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Review Article

Diabetes Mellitus and Early Detection of Pancreatic Cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is most often detected at an advanced stage due to a lack of symptoms at the first stage. PDAC is relatively uncommon, and screening of the asymptomatic population is not feasible or cost-effective. Therefore, screening of individuals in high-risk groups is recommended. Diabetes mellitus (DM) is associated with PDAC, and patients with DM are recognized as a high-risk group for PDAC. Here, we review the complex relationship between pancreatic cancer and DM, including the role of diabetes as a risk factor for pancreatic cancer and its role in inducing the destruction of islet β cells and insulin resistance. We also review the current study about discriminating DM with pancreatic cancer from normal DM and the model for early screening of pancreatic cancer in DM.

Pancreatic cancer and diabetes

Diabetes

Diabetes mellitus (DM) is a general term for heterogeneous disturbances of metabolism with the performance of chronic hyperglycemia.[1] Hyperglycemia results from defects in insulin secretion, insulin action, or both. Classification of DM depends on etiology and clinical manifestations. DM can be divided into three types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), and other specific types of diabetes.[2]

T1DM, once called insulin-dependent diabetes or juvenile-onset diabetes, is characterized as cellular-mediated autoimmune destruction of the β-cells in the pancreas. As β-cells are destructed, insulin is commonly deficient in T1DM patients. Different types of exogenous insulin are the primary treatment.[3] T1DM can occur at any age but usually in childhood and adolescence. Classic symptoms of T1DM (caused by insulin deficiency and hyperglycemia) usually start rapidly (days to weeks), including polyuria, polydipsia, weight loss, and ketoacidosis.[4]

T2DM accounts for the vast majority of those with diabetes, encompassing patients with insulin resistance and relative insulin deficiency.[5] So, T2DM patients do not need insulin treatment to control blood glucose levels for the first time.[6] Most patients with T2BD have obesity, which leads to some degree of insulin resistance.[7] Unlike T1DM, ketoacidosis seldom occurs spontaneously in this type of diabetes.

Other specific types of diabetes cannot be classified as T1DM or T2DM, including DM caused by genetic defects of β-cells, diseases of the exocrine pancreas (*e.g.*, pancreatitis, trauma, infection, pancreatectomy, and pancreatic cancer), hormones imbalance (*e.g.*, growth hormone, cortisol, epinephrine, and glucagon), infection (for instance, congenital rubella that can destruct β-cells in pancreas), and some drugs inducing DM.[2]

Pancreatic cancer

Pancreatic cancer is one of the most lethal malignancies, of which the main pathological component is pancreatic ductal adenocarcinoma (PDAC).[8] Because of the latency and lack of symptoms at an early stage, pancreatic cancer is usually detected at an advanced stage, and most treatment regimens are ineffective.[9] Therefore, early detection of pancreatic cancer is essential to improve prognosis. The cause of pancreatic cancer is complex and multifactorial. However, some factors have gradually been proven as risk factors for PDAC, for example, cigarettes and pancreatic cancer family history.[10] In recent years, researchers generally revealed that DM

Keywords: Pancreatic cancer; Diabetes mellitus; Early screening; Insulin resistance; Antidiabetic drugs.

Abbreviations: AM, adrenomedullin; BMI, body mass index; CSCs, cancer stem cells; CT, computed tomography; ddPCR, droplet digital PCR; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; EMT, epithelial-mesenchymal transition; ENDPAC, enriching new-onset diabetes for pancreatic cancer; ER, endoplasmic reticulum; FNA, fine-needle aspiration; GLP1-RA, glucagon-like peptide-1 receptor agonists; HIF-α, hypoxia-inducible factor-α; IGFs, insulin-like growth factors; IR, insulin receptor; MAPK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; mTOR, mechanistic target of rapamycin; NMR, nuclear magnetic resonance; NOD, new-onset diabetes; OPLS, orthogonal projection to latent structures; PCA, principal components analysis; PCRD, pancreatic cancer-related diabetes; PDAC, pancreatic ductal adenocarcinoma; SGLT-2, sodium-glucose co-transporter-2; T1DM, type 1 diabetes; T2DM, type 2 diabetes; TME, tumor microenvironment; UPR, unfolded protein response; VEGF, vascular endothelial growth factor; WHO, world health organization; WTP, willingness to pay.

