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Original Article

Diabetes associated with pancreatic ductal adenocarcinoma is just diabetes: Results of a prospective observational study in surgical patients

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ABSTRACT

Background: Identification of a specific diabetes signature associated to pancreatic ductal carcinoma (PDAC) could be a key to detect asymptomatic, early stage tumors. We aim to characterize the clinical signature and the pathogenetic factors of the different types of diabetes associated with PDAC, based on the time between diabetes and cancer diagnosis.
Methods: Prospective observational study on 364 PDAC patients admitted to a referral center for pancreatic disease. Hospital and/or outpatient medical records were reviewed. Blood biochemical values including fasting blood glucose, insulin and/or C-peptide, glycosylated hemoglobin and anti-islet antibodies were determined. Diabetes onset was assessed after surgery and during follow-up.
Results: The prevalence of diabetes in patients was 67%. Considering 174 patients (47.8%) already having diabetes when diagnosed with PDAC (long duration, short duration, concomitant), the clinical and biochemical profile was similar to that of patients with type 2 diabetes (T2D). Diabetes was associated with known risk factors (i.e., age, sex, family history for diabetes and increased BMI) and both beta-cell dysfunction and insulin resistance were present. Considering 70 patients (19.2%) with onset of diabetes after PDAC diagnosis (early and late onset), the strongest predictor was the loss of beta-cell mass following pancreatectomy in patients with risk factors for T2D.
Conclusion: Different types of diabetes according to the time between diabetes and PDAC diagnosis are clinical entities widely overlapping with T2D. Therefore, the success of a strategy considering diabetes onset as a marker of asymptomatic PDAC will largely depend on our ability to identify new diabetes-unrelated biomarkers of PDAC.

1. Introduction

The association between pancreatic ductal adenocarcinoma (PDAC) and diabetes [1,2] is of great clinical interest, because the identification of a specific diabetes signature associated to PDAC could be a key to detect asymptomatic, early stage tumors [3–5]. While long-duration diabetes is considered a risk factor for the development of PDAC [6], the pathogenesis of recent-onset diabetes associated with PDAC is still unknown. A first hypothesis suggests that the recent-onset diabetes is a paraneoplastic phenomenon caused by the cancer itself [7], which is capable to secrete diabetogenic products, such as amylin [8], S-100A8N-terminal peptide [9], adrenomedullin [10] and, more recently described, exosomes

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[11]. This hypothesis is supported by the high prevalence of diabetes in patients with PDAC [12,13], the temporal relationship between onset of diabetes and diagnosis of PDAC [14,15] and the resolution of diabetes after PDAC resection in a subgroup of patients [13]. According to this theory, the closer diabetes onset is to the diagnosis of PDAC, the lesser relevant in the pathogenesis of diabetes are the risk factors for "classical" type 2 diabetes (T2D) [3,13]. A second hypothesis to explain the development of diabetes closer to the diagnosis of PDAC is that diabetes and PDAC share one or more risk factors, such as hyperinsulinemia [8,16], genetic risk [17], obesity and lifestyle [18]. On a background of common risk factors, PDAC could unmask diabetes by inducing beta-cell dysfunction through either the direct destruction of normal pancreatic tissue (advanced stages) or the indirect reactive pancreatitis caused by the impairment of the pancreatic duct system. According to this second hypothesis risk factors for "classical" T2D should be relevant, regardless of the time between diabetes and PDAC diagnosis. We recently conducted a prospective observational study to describe the clinical features, risk factors and etiopathogenetic aspects of patients with diabetes associated with pancreas disease (T3cDM) [19]. In this work we compare the clinical signature and etiopathogenetic factors of diabetes in patients with PDAC, divided according to the time between diabetes and PDAC diagnosis.

2. Material and methods

2.1. Eligible patients

The studied population was represented by hospitalized patients with diagnosis of pancreatic disease proposed for both curative or not curative surgical treatment and admitted to the Pancreatic Surgical Unit of Scientific Institute San Raffaele (Milan, Italy). Patients who met all of the following criteria were eligible: >18 years of age, ability to provide written informed consent, presence of pancreatic disease. From January 2008 to December 2012, 787 adult incident cases of pancreatic disease were admitted to the Pancreatic Surgery Unit and 651 eligible patients accepted to participate (see Ref. [19]). Among eligible patients we selected those with a histologically or cytologically confirmed diagnosis of PDAC (364 cases). The local IRB approved the study and all patients provided a written informed consent to participate to the study.

