Diabetology & Metabolic Syndrome

REVIEW

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Targeting early diagnosis and treatment of pancreatic cancer among the diabetic population: a comprehensive review of biomarker screening strategies

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy characterized by challenging early diagnosis, limited therapeutic options, and a poor prognosis. Diabetes mellitus, marked by altered glucose metabolism, has emerged as a significant risk factor for PDAC development, highlighting a complex, bidirectional pathogenic relationship. This review systematically examines the intricate interactions between diabetes and PDAC, emphasizing their shared pathophysiological mechanisms. A comprehensive understanding of these mechanisms can inform the development of targeted therapeutic strategies, potentially improving patient outcomes by concurrently managing diabetes and pancreatic cancer. We further evaluate current biomarker screening approaches for PDAC within diabetic subpopulations, assess the effectiveness of screening programs among high-risk groups, and propose practical strategies for the early identification and monitoring of PDAC. Early detection in diabetic individuals through targeted biomarker screening followed by timely therapeutic intervention may significantly reduce mortality, improve survival rates, and extend patient longevity. In conclusion, an integrated approach combining early diagnosis, targeted treatments, and a detailed understanding of the underlying pathogenesis represents the most promising strategy for enhancing clinical outcomes and survival among diabetic patients diagnosed with pancreatic cancer.

Keywords Pancreatic cancer, Diabetes mellitus, Biomarker screening, Early diagnosis, Disease surveillance

Introduction

Pancreatic ductal adenocarcinoma (PDAC), one of the most aggressive and fatal forms of cancer, ranks as the 12 th most common malignancy and the 7 th leading cause of cancer-related mortality worldwide. In 2020 alone, more than 500,000 new PDAC cases were diagnosed globally, resulting in over 460,000 deaths. PDAC is notoriously termed the"King of Cancers"due to its high mortality rate and the devastating prognosis for affected patients, representing a major challenge in oncology research and clinical practice [1]. Up to 80% of patients present with advanced disease for which there is no effective treatment. Approximately 20% of cases eligible for surgery have a 5-year survival rate of less than 30% [2, 3].

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The main risk factors for PDAC can be categorized into non-modifiable risk factors, such as age, gender, blood type and genetic susceptibility, and modifiable risk factors, such as diet, obesity, infections and exposure to different chemicals and drugs [4]. Approximately 10% of PC is hereditary because of a known germline genetic predisposition and/or family history of PC. Genes associated with an increased risk of PC include hereditary breast cancer genes (BRCA1, BRCA2, ATM, and PALB2), CDKN2 A (Familial Atypical Multiple Staphylococcal Melanoma Syndrome—FAMMM), Lynch syndrome genes (MLH1, MSH2/EPCAM, MSH6), STK11 (Peutz-Jeghers syndrome), TP53 (Li-Fraumeni syndrome), and hereditary PC. Jeghers syndrome), TP53 (Li-Fraumeni syndrome) and hereditary pancreatitis genes such as PRSS1 [5]. It is estimated that 5–10% of all pancreatic cancers can be attributed to genetic risk factors.20 Several familial cancer syndromes have been identified that are associated with an increased risk of developing pancreatic cancer.Peutz-Jeghers syndrome is caused by mutations in the tumor suppressor, STK11 (also known as LKB1), and results in a 35% increased risk of developing pancreatic cancer [6]. Lifestyle and environment are modifiable risk factors and an important focus of disease prevention and health promotion strategies. Environmental factors contribute to PDAC through prolonged DNA damage and gene mutations. major genes involved in the progression of PDAC include KRAS, CDKN2 A, TP53, and SMAD4, as well as those involved in DNA repair, cell cycle regulation, chromatin remodeling, and axonal guidance [7]. KRAS mutations are observed in approximately 80% of PDAC cases, while TP53 mutations occur in around 50%, playing a crucial role in disease progression. Additionally, individuals diagnosed with precursor lesions, such as PanIN, intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), chronic pancreatitis, or diabetes mellitus, have a significantly higher risk of developing pancreatic cancer than the general population [8–10]. Among these precursor lesions, PanIN represents the earliest stage of malignant transformation, during which neoplastic cells penetrate the basement membrane, initiating PDAC development [10].

Diabetes mellitus, a metabolic disorder characterized by chronic hyperglycemia, affects approximately 537 million individuals globally, with approximately 6.7 million deaths attributable to diabetes in 2021, predominantly occurring in low- and middle-income countries [11]. The relationship between diabetes mellitus and pancreatic cancer has attracted significant research attention due to their intricate, bidirectional pathogenic interactions, which remain incompletely understood [11–14]. The primary objective of this review is to systematically analyze and synthesize existing evidence regarding the association between diabetes mellitus and pancreatic cancer. Specifically, the review aims to evaluate and highlight promising early biomarker-based screening strategies tailored for diabetic populations. By addressing these points, we seek to identify novel and practical approaches for the early detection and clinical management of pancreatic cancer, ultimately improving survival outcomes among this high-risk patient group.

Pancreatic cancer leads to type 3 C pancreaticogenic diabetes mellitus

Approximately 50–74% of PC-related diabetes is of recent onset (2–3 years duration). The prevalence of dysglycemia in PDAC is higher when diagnosis is made using a standard oral glucose tolerance test (OGTT) rather than fasting glucose levels. Abnormalities of glucose metabolism are frequently missed in PDAC. In this context, the importance of preoperative diagnosis of dysglycemia needs to be emphasized, as it has been shown to affect surgical strategy in up to 15% of patients! [10]. Although specific clinical guidelines defining pancreatic cancer complicated by diabetes remain lacking, the consensus is that new-onset diabetes occurring within 2–3 years before a pancreatic cancer diagnosis is frequently a paraneoplastic manifestation known as pancreatic cancer-new onset diabetes mellitus (PC-NODM) [6]. Often classified as type 3 C diabetes, this condition encompasses various pancreatic exocrine disorders and hyperglycemia resulting from distinct pathological mechanisms, including chronic pancreatitis, pancreatic ductal adenocarcinoma, hemochromatosis, cystic fibrosis, and previous pancreatic surgeries [15].

