Original Article

Risk factors for pancreatogenic diabetes after pancreaticoduodenectomy

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Backgrounds/Aims: Postoperative diabetes mellitus (DM) after pancreaticoduodenectomy (PD) may compromise the long-term quality of life in survivors after the operative procedure due to the treatment difficulty and its related complications. The aim of this study is to determine the incidence of new-onset pancreatogenic DM after PD and investigate the risk factors for this complication. **Methods:** Among 170 patients who had undergone PD between November 2003 and September 2009, 98 patients were selected for this study. The selected patients were non-diabetic prior to the operation and had undergone follow-up tests for glucose metabolism and an abdominal computed tomography (CT) scan 1 year after the operation. The clinical data of these patients were retrospectively analyzed by reviewing the medical records, radiologic images, and pathologic reports. **Results:** Postoperative pathology confirmed malignant tumors in 91 patients, borderline malignancy in 5, and benign tumor in 2. The tumor locations included the pancreatic head (n=30), the common bile duct (CBD) (n=30), ampulla of Vater (n=30), and the duodenum (n=8). New-onset DM occurred in 17 (17.4%) of the 98 patients during the first year after the operation. The comparative analysis between postoperative DM (+) and DM (−) groups revealed that the atrophy of the remaining pancreas was the only significant risk factor for development of postoperative DM after PD. **Conclusions:** This study suggests that the atrophy of the remaining pancreas increases the risk of pancreatogenic DM after PD, and efforts to prevent pancreatic atrophy are needed to decrease this complication. **(Korean J Hepatobiliary Pancreat Surg 2012;16:167-171)**

Key Words: Pancreaticoduodenectomy; Pancreatogenic diatetes mellitus; Pancreatic atrophy

INTRODUCTION

There is limited data on the long-term quality of life of the patients following the pancreaticoduodenectomy (PD), mainly due to the poor prognosis of the malignant disease constituting the major indications for this operative procedure, along with the high postoperative morbidity and mortality rates. However, the long-term survival rate has recently increased due to the refined surgical techniques, improvement in perioperative management, development of adjuvant treatments, and more frequent use of PD in benign and borderline malignant tumors.[1] The improved survival after PD has led to an increased concern regarding the long-term metabolic consequences.[2,3]

The loss of pancreatic parenchyma resulting from pan-

createctomy can lead to the abnormality in the glucose homeostasis known as pancreatogenic diabetes mellitus (DM). Impairment of the glucose metabolism after PD is difficult to predict and can range from minimal to major metabolic derangements. Although pancreatic insufficiency is generally known to occur when more than 80% of the pancreas is resected, new-onset DM has been reported to develop in 20-50% of the patients even after PD involving the removal of approximately 40-50% of pancreatic volume.[1,4] Pancreatogenic DM can compromise the long-term quality of life of the patients, because it is frequently associated with iatrogenic hypoglycemia resulting from increased peripheral sensitivity to insulin, unlike other types of DM; hence, it is difficult to control with medication. Long-term inadequate glycemic control can also cause nephropathy, neuropathy, and retinopathy.

Therefore, it is important to evaluate the incidence of pancreatogenic DM after PD, and identify the risk factors of developing this complication. Previous studies on pancreatogenic DM mainly examined the changes in hormone secretion or glucose metabolism after pancreatectomy.[2,5] There have been few clinical studies which have aimed to identify the risk factors associated with pancreatogenic DM.[6] In this study, we investigated the frequency of occurrence of new-onset pancreatogenic DM after PD, and analyzed the risk factors associated with the complication.

METHODS

Patients

The PD was performed in 170 patients between November 2003 and September 2009. Among those patients, 98 patients who had undergone follow-up tests for glucose metabolism at one year after the surgery were selected for this study. Among the patients, 48 patients with underlying DM and 24 patients who were lost to follow-up or died within one year after the operation were excluded from the study. The patients were divided into two groups, according to the postoperative development of DM; DM (＋) group (n=17) and DM (－) group (n=81). The clinical data of these patients were retrospectively analyzed by reviewing the medical records, radiologic images, and pathologic reports. To identify the risk factors for new-onset DM after PD, the following data were compared between the two groups: age, sex, body mass index (BMI), type of operation (Whipple vs. pylorus-preserving pancreatoduodenectomy [PPPD]), tumor site, pathologic diagnosis (benign or borderline malignancy vs. malignancy), T stage, N stage, amount of intraoperative blood loss, operation time, postoperative complication, postoperative hospital stay, size of postoperative pancreatic duct, underlying pancreatitis, postoperative atrophy of the remaining pancreas, history of adjuvant chemoradiation therapy, and recurrence.

