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Review Article

New perceptions of interrelationship between pancreatic cancer and diabetes

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Abstract: Pancreatic cancer is strongly associated with diabetes mellitus. About 80% of the patients with pancreatic ductal adenocarcinoma have glycometabolic alterations. On the contrary, patients with new-onset diabetes mellitus within 1-3 years have a significant increased risk of pancreatic neoplasm up to 5-8 folds. Long-standing diabetes increases the risk for pancreatic cancer, while pancreatic cancer also provokes the development of diabetes mellitus. The pancreatic cancer-induced glucose tolerance impairment is supposed to be paraneoplastic. However, the pathogenesis of this phenomenon remains unclear, which might be the key to develop novel therapeutic strategies. New-onset diabetes may indicate subclinical pancreatic neoplasm and potential reliable biomarkers are still to be explored.

Keywords: Pancreatic neoplasm, diabetes mellitus, relationship, early diagnosis, mechanism

Introduction

Pancreatic cancer (PaC) is a common digestive malignant tumor, which holds the fourth leading cancer-associated death in U.S. and the eighth to ninth worldwide [1, 2], with an overall five-year survival rate of 6% in the U.S. [3]. The term pancreatic cancer encompasses both exocrine and endocrine tumors, of which over 80% are pancreatic ductal adenocarcinomas (PDAC) [4]. A recent study held in urban China showed a standardized incidence rate at 6.70/100,000, with an overall 5-year survival rate at 4.1% and median survival time at 3.9 [95% Confidence Interval (CI) 3.8-4.0] months [5]. Despite the evolvement of cancer research over recent decades, the unique hope for cure of aggressive developing PDAC remains surgical operation, owing to the inconspicuous symptoms, high-degree malignancy and low-sensitivity to chemotherapy, whereas early resected small carcinomas (2 cm or less) disclosed significantly higher survival rates [6]. The poor prognosis reveals the late diagnosis of the malignancy, while most PDAC persist for about 20 years from intraductal papillary mucinous neoplasm (IPMN) to distant metastasis [7]. According to the statistics, the distant disease at diagnosis is an independent risk factor for the prognosis of PDAC with a hazard ratio (HR) at 1.257 [5]. Hence, the sine qua non of improvement of PDAC survival relies on early diagnosis.

Diabetes mellitus (DM) as a risk factor for carcinomas has long been well recognized. Epidemiological studies have consistently unveiled an increased incidence of multiple malignancies in patients classified as being diabetic. Peripheral insulin resistance and hyperinsulinemia have been suggested to promote tumor growth [8]. However, a distinctive phenomenon in pancreatic cancer compared to other malignant tumor is that about 85% of PDAC patients have glycometabolic disorders within three years before diagnosis of cancer [9]. This exclusive bidirectional interation between pancreatic cancer and new-onset diabetes mellitus (less than 3 years) has been acknowledged over the past decades, which showed a new emblem and potential approaches for the early diagnosis of PDAC.

Epidemiological evidence of association between PDAC and diabetes mellitus

Numerous epidemiological studies have investigated the correlation between PDAC and DM

