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Glucose Intolerance After Pancreatectomy Was Associated With Preoperative Hemoglobin A1c, Insulin Resistance, and Histological Pancreatic Fatty Infiltration

To the Editor:

The incidence of new-onset diabetes mellitus has been reported to be 18% to 39% after pancreaticoduodenectomy and 5% to 42% after distal pancreatectomy.¹ Although factors such as high body mass index (BMI),²⁻⁴ high resected pancreatic volume,^{2,3,5} operative procedure (distal pancreatectomy),^{3,6} presence of chronic pancreatitis,¹ glucose tolerance,^{5,6} and age³ are reported to contribute to glucose intolerance after pancreatectomy in preoperative nondiabetic patients, some of these factors are controversial, partly due to inaccurate or poor assessment of preoperative glucose tolerance. Moreover, the relationship between postoperative glucose intolerance and underlying conditions of glucose tolerance, such as insulin secretory capacity and insulin resistance or sensitivity, as well as histological characteristics of normal pancreatic tissue, have never been studied. We aimed to identify predictive factors of glucose intolerance after pancreatectomy, including histological factors, in preoperative nondiabetic patients whose glucose tolerance was examined in detail.

Fifty-six nondiabetic patients who underwent pancreatectomy in the Department of Gastroenterological Surgery, Osaka University Hospital, between April 2007 and September 2013, provided written comprehensive informed consent, and were followed up for at least 1 year were enrolled in our study. Preoperative diabetes was defined by (a) fasting plasma glucose level of 126 mg/dL or greater, (b) plasma glucose level at 120 minutes in a 75-g oral glucose tolerance test of 200 mg/dL or greater, (c) casual plasma glucose level of 200 mg/dL or greater, (d) hemoglobin A1c (HbA1c) of 6.5% or greater, or (e) presence of history of diabetes or use of antidiabetic drugs. Patients who either had relapses of the primary diseases or other active diseases; were diagnosed as having neuroendocrine tumors with positive immunostaining for either insulin or glucagon; were treated with

drugs affecting glucose tolerance, with underlying chronic pancreatitis, anemia, liver cirrhosis, or renal dysfunction; and were without preoperative data on HbA1c were excluded from the study. The maximum value of HbA1c (= postoperative MAX HbA1c) within 1 year after surgery was evaluated to be an index of glucose intolerance. Among the 56 patients, histological analyses of β -cell area and pancreatic fatty infiltration were performed in 36 patients whose normal pancreatic sections were isolated from near the resected margins and judged to be suitable for analyses, as determined by rejecting cancer elements and fibrosis changes. The ratio of β -cell area to the entire pancreatic section (excluding fat tissue) was defined as the relative β -cell area (%), and the ratio of the sum of the interlobular and intralobular fat-cell areas to the entire pancreatic section (including fat tissue) was defined as "fat-cell area" (%). Representative views of hematoxylin and eosin (HE)-stained pancreatic sections with the minimum (0.033%) and maximum (53%) values of fat-cell area are shown in Figures 1A and B, respectively, whereas the median value of fat-cell area in 36 subjects' specimens was 0.94%. Among the subjects of histological analyses, fat-cell area had the strongest correlation with postoperative MAX HbA1c ($r = 0.90$, $P < 0.0001$) of all of the preoperative clinical parameters that were correlated with postoperative MAX HbA1c, such as C-peptide index ($r = 0.51$, $P = 0.018$), HbA1c ($r = 0.52$,

$P = 0.0012$), fasting C-peptide ($r = 0.59$, $P = 0.0046$), BMI ($r = 0.66$, $P < 0.0001$), and homeostasis model assessment of insulin resistance (HOMA-R; $r = 0.68$, $P = 0.0001$). Multiple regression analyses revealed that fat-cell area, HOMA-R, and HbA1c were independently associated with postoperative MAX HbA1c and that fat-cell area had the strongest contribution (Table 1). Receiver operating characteristic curve analysis revealed that the cutoff value of fat-cell area for identifying subjects whose postoperative HbA1c deteriorated to diabetic state (HbA1c $\geq 6.5\%$, one of the criteria for diabetes in Japan) was 3.7%.

As for the reasons why fat-cell area was associated with postoperative glucose intolerance, the following explanations are given. First, fat-cell area in the pancreas may reflect insulin resistance. Indeed, fat-cell area had positive correlations with HOMA-R ($r = 0.56$, $P = 0.0031$) and BMI ($r = 0.64$, $P < 0.0001$) in this study, in line with previous studies.^{7,8} Second, fat-cell area may be related to another factor of glucose tolerance impairment other than insulin resistance because fat-cell area contributed to postoperative MAX HbA1c more strongly than HOMA-R. A previous study in humans revealed that the degree of pancreatic fatty infiltration was negatively correlated with indices of insulin secretory capacity,⁹ although this was not shown in this study. Further studies are needed to confirm the association of fatty infiltration and deterioration of β -cell function.

