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Original article

Diabetes mellitus and pre-diabetes are frequently undiagnosed and underreported in patients referred for pancreatic surgery. A prospective observational study

Geert Roeyen [a, *], Miet Jansen [a], Thiery Chapelle [a], Bart Bracke [a], Vera Hartman [a], Dirk Ysebaert [a], Christophe De Block [b]

[a] Department of Hepatobiliary, Endocrine and Transplantation Surgery, Antwerp University Hospital, Belgium
[b] Department of Endocrinology, Diabetology and Metabolism, Antwerp University Hospital, Belgium

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ABSTRACT

Objective: Previous reports on the prevalence of diabetes in pancreatic cancer and chronic pancreatitis patients are based on inconsistent and equivocal criteria. The objective of this study is to prospectively assess with conclusive methods the preoperative glycaemic status of patients undergoing pancreatic surgery. We hypothesise that most of those patients are unaware of these disturbances in glycaemic status and that the prevalence is underestimated.

Methods: During the last 2 years, patients referred for pancreatic surgery and without history of diabetes underwent a prospective preoperative screening with an oral glucose tolerance test (OGTT) and determination of the glycated haemoglobin level (HbA1c). The American Diabetes Association's criteria for diabetes and pre-diabetes were used. Beta-cell function and insulin sensitivity were calculated using HOMA2 indices. Impact on surgical policy has been scored.

Results: 99 patients were screened, 25 had a history of diabetes. The other 74 underwent an OGTT and HbA1c determination. Only 29.7% (22/74) had a normal glucose metabolism, while 8.1% (6/74) had impaired fasting glucose, 21.6% (16/74) had impaired glucose tolerance, 6.7% (5/74) had a combination of both, and 33.8% (25/74) had undiagnosed diabetes. In 15.2% (15/99) of the patients, this preoperative assessment had an impact on surgical policy.

Conclusions: 77.7% of patients referred for pancreatic surgery had some degree of (pre-)diabetes. In 70.3% of patients without a history of diabetes, these disturbances in glucose metabolism are a new finding. Physicians involved in pancreatic surgery should be aware of the frequently undiagnosed (pre-)diabetes and actively check for it. This prevalence is underestimated.

Introduction

Patients referred for oncologic pancreatic surgery or surgery for chronic pancreatitis often pose questions about their postoperative glucose metabolism and have concerns about becoming a diabetic patient. Many surgeons consider this postoperative pancreatogenic diabetes to be an unavoidable consequence of the intervention. However, since pancreatic surgery is nowadays more frequently performed for premalignant lesions (e.g. neuroendocrine tumours, intraductal papillary mucinous neoplasm or cysts) with prolonged survival, this type of diabetes gains importance [1]. If diabetes is diagnosed postoperatively, one might question whether this is indeed an unavoidable consequence of the surgical intervention, or whether this might be only a deterioration of an already pre-existing preoperative situation.

The correct preoperative glycaemic status might also influence the decision to perform surgery and the type of surgery.

Furthermore, strict perioperative glycaemic control has consequences for surgical recovery, postoperative mortality, morbidity, and long-term results [2].

Therefore, it seems necessary to have a correct prospective preoperative screening for abnormalities in glucose metabolism, to guide further examinations and treatment.

* Corresponding author. Department of Hepatobiliary, Endocrine and Transplantation Surgery, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium. Tel.: +32 3 821 43 27; fax: +32 3 821 41 17.
E-mail address: geert.roeyen@uza.be (G. Roeyen).

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The aim of this study is to prospectively assess, through OGTT and HbA1c, and strict application of the American Diabetes Association's criteria, the true preoperative prevalence of diabetes and pre-diabetes in patients referred for pancreatic surgery. We hypothesise that most of those patients are unaware of these disturbances in glycaemic status and that the prevalence of diabetes is much higher than in the background Belgian population.

Methods

During the last 2 years, all patients referred for pancreatic surgery were prospectively screened for abnormalities in glucose metabolism. Patients were questioned about history of diabetes, and those without a history of diabetes preoperatively underwent an oral glucose tolerance test (OGTT) and glycated haemoglobin (HbA1c) level determination. Following overnight fasting, an oral glucose load of 75 g (Glucomedics®) was administered, with blood sampling for plasma glucose and C-peptide subsequently performed at seven intervals of time (0, 15, 30, 45, 60, 90, 120 min). The results were interpreted according to the American Diabetes Association's criteria for diabetes and pre-diabetes [3]. Accordingly, diabetes was diagnosed if fasting plasma glucose $\geq$ 126 mg/dl, or if plasma glucose after 2 h during OGTT $\geq$ 200 mg/dl, or if the HbA1c level $\geq$ 6.5%. Pre-diabetes was diagnosed if fasting plasma glucose ranged between 100 and 125 mg/dl (impaired fasting glucose or IFG), or if plasma glucose after 2 h during OGTT ranged between 140 and 199 mg/dl (impaired glucose tolerance or IGT), or if HbA1c level ranged between 5.7 and 6.4%.

