Mini Review
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Pancreatic carcinoma and diabetes mellitus

Abstract

Pancreatic carcinoma (PaC) is a rare disease with one of the highest mortality rates and a continuously increasing incidence. Surgery is the only possibility 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 PaC. This article aims to review the connection between PaC and diabetes mellitus (DM), the potential screening group for PaC; to investigate the possibility of differentiating PaC-associated DM (PaCDM) from type 2 diabetes mellitus (T2DM); and to summarize the effect of metformin on PaC based on the results of the latest medical publications.

Keywords: pancreatic carcinoma, diabetes mellitus, screening, metformin

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Introduction

PaC accounts for only 3% of all cancer cases,[1] with a continuously increasing incidence.[2] Hungary is in the third place in Europe based on the incidence (10–15/100,000 persons per year) and prevalence of PaC.[3] The Central European region has the highest mortality rate from PaC in Europe.[4] PaC is the third leading cause of cancer-related death in the USA.[5]

The prognosis for PaC is extremely poor: it has the lowest five-year survival of all cancers, only 6%,[6] and this rate has not changed during the last 40years.[7] It depends on the late diagnosis of the disease: in the presence of the aspecific symptoms, PaC is often in an advanced stage, which means that the possibility of a curative surgical intervention is low. Screening PaC in an asymptomatic stage is recommended for a better outcome.[8] Population-wide screening is not feasible because the lifetime prevalence of PaC is low, only 1.39%.[9] In fact, screening of individuals under 70 who have a lifetime risk of PaC of 16% or greater is cost-effective.[10]

Connection between pancreatic cancer and diabetes mellitus

The connection between PaC and DM has been well known for decades.[11] Among risk conditions (such as hereditary pancreatitis or multiorgan cancer syndromes and a positive family history of PaC; Table 1. DM has the strongest link to PaC: 40–65% of pancreatic cancer patients meet the criteria for DM,[12] in contrast to these genetic factors, whose role in PaC is less than 10% (Lee 2,3). Based on a prospective study, the rate of DM among PaC patients is higher than in the normal population: in nearly 50% of PaC cases, DM was present as new-onset or concomitant at the time of the cancer diagnosis.[13] Retrospective studies with a huge number of cases showed that long-term DM and resultant hyperinsulinemia pose 2.17times the risk for developing PaC[14] 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). DM could be not only a cause, but also a consequence of the tumor: the new-onset (<36month) DM patients have an eightfold risk of contracting PaC within three years from the time of diagnosis of DM.[15] Based on the temporal relationship, two groups can be distinguished: in one, early-onset, long-term DM is the cause of PaC, and in the other, late-onset, short-term DM is the consequence of PaC.[16] The definition of new-onset DM has recently been changed: instead of 36months, DM identified 24months before PaC diagnosis is called new-onset DM.[17] It is not cost-effective to screen patients with long-term DM for PaC.[8] It is known that only 1% of newly diagnosed DM patients over 50 develop PaC within three years from the onset of DM,[10] but in these cases the tumor is often resectable.[18] We proved in our study that patients with new-onset DM constitute a feasible risk group for PaC screening. Unfortunately, we could not screen any early-stage PaC either with an imaging tool or an elevated level of tumor marker carbohydrate antigen 19-9.[19] Therefore, it is recommended that the tumor-specific differences and clinical manifestations of PaC be investigated for effective screening of early-stage tumors instead of doing instrumental examinations.

PaC: Pancreatic Carcinoma

The differentiation of PaCDM from "traditional" T2DM plays a key role in the screening method, thus leading to a number of studies that investigate this question. One of the relevant differences is the change in body weight. In PaCDM cases, patients lost weight before the onset of DM and continued losing weight despite antidiabetic therapy until they were diagnosed with PaC as compared to T2DM patients, who gained weight even after adequate DM therapy was implemented. Weight loss appeared earlier in PaCDM than other PaC 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 PaCDM, the escalation of antidiabetic therapy is required parallel to the weight loss, unlike in T2DM cases.[20] The investigation by Lee et al. strengthens the findings above with additional alarm signs: PaCDM patients were older and had more weight loss, lower premorbid BMI, more family history of PaC and less family history of DM compared to the 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 PaCDM than in T2DM,[21] and its level is similar to that of the normal healthy population.[22] Unfortunately, it is not sufficient to find a relatively small subgroup based on clinical manifestations of tumors eligible for screening if we cannot precisely differentiate between ill and healthy individuals. Because of the ineffectiveness of imaging tools and tumor markers for screening, the investigation of biomarkers came into view. It has been proved that there is a disparity between PaCDM and T2DM in the serum levels of neuroendocrine

