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 inoperable 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

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 40 years [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 multigran 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 2.17 times 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 (<36 month) 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 36 months, DM identified 24 months 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.

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 PaC 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 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-polyptic colorectal carcinoma     | 9                 | MLH1,MSH2,MSH6,PMS2   |
| Familial adenomatous polyposis                   | 4                 | APC                    |
| Fanconi anemia                                   | -                 | PALB2                  |
| Ataxia telangiectasia                            | 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               |                        |

PaC: Pancreatic Carcinoma

Citation: Illes D, Czako L (2017) Pancreatic Carcinoma and Diabetes Mellitus. Gastroenterol Hepatol Open Access 6(4): 00203. DOI: 10.15406/ghoa.2017.06.00203
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 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 [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 (>55 years) [19], low/normal BMI at the time of DM diagnosis, antidiabetic therapy-resistant weight loss, and PaC-positive and DM-negative family history. The BMI at the time of DM diagnosis, antidiabetic therapy-resistant weight loss, and PaC-positive and DM-negative family history. The only limitation of this drug is that its positive effects do not prevail if metastases are present [36].

References

1. Loc WS, Smith JP, Matters G, Kester M, Adair JH (2014) Novel strategies for managing pancreatic cancer. World J Gastroenterol 20(40): 14717-14725
2. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer Statistics. CA Cancer J Clin 64(1): 9-29
3. Szmol a R, Farkas G, Hegyi P, Csako L, Dubravcsek Z, et al. (2015) Pancreatic cancer: Evidence based management guidelines of the Hungarian Pancreatic Study Group. Orv Hetil 156(8): 326-339.
4. Hariri Haran D, Saied A Kocher HM (2008) Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford) 10(1): 58-62.
5. Cancer Statistics Center (2017) American Cancer Society.
6. Ferlay J (2013) GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. International Agency for Research on Cancer, Lyon, France.
7. Siegel R, Ma J, Zou Z, Jemal A (2014) Cancer statistics. CA Cancer J Clin 64(1): 9-29
8. Chari ST, Kelly K, Hollingsworth MA, Thayer SP, Ahliquist DA, et al. (2015) Early detection of sporadic pancreatic cancer: summative review. P e r a g r e a s 4 4 ( 5 ) : 6 9 3 - 7 1 2 .
9. National Cancer Institute. SEER cancer statistics review 1975-2006.
10. Chari ST (2007) Detecting early pancreatic cancer: problems and prospects. Semin Oncol 34(4): 284-294
11. Aggarwal G, Rab e KG, Petersen GM, Chari ST (2012) New-onset diabetes in pancreatic cancer: a study in the primary care setting. Pancreatology 12(2): 156-161.
12. Ben Q, Cai Q, Li Z, Yuan Y, Ning X, Deng S, Wang K (2011) The relationship between new-onset diabetes mellitus and pancreatic cancer risk: a case-control study. Eur J Cancer 47(2): 2 4 8 - 2 5 4 .
13. Dugnani E, Gandolfi A, Balzano G, Scavini M, Pasquale V, et al. (2016) Diabetes associated with pancreatic ductal adenocarcinoma is just diabetes: Results of a prospective observational study in surgical patients. Pancreatology 16(5): 8 4 4 - 8 5 2 .
14. A Yacoub, E Siegel, I Mak h ou l (2011) Pancreatic cancer and diabetes mellitus: A retrospective cohort study. J Clin Oncol 29(15_suppl): 4102.
15. Chari ST, Leibson CL, Rabe KG, Ransom J, Andrade M, et al. (2005) Probability of pancreatic cancer following diabetes: A population-based study. Gastroenterology 129(2): 504-511.
16. Mizuno S, Nakai Y, Isayama H, Yanai A, Takahara N, et al. (2013) Risk factors and early signs of pancreatic cancer in diabetes: screening strategy based on diabetes onset age. J Gastroenterol 48(2): 238-246.
17. Sah RP, Nagpal S, Mukhopadhyay D, Chari ST (2013) New Insights into pancreatic cancer-induced paraneoplastic diabetes. Nat Rev Gastroenterol Hepatol 10(7): 423-433.
18. Pelaz-Luna M, Takahashi N, Fletcher JG, Chari ST (2007) Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. Am J Gastroenterol. 102(10): 2157-2163
19. Illes D, Terz i n V, Holzinger G, Kosar K, Roka R, et al. (2016) New-onset type 2 diabetes mellitus--A high-risk group suitable for the screening of pancreatic cancer? Pancreatology 16(2): 266-271.
20. Hart PA, Kamada P, Rabe KG, Srinivasan S, Basu A, et al. (2011) Weight loss precedes cancer-specific symptoms in pancreatic cancer-associated diabetes mellitus. Pancreas 40(5): 768-772.
21. Lee JH, Kim SA, Park HY, Lee KH, Lee KT, et al. (2012) New-onset diabetes patients need pancreatic cancer screening? J Clin Gastroenterol 46(7): e58-61.

