Research on the relationships between pancreatic cancer and hyperglycemia in Chinese populations

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ABSTRACT

Aims/Introduction: Pancreatic cancer (PC) is related to diabetes. Long-standing diabetes should be a prerequisite, whereas new-onset hyperglycemia might be a result of PC. However, the association between diabetes and PC is still in dispute.

Materials and Methods: We investigated the relationship between glucose metabolism and other factors by retrospectively analyzing the clinical data of 331 PC patients. Any histopathological type was eligible. The patients were divided into three groups: group A, normal glucose metabolism; group B, hyperglycemia duration ≤ 6 months; and group C, diabetes duration > 24 months.

Results: The prevalence of hyperglycemia was 59.5%. Most patients were diagnosed with diabetes mellitus either concomitantly with cancer (39.0%) or within 6 months before cancer diagnosis (6.9%). There were more females in group C than group A (P = 0.005) and B (P = 0.018). Patients in group A were younger (A vs B, P < 0.001; A vs C, P = 0.032) and thinner (A vs B, P = 0.013; A vs C, P = 0.027). In group C, more individuals shared a family history of diabetes (A vs C, P = 0.004; B vs C, P = 0.023), but fewer smoked (A vs C, P = 0.027; B vs C, P = 0.020). Patients in group C had a larger proportion of poorly differentiated cancer (A vs C, P = 0.002; B vs C, P = 0.012). No differences in glucose metabolism were found among the different histological types.

Conclusions: We further support the notion that diabetes duration > 24 months might not be cancer related. Older and fatter PC patients were more likely to develop hyperglycemia. More patients with long-standing diabetes had poor tumor differentiation. We speculate that smoking and alcohol intake might advance PC onset. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2012.00237.x, 2013)

KEY WORDS: Diabetes duration, Pancreatic cancer, Risk factors

INTRODUCTION

More than one century ago, people began to notice that pancreatic cancer (PC) might be correlated with diabetes mellitus (DM). The increased prevalence of DM in PC patients has been well established. However, as both diseases have long latencies, the association between diabetes and PC, causal or consequential, is still in dispute.

The results of previous studies show that long-standing diabetes is a risk factor for the development of PC. The strength of this claim is only moderate. In a recent meta-analysis of 17 case-control and 19 cohort or nested case-control studies published between 1966 and 2005, the combined age and sex-adjusted odds ratio (OR) for PC associated with type 2 diabetes was 1.82 (95% confidence interval [CI] 1.66-1.89). Meanwhile, there is increasingly more evidence to support the notion that impaired glucose metabolism (IGM) might be an early symptom of PC. For individuals with a shorter history of diabetes (<4 years), the risk of PC was approximately 50% greater than the patients with more than 5 years of history (relative risk 1.5 vs 2.1; P = 0.005). New data show that diabetes or hyperglycemia is present in up to 40% of PC, which is usually detected soon before the clinical manifestations of PC, and can be improved or remitted after cancer resection.

Previous studies, pathologically, were mostly confined to pancreatic ductal adenocarcinoma (PDAC). In contrast, in the present study, any histopathological type was eligible. The present study was designed to investigate the relationship between glucose metabolism and other factors (e.g. pathological type, differentiation, tumor location, tumor markers, etc.) by retrospectively analyzing the clinical data of 331 PC patients. The differences between the clinical profiles of patients who do and do not develop DM might provide clues to the pathogenesis of pancreatic cancer-related DM.

MATERIALS AND METHODS

Study Population

Of the 904 PC patients hospitalized in Huashan Hospital, College of Medicine, Fudan University (Shanghai, China) from...
January 2000 to June 2010, 449 newly diagnosed patients who had undergone an operation, including radical operation, palliative operation with biopsy or exploratory operation, were considered eligible. Excluded patients included the following: (i) those who had neither preoperative fasting plasma glucose (FPG) test results nor a prior history of DM, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG; \( n = 8 \)); (ii) those who had no postoperative histopathological diagnosis \( (n = 18) \); (iii) those who had a previous history of cancer at another organ site \( (n = 23) \); (iv) primary tumor was not in the pancreas \( (n = 5) \); (v) those who had PC recurrence \( (n = 3) \); (vi) those who had borderline tumor \( (n = 3) \); or (vii) those who were lacking other important information \( (n = 58) \). Finally, 331 cases with histopathologically confirmed primary PC were included in the present clinical study, without any age or sex restriction (Figure 1).