Prior research consistently reports that approximately 80% of pancreatic cancer patients present glucose metabolism abnormalities, ranging from diabetes to impaired glucose tolerance [4]. Certain studies suggest pancreatic cancer may induce insulin resistance and compromise pancreatic beta-cell function through the secretion of circulating tumor proteins and cytokines, contributing to new-onset diabetes (NOD) [10, 14].

Pancreatic polypeptide (PP), secreted by PP cells within the islets of Langerhans, enhances insulin sensitivity and suppresses hepatic glucose production under physiological conditions. Recent studies have indicated marked differences in PP responses between patients with Type II Diabetes Mellitus (T2DM) and those with PDAC-associated diabetes mellitus (PDAC-DM), especially when tumors are located in the pancreatic head region. Specifically, PDAC-DM patients exhibited blunted PP responses 30 min postprandially, suggesting dysregulation of pancreatic hormone secretion and glucose metabolism [6]. Further analyses showed significantly lower fasting PP

concentrations ($P = 0.03$) and reduced PP levels at 15 min post-meal (median value: 1.869 vs. 3.283, $P < 0.01$) in PDAC-DM patients compared to the T2DM group [16].

Additional investigations revealed that patients with pancreatic cancer-associated non-obesity diabetes mellitus (PC-NODM) display increased peripheral insulin sensitivity alongside reduced insulin and C-peptide secretion relative to newly diagnosed diabetic patients [17]. These findings collectively underscore pancreatic beta-cell dysfunction rather than insulin resistance as the primary pathogenic mechanism in pancreatic cancer-induced diabetes.

In summary, pancreatic cancer frequently leads to type 3C diabetes through multiple mechanisms, notably pancreatic beta-cell dysfunction and paraneoplastic phenomena, highlighting the importance of targeted biomarker screening for early detection and intervention in diabetic patients at risk for pancreatic malignancies.

Diabetes as a risk factor for pancreatic cancer

Extensive research has consistently established diabetes and hyperglycemia as substantial risk factors contributing to the development of pancreatic cancer. A large prospective cohort study conducted in Sweden, which involved over 580,000 individuals, investigated the relationship between metabolic syndrome and pancreatic cancer. Through observation and monitoring of blood glucose levels alongside regular tumor screening, the study found a significant association between elevated fasting blood glucose levels and the development of pancreatic cancer. These findings highlight the pivotal role diabetes may play in facilitating pancreatic cancer progression [10]. Similarly, A meta-analysis showed that patients with type II diabetes had a twofold increased risk of pancreatic cancer (RR, 1.94; 95% CI, 1.66–2.27), and the relative risk of pancreatic cancer was negatively correlated with the duration of diabetes. In addition, the risk of pancreatic cancer increased more markedly when newly diagnosed diabetics had recently lost weight, with an HR as high as 6.75 (95% CI, 4.55–10.00) [7], showed in Fig. 1.

Multiple epidemiological studies further underscore a robust correlation between diabetes—particularly new-onset diabetes (NOD)—and pancreatic cancer. In 2011, a meta-analysis conducted by Ben involving 35 cohort studies reported a cumulative relative risk score (RR) of 1.94 for diabetic individuals developing pancreatic cancer. This risk varied according to diabetes duration: individuals diagnosed within one year, within five years, and within ten years had relative risk scores of 5.38, 1.95, and 1.49, respectively. The study emphasized that diabetes independently increases the risk for pancreatic cancer, regardless of geographical location, gender, study design, alcohol consumption, body mass index (BMI), or smoking status, with newly diagnosed diabetic patients within the first year exhibiting more than a five-fold increased risk [3].

Additionally, epidemiological research has expanded beyond Caucasian populations. Huang et al. conducted a comprehensive population-based cohort study from 2006 to 2016, involving approximately 1.5 million individuals of diverse ethnicities, including Caucasian, African American, Hispanic, and Asian participants from medical institutions in southern California. During this period, 2,002 pancreatic cancer cases were identified. The study confirmed that new-onset diabetes significantly elevated pancreatic cancer risk across various racial groups, with rapidly progressing hyperglycemia emerging as a key independent risk factor. Individuals recently diagnosed with diabetes exhibited a nearly seven-fold increased risk of developing pancreatic cancer compared to non-diabetic individuals [18]. Furthermore, Shreya and colleagues performed a case-control study utilizing polygenic risk scores derived from 1042 pancreatic cancer patients and 10,420 cancer-free controls from Biobank samples. Their findings indicated a robust association between common genetic variations related to pancreatic cancer and diabetes occurrence, underscoring the value of genetic risk profiling as a secondary screening method, particularly among newly diagnosed diabetic patients [19].

Additional research has identified a temporal association between diabetes and pancreatic ductal adenocarcinoma (PDAC). Approximately 25% of PDAC patients have diabetes, and 40% have pre-diabetes [10]. Time-stratified analyses suggest a markedly higher incidence of PDAC among patients newly diagnosed with diabetes (within two years) compared to those diagnosed 2–5 years earlier. Patients with long-standing diabetes mellitus (LSDM) have a 1.5-fold increased PDAC risk, whereas the risk in patients with NOD is 6–8 times greater [6]. Furthermore, a population-based cohort study reported a cumulative 3-year incidence of PDAC of 0.85% in newly diagnosed diabetic patients aged 50 and above, over six times higher than in the general population [7]. A meta-analysis further corroborated these findings, demonstrating a strong inverse relationship between diabetes duration and PDAC risk, highlighting the critical importance of NOD ($\leq$ 2 years duration) as an indicator of underlying pancreatic malignancy [3].

