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Pancreatic Carcinoma and Diabetes Mellitus

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Abstract

Pancreatic Ductal Adenocarcinoma (PDAC) is a rare disease with one of the highest mortality rates and a continuously increasing incidence. Surgery is the only option as a curative treatment, but, unfortunately, the tumor is often diagnosed in an inoperative stage because of its asymptomatic/aspecific progression. Until now, there is no feasible screening method for early-stage sporadic PDAC. This article aims to review the connection between PDAC and Diabetes Mellitus (DM) the potential screening group for PDAC; to investigate the possibility of differentiating PDAC-associated new-onset DM (PDACDM) from Type 2 Diabetes Mellitus (T2DM); and to summarize the effect of metformin on PDAC based on the results of the latest medical publications.

Keywords: Diabetes mellitus; Metformin; Pancreatic carcinoma; Screening

Introduction

Pancreatic Carcinoma (PDAC) accounts for only 3% of all cancer cases [1], with a continuously increasing incidence [2]. Hungary is in third place in Europe based on the incidence (10–15/100,000 persons per year) and prevalence of PDAC [3]. The Central European region has the highest mortality rate for PDAC in Europe [4]. PDAC is the third leading cause of cancer-related death in the USA [5]. The prognosis for PDAC is extremely poor: it has the lowest five-year survival of all cancers, only 6% [6], and this rate has not changed in the last 40 years [2]. It depends on the late diagnosis of the disease: in the presence of [a]specific symptoms, PDAC is often in an advanced stage; the possibility of a curative surgical intervention is thus low. Screening PDAC in an asymptomatic stage is recommended for a better outcome [7]. Population-wide screening is not feasible because the lifetime prevalence of PDAC is low, only 1.39% [8]. In fact, screening individuals under 70 who have a lifetime risk of PDAC of 16% or greater is cost-effective [9].

Link between pancreatic cancer and diabetes mellitus

Epidemiology: The connection between PDAC and DM has been well known for decades [10]. Among risk conditions (such as hereditary pancreatitis or multiorgan cancer syndromes and a positive family history of PDAC (Table 1),

Clinical Condition	Relative Risk (X)	Cumulative Risk at Age 70 (%)	Affected Gene
smoking	2,5		
chronic pancreatitis		15	
diabetes mellitus	2,2		
obesity		1,2	
Hereditary cancer syndromes			
• Peutz-Jeghers-syndrome	132	36	STK11/LKB1
• Hereditary atipical multiple mole melanoma	20-47	17	CDKN2A
• Hereditary breast/ovarium	3-10	3-6	BRCA2
• Hereditary nonpolyposis colorectal cancer	9	<5	MLH1,MSH2, MSH6, PMS2
• Familiary adenomatosus polyposis	4	<5	APC
• Fanconi anaemia			PALB2
• Ataxia teleangiectasia	3		ATM
• Li-Fraumeni syndrome	7		p53
Genetically predisposed chronic diseases			
• Hereditary pancreatitis	50-80	40	PRSS1/ SPINK1
• Cystic fibrosis	5	<5	CFTR
Familial cumulation of pancreatic cancer			
• PDAC in 3 < first-degree relatives	32	40	
• PDAC in 2 first-degree relatives	6,4	8-12	
• PDAC in 1 first-degree relative	4,5	2	

Table 1: Clinical conditions (affected gene) predisposing-, and their Relative Risk (RR) causing pancreatic cancer (PDAC).

DM has the strongest link to PDAC: 40-65% of pancreatic cancer patients meet the criteria for DM [11]. In contrast, genetic factors play a role in less than 10% of PDAC cases [2,3]. Type 2 diabetes is often associated with obesity, which independently increases the risk for developing pancreatic ductal adenocarcinoma. Obesity can also lead to increased insulin in the pancreatic microenvironment, which promotes tumor development [12]. Based on a prospective study, the rate of DM among PDAC patients is higher than in the normal population: in nearly 50% of PDAC cases, DM was present as new-onset or concomitant at the time of the cancer diagnosis [13].

Pathomechanism

Pancreatic cancer secondary to long-standing diabetes: Retrospective studies with a large number of cases have shown that long-term DM and resultant hyperinsulinemia pose 2.17 times the risk for developing PDAC [14,15]. through the effect of insulin as a growth factor and the elevated level of mitogen cell proliferation-enhancing Insulin-like Growth Factor-1 (IGF-1). Based on the temporal relationship, two groups can be distinguished by DM-onset age: in one, early-onset (<55 years), long-term (>2 years' duration) DM is the risk factor for PDAC, and in the other, late-onset (≥55 years), short-term DM is the consequence of PDAC [16]. The terminology "new-onset" has currently been used as a synonym for late-onset, short-term diabetes linked to PDAC in the literature. As already noted above, screening PDAC in an asymptomatic stage is recommended for a better outcome, but it is not cost-effective to screen patients with long-term DM for PDAC [7] because in these cases PDAC is not present when DM is diagnosed.