**Study Conduct and Data Collection**

According to the DM course, the study population can be divided into six groups: (i) normal glucose metabolism (NGM), that is FPG < 5.6 mmol/L on admission without DM history \( (n = 134) \); (ii) FPG \( \geq 5.6 \text{ mmol/L on admission without DM history} \ (n = 129) \); (iii) duration of DM \( \leq 6 \text{ months} \ (n = 23) \); (iv) duration of DM ranges from 7 to 24 months \( (n = 7) \); (v) duration of DM > 24 months \( (n = 26) \); and (vi) duration of DM unclear \( (n = 12) \); (Figure 1).

**Figure 1** | Flowchart of patients’ selection and grouping. FPG, fasting plasma glucose; DM, diabetes mellitus; IGM, impaired glucose metabolism; NGM, normal glucose metabolism; PC, pancreatic cancer.
In previous studies, DM duration ≤ 2 years was defined as ‘new-onset diabetes’\(^{4,6,8}\). However, a new concept of cancer-related IGM (i.e. hyperglycemia course ≤ 6 months) was more reasonable for the present study. First, the analysis of the chronology between hyperglycemia diagnosis and the clinical manifestation of PC supported this statement. For patients with DM duration > 24 months, at the time they met criteria for DM, none had previous cancer-related symptoms. For the patients with IGM duration ≤ 6 months, most (93.6%) already had cancer-related symptoms. Whereas for the middle part, half received the DM diagnosis first, and half had cancer-related symptoms first. Second, it was reported that PC was frequently undetectable or resectable on CT scans carried out before clinical diagnosis and seldom could be detected before 24 months\(^{3,10}\). Third, the natural history of PC was situated at before clinical diagnosis and seldom could be detected before 6 months\(^{7}\). A total of 30% of the patients died within 1 month of diagnosis, and 90% died within 1 year\(^{11}\). Therefore, the use of 6 months as the division to define cancer-related IGM might increase the specificity of the analysis. Accordingly, we regrouped the study population into three parts: group A, normal glucose metabolism (NGM), FPG < 5.6 mmol/L on admission without DM history \((n = 134)\); group B, cancer-related IGM, duration of DM ≤ 6 months or FPG ≥ 5.6 mmol/L on admission \((n = 152)\); and group C, long-standing DM, duration of DM > 24 months \((n = 26)\). The patients with DM duration that ranged from 7 to 24 months \((n = 7)\) were not included in the analysis between these three groups, as the relationship between DM and PC was obscure for them, and these patients only made up a small proportion in totality.

DM was defined as FPG ≥ 7.0 mmol/L on admission or a previous diagnosis of DM, according to the American Diabetes Association criteria of 2010. IFG was defined as FPG level ≥ 5.6 mmol/L and <7.0 mmol/L. NGM was defined as FPG level < 5.6 mmol/L without DM history. IGM was the general name for DM and IFG. The course of DM was calculated from the date of DM diagnosis to the date of PC diagnosis. For those diagnosed on admission, the course was recorded as less than 6 months. Serum glucose measurements were obtained after fasting for routine clinical purposes. Alcohol intake was estimated according to the patient’s report of duration and frequency. It was defined as consumption of beer, wine or liquor at least once per week for 1 year or more. Family history of PC was restricted to first-degree or second-degree relatives. The measurement of tumor size came from the greatest tumor diameter of the histopathological report. The histological classification was based on the World Health Organization classification of tumors of 2000\(^{13}\).

**Statistical Analysis**

Comparisons of continuous variables among the three groups were carried out using the Fisher’s exact test or chi-square test. Then the post-tests between each two subgroups were carried out with Bonferroni’s corrections. Statistical significance was defined as \(P < 0.05\), and all tests were two-sided. These tests were carried out with SPSS software, version 15.0 (SPSS, Chicago, IL, USA).