Collectively, these findings emphasize the need for targeted pancreatic cancer screening strategies among newly diagnosed diabetic populations, considering their significantly elevated risk. Such strategies are not only clinically valuable but economically beneficial as well,

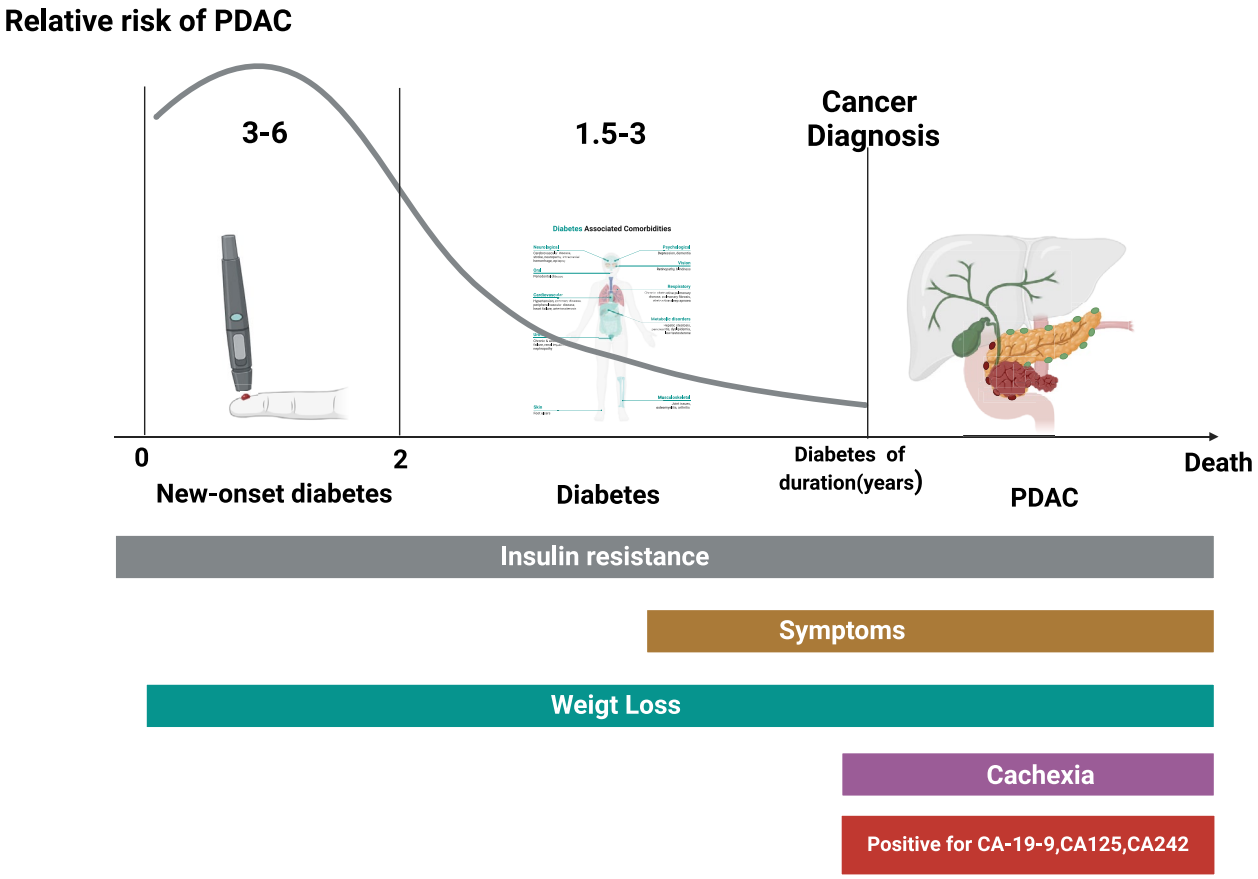

Fig. 1 The temporal relationship between diabetes and pancreatic cancer development. This figure illustrates the time-dependent association between diabetes and the progression to pancreatic ductal adenocarcinoma, highlighting key risk phases and clinical manifestations. The curve represents the relative risk of PDAC over time in diabetic individuals. New-onset diabetes carries the highest risk within the first two years, with a 3-6 fold increase in PDAC incidence, suggesting its potential role as an early indicator of pancreatic malignancy. As diabetes persists beyond two years, the relative risk gradually declines but remains elevated (1.5–3 times increase). Throughout disease progression, insulin resistance remains a persistent feature, contributing to systemic symptoms such as unexplained weight loss, a hallmark of early-stage pancreatic cancer. As PDAC advances, cachexia becomes more pronounced, leading to severe metabolic deterioration. The presence of tumor biomarkers (CA19-9, CA125, CA242) further aids in cancer detection and monitoring. This timeline underscores a critical window for early PDAC detection in diabetic patients, emphasizing the need for targeted screening strategies, particularly in individuals with new-onset diabetes, to improve early diagnosis and intervention

given the potential for earlier detection and improved patient outcomes.

Mechanisms underlying diabetes-related pancreatic cancer pathogenesis

The pathogenesis of PDAC associated with diabetes mellitus is multifaceted, involving complex interactions among hyperglycemia, insulin-like growth factor signaling, insulin resistance, hyperinsulinemia, and chronic inflammation [11]. These factors individually and collectively contribute to the initiation and progression of PDAC. We outline the critical pathogenic mechanisms and molecular pathways implicated in diabetes-induced pancreatic carcinogenesis, as illustrated in Fig. 2.

Hyperglycemia

Hyperglycemia and impaired glucose metabolism significantly facilitate PDAC development. Under hyperglycemic conditions, glucose accumulation leads to the formation of advanced glycation end products (AGEs). AGEs engage their receptor (RAGE), activating intracellular signaling cascades involving nuclear factor kappa-B (NF-κB). This activation exacerbates oxidative stress, promotes chronic inflammation, and causes cumulative cellular DNA damage, ultimately increasing carcinogenesis risk [20]. Menini et al. demonstrated in murine models that the AGE-RAGE interaction significantly accelerates the progression from pancreatic intraepithelial neoplasia to invasive PDAC [21].