Citation: Illes D, Csako L (2017) Pancreatic Carcinoma and Diabetes Mellitus. Gastroenterol Hepatol Open Access 6(4): 00203. DOI: 10.15406/ghoa.2017.06.00203
22. Skrha J, Busek P, Uhnova J, Hrabal P, Kmochova K, et al. (2016) Lower plasma levels of glucose-dependent insulinotropic peptide (GIP) and pancreatic polypeptide (PP) in patients with ductal adenocarcinoma of the pancreas and their relation to the presence of impaired glucose regulation and weight loss. Pancreatology 17(1): 89-94.

23. Michael N, VanSaun (2013) Molecular pathways: Adiponectin and leptin signaling in cancer. Clin Cancer Res 19(8): 1926-1932.

24. Pannala R, Basu A, Petersen GM, Chari ST (2009) New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol 10(1): 88-95.

25. Bassi D, Greco E, Fogo P, Pucci P, Flagiello A, et al. (2006) Pancreatic cancer-derived S-100A8 N-terminal peptide: a diabetes cause? Clin Chim Acta. 372(1-2): 120-128.

26. Andersen DK, Andren-Sandberg Å, Duell EJ, Goggins M, Korc M, et al. (2013) Pancreatitis - diabetes - pancreatic cancer: summary of an NIDDK-NCI workshop. Pancreas 42(8): 1227-1237.

27. Pollak M (2008) Insulin and insulin-like growth factor signaling in neoplasia. Nat Rev Cancer 8(12): 915-928.

28. Rosengurt E, Sinnett-Smith J, Kisfalvi K (2010) Cross-talk between insulin/insulin-like growth factor-1 receptors and G protein-coupled receptor signaling systems: a novel target for the antidiabetic drug metformin in pancreatic cancer. Clin Cancer Res 16(9): 2505-2511.

29. Jun Gong, Lori A Robbins, Aurelia Lugea, Richard T Waldron, Christie Y Jeon, et al. (2014) Diabetes, pancreatic cancer, and metformin therapy. Front Physiol 5: 426.

30. Dong L, Zhou Q, Zhang Z, Zhu Y, Duan T, et al. (2012) Metformin sensitizes endometrial cancer cells to chemotherapy by repressing glyoxalase I expression. J Obstet Gynaecol Res 38(8): 1077-1085.

31. Kawanami T, Takiguchi S, Ikeda N, Funakoshi A (2012) A humunized anti-IGF-1R monoclonal antibody (R1507) and/or metformin enhance gemcitabine-induced apoptosis in pancreatic cancer cells. Oncol Rep 27(3): 867-872.

32. Song CW, Lee H, Dings RP, Williams B, Powers J, et al. (2012) Metformin kills and radiosensitizes cancer cells and preferentially kills cancer stem cells. Sci Rep 2: 362.

33. Storozhuk Y, Hopmans SN, Sanli T, Barron C, Tsiani E, et al. (2013) Metformin inhibits growth and enhances radiation response of non-small cell lung cancer (NSCLC) through ATM and AMPK. Br J Cancer 108(10): 2021-2032.

34. Wang Z, Lai ST, Xie L, Zhao JD, Ma NY, et al. (2014) Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 106(1): 19-26.

35. Sadeghi N, Abbruzzese JL, Yeung SC, Hassan M, Li D (2012) Metformin Use is Associated with Better Survival of Diabetic Patients with Pancreatic Cancer. Clin Cancer Res 18(10): 2905-2912.

36. Choi Y, Kim TY, Oh DY, Lee KH, Han SW, et al. (2016) The Impact of Diabetes Mellitus and Metformin Treatment on Survival of Patients with Advanced Pancreatic Cancer Undergoing Chemotherapy. Cancer Res Treat 48(1): 171-179.