**RESULTS**

**Characteristics of the Study Population**

Of the 331 PC patients we studied (188 male [56.8%] and 143 female [43.2%]), the mean age was 60.85 years (range 20–83), and the mean body mass index (BMI) was 22.84 ± 3.00 kg/m\(^2\). A total of 51 patients (15.4%) had a history of alcohol intake. A total of nine patients (2.7%) reported to have a family history of DM. A large proportion (39.5%) met the criteria for DM (36.5%) or IFG (23.0%). Most were diagnosed with DM either concomitantly with cancer (39.0%) or within half a year before cancer diagnosis (6.9%); therefore, the prevalence of cancer-related IGM was 45.9%. Long-standing DM accounted for approximately 7.9%. NGM cases represented 40.5% (Figure 2). Glucose metabolism of different histological types is shown in detail in Table 1, and no statistically significant differences were found among groups \((P = 0.354)\). Most histological reports were moderately (45.6%) or poorly (17.5%) differentiated. The median tumor diameter of the entire PC group was 40 mm (range 8–150 mm). A total of 27 patients (8.2%) were found to among the three groups were carried out using the Fisher’s exact test or chi-square test. Then the post-tests between each two subgroups were carried out with Bonferroni’s corrections. Statistical significance was defined as \(P < 0.05\), and all tests were two-sided. These tests were carried out with SPSS software, version 15.0 (SPSS, Chicago, IL, USA).

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have hepatic metastasis during surgery. Of the 26 diabetics in group C, six had never been treated with any hypoglycemic agents; eight had used insulin by itself or with other drugs.

The characteristics of the three groups are presented in Table 2. The sex composition was different among the three groups; more females were found in group C ($P = 0.016$). For the patients without a previous history of DM, those who developed cancer-related IGM were found to be older, fatter and larger in tumor size than the patients who did not ($P = 0.001, 0.038$ and $0.019$, respectively). Additionally, group C had a higher level of carcinoembryonic antigen (CEA) and worse histological differentiation than the others.

As pancreatic endocrine tumors might have different characteristics based on the cellular origin and affect the glucose metabolism independently through endocrinological processes, we repeated the comparison after ruling out these pancreatic endocrine tumors from groups A, B and C. Then there were 125, 147 and 26 patients left in groups A’, B’ and C’, respectively (Table 3), and the results of comparison were quite similar to the previous comparison (Table 2).

Besides the comparisons based on glucose metabolism, the mean age of smoking patients when diagnosed with PC was 59.04 years, whereas the mean age of non-smoking patients was 61.51 years ($P = 0.026$). The mean age of alcoholic patients when diagnosed with PC was 57.96 years, and the mean age of non-alcoholism was 61.37 years ($P = 0.022$). Undifferentiated carcinoma had the largest tumor diameter (median 8.5 cm) compared with well- (median 3.0 cm), moderately- (median 3.0 cm) and poorly-differentiated (median 3.5 cm) carcinomas ($P = 0.030$). Tumors located in the pancreatic body and tail had a bigger size (median 4.33 cm) than those in the pancreatic head (median 3.65 cm) and the uncinate process (median 3.09 cm; $P < 0.001$). Focusing on adenocarcinoma, mucinous cystadenocarcinoma was larger in tumor size (median 6.5 cm) than PDAC (median 3.36 cm), serous cystadenocarcinoma (median 4.0 cm) and intraductal papillary mucinous carcinoma (median 3.0 cm; $P = 0.023$). PDAC had the highest level of carbohydrate antigen 19-9 (median 153.9 U/mL) in adenocarcinoma ($P = 0.015$).

**DISCUSSION**

A national study carried out in China in 2008 showed that 9.7% of adults were diabetics. In the present study, 59.5% of PC patients had IGM, which was much higher than in the general population. Thus, the high prevalence of IGM could not simply contribute to type 2 diabetes mellitus or type 1 diabetes mellitus, indicating that there must be some relationship with pancreatic cancer.

In the present study, the proportion of long-standing diabetics was 7.9% of all the cases. There were 12 diabetics for whom we could not determine their DM course from the clinical records. Taking them into consideration, the real proportion of long-standing diabetes should range from 7.9 to 11.5%, which was quite close to the prevalence of DM in the