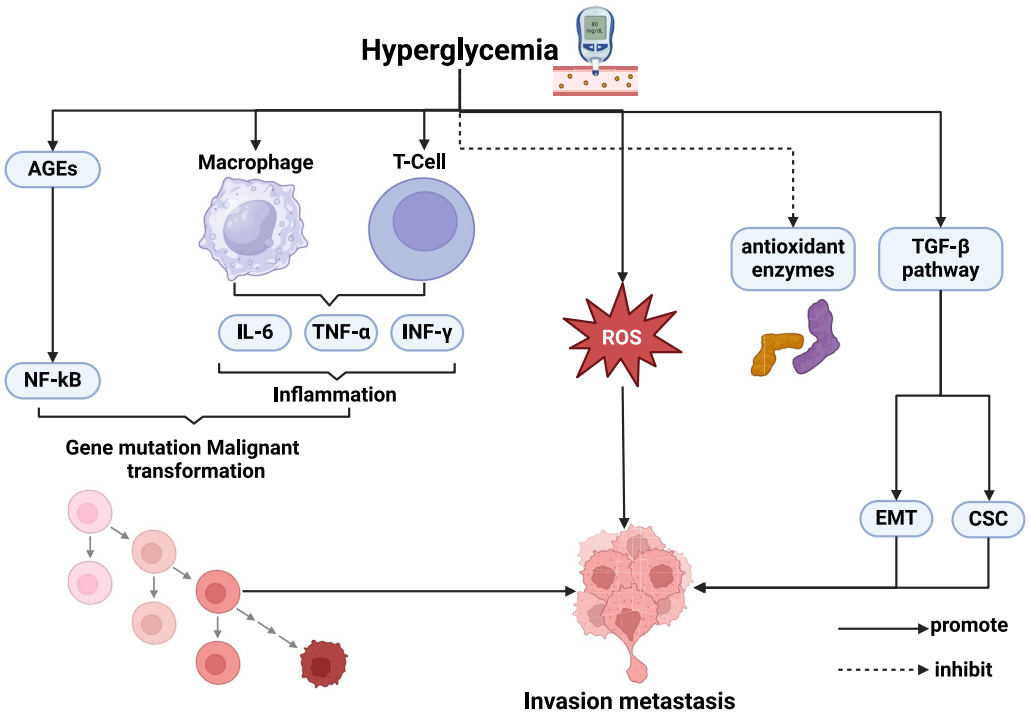

Fig. 2 Mechanisms underlying pancreatic cancer pathogenesis induced by diabetes. Hyperglycemia drives pancreatic tumorigenesis through oxidative stress, inflammation, and signaling dysregulation. Excess glucose promotes reactive oxygen species (ROS) production, accelerating tumor proliferation and metastasis while impairing antioxidant enzyme activity. It also activates TGF-β signaling, inducing epithelial-mesenchymal transition (EMT) and a cancer stem cell (CSC)-like phenotype, key processes in pancreatic ductal adenocarcinoma (PDAC) initiation. Hyperglycemia triggers a pro-inflammatory response, stimulating macrophages and T-cells to release IL-6, TNF-α, and IFN-γ, fostering a tumor-supportive microenvironment. Additionally, the accumulation of advanced glycation end-products (AGEs) activates NF-κB, further amplifying inflammation, oxidative stress, and malignant transformation.These interconnected mechanisms create a tumorigenic niche, significantly increasing pancreatic cancer risk in diabetic individuals

Additionally, hyperglycemia promotes epithelial-mesenchymal transition (EMT) and enhances stem cell-like properties of pancreatic ductal epithelial cells via activation of transforming growth factor-beta (TGF-β) signaling pathways [22]. Elevated glucose conditions enhance reactive oxygen species (ROS) production, triggering EMT and fostering metastasis by stimulating osteopontin expression and secretion in pancreatic cells. Furthermore, ROS accumulation resulting from hyperglycemia suppresses the c-Jun N-terminal kinase (JNK) pathway, promoting pancreatic cancer cell proliferation [23]. Hyperglycemia also disrupts the tumor-suppressive function of Ten-eleven translocation 2 (TET2), a critical regulator of DNA methylation, thus contributing to carcinogenesis [24]. Additionally, Li et al. revealed that hyperglycemia increases hypoxia-inducible factor 1-alpha (HIF-1α) expression, exacerbating tumor hypoxia and metastatic potential in pancreatic cancer [25]. Thus, hyperglycemia and its downstream metabolic consequences constitute critical factors in PDAC pathogenesis.

Insulin-like growth factor-1 signaling

Insulin-like growth factor-1 (IGF-1) signaling significantly influences pancreatic cancer development and progression. High expression of the IGF-1 receptor (IGF-1R) in pancreatic tumors correlates with poor differentiation and prognosis [26]. Hyperinsulinemia indirectly enhances IGF-1 bioavailability by inhibiting IGF-binding proteins, promoting cell proliferation, differentiation, and thereby increasing pancreatic cancer susceptibility [26]. Under physiological conditions, IGF-1R primarily regulates cellular proliferation, whereas insulin receptor (IR) signaling modulates metabolic responses. However, in PDAC, aberrant activation of both IGF-1R and IR by IGF-1 or paracrine insulin triggers downstream signaling via mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3 K)/Akt/mTOR pathways, promoting cellular proliferation and inhibiting apoptosis [26, 27]. Interestingly, animal studies suggest that pharmacological inhibition of the PI3 K pathway can paradoxically induce compensatory hyperinsulinemia, which can be

mitigated by dietary interventions, such as ketogenic diets, to maximize therapeutic efficacy [28].

Insulin resistance and hyperinsulinemia

Insulin resistance (IR)—characterized by impaired peripheral insulin responsiveness—is implicated in increased pancreatic cancer risk. Clinical studies indicate that mitigating IR, such as with metformin treatment, significantly reduces pancreatic cancer incidence among diabetic patients. Notably, post-surgical improvement in insulin sensitivity correlates positively with enhanced survival rates in PDAC patients [29]. At the molecular level, IR contributes to hyperinsulinemia by inducing serine phosphorylation of insulin receptor substrates, activating kinases that downregulate insulin signaling pathways [11]. This state of hyperinsulinemia perpetuates IR, establishing a detrimental feedback loop. Epidemiological evidence demonstrates a clear association between elevated fasting insulin levels (OR = 1.66, 95% CI: 1.05–2.63) and pancreatic cancer incidence, underscoring the significance of hyperinsulinemia as an oncogenic factor [30].

Hyperinsulinemia promotes pancreatic fibrosis and connective tissue hyperplasia, profoundly altering the tumor microenvironment and influencing therapeutic outcomes. In type 2 diabetic patients, hyperinsulinemia activates pancreatic stellate cells, enhancing extracellular matrix (ECM) deposition, fibrosis, and connective tissue proliferation, thus fostering PDAC development [12]. Typically, stellate cells remain quiescent, secreting minimal ECM. However, during pancreatic intraepithelial neoplasia, activated stellate cells release substantial ECM components, facilitating tumor progression, metastasis, and immune evasion [31]. Consequently, hyperinsulinemia-induced microenvironmental alterations critically modulate pancreatic cancer progression and prognosis.