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mediators: the mean plasma level of leptin, pancreatic polypeptide (PP) and glucose-dependent insulinotropic peptide (GIP) is significantly lower in PaCDM than that in T2DM, and the level of adiponectin is higher. This significance is more explicit if the PaCDM group is further restricted to patients with new-onset DM and >2kg weight loss compared to the "simple" T2DM cases.[22] The lower serum levels of GIP and PP were present among PaC patients with normal glucose tolerance, suggesting that these findings are rather the consequence of PaC 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.[23] These facts suggest that the lower level of leptin and the higher level of adiponectin are a compensatory response of the human body itself to the tumor process. Škrha et al.,[22] found these differences in advanced-stage PaC cases, thus confirming this theory. One of the limitations of their study is that they lack data from early-stage PaC cases. It remains unclear whether the divergence in serum levels of neuroendocrine mediators is appropriate for the screening of early-stage PaC. Most of the studies suggest that PaCDM 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 PaC. 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. The 14 amino acid peptide from S100A8 impairs the catabolism of glucose with myoblasts in vitro and may cause hyperglycemia in vivo.[17,22,24–26] The investigation of complex connections between PaC and DM resulted in an important question: does antidiabetic therapy influence the tumor development/process, and if so, how?

Table 1 Clinical conditions with elevated risk for pancreatic carcinoma (responsible gene) and the relative risk

Clinical Conditions	Relative Risk (x)	Responsible Gene
Smoking	2.5	
Chronic pancreatitis	15	
Diabetes mellitus	2.2	
Obesity	1.2	
Peutz-Jeghers syndrome	132	STK11/LKB1
Hereditary atypical multiple mole melanoma	20-47	CDKN2A
Hereditary breast/ovarium cancer	3-10	BRCA2
Hereditary non-polypotic colorectal carcinoma	9	MLH1,MSH2,MSH6,PMS2
Familial adenomatosus polyposis	4	APC
Fanconi anemia	-	PALB2
Ataxia teleangiectasia	3	ATM
Li-Fraumeni syndrome	7	p53
Hereditary pancreatitis	50-80	PRSS1/SPINK1
Cystic fibrosis	5	CFTR
3<First relative with PaC	32	
2 First relative with PaC	6.4	
1 First relative with PaC	4.5	

Metformin and pancreatic cancer

Long-term DM increases the risk of developing PaC through hyperinsulinemia and overexpression of insulin and insulin-like growth factor-1 (IGF-1) receptors.[27]. The "first choice" antidiabetic in T2DM, metformin interacts with the signaling pathway of insulin and IGF-1.[28] 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. The inhibition of mTOR decreases protein synthesis and the intensity of cell growth, processes which play an important role in survival. AMPK promotes the function of tumor suppressor p53 and reduces the serum levels of insulin and IGF-1.[29] Some studies showed that metformin can sensitize cancer cells to both chemotherapy[30,31] and radiotherapy.[32,33] Metformin is increasingly accepted as an antitumor agent. It can lessen the risk of T2DM patients developing PaC if used continuously over a long period: a meta-analysis based on 11 studies showed that using metformin lowered the risk of PaC by 37% compared to other antidiabetics.[34] It influences the survival of PaCDM 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 PaC patients.[35] Metformin can improve survival even in the case of advanced-stage PaC treated with palliative chemotherapy compared to the non-diabetic PaC patients not taking metformin (overall survival was 11months, 7.5months and 7.9months in these groups, respectively). The only limitation of this drug is that its positive effects do not prevail if metastases are present.[36]

Summary

The connection between PaC and DM is complex and bidirectional. Screening for early-stage PaC is recommended for high-risk group patients with new-onset DM who present with the following alarm signs: old age (>55years) (19), low/normal BMI at the time of DM diagnosis, antidiabetic therapy-resistant weight loss, and PaC-positive and DM-negative family history. The low level of insulin resistance may be a potential differentiating factor between PaCDM and T2DM. The search for biomarkers that are specific only to PaC, thus making early stage cancer screening possible, is still in progress. The effect of metformin in tumor prevention and in survival improvement has

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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.

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Conflicts of interest

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