[10]. A recent meta-analysis based on 97 studies demonstrated an increased hazard ratio at 1.51 (1.24-1.83) in patients with diabetes for deaths owing to pancreatic cancer [11]. In a prospective cohort study with follow-up durations more than 20 years, an increased risk of pancreatic cancer among subjects with high post-load plasma glucose levels is observed [12]. Also, a meta-analysis noticed an excessively high risk of pancreatic cancer related to high levels of circulating C-peptide/insulin and hyperglycemia [13]. On the other hand, a meta-analysis consisted of 17 case-control and 19 cohort or nested case-control studies with information on 9220 individuals with pancreatic cancer from 1966 to 2005 showed that Individuals in whom diabetes had only lately been diagnosed (< 4 years) had a 50% greater risk of the malignancy compared with individuals who had diabetes for ≥ 5 years [14]. A population-based study showed that the prevalence of pancreatic cancer in patients with new-onset diabetes had an 8-fold higher risk than the general population [15]. Chari et al [16] reviewed the medical records of fasting blood glucose (FBG) up to 60 months of 736 PDAC cases and 1875 controls and confirmed a greater proportion of cases than controls met criteria for diabetes in the group with 36 months before the diagnosis of PDAC. A retrospective cohort study including 512 newly diagnosed pancreatic cancer cases (243 diabetic and 269 non-diabetic) and 933 controls revealed that DM was more prevalent (47% vs 7%; $P < .001$) and predominantly of new onset (< 2-year duration) (74% vs 53%; $P = .002$) among cases compared with controls [17]. The latest meta-analysis, which included a total of 35 cohort studies, also support that diabetes is associated with an increased risk of pancreatic cancer in both males and females and that DM is both an early manifestation and an etiologic factor for pancreatic cancer, with a relative risk of pancreatic cancer negatively correlated with the duration of DM, which is highest within less than 1 year [18]. Based on the above data, long-term diabetes mellitus is a probable risk factor for pancreatic cancer, but new-onset diabetes (especially within 1-3 years) shows a more compact correlation to the risk of pancreatic cancer. New-onset diabetes is considered mostly as a cancer related symptom.

Classification of pancreatic cancer-induced diabetes

According to the classification of diabetes mellitus established by the American Diabetes Association (ADA), pancreatic cancer-induced diabetes belongs to type 3c diabetes mellitus (T3cDM) that is caused by inherited or acquired pancreatic exocrine disease [19]. T3cDM holds 10% in western diabetic population [20], which is most likely caused by destruction of pancreatic islets in chronic pancreatitis, trauma or infections compared to type 1 and type 2 diabetes. The characteristics of this type are hypoinsulinemia, lack of pancreatic polypeptide, hepatic insulin resistance and increased peripheral insulin sensitivity, etc. Nevertheless, the symptoms caused by pancreatic cancer-induced diabetes, accounting for 9% in T3cDM [21], are different from other pancreatogenic diabetes by slightly hyperinsulinemia and peripheral insulin resistance [22]. Therefore, the mechanism of pancreatic cancer-induced diabetes is not supposed to be limited to the diminution of islets quantity.

Clinical manifestation of pancreatic cancer-induced diabetes

In over a fifth of PaC, the onset of DM occurs when the cancer is asymptomatic [23]. The clinical manifestation of pancreatic cancer-induce diabetes also differs from traditional type 2 diabetes mellitus (T2DM). At the onset of DM, 59% of PCDM subjects lost weight versus 30% of T2DM subjects while 56% of T2DM subjects gained weight versus 31% of PCDM subjects. By index date, PCDM subjects lost more weight than T2DM subjects did. Loss of weight usually has a negative correlation with FBG level in T2DM, while such an interrelationship is not obvious but even inverse in pancreatic cancer-induced diabetes [24]. Furthermore, PCDM patients tended to have higher FBG values compared to controls with DM, but were of similar age and gender distribution, and did not differ significantly in terms of self-reported usual adult BMI and family history of DM [17]. A controversial issue is that whether DM can resolve or not after pancreaticoduodenectomy (PD). Pannala et al showed that DM resolved in 17 of 30 patients (57%) with new-onset DM, its prevalence was unchanged in patients with long-standing DM (n = 11) ($P = .009$), indicating that

new onset diabetes may be induced by pancreatic cancer [17]. While another group demonstrated that DM resolved after PD in some patients both with and without PDCA, suggesting that PD-associated anatomic change may also play a role in resolution of DM after PD [25].

The influence of associated diabetes to PDAC and clinical outcomes

An important controversy is whether accompanied diabetes influences the mortality of PDAC. Some studies found that DM impacts little on the mortality of pancreatic cancer [26] or overall survival time [27, 28], although others found that accompanied DM significantly reduced survival durations [29, 30].

For the anti-diabetic medications, several lines of evidence showed that metformin has a protective effect for cancer. Metformin is associated with a decreased risk of cancer incidence compared with other treatments among diabetic patients, according to two meta-analyses, consisting of 11 studies and 17 studies, respectively [31, 32]. In contrast, new use of insulin or insulin glargine was associated with an increased risk of pancreatic cancer, shown by a meta-analysis including 1,332,120 people and 41,947 cancers [33]. However, another meta-analysis composed by 11 studies including 448,928 study subjects and 19,128 cancer patients reported no significant link between insulin glargine and increased pancreatic cancer risk [34]. Further studies should be designed to clarify the question. For thiazolidinediones (TZDs), a meta-analysis of 17 studies showed no association with pancreatic cancer [35].