Inflammatory response

Chronic inflammation is pivotal in diabetes-associated pancreatic carcinogenesis. In type 2 diabetic individuals, systemic inflammation results from adipose tissue expansion and immune cell accumulation, establishing a pro-tumorigenic microenvironment that predisposes pancreatic tissues to malignant transformation [11].The interaction between inflammatory responses and pancreatic cancer is manifested in various stages of the pancreatic cancer process [32]. Epidemiological evidence from a comprehensive Danish cohort study (approximately 250,000 participants) spanning over three decades highlighted acute pancreatitis as a significant pancreatic cancer risk factor, demonstrating the profound implications of inflammation in pancreatic carcinogenesis [33].

At the cellular level, chronic inflammation facilitates pancreatic cancer by driving oxidative stress, activating inflammatory signaling pathways, including cyclooxygenase-2 (COX-2), NF-κB, and signal transducer and activator of transcription 3 (STAT3), thus accelerating pancreatic acinar cell transformation and promoting malignancy [34]. Furthermore, persistent inflammatory stimuli exert autocrine and paracrine effects within epithelial and mesenchymal compartments, enhancing tumor growth, immune suppression, and metastatic capacity [35, 36]. Collectively, inflammation serves as a critical intermediary connecting diabetes mellitus and pancreatic cancer progression.

In summary, the pathogenic mechanisms underlying diabetes-related pancreatic cancer encompass hyperglycemia-induced molecular dysregulation, IGF-1 signaling alterations, insulin resistance and hyperinsulinemia, and persistent inflammatory responses. Comprehensive understanding of these interconnected pathways is essential for developing targeted preventive and therapeutic strategies against PDAC in diabetic populations.

Biomarker detection for pancreatic cancer

Pancreatic cancer is a highly lethal malignancy with extremely poor overall survival, underscoring the urgent need for early screening, accurate diagnosis, reliable prognostic assessment, and effective prediction of treatment response. The effective management of tumor prevention and therapy depends on meticulous screening, precise diagnosis, accurate staging, reliable prognosis, and consistent monitoring [37]. Early detection and intervention significantly improve survival rates. A range of tumor-related molecules has emerged as valuable clinical biomarkers for early tumor identification. Currently, key methods for screening, diagnosing, prognosing, and predicting pancreatic cancer involve detecting disease-associated biomarkers such as CA19-9, CA125, CA242, CEA, MUC5 AC, ubiquitin enzyme Vanin-1 (VNN1), adrenomedullin (AM), S100 calcium-binding protein A8 (S100 A8), thrombospondin-1 (TSP-1), angiopoietin-like protein 2 (ANGPTL2), osteoprotegerin, and ratios such as the circulating neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and lymphocyte-monocyte ratio (LMR) [38–41], as show in Table 1.

Diagnostic markers

Carbohydrate antigen 19-9 (CA19-9)

Carbohydrate Antigen 19-9 is the most widely used and efficient biomarker for pancreatic cancer, acting as a reliable indicator of aberrant glycosylation. Approximately 85% of pancreatic cancer patients show elevated serum CA19-9, making it crucial for both diagnosis and prognostic evaluation [42]. In practical applications, its

Table 1 Diagnostic performance of biomarkers for pancreatic cancer detection

Biomarkers	Material	Sensitivity (%)	Specificity (%)	References
CA19-9	Blood	79	82	Luo et al. [43]
CEA	Blood	61	85	Wang et al. [44]
CA242	Blood	87	83	Zhao et al. [45]
CA125	Blood	42	93	Laura et al. [46]
MUC5 AC	Pancreatic cell	78	77	Laura et al. [46]
MIC-1	serum	80	85	Robert et al. [47]
ctDNA	Blood	64	92	Zhu et al. [48]
Exosomes	Blood	72	92	Lan et al. [49]

screening sensitivity can reach 80%, though false positives can arise from conditions such as pancreatitis and hyperbilirubinemia, as well as certain non-pancreatic diseases [49]. In addition, Lewis antigen-negative patients may have falsely negative results due to limited or absent CA19-9 expression [50]. Although NCCN guidelines indicate that CA19-9 is undetectable in Lewis antigen-negative patients, a Fudan University study of 1482 Lewis antigen-negative cases found 24% had significantly elevated CA19-9 (> 37 U/mL), suggesting diagnostic relevance in this subgroup [50]. Furthermore, in patients who are Lewis antigen-negative, evidence from a study conducted in Japan suggests that Duke pancreatic monoclonal antigen type 2 (DUPAN-2) may serve as a complementary biomarker to CA19-9 in pancreatic cancer, particularly among patients presenting with normal CA19-9 levels. Incorporating DUPAN-2 assessment could thus improve diagnostic accuracy and enhance clinical management strategies for this subgroup [51].

Carbohydrate antigen 125 (CA125)

Carbohydrate antigen 125 shows strong potential for diagnosing and managing pancreatic cancer. It is expressed in peritoneal, pleural, and pericardial membrane tissue cells and is commonly elevated in several malignancies, including gastric cancer. Patients with cirrhosis, particularly in the decompensated phase, can also exhibit high serum CA125. Jiang et al. examined CA125 using immunohistochemical methods in benign pancreatic tissue and pancreatic cancer, revealing a notable and consistent upregulation of CA125 as benign tissue transitioned to malignancy [52].

Carbohydrate antigen 242 (CA242)

Carbohydrate Antigen 242 is a sialylated mucin-type antigen, characterized by sugar chain epitopes commonly found on mucins. Its strong association with pancreatic, gallbladder, and colon cancers highlights its potential as a valuable tumor marker. As a novel biomarker, CA242 holds significant promise for malignancy diagnosis. While it shares certain epitopes and sensitivity with CA19-9, there are marked differences in its expression among benign and malignant conditions. A study of patients with pancreatic cancer, benign pancreatitis, and healthy controls showed CA19-9 had the greatest sensitivity, whereas CA242 had superior specificity; notably, CA242's false-positive rate was substantially lower than CA19-9's [53]. Extensive research indicates CA242 provides better diagnostic efficiency compared to CA19-9 and CEA. Specifically, CA19-9 exhibits higher specificity against healthy controls, whereas CEA is more specific for benign pancreatic disease. The diagnostic accuracy of CA19-9 and CEA varies with different reference populations, but CA242 remains consistently accurate regardless of the patient's condition [54].