Diabetes mellitus caused by pancreatic cancer (PDACDM): DM could be not only a cause of the tumor, but also a consequence: new-onset DM patients have an eightfold risk of contracting PDAC within 36 months of the time they are diagnosed with DM [17]. The definition of new-onset DM has recently been changed: instead of 36 months, DM identified within 24 months of the PDAC diagnosis is called new-onset DM [18]. We know that only 1% of newly diagnosed DM patients who are over 50 years old develop PDAC within three years of the onset of DM [9], but in these cases the tumor is often resectable [19]. In this article, PDACDM is used as a synonym for PDAClinked new-onset DM. In other studies, an even higher prevalence of PDACDM [5.2-13.6%] was revealed in patients with recently diagnosed diabetes [20]. In our study we proved that patients with new-onset DM constitute a feasible risk group for PDAC screening. Unfortunately, we could not screen any early-stage PDAC either with an imaging tool or an elevated level of tumor marker carbohydrate antigen 19-9 [21]. Therefore, it is recommended to investigate the tumor-specific biomarkers of PDAC for effective screening of early-stage tumors instead of performing imaging examinations.

Type 3c Diabetes Mellitus (T3cDM)

The differentiation of PDACDM from "traditional" T2DM plays a key role in the screening method, thus leading to a number of studies that investigate this question. PDACDM belongs to the T3cDM group (pancreatogenic or secondary diabetes) which contains diabetic conditions due to diseases of the exocrine pancreas: benign and malign conditions such as acute, relapsing and chronic pancreatitis of any etiology, hemochromatosis, cystic fibrosis, fibrocalculous pancreatopathy, pancreatic trauma, pancreatectomy, pancreatic agenesis and pancreatic cancer [22]. Although T3cDM accounts for approximately 5-10% of Western diabetic populations, its diagnosis is often missed and T3cDM patients are misclassified as T2DM. This might be due to the very poor awareness of this type of diabetes even among well-trained physicians or to the lack of commonly accepted diagnosis criteria. The recommended criteria are listed in (Table 2) [23]. It is not enough for early diagnosis of PDACDM to know the T3cDM criteria, tumor-specific differences must be investigated to clearly separate PDACDM from the other types of DM.

Proposed major criteria (all must be fulfilled):

- Presence of exocrine pancreatic insufficiency (according to the monoclonal fecal elastase-1 test or direct function tests).
- Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT).
- Absence of type 1 diabetes mellitus associated autoimmune markers.

Minor criteria:

- Impaired beta cell function (e.g. HOMA-B, C-peptide/glucose-ratio).
- No excessive insulin resistance (e.g. HOMA-IR).
- Impaired incretin secretion (e.g. GLP-1, pancreatic polypeptide).
- Low serum levels of lipid soluable vitamins (A, D, E, and K)

Table 2: Suggested diagnostic criteria of T3cDM.

PDACDM Differentiation from T2DM-What Do We Know?

One of the relevant differences is the change in body weight. In PDACDM cases, patients lost weight before the onset of DM and continued losing weight despite antidiabetic therapy until they were diagnosed with PDAC as compared to T2DM patients, who gained weight even after adequate DM therapy was implemented. Weight loss appeared earlier in PDACDM than other PDAC symptoms [abdominal pain, fatigue and anorexia], evidence that it is not a consequence of cachectization. It has been proposed that weight loss results from overproduction of a "lipid-mobilizing factor" Zink-Alpha-2-Glycoprotein(ZAG) and resultant fatty acid mobilization. In the case of PDACDM, the escalation of antidiabetic therapy is required parallel to the weight loss, unlike in T2DM cases [24]. An investigation by Lee et al. strengthens the findings above with additional alarm signs: PDACDM patients were older and had more weight loss, lower premorbid BMI, more family history of PDAC and less family history of DM compared to new-onset T2DM patients. With regard to Insulin Resistance (IR), the two groups exhibited further differences, which are confirmed by the homeostatic model assessment index: IR is lower in PDACDM than in T2DM [25], and its level is similar to that of the normal healthy population [26].