Definition of parameters

All patients underwent glucose metabolism tests, including oral glucose tolerance test (OGTT), as well as an abdominal computed tomography (CT), before and one year after the operation. In the OGTT, the blood glucose was measured after fasting and two hours after drinking a glucose-rich beverage. Pancreatogenic DM was defined as the presence of diabetes symptoms, a random glucose level ＞200 mg/dl, fasting blood sugar (FBS) ＞126 mg/dl, or postprandial glucose level ＞140 mg/dl. The pancreatic-duct was defined to be dilated when it was five mm or more in diameter on the postoperative CT images. The thickness of the pancreatic parenchyma near the pancreatoenteric anastomosis site was measured using an abdominal CT, before and one year after the operation. Pancreatic atrophy was confirmed when the postoperative parenchymal thickness was reduced to ＜50% of the preoperative value. The presence of pancreatitis was evaluated by postoperative pathologic examination.

Statistics

In order to determine the risk factors for development of diabetes, the categorical variables were compared using chi-square test, and the continuous variables were compared using the non-parametric Mann-Whitney U test. All the statistical analysis was performed using the SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). A p-value less than 0.05 was considered statistically significant.

RESULTS

Demographic characteristics

The demographic characteristics of the study population were summarized in Table 1. The study included 61 male and 37 female patients, with a mean age of 66.2 years (range: 18-78 years). Twenty-three patients (23.5%) had BMI of 25 or more. The tumor locations included the pancreatic head (n=30, 30.6%), the common bile duct (n=30, 30.6%), ampulla of Vater (n=30, 30.6%), and the duodenum (n=8, 8.2%). PPPD was performed in 86 patients (87.8%) and the Whipple procedure in 12 patients (12.2%). Postoperative pathology confirmed: malignancy in 91 patients (adenocarcinoma, ductal adenocarcinoma, signet ring cell carcinoma, acinar cell carcinoma, metastatic renal cell carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells); borderline malignancy in five patients (intraductal papillary mucinous adenoma [IPMN] with low/high grade dysplasia); and benign disease (serous microcystic adenoma, and well differentiated endocrine tumor) in two patients. Postoperative complica-

Table 1. Demographic characteristics of the patients

	No. (%)
Age (mean±SD, years)	66.2±11.8
Sex	
Male	61 (62.3%)
Female	37 (37.7%)
BMI (kg/m^2)	
<25	75 (76.5%)
≥25	23 (23.5%)
Location	
Pancreas	30 (30.6%)
Common bile duct	30 (30.6%)
Duodenum	8 (8.2%)
Ampulla of Vater	30 (30.6%)
Pathologic diagnosis	
Malignancy	91
Borderline malignancy	5
Benign	2
Type of operation	
PPPD	86 (87.8%)
Whipple	12 (12.2%)
Postoperative hospital stay (days)	25.5±7.5
T staging	
T1	37
T2	25
T3	23
T4	13
N staging	
N0	51
N1	47
Postoperative complication	40 (40.8%)
Pancreatic fistula	17
Wound complication	6
Intraabdominal fluid collection	4
Bleeding complication	4
Delayed gastric emptying	4
Others (ileus, pneumonia, pleural effusion, and voiding difficulty)	5

BMI, body mass index; PPPD, pylorus-preserving pancreatoduodenectomy

tions developed in 40 patients (40.8%), including pancreatic fistula (n=19), delayed gastric emptying (n=4), intraabdominal fluid collection (n=5), bleeding (n=4), and wound complication (n=6) (Table 2). The mean length of the postoperative hospital stay was 25.5 days (range: 15-36 days).

Risk factors for postoperative DM

In the follow-up of one year after the operation, postoperative new-onset DM (NODM) had developed in 17 (17.4%) of the 98 patients. Table 2 shows the comparative analysis of the risk factors for postoperative DM after PD two. Age, sex, BMI, type of operation, tumor site, patho-

logic diagnosis, T stage, N stage, amount of intraoperative blood loss, operation time, postoperative complication, postoperative hospital stay, postoperative pancreatic-duct size, underlying pancreatitis, history of adjuvant chemoradiation therapy, and recurrence were not significantly different between the NODM group and no-NODM group. Pancreatic atrophy was found to be the only significant risk factor for the development of postoperative DM after PD, with 10 patients (58.8%) in the NODM group vs. 18 patients (22.2%) in no-NODM group (p=0.004).