Carcinoma embryonic antigen (CEA)

Carcinoembryonic Antigen is an acidic protein marker linked to human embryonic antigen determinants. While primarily produced by endothelial cells, CEA secreted by tumor cells is commonly found in lymph and blood, with elevated expression across various malignancies. High CEA levels disrupt normal cell adhesion, impair epithelial integrity, and promote the adhesion, metastasis, and tissue infiltration of cancer cells. Studies have shown that in evaluating serum CEA and CA19-9 for predicting advanced pancreatic cancer, CEA demonstrated greater accuracy than CA19-9 in identifying advanced disease [55].

Mucin 5 AC (MUC5 AC)

MUC5 AC is a high-molecular-weight glycoprotein produced by goblet cells in the airway epithelium and mucous cells beneath the submucosa. Under normal conditions, mucin plays vital roles in maintaining epithelial integrity, promoting cellular differentiation and proliferation, regulating cell adhesion, and facilitating signal transduction. Among mucin family members, secretory

MUC5 AC is notably overexpressed in the earliest stage of pancreatic intraepithelial neoplasia (PanIN-I), a precursor lesion. As PanIN and pancreatic cancer progression models become better understood, MUC5 AC's diagnostic significance has gained attention [56]. Marek applied semi-quantitative immunohistochemical techniques to assess mucin expression in PDAC, chronic pancreatitis, and normal tissue specimens. By multiplying staining intensity by the percentage of positive cells, the analysis revealed that MUC5 AC had an elevated median score in PDAC [56].

Macrophage inhibitory cytokine-1 (MIC-1)

Macrophage inhibitory cytokine-1, a key member of the TGF-β superfamily, is crucial for embryonic development and regulates cellular responses to stress and inflammation. It plays a significant role in tissue repair after acute injury [57]. MIC-1's expression, secretion, and function, in conjunction with other growth factors, govern cellular behavior through complex regulatory networks. Dysregulation of MIC-1 signaling is implicated in various disorders, particularly in cancer progression, which is involved in cancer cell proliferation, migration, invasion, metastasis, drug resistance, and anorexia-induced weight loss in advanced stages. As a secreted cytokine, MIC-1 holds promise as both a biomarker and a therapeutic target with significant clinical implications [58].

Circulating tumor DNA (ctDNA)/cell-free DNA (cfDNA)

Studies have shown that apoptosis and necrosis during tumor initiation and progression release ctDNA into peripheral blood, which closely reflects the genetic and epigenetic profiles of primary tumor cells. Utilizing ctDNA methylation analysis, researchers have established a diagnostic model for early pancreatic cancer detection, achieving 76% sensitivity and 83% specificity. Between December 2014 and October 2019, Mayo Clinic collected 357 samples from 282 patients with pancreatic cancer for comprehensive ctDNA analysis, representing the largest cohort study to date demonstrating the diagnostic utility of ctDNA in pancreatic cancer [59]. A 2019 study published in Nature indicated that cfDNA fragmentation patterns in healthy individuals typically reflect leukocyte-derived nucleosome positioning, whereas these patterns are altered in cancer patients. Combining cfDNA analysis with DNA evaluation of fragments for early interception (DELFI) significantly improves specificity to approximately 98% [60].

Exosomes

Exosomes serve as a crucial constituent of the tumor microenvironment, exerting significant influence on oncogenes and tumor suppressor genes, such as tumor cell proliferation, apoptosis, invasion, and migration [61]. Studies have showed Glypican-1 (GPC-1) detected in exosomes from pancreatic cancer patients has exhibited 100% specificity and accuracy for early detection. Additionally, diabetes onset may indicate early pancreatic cancer, potentially driven by exosome-borne genes that alter insulin resistance in skeletal muscle and disrupt the PI3 K/Akt/FoxO1 pathway [62].

Other biomarkers

Additional biomarkers—VNN1, AM, S100 A8, TSP-1, ANGPTL2, OPG, and others are also valuable for screening and diagnosing pancreatic cancer. VNN1 can impair insulin-secreting cells by increasing oxidative stress, potentially serving as a biomarker for early detection of pancreatic cancer-related diabetes [63]. Plasma AM levels can distinguish PDAC from type 2 diabetes mellitus without PDAC [64]. S100 A8 may be a screening target due to its role in both tumor growth and hyperglycemia [65]. TSP-1 levels drop around two years before pancreatic cancer is diagnosed, significantly aiding CA19-9 in early detection [66]. ANGPTL2 demonstrates sensitivity on par with, or better than, CA19-9, and their combined use enhances both sensitivity and specificity [67]. OPG, belonging to the tumor necrosis factor receptor superfamily (TNFRSF), serves as an apoptosis ligand induced by tumor necrosis factor (TNF), which has emerged as a potential diabetes-associated biomarker for early PDAC detection [68].

Prognostic markers

Most biomarkers described in Sect. 4.1 function both as diagnostic indicators and prognostic markers. Diagnostic biomarkers facilitate early disease detection and classification, while prognostic markers predict disease progression, treatment response, and patient survival. These prognostic insights allow clinicians to stratify patient risk, personalize treatment, and closely monitor disease progression. This section highlights the biomarkers'prognostic significance and clinical utility.

CA19-9

As widely recognized, CA19-9 is elevated in approximately 85% of pancreatic cancer patients, serving as a key biomarker for both diagnosis and prognosis [42]. Elevated CA19-9 levels significantly correlate with disease presence, and patients presenting with normal CA19-9 levels typically exhibit improved long-term survival outcomes. Furthermore, CA19-9 is instrumental in monitoring biological disease progression, guiding therapeutic decisions, and providing insights into treatment efficacy and disease recurrence risk.

CA125

CA125 correlates strongly with pancreatic cancer metastasis. Patients with metastatic disease typically present much higher serum CA125 levels than those without metastasis. Furthermore, CA125 rises with lymph node and distal organ metastasis, particularly to the liver. Patients showing elevated baseline CA125 often develop early distant metastasis post-resection. CA125 levels above 22.035 U/mL predict worse surgical outcomes [69]. Thus, CA125 serves as a noninvasive biomarker associated with metastatic potential and prognosis.