Unfortunately, it is not sufficient to find a relatively small subgroup based on clinical manifestations of tumors eligible for screening if we cannot differentiate precisely between ill and healthy individuals. Because of the ineffectiveness of imaging tools and tumor markers for screening, the investigation of biomarkers has come into view. It has been proved that there is a disparity between PDACDM and T2DM in the serum levels of neuroendocrine mediators: the mean plasma level of leptin, Pancreatic Polypeptide (PP) and Glucose-Dependent Insulinotropic Peptide (GIP) is significantly lower in PDACDM than that in T2DM, and the level of adiponectin is higher in PDACDM than in T2DM. This significance is more explicit if the PDACDM group is further restricted to patients with new-onset DM and >2kg weight loss compared to the "simple" T2DM cases [26]. The lower serum levels of GIP and PP were present among PDAC patients with normal glucose tolerance, suggesting that these findings are rather the consequence of PDAC only. Leptin increases cell proliferation, migration and tumor cell invasion, while adiponectin inhibits cell growth, invasion and tumor progression through stimulation of tumor cell apoptosis [27]. These facts suggest that the lower level of leptin and the higher level of adiponectin are a compensatory response to the tumor process in the human body itself. Škrha et al. found these differences in advanced-stage PDAC cases, thus confirming this theory [28]. One of the limitations of their study is that it lacks data from early-stage PDAC cases. It remains unclear whether the divergence in serum levels of neuroendocrine mediators is appropriate for the screening of early-stage PDAC. Most studies suggest that PDACDM is a paraneoplastic sign caused by tumor-produced factors, such as adrenomedullin, a potential mediator of β-cell dysfunction in pancreatic cancer-induced diabetes, and an increased expression of proteases, such as fibroblast-activation protein alpha and dipeptidyl peptidase 4, which can cause a lower GIP level in PDAC.

In a study by Basso et al., daily intraperitoneal injection of supernatant from pancreatic cancer cell line MIA PaCa2 into immunodeficient mice led to a significant increase in blood glucose levels and significantly reduced glucose tolerance compared to control mice injected with saline [28]. The 14-amino-acid peptide corresponding to the N-terminal of the S100 calcium-binding

protein A8 (S100A8 or calgranulin A) was detected in PDACDM cases, but not in PDAC or samples from non-neoplastic subjects, and it impairs the catabolism of glucose with myoblasts in vitro and may cause hyperglycemia in vivo [18, 26, 28-30]. S100A8 is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and are involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation [28].

Independent of the fact that DM is a cause or a consequence of PDAC, hyperglycemia (HG) has an effect on PDAC progression. HG promotes the growth and metastasis of tumor cells [31]. Wang et al. studied the tumor progression effect of DM and its accompanying chronic inflammation. They found that HG stimulated the proliferation of PDAC cells in a concentration- and time-dependent manner due to an increase in the phosphorylation of p38 mitogen-activated protein kinase. HG decreased the apoptotic potential of tumor cells, reduced E-cadherin expression and increased vimentin expression, thereby inducing epithelial-mesenchymal transition, which is an important step in tumor progression [32].

In addition to eliminating HG and thus decreasing endogenous hyperinsulinemia, reducing the dose of exogenous insulin is essential for a better outcome for PDAC. Long-term DM increases the risk of developing PDAC through hyperinsulinemia and overexpression of insulin and Insulin-Like Growth Factor-1 (IGF-1) receptors [33].

Antidiabetic treatment and the risk of PDAC

Metformin and pancreatic cancer

The "first choice" antidiabetic in T2DM, metformin interacts with the signaling pathway of insulin and IGF-1 [34]. Metformin operates through the activation of Adenosine Monophosphate-Activated Protein Kinase (AMPK), which leads to the inhibition of the mammalian Target of Rapamycin (mTOR), stops the insulin/IGF-1 pathway and results in the inhibition of their mitotic effects and tumor progression (Figure 1), (35). Inhibiting mTOR decreases protein synthesis and the intensity of cell growth, thus playing an important role in survival. AMPK promotes the function of tumor suppressor p53 and reduces the serum levels of insulin and IGF-1 [36]. Some studies have shown that metformin can sensitize cancer cells to both chemotherapy [37,38] and radiotherapy [39,40]. Metformin is increasingly accepted as an antitumor agent. It can lessen the risk of T2DM patients developing PDAC if used continuously over a long period: a meta-analysis based on 11 studies showed that using metformin lowered the risk of PDAC by 37% compared to other antidiabetics [41]. It influences the survival of PDACDM patients as an independent predictor of improved outcome in this group. The two-year survival was 30% in the metformin group compared to 15% in the non-metformin group among PDACDM patients [42]. Metformin can improve survival even in the case of advanced-stage PDAC treated with palliative chemotherapy compared to non-diabetic PDAC patients not taking metformin [overall survival was 11 months, 7.5 months and 7.9 months in these groups, respectively]. The only limitation of this drug is that its positive effects do not prevail if metastases are present [43,44].