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had a close association with PDAC, and early detection of PDAC depending on DM seems possible.[11] This review will discuss the relationship between DM and PC in detail and analyze the role of DM in the early detection of pancreatic cancer.

DM and the risk of PDAC

The relationship between DM and pancreatic cancer has been studied for years. Plenty of evidence supports that type 2 diabetes is a risk factor for developing pancreatic cancer. A meta-analysis involving 26 cohort studies raised that DM was associated with an increased risk of PDAC (relative risk [RR] = 3.69; 95% confidence interval [CI] = 3.12–4.37, $p < 0.05$).[12] Multiple mechanisms may explain the role of diabetes in promoting cancer initiation progression. On the one hand, a pathological state of diabetes leads to the initiation and progression of PDAC. On the other hand, some antidiabetics are also shown to be associated with the risk of PDAC.

Diabetes: a risk factor of PDAC

Hyperglycemia and the risk of PDAC incidence

Hyperglycemia is a risk factor of PDAC. A prospective, nested case-control study involving 449 case patients and 982 control subjects showed that a higher level of HbA1c was associated with an increased risk for pancreatic cancer (highest vs. lowest quintiles of HbA1c, odds ratio [OR] = 1.14, 95%CI = 1.17 to 2.72, $p = 0.04$).[13] Another nested case-control study of 278 cases and 826 matched controls found that long-term patterns of higher fasting blood glucose (FBG) are associated with a higher risk of PDAC (individuals with long-standing hyperglycemia vs. consistently normoglycemic individuals, OR = 2.02, 95%CI = 1.24–3.31, $p < 0.05$).[14] A dose-response meta-analysis evaluating blood glucose concentration and risk of pancreatic cancer showed that a strong linear dose-response association between fasting blood glucose concentration and the rate of pancreatic cancer was detected (per 0.56 mmol/L, RR = 1.14, 95%CI = 1.06–1.22; $p < 0.001$).[15] Preconditioning PDAC cells with glucose medium showed that a high-glucose environment increased cell viability and sphere formation.[16]

Many theories explain its role as a carcinogen, including initiation, progression, and metastasis. Chen *et al*. reported that hyperglycemia promotes PDAC initiation and progression by activating the wingless/integrated (Wnt)/β—catenin signaling pathway.[17] Sato *et al*. found that hyperglycemia in PDAC cells could strengthen the STAT3 phosphorylation and MYC expression, aggravating cancer progression.[16] Apart from tumor initiation and progression, hyperglycemia can also promote epithelial-mesenchymal transition (EMT) of PDAC. A study showed that hyperglycemia could stimulate HIF-1α expression in PDAC, leading to hypoxia in the pancreatic parenchyma and promoting the metastatic ability in PDAC.[18] Another study raised that hyperglycemia could promote the EMT of PDAC via stimulating hydrogen peroxide, as hyperglycemic mice contain a higher plasma hydrogen peroxide level, while hydrogen peroxide scavenger could reverse hyperglycemia-induced tumor metastasis.[19] In addition, hyperglycemia promotes the acquisition of pancreatic cancer stem cells (CSCs), essential for EMT.[20]

Hyperinsulinemia, insulin resistance, and the risk of PDAC incidence

Insulin resistance and hyperinsulinemia are risk factors of PDAC, and they can be detected in most T2DM patients.[21] The relationship between insulin resistance and hyperinsulinemia is complex. Traditionally it was believed that insulin resistance provoked the development of hyperinsulinemia in T2DM patients, while in recent years, some researchers came up with a reverse order and placed hyperinsulinemia upstream of insulin resistance.[21]