DISCUSSION

There have been contradictory reports on the development of pancreatogenic DM after PD.[1,3,5,7-10] The degree of glucose metabolism impairment after pancreatectomy is related to the extent of pancreatic parenchyma resection, underlying pancreatic disease, and duration of follow-up.[2,5,11] Assuming that PD involves the removal of similar volume (approximately 40-50%) of pancreatic parenchyma, the development of DM after PD can be mainly determined by the latter two factors.[1,4] However, most studies on this subject had variable follow-up durations after the operation or included patients with different endocrine function of the pancreatic parenchyma prior to surgery. Some previous studies with a short-term follow-up suggested that DM was unlikely to develop after PD, while long-term follow-up studies reported the incidence of postoperative DM ranging from 20-50%.[1] In addition, many studies included patients with underlying chronic pancreatitis or preoperative DM, making it difficult to determine the effect of PD on the glucose metabolism of the remaining pancreatic parenchyma.[6,12-18]

To control the possible bias, this study was designed with patients who were non-diabetic preoperatively, with the evaluation of their glucose metabolism function at the same time-interval after operation. The results show that NODM occurred in 17% of the non-diabetic patients who underwent PD during the follow-up of one year after the operation. This is consistent with the results of the previous studies that reported the incidence rate of 9-20% of pancreatogenic diabetes after PD.[3,19] This finding indicates that the impairment of pancreatic endocrine function may develop after some degree of resection, unlike the exocrine function that may not be hampered even after the

Table 2. Comparison of clinicopathologic factors between new-onset diabetes mellitus (NODM) group and no-NODM group

	NODM group	No NODM group	p-value
Age, mean (years)	67±14.5	65±15.2	0.314
Sex			0.391
Male	12	49	
Female	5	32	
Intraoperative blood loss (ml)	782±322	815±575	0.902
Length of stay (days)	28.5±3.2	21.9±4.1	0.234
Operation time (minutes)	420±82	436±78	0.532
Operation name			0.648
PPPD	14	72	
Whipple	3	9	
Cancer site			
Pancreas	7	23	0.623
Common bile duct	7	23	0.395
Duodenum	0	8	0.999
Ampulla of Vater	3	27	0.188
Transfusion			0.969
Yes	12	61	
No	5	20	
BMI			0.301
<25	14	61	
≥25	3	20	
Postoperative complication			0.770
Yes	6	34	
No	11	47	
Postoperative pancreatic duct dilatation			0.085
Yes	11	45	
No	6	36	
Pancreatitis			0.824
Yes	4	25	
No	13	56	
Pancreatic atrophy			0.004
Yes	10	18	
No	7	63	
Adjuvant therapy			0.402
Yes	4	25	
No	13	56	
T staging			0.457
T1/T2	12	50	
T3/T4	5	31	
N staging			0.332
N0	9	42	
N1	8	39	
Recurrence			0.245
Yes	5	32	
No	12	49	

BMI, body mass index; PPPD, pylorus-preserving pancreatoduodenectomy

resection of a considerable portion of the pancreas. Moreover, this incidence is expected to increase throughout the remaining life of the patients, because glucose tolerance function naturally decreases with age, and the process of pancreatic atrophy may continue over time.[9] Therefore, the endocrine function of patients with a long life expectancy after PD should be carefully monitored in order to early detect diabetes and to avoid the long-term complications caused by inadequate glycemic control.

Another important finding of this study is that among various clinicopathologic factors, postoperative pancreatic atrophy was the only risk factor for pancreatogenic DM after PD. The pancreatic atrophy after pancreatic head resection resulted in the loss of endocrine function of pancreas.[3,9] This finding is contradictory to the previous study of You et al.[3] which showed that the volume of the remnant pancreas was not associated with pancreatogenic diabetes. These inconsistent results can be explained by the differences in the study design. The study of You et al.[3] included 55 patients who had survived, after a median follow-up duration of no less than 55 months, among the 168 patients who had undergone PD; and the results of pancreatic endocrine function of the remaining patients were not presented. In comparison, this study evaluated the pancreatic endocrine function of all patients who had the follow-up period of more than one year. As such, the selection bias cannot be excluded in the previous study of You et al. Nonetheless, considering the small number of patients in this study, further prospective studies with a larger number of patients are needed to clarify the effects of pancreatic atrophy on pancreatogenic DM after PD.

Atrophy of the remnant distal pancreas after PD commonly occurs, and there have been several animal and human studies in the attempts of preventing the pancreas atrophy.[9] Although the mechanism is not well elucidated, a suggested mechanism involves the loss of gastrointestinal hormones with the trophic effect on the pancreas, such as cholecystokinin and gastrin, resulting from the resection of the duodenum and the distal stomach. Jang et al. reported that induced hypergastrinemia can prevent pancreatic atrophy after PPPD, likely via a mechanism of the regenerative activity of the pancreas stimulated by gastrin.[9] Additionally, a recent animal study showed that control of serum glucose levels play an important role in preventing pancreatic atrophy.[10] Based on the result of these studies, the efforts to prevent pancreatic atrophy should be continued and clinically applied to de-

crease the incidence of pancreatogenic DM after PD.

In conclusion, this study suggests that pancreatogenic DM is not an uncommon complication after PD, and that postoperative atrophy of the remaining pancreas significantly increases the risks of this complication. As such, patients who undergo PD need to be carefully followed up, in order to monitor the glucose metabolism function in avoiding the DM related long-term complications and improving their quality of life. In addition, various efforts to prevent the atrophy of the remaining pancreas are required to decrease this complication.

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