic phenomenon is the improvement or resolution of DM with cancer-related treatments. Although it is anticipated patients with PDAC would have increased likelihood of developing DM postoperatively, there is often paradoxical improvement in the glycemic status. While PDAC patients with long-standing DM have

persistent DM following pancreatic resection, patients with PDAC and new-onset DM often experience resolution of diabetes in the postoperative setting (**Figure 3**) (11, 28). Additionally there is often resolution of pre-operative glucose intolerance and peripheral insulin resistance (11, 30). Similarly, in those with new-onset DM undergoing neoadjuvant chemotherapy increased tumor destruction was associated with greater odds of DM resolution (13). Although either treatment could contribute to worsened DM, the commonly observed resolution of DM favors a tumor-mediate diabetic state in some patients with PDAC.

DM occurring in the setting of PDAC is generally believed to be the result of both β-cell dysfunction and peripheral insulin resistance, however the mechanisms of disease are not fully understood. Adrenomedullin is a hormone with receptors on β-cells that has recently been proposed mediator as a of β-cell dysfunction in PaCDM (2). Adrenomedullin was demonstrated to inhibit insulin secretion when examined in both *in vitro* and *in vivo* tumor models. Additionally, plasma levels of adrenomedullin where increased in patients with PDAC compared to diabetic and non-diabetic controls, and those with PaCDM had higher levels than those with PDAC without DM. It has previously been shown that adrenomedullin is upregulated in the setting of hypoxia or hypoglycemia, suggesting this is a mediator of β-cell dysfunction in response to the PDAC tumor microenvironment (22, 26).

Other potential mediators of insulin resistance in PDAC including islet amyloid polypeptide and S-100A8 N-terminal peptide have been investigated; however, there are no compelling data in humans confirming their role (3, 5, 7). Pancreatic polypeptide (PP) is a hormone that appears to respond to stimulation differently in PDAC. This hormone normally mediates hepatic sensitivity to insulin; subcutaneous infusion of PP enhances insulin sensitivity and decreases insulin requirements (32, 39). A recent proof of concept study demonstrated a blunted PP response to mixed meal stimulation test in those with PDAC-induced DM compared to T2DM (15). Notably, the abnormal response was only observed in those with a tumor located in the head or body of the pancreas, so it is uncertain whether the decreased PP responsiveness is a consequence of mass destruction of the ventral pancreas or an alternate mediating factor.

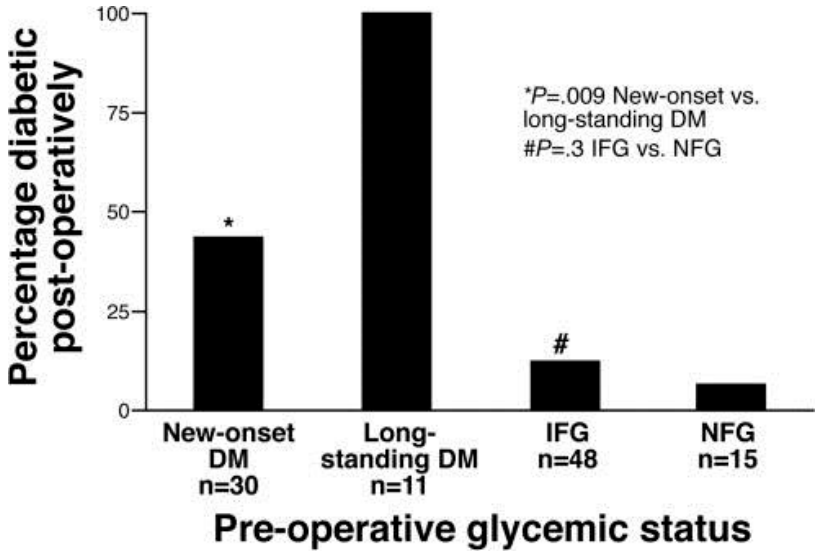

Figure 3. Prevalence of DM after pancreaticoduodenectomy for PDAC. New-onset DM was defined as a duration of ≤2 years duration in this study. Impaired fasting glucose (IFG) (100-125 mg/dL); Normal fasting glucose (NFG), ≤99 mg/dL). Adapted with permission from Pannala *et al* (28); with permission from Elsevier.

Thus, although a biochemical mediator of insulin resistance in PDAC remains under consideration, there is currently no direct evidence of this relationship. Another emerging possible mechanism of insulin resistance involves the interaction between PDAC and adipose tissue. Proposed pathways include adipose tissue inflammation, with resultant alterations of secreted adipokine levels (particularly adiponectin and leptin), inflammasome-mediated cytokine release (including tumor necrosis factor, IL-6, and monocyte chemoattractant protein 1), and the generation of non-esterified fatty acids (33).

DM Following Pancreatic Surgery for Pancreatic Cancer

DM onset following pancreatic resection is another important consideration. The timing of DM onset after surgery is in contrast to the previous discussions of PaCDM, which refers to DM prior to cancer treatment. DM secondary to pancreatic resection is primarily a consequence of decreased β-cell mass, and is not unique to cancer. The prevalence of post-operative DM is dependent on several factors including the type of resection, extent of resection, and whether or not there is residual disease, such as chronic pancreatitis, in the remnant pancreas. The prevalence of pancreatogenic DM following distal pancreatectomy for tumors (malignant or benign) is approximately 5-15% (10, 23, 25, 37). However, in those undergoing distal pancreatectomy for chronic pancreatitis, the risk of DM is higher (>25%) (19, 35). Despite physiologic changes favoring improved glucose tolerance, including delayed gastric emptying and weight loss, after proximal pancreatic resections (i.e., pancreaticoduodenectomy or duodenum-preserving pancreatic head resection) a higher proportion of patients develop post-operative DM compared to distal pancreatectomy. The reported prevalence of pancreatogenic DM in those undergoing surgery for chronic pancreatitis (20-50%) (21, 34, 40) remains higher than for those undergoing proximal resection for a tumor (20-30%) (10, 18).

4. Summary

The interaction between DM and PDAC is complex, and DM as a result of PDAC remains an intriguing area of interest. Many patients with PDAC develop DM shortly prior to cancer diagnosis, which is often paradoxically ameliorated by surgical resection. In combination with an increased risk for PDAC in those with new-onset DM, these data suggests the tumor itself may induce DM. There are emerging data supporting this concept of PDAC-induced paraneoplastic DM, including the identification of adrenomedullin, a potential humoral mediator of β-cell dysfunction. Further investigations into the mechanisms of β-cell dysfunction and peripheral insulin resistance in PaCDM may lead to additional insights into early detection and treatment of PDAC.

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