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ORIGINAL ARTICLE

Perioperative C-peptide index is associated with the status of diabetes management after pancreatectomy

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ABSTRACT

Aims/Introduction: This study aimed to identify the clinical factors affecting postoperative residual pancreatic β-cell function, as assessed by the C-peptide index (CPI), and to investigate the association between perioperative CPI and the status of diabetes management after pancreatectomy.

Materials and Methods: The associations between perioperative CPI and clinical background, including surgical procedures of pancreatectomy, were analyzed in 47 patients who underwent pancreatectomy, and were assessed for pre-and postoperative CPI. The association between perioperative CPI and glycemic control after pancreatectomy was investigated.

Results: The low postoperative CPI group (CPI <0.7) had longer duration of diabetes (17.5 ± 14.5 vs 5.5 ± 11.0 years, *P* = 0.004), a higher percentage of sulfonylurea users (41.7 vs 8.7%, *P* = 0.003) and a greater number of drug categories used for diabetes treatment (1.9 ± 1.1 vs 0.8 ± 0.8, *P* <0.001) than did the high postoperative CPI group. Postoperative CPI was higher (1.4 ± 1.2 vs 0.7 ± 0.6, *P* = 0.039) in patients with low glycosylated hemoglobin (<7.0%) at 6 months after pancreatectomy; preoperative (2.0 ± 1.5 vs 0.7 ± 0.5, *P* = 0.012) and postoperative CPI (2.5 ± 1.4 vs 1.4 ± 1.1, *P* = 0.020) were higher in non-insulin users than in insulin users at 6 months after surgery.

Conclusions: The duration of diabetes and preoperative diabetes treatment were associated with residual pancreatic β-cell function after pancreatectomy. Furthermore, perioperative β-cell function as assessed by CPI was associated with diabetes management status after pancreatectomy.

INTRODUCTION

Diabetes as a result of exocrine pancreatic disease occurs in >8% of the general diabetes patient population[1]. The morbidity and mortality of pancreatic cancer are increasing over time, and over the past decade, the number of deaths due to pancreatic cancer in Japan has increased by 1.4-fold[2]. As patients with pancreatic cancer have reduced endogenous insulin secretion, glucose intolerance in these patients is often induced[3]. In addition, when glucagon secretion is decreased, treating diabetes might become difficult, owing to unstable blood glucose fluctuations[4]. With an increase in the number of patients with pancreatic cancer, the opportunity for diabetologists to treat glucose intolerance or diabetes after pancreatectomy is also increasing, and considerable attention should be paid to patients not only after pancreatectomy, but also before the operation.

The C-peptide index (CPI) represents endogenous insulin secretion and shows pancreatic β-cell function in type 2 diabetes[5,6]. In terms of the association between endogenous insulin secretion and the status of diabetes management in type 2

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diabetes patients, Iwata *et al.*[7] reported that insulin therapy was required with a specificity of >80% if CPI was <1.0. Although previous studies have identified preoperative glycosylated hemoglobin (HbA1c), body mass index (BMI), age and the procedure of pancreatic resection as risk factors for the development of diabetes after pancreatic resection[8–10], the association between perioperative residual β-cell function evaluated using CPI and the status of diabetes management, including glycemic control and requirement for insulin therapy, after pancreatectomy has not yet been investigated.

The present study aimed to explore the clinical background, including the history of diabetes and the surgical procedures of pancreatectomy, which affected perioperative residual β-cell function, as assessed by the CPI. Furthermore, we investigated the association between perioperative CPI and diabetes management status, including glycemic control and the requirement for insulin therapy.

MATERIALS AND METHODS

Study design and ethical approval

The present study used a retrospective, observational, single-center design. All study procedures were carried out in accordance with the 1964 Helsinki Declaration and its later amendments, and the 'Ethical Guidelines for Medical and Health Research Involving Human Subjects' published by the Ministry of Health, Labor and Welfare of Japan. The ethics committee of the Toyama University Hospital approved the study protocol (approval number R2020207) and waived the requirement for informed consent, owing to the retrospective nature of the study. The document describing the study information was disclosed on the website of the Toyama University Hospital, and the study participants had the opportunity to object to the use of their data for scientific research after reading the document.

Study participants

Patients who underwent pancreatectomy operation, including pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy and partial pancreatectomy, at the Toyama University Hospital from December 2015 to April 2021 were enrolled in the present study. The inclusion criteria were as follows: (i) data on fasting plasma glucose and serum C-peptide immunoreactivity (CPR) levels measured before and after pancreatectomy; and (ii) receipt of diabetes treatment at the Department of Diabetology, Metabolism and Endocrinology of the Toyama University Hospital. Patients who objected to the use of their data in the present study were excluded.