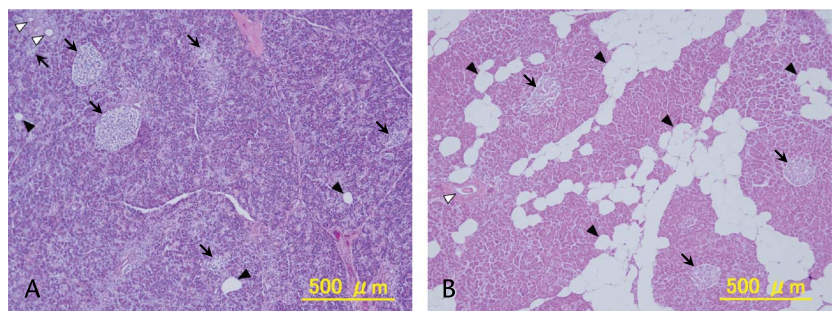


FIGURE 1. Views of HE-stained pancreatic sections with the minimum fat-cell area (0.033%; A) and maximum fat-cell area (53%; B). Fat-cell area (black arrowhead) was found scattered or spread in normal pancreatic structure of islets (black arrow) and exocrine tissue. Fat-cell area was distinguished from lymph ducts or vessels (white arrowhead) by the absence of surrounding connective tissue and endothelial cells. A, A representative low-magnification view of a HE-stained pancreatic section with the minimum fat-cell area (0.033%) from a 55-year-old woman, whose BMI and HOMA-R were 22.3 kg/m² and 1.1, respectively. Her postoperative MAX HbA1c was 6.2%. B, A representative low-magnification view of a HE-stained pancreatic section with the maximum fat-cell area (53%) from a 29-year-old woman, whose BMI and HOMA-R were 34.3 kg/m² and 3.8, respectively. Her postoperative MAX HbA1c was 13.3%.

TABLE 1. Multiple Regression Analyses for Postoperative MAX HbA1c (%)

	Coefficient	SE	Standardized Coefficient	t	P
(Model 1, n = 26)					
Fat-cell area, %	0.101	0.014	0.709	7.38	<0.0001
BMI, kg/m ²	0.069	0.047	0.140	1.49	0.1516
HOMA-R	0.433	0.151	0.215	2.87	0.0090
(Model 2, n = 36)					
Fat-cell area, %	0.110	0.011	0.780	9.88	<0.0001
BMI, kg/m ²	0.026	0.036	0.059	0.73	0.4733
HbA1c, %	0.729	0.173	0.276	4.21	0.0002
(Model 3, n = 21)					
Fat-cell area, %	0.109	0.017	0.760	6.61	<0.0001
BMI, kg/m ²	0.067	0.059	0.134	1.14	0.2699
F-CPR, nmol/L	1.776	0.976	0.154	1.82	0.0866
(Model 4, n = 26)					
Fat-cell area, %	0.110	0.009	0.767	11.98	<0.0001
HOMA-R	0.339	0.135	0.168	2.51	0.0199
HbA1c, %	0.569	0.176	0.193	3.23	0.0039
(Model 5, n = 21)					
Fat-cell area, %	0.112	0.011	0.775	9.89	<0.0001
HOMA-R	0.682	0.268	0.311	2.54	0.0211
F-CPR, nmol/L	-0.459	1.297	-0.040	-0.35	0.7276
(Model 6, n = 21)					
Fat-cell area, %	0.115	0.011	0.799	10.72	<0.0001
HbA1c, %	0.606	0.232	0.194	2.61	0.0184
F-CPR, nmol/L	1.288	0.878	0.112	1.47	0.1607

Bold values are statistically significant.

The multiple regression analyses revealed that fat-cell area was independently associated with postoperative MAX HbA1c in all models. Although HOMA-R and/or HbA1c were also revealed to be independent factors in models 1, 2, 4, 5, and 6, the absolute values of standardized partial regression coefficients of fat-cell area were larger than those of HOMA-R and HbA1c. Sample size of multiple regression analysis differed among the models because values of F-CPR and HOMA-R were missing in some patients.

F-CPR indicates fasting C-peptide.

Unexpectedly, postoperative MAX HbA1c was not associated with relative β -cell area, an index reflecting insulin secretory capacity.¹⁰ This result may suggest that insulin secretory capacity contributed less to postoperative glucose tolerance within 1 year than insulin resistance in preoperative nondiabetic patients. Longer follow-up studies might clarify the contribution of relative β -cell area to postoperative glucose tolerance.