Hyperinsulinemia is associated with a higher risk of PDAC. A prospective, nested case-control study involving 449 case patients and 982 control subjects revealed that hyperinsulinemia was associated with an increased risk for pancreatic cancer (highest vs. lowest quintiles of insulin, OR = 1.57, 95%CI=1.08–2.30, $p = 0.002$).[13] A case-cohort prospective study of 29,133 male Finnish smokers aged 50 to 69 years showed that higher insulin concentrations and insulin resistance might lead to a higher risk of pancreatic cancer (insulin: highest vs. lowest quartile, HR = 2.90; 95%CI = 1.22–6.92; $p = 0.005$; insulin resistance: highest vs. lowest quartile, HR = 2.71; 95%CI = 1.22–6.92; $p = 0.006$).[22]

Insulin is thought to promote carcinogenesis in many kinds of cancer, including prostate, colorectal, breast, and pancreatic cancer, by stimulating insulin receptors (IRs) and insulin-like growth factors (IGFs) receptors and then stimulating the mitogen-activated protein kinase (MAPK) pathway.[23,24] Yang *et al*. reported that insulin could enhance cell proliferation and fibrosing responses in cultured activated pancreatic stellate cells by stimulating IR/IGF-1R and then Akt/mechanistic target of rapamycin (mTOR)/p70S6K signaling pathway.[25]

Obesity and the risk of PDAC incidence

Obesity is closely associated with T2DM. Obesity is believed to be a promoter of T2DM that can stimulate excessive fat accumulation and obesity.[26] The most commonly used criterion for determining obesity is the body mass index (BMI). According to the World Health Organization (WHO), obesity is defined as a BMI of 30 kg/m^2 or greater. Clinical studies have revealed that obesity could increase the risk of PDAC. A study analyzing the National Cancer Institute Pancreatic Cancer Cohort Consortium (PanScan) reported a positive association between BMI and pancreatic cancer risk (the highest vs. lowest quartile of BMI, OR = 1.33, 95%CI = 1.04–1.69; $p < 0.03$).[27] Similar conclusion was drawn from many other studies and meta-analyses.[28–30]

Multiple molecular mechanisms and signaling pathways seem to be involved in the association of obesity with PDAC.

Leptin is a kind of adipokines synthesized primarily in white adipose tissue. Obesity is often associated with leptin resistance and overexpressed leptin.[31] Epidemiology studies suggested that leptin may be associated with the incidence of PDAC in the obesity group. A pool analysis from three cohorts revealed an association between increasing leptin concentration and pancreatic cancer (quintile 5 *vs.* quintile 1: OR = 2.55, 95%CI = 1.23–5.27, $p = 0.004$).[32] However, a meta-analysis involving 17 articles drew an opposite conclusion that circulating leptin levels were significantly lower in patients with PC than in those without PC (SMD=0.830, 95%CI = 0.497–1.164, $p<0.001$), although they reported that the level of AdipoQ (another kind of adipokines) was significantly higher in PC patients in the same time.[33] Furthermore, the article explored the possible reasons for the unusual decrease of leptin in PC patients and found that PC patients with cachexia showed a significantly lower leptin level compared with those without cachexia, suggesting that cachexia may lead to the consumption of leptin.[33]

Many studies have proved that leptin showed oncogenic roles at the cell level. Xu *et al*. found that in PDAC cells, leptin could promote cell proliferation and increase glucose uptake by stimulating

the ATK signal pathway, as the AKT inhibitor significantly counteracted the effects of leptin stimulation.[34] In addition, researchers found that leptin treatment promoted the expression of the Notch signaling pathway, which plays a critical role in cell proliferation, suggesting that the leptin-Notch axis may also play an important part.[35]

Studies proved that obesity promoted pro-inflammatory response (including increased expression of IL-1β, IL-6, TNF-α, IL-12, or CXCL1) and immune cell infiltration in PDACs.[36] Furthermore, obesity-induced IL-1β mediated PSC activation and PDAC progression.[36] In addition, the study also revealed that obesity could induce a steatotic and fibrotic microenvironment in PDACs, which could also be enhanced by inflammation, and then augmented desmoplasia and tumor growth.