A recent retrospective study containing 111 PDAC with new onset DM reported that the median duration of DM prior to pancreatic cancer diagnosis was 6.5 (0.5-35) months, and the median delay between onset and physician diagnosis of DM was 2.5 (0.25-14) months, which decreased from 8.8 (3.5-14) months in patients with DM onset between 1995 and 1999 to 0 (0-2) months, in patients with DM onset between 2004 and 2009. However, the proportion of patients with undiagnosed DM (~33%) remained unchanged [23]. Mizuno et al [36] retrospectively reviewed 540 patients with pancreatic cancer and noted that asymptomatic patients had smaller primary tumor and were diagnosed at an earlier stage. The prognosis of pancreatic cancer patients complicated with DM did not differ from that of patients without DM; however, patients had better prognosis if they were diagnosed in association with DM alone (median survival time, 20.2 months), compared with patients diagnosed by other symptoms (10.2 months, $P < 0.01$), proposing that patients diagnosed in association with DM had better survival than otherwise symptomatic patients. Thus, DM can be a useful diagnostic clue for screening and lead to improvement of prognosis in pancreatic cancer patients.

Mechanisms of pancreatic cancer induced-diabetes

As the impact of diabetes mellitus on tumor growth has long been recognized, the mechanisms of which has been researched in depth, including metabolic, hormonal, immunological alterations that influence tumor proliferation [37]. On the opposite, the knowledge of how neoplasms affect glycometabolism remains relatively insufficient. The primary causes of glycometabolic disorders involve dysfunction of beta-cells, peripheral insulin resistance and lipotoxicity in the domain of T2DM researches [38]. A similar occurrence was demonstrated in pancreatic cancer induced-diabetes [39], but the mediators of the interaction secreted directly by cancerous tissues remains indeterminate. In a recent study, Wang et al identified the proteins implicated in the development of PC-associated DM in PC tissues with DM using isobaric tags for relative and absolute quantitation (iTRAQ) coupled with two-dimensional liquid chromatography-tandem mass spectrometry to compare protein expression in PC tissues with DM with that in PC tissues without DM and in adjacent non-tumor tissues with or without DM [40]. This result may serve as a foundation to better understand and further explore the etiology and pathogenesis of PC-associated DM.

Dysfunction of beta-cell

Recent studies focused on adrenomedullin (ADM), a peptide originally isolated from human pheochromocytoma tissues, consisting of 52 amino-acids and sharing homology with the calcitonin gene-related peptide (CGRP) and amylin [41]. It is synthesized by different types of cells

and acts by binding calcitonin receptor-like receptor (CRLR) and members of the receptor activity-modifying protein (RAMP) family. ADM is widely expressed in heart, lung, kidney and pancreas, regulating cell growth, differentiation and migration. ADM is induced by hypoxia and over-expressed in PDAC and might therefore serve as a potential tumor marker. Furthermore, ADM increases invasiveness of some pancreatic cancer cells and might influence angiogenesis [42]. Meanwhile, ADM is abundantly expressed on pancreatic islets beta-cell and can inhibit insulin secretion at both basal (3 mM) and high (15 mM) glucose concentrations [43]. Using microarray analysis, Aggarwal et al identified ADM as a potential mediator of diabetes in patients with pancreatic cancer. To confirm the role of ADM in the relationship of pancreatic cancer and glycometabolism, protein and mRNA levels of ADM were evaluated which showed elevated in human pancreatic cancer samples compared to controls. ADM inhibited glucose-stimulated insulin secretion from beta cell lines and islets isolated from mice [44]. These findings directly defined the fact that ADM is up-regulated in patients with pancreatic cancer and causes insulin resistance in beta cells and mice.