In conclusion, glucose intolerance within 1 year of pancreatectomy could be predicted by preoperative HbA1c, HOMA-R, and especially pancreatic fat-cell area in preoperative nondiabetic patients.

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Adjuvant Treatment in Potentially Curable Pancreatic Cancer Need to Include Tumor Location in the Equation?

To the Editor:

Pancreatic cancer is currently the fourth, but projected to be the second, leading cause of death from cancer in the United States, with an estimated 53,000 new cases and 43,000 deaths in 2017.^{1,2} About 70% of patients with pancreatic cancer die within the first year after diagnosis, with 5-year survival being only 8%.¹ Pancreatic cancer also remains one of the few malignancies with increasing incidence, despite advances in diagnostic imaging, surgical techniques, and systemic treatments.²

Pancreatic cancer may present in the head or body/tail region of the organ. Patients with tumors located in the pancreatic head

constitute 65% to 70% of all patients with pancreatic cancer, with the remainder having tumors localized to the body/tail or involving the entire pancreas.³ Although patients with head and body/tail tumors are generally treated similarly, it is important to note that patients with cancer of the head of the pancreas have a different disease presentation and prognosis than those with body/tail tumors. Patients with pancreatic head tumors most commonly present with painless obstructive jaundice, even when the tumor is of a small size and are likely to get diagnosed earlier in the disease course. On the other hand, patients with body/tail tumors tend to get diagnosed with delay owing to lack of obvious symptoms such as jaundice. In fact, jaundice in patients with body/tail tumors may be secondary to hepatic metastases, thereby reflecting an advanced stage of disease.⁴ Interestingly, both overall and tumor-free survival has been found to be better in patients with localized body/tail cancers compared with those with head cancers,^{5,6} possibly suggesting that head tumors may be biologically different with a more

TABLE 1. Summary of Adjuvant Chemotherapy and Chemoradiation Trials Comparing Treatment Modalities for Pancreatic Cancer

Group/Trial	Author, Year	Comparison Group	Conclusion	Location-Related Comment
GITSG ⁴	Kalser, 1985	Adjuvant 5-FU + radiation vs observation	Survival benefit with adjuvant 5-FU and radiation	Survival not stratified by tumor location
CONKO-001 ¹¹	Oettle, 2013	Adjuvant gemcitabine vs observation	Survival benefit with adjuvant gemcitabine	Survival not stratified by tumor location
EORTC 40891 ¹²	Smeenk, 2007	Adjuvant 5-FU + radiation vs observation	Survival benefit with chemoradiation	Study restricted to patients with head and periampullary cancers; no data on body/tail tumors
RTOG 9704 ¹³	Regine, 2011	Adjuvant prechemoradiation and postchemoradiation 5-FU vs gemcitabine	No survival benefit overall G vs 5-FU, but in patients with head G better than 5-FU	Trial compared head vs overall tumors and found difference
JSAP 02 ¹⁴	Ueno, 2009	Adjuvant gemcitabine vs observation	Survival benefit with adjuvant gemcitabine	Survival not stratified by tumor location
ESPAC-1 ¹⁵	Neoptolemos, 2004	5-FU vs observation	Survival benefit with 5-FU	Survival not stratified by tumor location
ESPAC-1+ ^{16*}	Neoptolemos, 2009	5-FU/FA vs observation	Survival benefit with 5-FU	Survival not stratified by tumor location
ESPAC 3v1 ¹⁶	Neoptolemos, 2009	5-FU/FA vs observation	Survival benefit with 5-FU	Survival not stratified by tumor location
ESPAC 3v2 ¹⁷	Neoptolemos, 2010	5-FU/FA vs gemcitabine	Survival benefit with gemcitabine	Survival not stratified by tumor location
ESPAC 4 ¹⁸	Neoptolemos, 2017	Adjuvant gemcitabine and capecitabine with gemcitabine monotherapy	Survival benefit with adjuvant gemcitabine + capecitabine	No comparison based on type of surgery, although surgery data available
JASPAC-01 ¹⁹	Uesaka, 2016	Adjuvant S-1 vs gemcitabine	Survival benefit with S-1	Improvement in relapse-free (but not overall survival) nonsignificant in patients undergoing distal pancreatectomy

*ESPAC-1+ was a randomized comparison of 192 patients enrolled from within the total 550 for ESPAC-1 (2004).

CONKO-001 indicates Charité Onkologie 001; EORTC, European Organisation for Research and Treatment of Cancer; ESPAC, European Study Group for Pancreatic Cancer; GITSG, Gastrointestinal Tumor Study Group; JASPAC, Japan Adjuvant Study Group of Pancreatic Cancer; JSAP, Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer; RTOG, Radiation Therapy Oncology Group.