Data collection

Data used in the present study were retrospectively collected from the electronic medical records of the study participants. Changes in endogenous insulin secretion were evaluated based on fasting plasma glucose and fasting serum CPR levels collected before and after pancreatectomy. Serum CPR levels were measured using the chemiluminescent enzyme immunoassay. CPI was calculated as follows: CPR (ng/mL)/plasma glucose (mg/dL) × 100. Preoperative clinical parameters, including age, BMI, history, duration and treatment of diabetes, surgical procedures of pancreatectomy, and HbA1c values, were also collected to investigate the associations between postoperative pancreatic β-cell function and these parameters. Furthermore, we examined the HbA1c values and the requirement for insulin therapy of the participants at 1 month and 6 months after pancreatectomy to investigate the associations between these postoperative factors related to glycemic control, and preoperative and postoperative pancreatic β-cell function, surgical procedures or other metabolic factors.

Sample size calculation

The sample size was calculated based on the CPI values. We found that a sample size of 45 patients would be sufficient to detect a 0.8% difference in postoperative CPI between the groups with low and high HbA1c at 6 months after pancreatectomy, assuming a standard deviation of 0.95, $a = 0.05$ and power of 80%. These calculations were carried out using the CRAB SWOG Statistical Tools Calculator (Cancer Research and Biostatistics, Seattle, WA, USA; https://stattools.crab.org).

Statistical analysis

To compare metabolic parameters and surgical procedures, postoperative CPI and HbA1c levels were divided into two groups using the median of each value. Student's *t*-test or the Mann–Whitney *U*-test was used for bivariate analysis, depending on the distribution of the variables. Depending on the number of examples of categorical variables, Fisher's exact test, the χ^2-test or the Kruskal–Wallis test was used for comparison. Correlations between the number of categories of drugs used to treat diabetes and CPI were analyzed using Spearman's correlation coefficient. A multivariate analysis to evaluate the relationship between the number of drug categories used for diabetes treatment and CPI was also carried out by adjusting for demographic factors. Statistical significance was set at $P < 0.05$. All statistical analyses were carried out in Python version 3.8.8 (Python Software Foundation, Beaverton, OR, USA)[11] and TableOne (Python Software Foundation)[12].

RESULTS

Clinical characteristics of the study participants

As shown in Table 1, 47 patients who underwent pancreatectomy participated in the present study. The mean age of the patients was 71.3 ± 10.8 years, and 33 patients (70.2%) were men. A total of 33 (70.2%), nine (19.1%), three (6.4%) and two (4.2%) patients underwent pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy and partial pancreatectomy, respectively. There were 37 (78.7%) patients with diabetes, and 11 patients (23.4%) received insulin therapy before pancreatic surgery. The mean preoperative HbA1c value was 7.7 ± 1.2%, and that of the fasting CPI was 1.6 ± 1.1. Preoperative and postoperative serum CPR levels were measured at 22.0

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Table 1 | Clinical characteristics of the study participants

Characteristics	Overall (*n* = 47)	With preoperative diabetes (*n* = 37)
Age, years (mean ± SD)	71.3 ± 10.8	73.2 ± 8.0
Male, *n* (%)	33 (70.2)	28 (75.7)
BMI, kg/m^2 (mean ± SD)	23.4 ± 5.1	22.8 ± 4.8
Duration of diabetes, years (mean ± SD)	11.3 ± 14.0	14.8 ± 14.4
Surgical procedure, *n* (%)		
Pancreaticoduodenectomy	33 (70.2)	28 (75.7)
Distal pancreatectomy	9 (19.1)	6 (16.2)
Total pancreatectomy	3 (6.4)	2 (5.4)
Partial pancreatectomy	2 (4.2)	1 (2.7)
Preoperative data		
Insulin user, *n* (%)	11 (23.4)	11 (29.7)
Fasting plasma glucose, mg/dL (mean ± SD)	160.6 ± 60.0	168.7 ± 59.5
Fasting C-peptide, ng/mL (mean ± SD)	2.3 ± 1.6	2.2 ± 1.7
Fasting CPI (mean ± SD)	1.6 ± 1.1	1.3 ± 1.0
HbA1c, % (mean ± SD)	7.7 ± 1.2	8.0 ± 1.0

Total *n* = 47. BMI, body mass index; CPI, C-peptide index; HbA1c, glycosylated hemoglobin; SD, standard deviation.