VEGF also seems to play a role in obesity-induced tumor initiation. Obesity was reported to be associated with a higher level of vascular endothelial growth factor (VEGF). Research showed that obesity could induce local hypoxia and then the overexpression of VEGF.[37] In PDAC, VEGF stimulation led to hypoxia-inducible factor-α (HIF-α) up-regulation, which promoted glycolysis and PDAC progression.[38]

Antidiabetics and the risk of PDAC incidence

At present, there are various kinds of antidiabetic drugs, including biguanides, sulphonylureas, thiazolidinediones, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP1-RA), dipeptidyl peptidase-4 (DPP-4) inhibitors, and alpha-glucosidase inhibitors.[39] Studies have shown that multiple antidiabetic drugs are associated with the incidence of PDAC.

Metformin and the risk of PDAC

Metformin is the recommended first-line treatment for T2DM and is widely prescribed worldwide.[40] Metformin traditionally functions as an antidiabetic drug by reducing hepatic gluconeogenesis.[41] In recent years, various epidemiologic studies revealed that metformin might have a relationship with a reduced risk of PDAC. For example, a case-control study involving 973 patients with pancreatic adenocarcinoma and 863 controls showed that people with diabetes taking metformin had a significantly lower risk of pancreatic cancer than those without metformin (OR = 0.38; 95% CI = 0.22–0.69; $p = 0.001$).[42] Similar conclusion was drawn by another case-control study in 2015 (OR = 1.46; 95% CI = 0.85–2.52).[43] A meta-analysis in 2013 containing 37 studies concluded that metformin use led to a 46% risk reduction of PDAC.[44] Some mechanisms may explain the anticancer effect of metformin. For example, Ren *et al*. reported that metformin might activate the STING/IRF3/IFN-β pathway by inhibiting AKT signaling in PDAC cells and then promote the infiltration of immune cells in the tumor microenvironment (TME).[45] Zhao *et al*. found that metformin could induce the expression of pro-apoptosis proteins caspase-3 and Bax and reduce the expression of anti-apoptosis protein Bcl-2 through the MTOR signaling pathway, leading to the suppression of PDAC.[46] In conclusion, metformin has shown its function as an anticancer drug in PDAC patients.

GLP1-RAs and the risk of PDAC

Glucagon-like peptide-1 (GLP-1) is an incretin secretory molecule secreted after eating, which can lower glucose concentrations by stimulating insulin secretion and suppressing glucagon release.[47]

Apart from the function as a kind of antidiabetic drug, GLP-RAs (GLP-receptor agonists) have been associated with PDAC in recent years. A study reported that using GLP-RAs was linked to a higher risk of PDAC.[48] Koehler *et al*. studied the effect of GLP1 in mice and found that GLP1 could activate the growth and survival of PDAC. In addition, they reported that pancreatic cancer cells expressed GLP1 receptors.[49] However, some later studies drew a contradictory conclusion that incretin use was not associated with pancreatic cancer.[50] A meta-analysis containing twelve trials revealed that GLP1-RA did not increase the risk of PDAC compared to other treatments (OR 1.06; 95% CI = 0.67–1.67; I^2 14%).[51] One limitation of current studies is that the follow-up duration may be insufficient to draw a convincing conclusion. More studies with long-term follow-up are needed to ensure the safety of incretin therapy.

DPP4-inhibitor and the risk of PDAC

Dipeptidyl peptidase-4 (DPP4) is a serine protease that promotes the degradation of GLP-1.[52] Therefore, DPP4-inhibitor (DDP4i) can suppress the degradation of GLP-1 and be used as a kind of hypoglycemic agent.

A cohort in 2014 with a six-month follow-up showed that the risk of pancreatic cancer with DPP-4 inhibitor treatment was not higher than with other antidiabetic treatments.[53] A cohort study in 2019, including 33,208 patients newly diagnosed with type 2 diabetes who were treated with antidiabetic drugs, revealed that DPP4i use is associated with increased risks of pancreatic cancer (HR 1.81, 95% CI = 1.16–2.82; $p = 0.009$).[54] So far, no studies have explained the relationship. However, a meta-analysis in 2020 involving 157 trials suggested that DDP4i were not associated with an increased risk of pancreatic cancer (OR = 0.86, 95% CI = 0.60–1.24).[55] Therefore, more large-scale RCT studies are needed to clarify the association between DD4Pi and PDAC.