CA242

Studies have demonstrated that elevated levels of CA242 are positively correlated with disease progression, indicating its potential as a biomarker for tumor burden and aggressiveness. Notably, a significant increase in CA242 levels is associated with a poorer prognosis, as it reflects advanced disease stages, increased metastatic potential, and reduced overall survival [53].

CEA

Elevated preoperative carcinoembryonic antigen (CEA) levels serve as a reliable prognostic indicator for pancreatic ductal adenocarcinoma, particularly in patients undergoing radical resection. Higher CEA concentrations effectively predict postoperative outcomes, correlating closely with an increased risk of recurrence, decreased survival rates, and poorer long-term prognosis [70].

Mucin 5 AC

Overexpression of MUC5 AC has been linked to more aggressive progression of pancreatic cancer, suggesting its potential involvement in facilitating tumor growth, invasion, and metastasis. Upon investigation, it was discovered that the expression of MUC5 AC may have a significant association with the aggressive advancement of PDAC, hinting at a potential function of MUC5 AC in facilitating the progression of pancreatic cancer [71].

Neutrophils, platelets, and lymphocytes

Studies indicate that neutrophils play a crucial role in the microenvironment and progression of pancreatic cancer, strongly correlating with its prognosis. N2 neutrophils, in particular, can promote tumor metastasis and angiogenesis. For instance, neutrophil elastase and matrix metalloproteinase 9 may activate dormant metastatic cancer cells, leading to overt metastases [72]. The intertwined relationship between platelets and tumor cells is indispensable. Studies have revealed that pancreatic cancer cells have the ability to stimulate platelet aggregation by activating thrombin and podoplanin, which are expressed by fibroblasts associated with pancreatic cance [73]. Platelet-related protein levels differ notably between healthy individuals and patients with early-stage pancreatic cancer [74]. Meanwhile, the distribution of T cells (CD4+ and CD8+) affects overall survival, and tumor cells secreting CXCL1 can avoid immune surveillance by impairing T-cell activity [75, 76]. Furthermore, evaluating the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) holds clinical value in diagnosing or predicting malignancies of the digestive system [77, 78].

Other biomarkers

High MIC-1 expression has been strongly linked to poorer patient prognosis and reduced survival. As aggressive cancers progress, MIC-1 levels rise in cancer cells, serum, and cerebrospinal fluid. Elevated MIC-1 expression is strongly associated with poor prognosis and reduced survival, exerting pleiotropic effects throughout carcinogenesis [58]. Meanwhile, circulating tumor DNA (ctDNA) serves as a real-time indicator of tumor burden, enabling clinicians to evaluate treatment efficacy and predict patient outcomes [79]. In addition, exosomes released by pancreatic cancer cells significantly contribute to tumor progression, invasion, and metastasis, highlighting their prognostic relevance in pancreatic cancer management.

Predictive markers for treatment response

In addition to their diagnostic and prognostic utility, several biomarkers serve as valuable predictive indicators for treatment response in pancreatic cancer. CA19-9, traditionally recognized for its diagnostic and prognostic roles, presents therapeutic opportunities through targeted approaches, including therapeutic antibodies, cancer vaccines, CA19-9-directed nanoparticles, and inhibition of CA19-9 biosynthesis [42]. Similarly, CA125 demonstrates predictive capabilities superior to CA19-9 in assessing resectability of pancreatic tumors, exhibiting a significantly higher area under the ROC curve (0.81 vs. 0.66) and a more favorable predictive cut-off (19.70 U/mL vs. 289.40 U/mL). Furthermore, baseline CA125 levels exceeding 26.95 U/mL predict adverse surgical outcomes [69, 80].

MIC-1 also emerges as a promising predictive marker, significantly influencing tumor proliferation, migration, invasion, metastasis, drug resistance, and terminal cachexia. The secreted form of MIC-1 underscores its potential as both a predictive biomarker for therapeutic response and a direct therapeutic target [58]. Circulating tumor DNA (ctDNA/cfDNA) offers a real-time reflection of ongoing tumor burden, thus enabling clinicians to assess therapeutic efficacy dynamically and predict clinical outcomes [79]. Additionally, systemic inflammatory

indicators, such as neutrophils, platelets, and lymphocytes, particularly platelet-related protein concentrations, differ notably between healthy individuals and early-stage pancreatic cancer patients. These markers frequently normalize or decrease post-tumor resection, indicating their potential role in evaluating treatment efficacy and predicting patient response [74].

Screening strategies, future prospect, and therapeutic interventions

Early detection of pancreatic cancer in diabetic populations remains challenging yet critical for improving clinical outcomes. Advances in clinical screening, artificial intelligence-based biomarker discovery, and targeted therapeutic interventions promise significant progress in this domain.

Early screening in diabetic patients

Early screening for pancreatic cancer among individuals experiencing new-onset or worsening diabetes has attracted considerable attention due to its potential to detect malignancies at more manageable stages [11]. Several observational clinical trials are currently exploring effective screening methods for this high-risk group. For example, the ongoing "PANDOME" study (NCT03937453, https://clinicaltrials.gov/study/NCT03937453) investigates the association between new-onset or deteriorating diabetes and pancreatic cancer, utilizing Magnetic Resonance Imaging (MRI), Magnetic Resonance Cholangiopancreatography (MRCP), and periodic blood sampling for biomarker analysis. Similarly, the "NODES" trial (NCT04164602, https://clinicaltrials.gov/study/NCT04164602) specifically targets elderly patients (over 60 years old) recently diagnosed with diabetes mellitus. This study aims to develop a diagnostic biomarker panel capable of distinguishing pancreatic cancer from chronic pancreatitis or benign diabetes-related changes, focusing on markers such as C-peptide, glutamic acid decarboxylase (GADA) antibodies, and other pancreatic autoantibodies. Additionally, the prospective observational trial conducted by Shanghai Changzheng Hospital (NCT06585072, https://clinicaltrials.gov/study/NCT06585072) investigates alterations in glucose metabolism and endocrine-exocrine secretory functions after pancreatic cancer surgery. Collectively, these studies emphasize the importance of precise screening protocols and biomarker discovery to facilitate early diagnosis and effective clinical management of pancreatic cancer in diabetic populations.