Sulfonylurea and pancreatic cancer

Sulfonylureas (SU) act by increasing insulin release from the beta cells in the pancreas [45], leading to an increased level of insulin in the body. SU seems to be associated with an increased all-cancer risk in cohort studies, though data from randomized controlled trials and case-control studies failed to demonstrate a statistically significant effect. Meta-analyses suggest that SU may be tied to increased cancer risk in subjects with T2DM [46], but its harmful effect on risk of PDAC is disputed [47].

Insulin and Pancreatic Cancer

Numerous studies have investigated the effect of insulin on the risk of cancer genesis/progression. In addition to the pathways noted above, overexpression of insulin receptor substrates-1 and -2 activates the oncogenic PI3 kinase pathway, leading to reduced cell adhesion [48], the phosphorylated insulin receptor is expressed at significantly higher frequencies in low-grade carcinomas, and higher insulin levels are evident in patients with dysplastic lesions [49]. Several meta-analyses have demonstrated that insulin treatment was associated with an increased risk of overall cancer, and the association was even stronger for pancreatic cancer [50,51].

Incretin Analogs and Pancreatic Cancer

Glucagon-like peptide-1 Receptor Agonists (GLP-1RAs) are a novel class of injectable antidiabetic drugs with an extensive effect on glucoregulation: they enhance glucose-dependent insulin secretion, suppress glucagon secretion and slow gastric emptying in addition to preserving beta-cell function [52]. Nevertheless, the U.S. Food and Drug Administration has indicated a potential long-term action of the drug in promoting PDAC after a study of the adverse events database of studies investigating GLP-1RAs [53]. Several reviews have examined the effects of GLP-1RAs on the risk of PDAC in diabetic patients. They found different results from those of the FDA: GLP-1RAs do not increase tumor risk in any tissue; however, there is a lower incidence of PDAC in the incretin-based group than in the placebo or non-incretin-based anti-diabetic drugs groups in investigations with a study period longer than 104 weeks [54]. However, long-term results are not yet available with incretins.

Diabetes Mellitus and Pancreatic Cancer Surgery

Surgery is the only curative treatment for PDAC. Early diagnosis can lead to surgical intervention (e.g. to pancreatectomy), which can influence the diabetic condition of the patient and

vice versa. Xinghua et al. investigated the impact of DM on postoperative outcomes and long-term survival after cancer resection. In their meta-analysis, they found that DM does not seem to affect perioperative outcomes in patients undergoing surgery for pancreatic cancer. However, after stratification by DM type, they concluded that new-onset DM was associated with reduced survival compared to long-term diabetes [55]. Other studies have shown different results: diabetes mellitus was accompanied by reduced survival following pancreatic cancer resection and adjuvant chemotherapy. Diabetic PDAC patients were older, they had more co-morbidities, and the maximum tumor size in diabetic patients was larger at randomization [56-58].

Raghavan et al. found that even postoperative complication rates are higher among patients with DM and confirmed that patients with new-onset non-insulin-dependent DM have a worse long-term survival rate and a higher rate of postoperative complications [59]. After curative resection, the symptoms and the diabetic condition of PDACDM disappear in the case of new-onset diabetes, but persist among patients with long-term diabetes [60], thus demonstrating that new-onset DM-linked PDAC and long-term DM-linked PDAC are different entities with different pathomechanisms.

Conclusion

The link between PDAC and DM is complex and bidirectional. Screening for early-stage PDAC is recommended for high-risk group patients with new-onset DM who present with the following alarm signs: old age (>55 years) [21], low normal BMI at the time of the DM diagnosis, antidiabetic therapy-resistant weight loss, and PDAC-positive and DM-negative family history. The low level of insulin resistance may be a potential differentiating factor between PDACDM and T2DM. The search for biomarkers that are specific only to PDAC, thus making early-stage cancer screening possible, is still in progress. The effect of metformin in tumor prevention and in survival improvement has been confirmed by numerous studies. It is important to emphasize that these effects are present not only in diabetic patients, but also in non-diabetics. Thus, in the case of non-metastatic pancreatic cancer, it is recommended that metformin be integrated into the therapy. Among antidiabetic drugs, the use of GLP-1RAs seems safe and insulin treatment increases the risk of PDAC. A number of studies have shown that DM is associated with reduced survival following pancreatic cancer resection compared to non-diabetic PDAC patients. Among diabetic PDAC patients, those with new-onset DM have a worse long-term survival rate and a higher rate of postoperative complications.

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