In conclusion, diabetes can induce the incidence of pancreatic cancer in many ways.

PDAC and the risk of DM

As the review mentioned in section 1.1, specific types of DM contain diabetes caused by diseases of the exocrine pancreas, for instance, pancreatic cancer. The relationship between pancreatic cancer and the incidence of DM is far more complex, which can not be explained simply by the destruction of pancreatic β-cells due to PDAC. This section will discuss the role of PDAC as a risk factor for DM and the possible function of DM in the early detection of pancreatic cancer.

PDAC as a risk factor of diabetes

While type 2 diabetes has been recognized as a risk factor for pancreatic cancer, shreds of evidence showed that diabetes might be a manifestation of pancreatic cancer.[56] Diabetes is present in about 80% of patients with PDAC.[57] A study on the prevalence of diabetes mellitus in pancreatic cancer found that patients with PDAC had a significantly higher prevalence (68%, $p < 0.0001$) of DM compared with patients with other kinds of cancers and noncancer controls (23.5%).[58] Another study comparing PC patients and controlled people found that DM was more prevalent (47% *vs.* 7%; $p < 0.001$) among cases compared with control, and the DM was predominantly new onset DM.[59]

PDAC and β cells dysfunction

Patients with PDAC are usually accompanied by a decrease in the size of islets and a reduction in the number of β cells.[60] The β cell response (including response to an oral glucose load, hyperglycaemic clamp, or glucagon stimulation) was also impaired in PDAC

Table 1. Studies about pancreatic cancer and DM with different topics

Topic	Study
Diabetes: a risk factor of PDAC	
Hyperglycemia and the risk of PDAC incidence	13–19
Hyperinsulinemia and the risk of PDAC incidence	13,22
Insulin resistance and the risk of PDAC incidence	23–25
Obesity and the risk of PDAC incidence	27–30,32–38
Antidiabetics and the risk of PDAC incidence	
Metformin	42–46
GLP1-RAs	48–51
DPP4-inhibitor	53–55
PDAC: a risk factor of diabetes	
PDAC as a risk factor of diabetes	58,59
PDAC and β cells dysfunction	60–63
PDAC and insulin resistance	64–68

DM, diabetes mellitus; DPP4, dipeptidyl peptidase-4; GLP1-RA, glucagon-like peptide-1 receptor agonists; PDAC, pancreatic ductal adenocarcinoma.

patients.[61] Using a mouse model of KrasG12D-driven PDAC, Parajuli *et al*. reported that PDAC progression led to an increased expression of TGF-β signaling pathway, and then caused erosion of β-cell mass through apoptosis.[62] Exosomes from conditioned media of pancreatic cancer could enter β cells and inhibit insulin secretion, suggesting that PC causes paraneoplastic β-cell dysfunction by improving exosomes into circulation that inhibit insulin secretion.[63] Exosomes mediated adrenomedullin (AM) production, which was delivered to the β-cell, induced endoplasmic reticulum (ER) stress, a failure of the unfolded protein response (UPR), and increased β-cell dysfunction and death.

PDAC and insulin resistance

A study reported that PDAC might produce substances that induce insulin resistance. Insulin resistance was relieved after subtotal pancreatectomy for pancreatic cancer.[64] According to skeletal muscle biopsies from pancreatic cancer patients with or without diabetes, insulin receptor (IR) binding, IR mRNA, and IR substrate-1 content were all normal in PC patients. However, the fractional velocity of glycogen synthase was decreased in the diabetic pancreatic cancer group, suggesting that the PC-related insulin resistance was associated with a post-IR defect.[65]