Autoantibodies against insulin and beta-islet cells [45] or islet amyloid polypeptide (IAPP, normally secreted with insulin by beta cells and could be stimulated to release by pancreatic cancer) [46] were also supposed to mediate the impairment of glucose tolerance in PDAC, both of which lack further evidence to support. Furthermore, signal pathway analysis of genome-wide association suggested an association between susceptibility for PDAC and pancreatic development genes like HNF1A, HNF1B, PDX1 or NR5A2, some of which are also implicated in DM [47]. All the data demonstrate the complex relationship between DM and pancreatic cancer.

Peripheral insulin resistance

Similar to T2DM, the insulin resistance associated with pancreatic cancer is associated with a post-insulin receptor (IR) defect, which impairs skeletal muscle glycogen synthesis and glycogen storage [48]. S100A8 N terminal peptide [49] and IAPP [50] are also suggested to mediate peripheral insulin resistance in PDAC. Both were shown to cause insulin resistance in vitro, but the importance and discriminative ability were not authorized [47, 51, 52].

A systemic inflammatory response is often seen in PaC. In PaC, high level of IL-6 is associated with cachexia [53]. It seems that inflammatory cytokines are released and play an important role in the development of peripheral insulin resistance in PaC, considering that sepsis results in hyperglycemia and insulin resistance, and central in the development of the latter is the expression of inflammatory cytokines such as tumor necrosis factor-alpha, IL-1 beta, IL-6 [54].

Other hypothesis

A small study composed of 64 patients with newly diagnosed PaC reported that newly diagnosed PaC was characterized with lower leptin concentrations and higher adiponectin/leptin ratio in comparison with controls or T2DM individuals, which could help in the screening of persons in high risk for PaC, especially in those with diabetes [55]. Another hypothesis presumed that diabetes was caused by biliary obstruction and distal pancreatitis associated with a tumor, based on the evidences that insulin resistance and diabetes improved markedly after tumor resection [30, 56].

Potential biomarkers in the development of pancreatic cancer and glycometabolic disorders

CA19-9 is a classic biomarker for the diagnosis of pancreatic neoplasm. When the value of CEA and CA 19-9 was analyzed as a dichotomous variable, elevated CEA (≥ 5 ng/ml) and CA 19-9 (≥ 500 U/ml) levels were strongly correlated with the presence of diabetes in PDAC patients. Thus, new-onset DM combined with higher CA 19-9 and/or CEA might be regarded as a useful tool to screen early pancreatic cancer [57]. IAPP was considered to be a candidate marker of pancreatic cancer associated with DM, but a study showed its sensitivity only at 40% for pancreatic cancer, 50% for pancreatic cancer with DM and 27% for resectable cancer. Hence, IAPP is not a satisfactory marker for early detection [51]. As mentioned above, ADM is likely to be a potential biomarker for the early diagnosis of PDAC, with higher plasma levels in patients with pancreatic cancer compared with patients with diabetes or controls. Moreover, plasma

levels of adrenomedullin were higher in patients with pancreatic cancer who developed diabetes compared those who did not [44]. But the diagnostic utility of ADM should be further explored in further studies. Adiponectin/leptin ratio, as well as glucagon/insulin ratio, is also supposed to be potential biomarkers for pancreatic cancer in patients with new-onset diabetes mellitus [55, 58]. Zhou et al found that the regenerating gene (REG) I-alpha and transgelin are involved in pancreatic cancer. These two proteins were preferentially expressed in cancerous tissues and pancreatic cancer cell lines, modulating cell proliferation, migration and invasion. Interestingly, both of them had a significant correlation between diabetes [59, 60]. Recently, our group profiled the genome-wide microRNA expression in patients with pancreatic cancer and DM, T2DM and healthy controls, which demonstrated that a combination of multiple serum microRNA serves as a more comprehensive indicator for pancreatic cancer detection (data not shown).

Conclusion

The relationship between pancreatic cancer and DM is complex. The mechanism of pancreatic cancer-induced DM remains unclear. The investigation into the pathogenesis of PaC associated DM may help develop novel preventive and therapeutic strategies. The research on developing reliable biomarkers of high sensitivity and specificity to distinguish early pancreatic cancer in new-onset DM might immensely increase the survival rate of this deadly disease.

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