| Table 1 | Glucose metabolism of different histological type |
|---------|---------------------------------------------|
| Normal | ≤ 6 m | 7–24 months | >24 months | Total |
| Cancers of the exocrine pancreas | | | | |
| Adenocarcinoma (NOS) | 66 | 64 | 4 | 9 | 143 |
| Ductal adenocarcinoma | | | | |
| Ductal adenocarcinoma (NOS) | 42 | 64 | 1 | 11 | 118 |
| Mucinous non-cystic carcinoma | 4 | 4 | 1 | 9 |
| Signet-ring cell carcinoma | | | 1 | |
| Adenosquamous carcinoma | 2 | 3 | 1 | 6 |
| Undifferentiated carcinoma | | | 1 | 2 |
| Mixed ductal-endocrine carcinoma | | | 1 | 1 |
| Serous cystadenocarcinoma | 1 | | | 1 |
| Mucinous cystadenocarcinoma | 3 | 1 | 1 | 5 |
| Intraductal papillary mucinous carcinoma | 1 | 2 | 1 | 4 |
| Acinar cell carcinoma | | | | |
| Acinar cell carcinoma (NOS) | 2 | 4 | | 6 |
| Mixed acinar-endocrine carcinoma | 1 | | | 1 |
| Solid-pseudopapillary carcinoma | 2 | | | 2 |
| Squamous cell carcinoma | 2 | | | 2 |
| Cancers of the endocrine pancreas | | | | |
| Islet cell carcinoma | 1 | | | 1 |
| Neuroendocrine carcinoma | 8 | 5 | 1 | 14 |
| Others | 1 | 1 | 3 | 3 |
| Total | 134 | 152 | 7 | 26 | 319 |

NOS, not otherwise specified.
general population. Additionally, we noticed that more patients have family histories of DM in group C than in both A and B. This observation implied that there was a genetic component in long-standing DM rather than it arising as a result of PC. Both results support the notion that long-standing DM is a pre-existing condition belonging to type 2 diabetes mellitus, and is not likely to be cancer related.

The prevalence of cancer-related IGM in the present study was 45.9%, which was lower than expected. The reasons were as follows. First, as 2-h plasma glucose was not routinely tested, glucose tolerance was not well evaluated. Thus, many IGT cases might have been ignored. Second, the diagnosis of IGM was based on a single FPG test without a glycated hemoglobin value. It was difficult for us to obtain a general view of each patient’s glucose metabolism. Third, the reported incidence of ectopic pancreas ranged from 0.55 to 13.7% based on autopsy or laparotomy. β-cells were proved to exist in the ectopic pancreas by histological examination, which might be supposed to benefit glycemic regulation. Therefore, for PC patients, the
existence of ectopic pancreas might conceal the true extent of IGM resulting from a tumor.

The analysis of sex differences, both groups A and B had more males than females, whereas group C was the opposite. According to the annual Surveillance, Epidemiology and End Results (SEER; a premier source for cancer statistics in the USA) program on PC, males always make up the majority. We speculate that females with long-standing DM have a greater risk in developing PC.