Further research found that PC- derived-exosomes inhibit insulin-PI3K-Akt signaling and thereby interfere with GLUT4 uptake, which may explain why PC could induce insulin resistance in skeletal muscle.[66] In addition, Sagar *et al*. reported that pancreatic cancer exosomes were readily internalized into adipocytes, leading to lipolysis in adipose tissue.[67] This process was mediated by exosomal adrenomedullin, which interacted with its receptor on the adipocytes. It activated p38 and extracellular signal-regulated (ERK1/2) mitogen-activated protein kinases and promoted lipolysis by phosphorylating hormone-sensitive lipase. Meanwhile, adipocyte lipolysis is associated with insulin resistance in T2DM.[68]

New-onset DM as an early sign of pancreatic cancer

As pancreatic cancer is a risk factor of DM, new-onset DM may be a vital early sign of PC. A cohort study of 48 995 African Americans and Latinos examining the relationships between new-onset diabetes and PC incidence showed that diabetes was associated with a higher risk of PC (HRage75 = 2.39, 95%CI = 1.91–2.98). The association for recent-onset diabetes (three or fewer years) was 2.3-fold greater (HR = 3.71, 95%CI = 2.83–4.88) than for long-standing diabetes (more than three years; HR = 1.61, 95%CI = 1.18–2.21).[69] The researchers conducted a population-based cohort study of different races, which showed that individuals who received a recent diagnosis of diabetes had an almost 7-fold increase in the risk of pancreatic cancer (RR = 6.91; 95%CI = 5.76–8.30).[56]

We concluded studies about pancreatic cancer and DM with different topics (Table 1).[13–19,22–25,27–30,32–38,42–46,48–51,53–55,58–68]

DM in the early detection of PC

In recent years, DM has gradually been regarded as a manifestation of pancreatic cancer. However, more importantly, DM appears typically 2–3 years earlier than PC, making DM important in early PC detection.

Diagnosis of PC

Numerous international guidelines recommend computed tomography (CT) as an initial measure for diagnosing suspected PC.[70,71] Because of its low cost, CT is preferred over magnetic resonance imaging (MRI) as the first-line modality. In the CT set, the tumor detection rates were about 90%, and MRI shared a similar sensitivity.[72] The classic CT feature of PC includes a hypoattenuating pancreatic mass, pancreatic duct dilatation, and atrophy of the upstream pancreas. Therefore, CT is also applied to screen patients at high risk for PC.[73] In the early stage of PC, inhomogeneous parenchyma, interruption of the pancreatic duct, and loss of fatty marbling can be seen in the CT set, which was helpful for early detection of PC.[74,75] Other measures for the diagnosis of PC include magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS).

Early detection of PC in DM patients

Given that the prevalence of PDAC in the general population is relatively low, population CT screening is cost-inefficient and

Table 2. Advances in the early detection of PDAC in NOD

Topic	Study	Conclusion
END-PAC	Sharma *et al*[78]	END-PAC* can evaluate the risk of pancreatic cancer in patients with new-onset diabetes according to change in blood glucose, change of weight, and age at glycemically-defined new-onset diabetes
	Boursi *et al*[79]	The sensitivity, specificity, positive predictive value, and negative predictive value of the END-PAC model were 54.2%, 76.98%, 2.57%, and 99.4%, respectively.
	Chen W. *et al*[80]	At the 3+ threshold, the sensitivity, specificity, PPV, and NPV of the END-PAC model were 62.6%, 78.5%, 2.0%, and 99.7%.
Cost-effectiveness	Wang L., *et al*[84]	Considering a WTP* threshold between $100,000 and $150,000 per quality-adjusted life-year, a minimum predicted 3-year PDAC risk of 1.0% to 2.0% may be cost-effective

END-PAC, enriching new-onset diabetes for pancreatic cancer; NOD, new-onset diabetes; PDAC, pancreatic ductal adenocarcinoma; WTP, a willingness to pay.

challenging to achieve. Therefore, the identification of high-risk populations for pancreatic cancer is essential.