2.2. Medical history

At entry into the study both inpatient and outpatient medical records of each participant were reviewed to abstract the variables of interested and the date of diagnosis of PDAC. In patients with a previous diagnosis of diabetes the medical records were also reviewed to compute disease duration and diabetes medications. All abstracted data were double-checked with either the patient and/or a relative.

2.3. Follow-up

Outpatient's visits were scheduled one month after hospital discharge and every six months thereafter for 10 years. Follow-up data were collected for all patients by reviewing electronic medical records and/or telephone interviews. Adjuvant chemo- or radiotherapy was administered when indicated and CT scan and blood tumor markers were performed every three or six months, based on the risk of recurrence.

2.4. Definition of diabetes and diabetes duration

Study participants were defined as having diabetes if they had at least one FPG $\geq$126 mg/dl (7.0 mmol/l) or HbA1c $\geq$ 6.5% (48 mmol/mol) or they were taking diabetes medications. At admission, participants were classified as having: (a) long-duration diabetes if they had a documented diagnosis of diabetes for $\geq$ 48 months (i.e., a time period during which an existing pancreatic disease would have likely become manifest [12]); (b) short-duration diabetes if they had a documented diagnosis of diabetes for < 48 months; (c) concomitant diabetes if participants were diagnosed with diabetes at the time of the diagnosis of PDAC; (d) diabetes of uncertain duration if participants had a documented diagnosis of diabetes prior to the diagnosis of pancreatic disease, but disease duration was unknown. During follow-up, participants were classified as having: (a) early new-onset diabetes if a documented diagnosis of diabetes was made within 90 days from discharge after PDAC diagnosis; (b) late new-onset diabetes if a documented diagnosis of diabetes was made after 90 days from discharge after PDAC diagnosis; (c) remission of diabetes if the patient had a documented diagnosis of diabetes prior to admission, but blood glucose returned to normal thereafter without being on diabetes medication during all the follow up.

2.5. Determination of the clinical signature and the etiopathogenic factors of the different types of diabetes classified according to the time from pancreatic ductal adenocarcinoma diagnosis

Medical records of each participant were reviewed to abstract the following variables: gender, age, height, weight and BMI [both actual and 12 month before surgery (defined as the usual BMI)], family history of diabetes in first-degree relatives, PDAC presenting sign/symptoms, concomitant diseases (classified as ever/never: non-pancreatic tumor, dyslipidaemia, hypertension, coronary artery disease, hepatic diseases, autoimmune diseases, thyroid dysfunction), tumor treatment (surgery, neoadjuvant CT, adjuvant CT/RT), tumor size and localization, tumor grade, tumor stage and TNM classification. Fasting blood samples were obtained during the preoperative work-up [upon or just before hospital admission, median 6 days (1–13) before surgery] and prior to hospital discharge [median 9 (6–12) days after surgery]. Baseline hemoglobin A_{1c} (HbA_{1c}), baseline and discharge fasting plasma glucose (FPG) and baseline and discharge serum creatinine were measured in all patients. Serum insulin (AIA-PACK IRI; Tosoh, Tokyo, Japan) was measured upon admission and prior to hospital discharge in 291 and 122 out of 364 patients, respectively. C-peptide (AIA-PACK C-Peptide; Tosoh) was measured at baseline and prior to hospital discharge in 135 and 67 out of 364 patients, respectively. Autoantibodies to glutamic acid decarboxylase (GADA), insulinoma-associated protein 2 (IA-2A), insulin (IAA) and zinc transporter 8 antigen (ZnT8A) were measured in 300 out of 364 patients by radiobinding and immunoprecipitation assays as previously described [20]. Insulin resistance and beta-cell function were estimated using the HOMA2 model (available from www.OCDEM.ox.ac.uk) according to the recommendations for its appropriate use [21]. Glomerular filtration rate (eGFR) was estimated using the simplified Modification of Diet in Renal Disease (MDRD) formula [22]. To asses inflammatory biomarkers we calculated peripheral neutrophil-to-lymphocyte ratio (NLR) [23] and platelet-to-lymphocyte ratio (PLR), both reported as poor prognostic indicators in several malignancies, and lymphocyte-to-monocyte ratio (LMR) previously associated with a favorable prognosis for specific hematologic and solid tumors [24]. Preoperative nutritional status was evaluated in all study participants using Onodera's prognostic nutrition index (PNI) calculated as 10 $\times$ serum albumin (g/dl) + 0.005 $\times$ total lymphocyte count (per mm^3) [25]. To grade nutritional status we computed the Geriatric Nutritional Risk Index (GNRI) [1.519 $\times$ albumin (g/L) + 41,7 $\times$ (weight/ideal weight)] [26].