### Table 3 | Features of pancreatic exocrine tumor patients among the three groups

| Group | n | Features of pancreatic exocrine tumor patients among the three groups | P (A`B`) | P(A`B`) | P(A`C`) | P (B`C`) |
|-------|---|---------------------------------------------------------------------|----------|---------|---------|----------|
| Male/female | | Male/Female | | 0.012 | 1.000 | 0.009 | 0.026 |
| Age | | 58.01 ± 11.46 | 62.81 ± 9.92 | 63.08 ± 7.62 | <0.001 | 0.001 | 0.075 | 1.000 |
| BMI, kg/m² (n)* | | 22.18 ± 2.96 (113) | 23.12 ± 3.04 (138) | 23.64 ± 2.95 (25) | 0.015 | 0.039 | 0.080 | 1.000 |
| Weight loss (kg) | | 0.00 (117) | 0.00 (138) | 1.00 (22) | 0.176 | | | |
| Weight loss/usual weight (%) | | 0.00 (111) | 0.00 (133) | 1.39 (22) | 0.117 | | | |
| Family history of DM (%)‡ | | 0 | 1.4 | 11.5 | <0.001 | 1.000 | <0.001 | 0.013 |
| Smoking (%) | | 36.0 | 23.8 | 11.5 | 0.012 | 0.082 | 0.044 | 0.483 |
| Alcohol intake (%)† | | 19.2 | 12.9 | 3.8 | 0.090 | | | |
| FPG (mmol/L)‡ | | 5.1 (125) | 6.5 (146) | 8.0 (23) | <0.001 | <0.001 | <0.001 | <0.001 |
| Tumor size (cm)‡★★ | | 3.00 (125) | 4.00 (146) | 3.5 (25) | 0.030 | 0.015 | 0.383 | 1.000 |
| Tumor marker | | | | | | | | |
| CA125 (U/mL)‡ | | 35.0 (90) | 35.0 (112) | 35.0 (15) | 0.427 | | | |
| CA19-9 (U/mL)‡ | | 78-84.5 | 66-170.8 | 72-175.8 | 0.028 | 0.052 | 0.191 | 1.000 |
| CEA (ug/L)‡ | | 2.6 (100) | 2.8 (110) | 5.6 (17) | 0.012 | 1.000 | 0.014 | 0.020 |
| CA50 (U/mL)‡ | | 293.8 (84) | 674.96 (96) | 83.1 (15) | 0.089 | | | |
| CA242 (U/mL)‡ | | 15.0 (60) | 244.71 (71) | 17.0 (9) | 0.625 | | | |
| Tumor location | | | | | | | | |
| Diffuse | | 1 | 3 | 1 | 0.080 | | | |
| Head | | 55 | 73 | 13 | | | | |
| Uncinate process | | 19 | 24 | 0 | | | | |
| Body and tail | | 36 | 43 | 10 | | | | |
| Ampulla of Vater | | 14 | 4 | 2 | | | | |
| Differentiation | | | | | | | | |
| Well | | 6 | 6 | 4 | | | | |
| Moderate | | 65 | 73 | 5 | | | | |
| Poor | | 28 | 23 | 7 | | | | |
| Undifferentiated | | 0 | 3 | 1 | | | | |
| Hepatic metastasis (%) | | 6.8 | 10.5 | 0 | 0.198 | | | |

Values of P<0.05 are considered statistically significant (in bold). *Body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. †Variables are reported as medians (n), and 5–95% percentiles for these non-normally distributed continuous variables. ‡Family history of pancreatic cancer is restricted to first-degree or second-degree relatives. §Alcohol intake is defined as consumption of beer, wine or liquor at least once per week for 1 year or more according to patient’s report. ★★The measurement of tumor size comes from the greatest tumor diameter of histopathological report. DM, diabetes mellitus; FPG, fasting plasma glucose.
drinking after being diagnosed with DM. Even though no significant differences were noted among groups on alcohol intake, we still noticed that fewer patients in group C drank alcohol. Smoking and alcohol intake are risk factors of many diseases. The age of PC patients with the addiction to smoking and alcohol was shown to be younger than those without. Therefore, smoking and alcohol could have an effect of advancing PC onset.

In previous studies, tumor size was thought to be related to IGM in PC patients. The bigger the tumor size was, the greater influence there would be on glucose metabolism. Later on, however, one study reported that 60.8% of the patients with small pancreatic cancers (<20 mm in size) had abnormal glucose tolerance,16 bringing the claim of tumor size into question. Until recently, it appeared that the development of IGM was associated with peripheral insulin resistance, abnormal inflammatory mediators and impaired islet cell function, either directly or indirectly induced by cancer cells.5,17,21 In the present study, the median tumor size of group B was significantly bigger than group A ($P = 0.015$), so we supported that tumor size could be one mechanism behind the development of IGM in PC.

We also noted the distinctions of tumor differentiation among groups. There was a larger proportion of poorly-differentiated cases in group C than the other groups. Thus, it appears that the long duration of hyperglycemia might have a negative effect on tumor differentiation.

All of the tumor markers investigated in the present study are glycoproteins. As glycoproteins, they could be affected by plasma glucose level and be increased in a hyperglycemia situation. A higher level of CEA was found in group C than the other two groups, which might be attributed to long-standing hyperglycemia. However, no correlation was observed between CEA and tumor differentiation in the present study.

The strengths of the present study included a large sample size with a clear histological diagnosis and detailed surgery information. As the present study of clinical data was retrospective, the main limitation was the inevitable loss of some information (e.g. the evaluation of glucose tolerance, the postoperative follow up).

In conclusion, from the present study, we found that the prevalence of hyperglycemia and cancer-related IGM were 59.5 and 45.9%, respectively. We further support the notion that glucose metabolism after subtotal pancreatectomy for pancreatic cancer. A meta-analysis. JAMA 1995; 273: 1605–1609.

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