The key to early PC detection in DM patients is differentiating pancreatic cancer-related diabetes (PCRD) from common DM. New onset diabetes in PDAC often differs from T2DM in significant ways. For example, PCRD is usually concomitant with weight loss, while T2DM is commonly associated with weight gain.[76] Besides, diabetes can be better controlled by weight loss in common DM, which is barely seen in PCRD. A cohort study using multivariate logistic regression analysis reported that BMI, the age of onset of diabetes, HBV infection, TBIL, ALT, Cr, APO-A1, and WBC are factors that could differentiate PC + DM from common DM.[77]

NOD is vital in the early diagnosis of pancreatic cancer. Sharma *et al*. developed a model called enriching new-onset diabetes for pancreatic cancer (END-PAC) to evaluate the risk of pancreatic cancer in patients with new-onset diabetes.[78] The model contains the change of blood glucose, change of weight, and age at glycemically-defined new-onset diabetes. More significant changes in blood glucose, lower change of weight, and higher age lead to a higher risk of PC in patients with new-onset diabetes. Several studies have validated the END-PAC model. For example, a study by Boursi *et al*. focused on 5,408 patients with NOD, and according to their research comparing the high-risk group compared with the low-risk group, the sensitivity, specificity, positive predictive value, and negative predictive value of the model were 54.2%, 76.98%, 2.57%, and 99.4%, respectively.[79] Similarly, a study of 13,947 NOD patients in a healthcare setting validated the END-PAC model. At the 3+ threshold, the sensitivity, specificity, PPV, and NPV were 62.6%, 78.5%, 2.0%, and 99.7%, respectively.[80] In conclusion, current studies supported the robustness, generalizability, and clinical applicability of the END-PAC model. However, the original investigation and validation studies have some limitations. For instance, the definition of NOD was restricted and may exclude certain patients who truly had NOD. Besides, all the studies were retrospective. Therefore, more efforts are needed to validate the screening strategies for patients with NOD in real-world settings.

In recent years, many other metabolites have been shown to play a role in the discrimination of DM from PC+DM. With the help of ^{1}H mass spectrometry and nuclear magnetic resonance (NMR) spectroscopy, alterations of many plasma metabolite concentrations can discriminate T2DM and PC, suggesting that some proposed plasma metabolite biomarkers can be included in the model to evaluate the risk of pancreatic cancer in patients with new-onset diabetes.[81] Similarly, He *et al*. analyzed their data using principal components analysis (PCA) and orthogonal projection to latent structures (OPLS). They identified 62 differential metabolites that may function as individual biomarkers of PC.[82] The droplet digital PCR (ddPCR) confirmed that miR-20b-5p, a kind of miRNA, showed a higher level in PC patients with new-onset diabetes, suggesting that miR-20b-5p achieved higher diagnostic accuracy than PC with new-onset diabetes.[83]

A study evaluated the cost-effectiveness of PDAC early detection strategy targeting high-risk new-onset diabetes patients using MRCP and positive MRI underwent EUS/fine-needle aspiration (FNA). They found out that considering a willingness to pay (WTP) threshold between $100,000 and $150,000 per quality-adjusted life-year, a minimum predicted three-year PDAC risk of 1.0% to 2.0% may be cost-effective.[84] Advances in the early detection of PDAC in NOD were concluded in Table 2.[78–80,84]

Conclusions

Substantial studies have focused on the complex relationship between PC and DM. On the one hand, DM is a risk factor of PC, as hyperglycemia, hyperinsulinemia, insulin resistance, and obesity all improve PC initiation and progression. On the other hand, DM seems to be a manifestation of PC, considering that PC can lead to the destruction of islet β cells and insulin resistance. The incidence of PC in patients with DM is apparently higher than in normal people, suggesting that early PC screening in patients with DM is significant. The END-PAC model can help to identify people at high risk for PC in patients with new-onset diabetes. In addition, some metabolites have been shown to help discriminate PC + DM from normal DM. In conclusion, these methods can help identify the high-risk population of PC in diabetic patients and diagnose PC earlier. However, the practical application value and effect still need clinical verification.

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Conflict of interest

TPZ has been an associate editor of *Cancer Screening and Prevention* since March 2022. The authors declare no other competing interests.

Author contributions

YBF performed literature searches, drafted the literature review, and revised and finalized the manuscript. GY revised the manuscripts. JDQ revised the manuscripts. TPZ conceptualized, revised, and finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

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