Future prospect

Artificial intelligence (AI) is revolutionizing cancer diagnostics and biomarker discovery, creating unprecedented opportunities for early detection and accurate risk stratification in pancreatic cancer. Machine learning algorithms leverage comprehensive datasets—including genomic, proteomic, metabolomic, and imaging profiles—to identify and validate predictive biomarkers and diagnostic signatures.

Recent reviews highlight AI's expanding role in pancreatic cancer management. One comprehensive review emphasized AI's potential in predicting and monitoring responses to immune checkpoint inhibitor therapies, thereby enabling personalized and optimized treatments based on individual patient profiles [81]. Another recent review demonstrated how integrating AI with biomarkers and multi-omics data substantially enhances early pancreatic cancer detection capabilities, especially by analyzing electronic health records and social media data to identify high-risk populations [82].

Large-scale clinical trials, such as the PANDA (NCT06528223, https://clinicaltrials.gov/study/NCT06528223) and PANDA PLUS (NCT06643715, https://clinicaltrials.gov/study/NCT06643715) studies, further explore AI-based screening models utilizing deep-learning algorithms on real-time computed tomography (CT) imaging data. These trials aim to assess clinical applicability, diagnostic accuracy, and predictive potential of AI tools, ultimately enhancing early diagnosis and patient outcomes.

Therapeutic interventions

Emerging evidence indicates diabetes-related metabolic changes, including hyperglycemia, insulin resistance, and chronic inflammation, may contribute to pancreatic cancer progression by fostering a pro-tumorigenic microenvironment. Thus, interventions targeting these pathways have become promising strategies for improving outcomes in diabetes-associated pancreatic cancer.

Metformin and other antihyperglycemic agents

Metformin exerts antitumor effects primarily via activation of AMP-activated protein kinase (AMPK) and inhibition of the mammalian target of rapamycin (mTOR) pathway. Clinical data suggest improved survival and enhanced treatment responses in diabetic pancreatic cancer patients treated with metformin; however, findings remain inconsistent, necessitating validation through randomized controlled trials [83].

GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, widely used for glycemic control in type 2 diabetes, have demonstrated promising antitumor activity in preclinical studies. These agents may suppress pancreatic cancer cell proliferation and migration while modulating

inflammation within the tumor microenvironment [84]. Further clinical investigations are required to clarify their therapeutic potential and effectiveness in diabetic pancreatic cancer patients.

Combination approaches with chemo- or immunotherapy

Given that insulin resistance and hyperinsulinemia accelerate cellular proliferation, combining insulin-sensitizing therapies such as metformin or pioglitazone with chemotherapy or immunotherapy has become an active area of research [85, 86]. By restoring metabolic balance and reducing hyperinsulinemia-driven tumor signals, these combined approaches could enhance the efficacy of standard cancer treatments.

Anti-inflammatory pathway modulation

Chronic inflammation links diabetes to pancreatic cancer, highlighting the potential for therapeutic interventions targeting inflammatory cytokines (IL-6, TNF-α) and signaling pathways (NF-κB). Combining these approaches with antidiabetic medications that reduce systemic inflammation shows significant promise[87].

CAR-based cell therapies

Chimeric antigen receptor (CAR)-based cell therapies, traditionally explored in type 1 diabetes mellitus (T1DM), utilize cytotoxic T cells and regulatory T cells as targets. More recently, macrophages with their potent immunomodulatory capabilities have been proposed as novel CAR targets. Given that both macrophages and T cells play pivotal roles in diabetes-associated pancreatic cancer, CAR-modified immune cells offer a novel therapeutic avenue [88]. Specifically, macrophages, the earliest immune cells to infiltrate pancreatic tissue during T1DM onset, exhibit plasticity between inflammatory (M1) and anti-inflammatory (M2) phenotypes upon exposure to specific cytokines (e.g., IL-4, IL-13, IL-10). M2 macrophages, due to their anti-inflammatory properties, represent promising CAR-therapy targets and could become instrumental in preventing pancreatic cancer progression in T1DM patients [88].

Conclusion

Pancreatic cancer and diabetes affect a substantial portion of the global population, posing significant societal and individual healthcare challenges. Elucidating the intricate relationship between these two conditions is crucial for advancing diagnosis, treatment, and prevention strategies. Accumulating evidence underscores a bidirectional association, emphasizing the importance of proactive pancreatic cancer screening in diabetic populations. Despite this recognition, pancreatic cancer's complexity and incompletely understood pathogenesis continue to hinder timely diagnosis and effective treatment.

To overcome these challenges, it is essential to develop comprehensive diagnostic models that integrate multiple tumor biomarkers, thereby enhancing sensitivity and specificity in disease monitoring. Additionally, prioritizing targeted screening efforts for high-risk groups, particularly individuals with diabetes, can significantly improve early detection rates. Effective management of diabetic patients extends beyond glycemic control and must incorporate strategies specifically designed to mitigate the risk of pancreatic ductal adenocarcinoma (PDAC).

Future research should concentrate on elucidating the molecular and pathological mechanisms linking diabetes and pancreatic cancer, alongside expanding and refining innovative early detection techniques such as liquid biopsy, advanced imaging, and artificial intelligence-driven diagnostic tools. These efforts are expected to yield novel biomarkers, precise diagnostic approaches, and tailored therapeutic interventions. Ultimately, these advancements promise to enhance early diagnosis, optimize clinical outcomes, and usher in a new era of precision medicine tailored specifically for pancreatic cancer patients.

Study limitations

This review is limited by the variability in study designs and sample sizes. Some studies lacked long-term follow-up, and retrospective data may introduce bias. Larger, prospective studies are needed for more robust conclusions.

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Author contributions

Huijuan Cheng and Guodong Sun conceptualized and designed the study. Jie Yang and Chengming Wen drafted the manuscript, while Hongkai Guo and Yahui Chai contributed to visualization and literature review. Huijuan Cheng and Guodong Sun critically reviewed and revised the manuscript for significant intellectual content. All authors have read and approved the final version of the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent and publication
All authors have reviewed and approved the final version of the manuscript and consent to its publication.

Competing interests
The authors declare no competing interests.

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