Beta-cell function and insulin sensitivity (HOMA2-%B and HOMA2-%S respectively) were assessed using HOMA2 (homoeostasis model assessment 2) indices calculation through the computer application provided by the Oxford Centre for Diabetes, Endocrinology and Metabolism [4,5], based on fasting plasma glucose and C-peptide levels.

Weight and height were measured by a qualified nurse at the outpatient clinic or on admission to the hospital, and body mass index was subsequently calculated.

The impact of this prospective preoperative assessment of the glycaemic status on surgical policy has also been scored by comparing the final surgery performed (considering the preoperative OGTT and HbA1c results) with the type of surgery planned during tumour board meeting (for malignancies and premalignancies) or during multidisciplinary discussion (for chronic pancreatitis patients).

Both informed consent and the approval of the local Ethical Committee were acquired (Belgian registration number: BE300201318590). This study was conducted according to the ethical principles stated in the 'Declaration of Helsinki' and in 'Good Clinical Practice'.

Statistical analysis

Results were analysed using SPSS (version 21.0, Chicago, IL), with the data expressed as means (standard deviation) for normally distributed continuous variables and medians (range) for non-normally distributed continuous variables. Categorical data are expressed as numbers (%). The normal distribution of continuous variables was assessed using the Kolmogorov–Smirnov method. To compare means and medians for polychotomous outcome parameters, we used the One-Way ANOVA with Bonferroni correction for normally distributed variables, and the Kruskal–Wallis method for non-normally distributed variables. To assess potential significant differences between the groups for categorical variables, a contingency table was generated and the Fisher's exact test applied. A two-tailed P-value < 0.05 was considered significant. Stepwise forward logistic regression analysis was done to assess the strength and independency of associations.

Results

During the study period, 99 patients were evaluated (43 females and 56 males) with a mean age of 64 ± 12 years and median BMI of 24.5 kg/m^2 (range: 16.2–35.6). Seventy patients were referred for surgery for a proven or presumed malignancy (e.g. pancreatic adenocarcinoma, distal bile duct carcinoma, periampullary malignancies), while 16 were referred for a premalignant lesion (e.g. intraductal papillary mucinous neoplasm, neuroendocrine tumours larger than 2 cm, suspicious cysts) and 13 for chronic pancreatitis. In most patients, the lesion to be resected was localised in the pancreatic head (71/99) (Fig. 1). In patients with a malignancy, the lesion was also more frequently located at the pancreatic head ($p = 0.021$). This subgroup was also older in age compared to the subjects undergoing surgery for chronic pancreatitis ($p = 0.002$). HbA1c levels, fasting glucose levels, C-peptide levels, and measures of beta-cell function (HOMA2-%B) and insulin sensitivity (HOMA2-%S) did not differ significantly between subjects with malignant disease, premalignant lesions or chronic pancreatitis. Significant differences between groups were observed for glucose level after 2 h ($p = 0.042$) (Table 1).

Twenty-five patients (Fig. 2) were known to have diabetes, but in 11 of those, diabetes had been diagnosed within two years prior to surgery. None of the patients had type-1 diabetes. In the remaining 74 patients, glucose metabolism was prospectively evaluated through OGTT and HbA1c determination. Only 29.7% (22/74) had normal glucose tolerance. Surprisingly, 33.8% (25/74) had newly diagnosed diabetes, while 21.6% (16/74) had impaired glucose tolerance (IGT), 8.1% (6/74) had impaired fasting glucose (IFG), and 6.7% (5/74) had a combination of impaired fasting glucose and impaired glucose tolerance (IFG + IGT).

Screening patients for glycaemic disturbances based on history and fasting glucose alone, as usually reported in the literature, would misclassify 28.4% (21/74) of the patients, thus giving them false reassurance. Indeed, these patients were shown to have IGT or newly diagnosed diabetes based on the OGTT and HbA1c results. Herein lies the added value of performing these tests.

In 15.2% (15/99) of the patients, this correct assessment of the preoperative glycaemic status had a direct impact on surgical policy: e.g. in patients with significant comorbidity or when confronted with technical difficulties during the operation, the surgeon decided to perform a total pancreatectomy because diabetes had already been diagnosed preoperatively or on the other hand, when glycaemic status was undisturbed, more tissue-sparing techniques were applied.

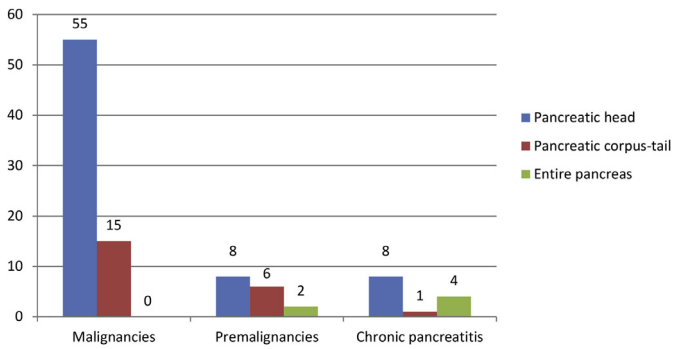

Fig. 1. Patient characteristics prior to surgery: number of patient according to localisation of the lesion ($p = 0.021$ Kruskal–Wallis test).

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