(12.5–68.0; median [interquartile]) days before pancreatectomy and 14.0 (9.0–22.5) days after pancreatectomy, respectively. At the time of preoperative CPR measurement, 11 (23.4%), 12 (25.5%), 24 (51.1%), 2 (4.3%) and 0 (0%) patients used glucagon-like peptide-1 receptor agonists, insulin, sulfonylureas, dipeptidyl peptidase-4 inhibitors and sodium–glucose transporter 2 inhibitors, respectively. At the time of postoperative CPR measurement, 39 (83.0%), one (2.1%), six (12.8%), one (2.1%) and one (2.1%) patients used glucagon-like peptide-1 receptor agonists, insulin, sulfonylureas, dipeptidyl peptidase-4 inhibitors and sodium–glucose transporter 2 inhibitors, respectively. Among patients with preoperative diabetes (*n* = 37), the mean age was 73.2 ± 8.0 years, and 28 (75.7%) were men. The mean preoperative HbA1c value was 8.0 ± 1.0%, and that of the fasting CPI was 1.3 ± 1.0.

Clinical factors contributing to residual pancreatic β-cell function after pancreatectomy

We compared the metabolic parameters and surgical procedures in the groups with low (CPI <0.7) and high postoperative CPI (CPI ≥0.7; Table 2). In the analyses involving all participants, the low postoperative CPI group had a higher percentage of diabetes patients (91.7 vs 65.2%, $P = 0.036$) and a longer duration of diabetes (17.5 ± 14.5 vs 5.5 ± 11.0 years, $P = 0.004$) than the high postoperative CPI group. Preoperative CPI was reasonably lower in patients with low postoperative CPI than in those with high postoperative CPI (1.1 ± 0.6 vs 2.0 ± 1.3, $P = 0.005$). Among patients with preoperative diabetes, preoperative CPI was lower in those with low postoperative CPI than in those with high postoperative CPI (1.0 ± 0.5 vs 1.8 ± 1.3, $P = 0.046$). Of note, the low postoperative CPI group had a significantly higher number of drug categories used for diabetes treatment (2.0 ± 1.0 vs 1.2 ± 0.7, $P = 0.003$) before pancreatectomy than did the high postoperative CPI group.

Among all participants, Spearman's rank correlation coefficient showed that the number of drug categories used for diabetes treatment was inversely correlated with both preoperative ($r = -0.42$, $P < 0.005$; Figure 1a) and postoperative CPI values ($r = -0.45$, $P < 0.005$; Figure 1b). Among patients with preoperative diabetes, Spearman's rank correlation coefficient showed that the number of drug categories used for diabetes treatment was not correlated preoperatively ($r = -0.22$, $P = 0.20$; Figure 1c). Furthermore, Spearman's rank correlation coefficient showed that the number of drug categories used for diabetes treatment was inversely correlated postoperatively ($r = -0.36$, $P = 0.028$; Figure 1d). We also carried out a multivariate analysis using the least squares method; when adjusted by age and BMI, the number of preoperative treatments was not correlated with preoperative CPI (coefficient –2.04, $P = 0.216$), but was correlated with postoperative CPI (coefficient –0.286, $P = 0.0216$; Table S1). In the comparison of clinical factors among the groups with several drug categories used for diabetes treatment in patients with preoperative diabetes by using the analysis of variance, preoperative HbA1c ($P = 0.143$) and CPI ($P = 0.566$) were not significantly different among the groups (Table S2). The number of drug categories was associated with diabetes duration ($P = 0.042$), use of sulfonylureas ($P = 0.006$) and use of sodium–glucose transporter 2 inhibitors ($P < 0.001$).

The frequency of each surgical procedure was not significantly different between the groups (Table 2). In addition, preoperative and postoperative CPI values were not significantly different between patients who underwent pancreaticoduodenectomy and those who underwent distal pancreatectomy (Figure S1a,b). However, preoperative CPI tended to be higher in patients who underwent distal pancreatectomy than in those

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Table 2 | Characteristics of patients stratified by low and high postoperative C-peptide index before pancreatectomy

Characteristics	Overall (*n* = 47)			With preoperative diabetes (*n* = 37)		
	Low postoperative CPI (<0.7) (*n* = 24)	High postoperative CPI (≥0.7) (*n* = 23)	*P*	Low postoperative CPI (<0.7) (*n* = 22)	High postoperative CPI (≥0.7) (*n* = 15)	*P*
Age, years (mean ± SD)	73.5 ± 7.6	69.0 ± 13.2	0.172	74.5 ± 6.9	71.4 ± 9.4	0.142
Male, *n* (%)	20 (83.3)	13 (56.5)	0.091	18 (81.8)	10 (66.7)	0.438
BMI, kg/m^2 (mean ± SD)	22.2 ± 3.9	24.6 ± 6.0	0.119	21.6 ± 2.9	24.7 ± 6.3	0.029
Duration of diabetes, years (mean ± SD)	17.5 ± 14.5	5.5 ± 11.0	0.004	19.3 ± 14.0	8.6 ± 12.8	0.011
Surgical procedure, *n* (%)						
Pancreaticoduodenectomy	18 (75.0)	15 (65.2)	0.181	17 (77.3)	11 (73.3)	0.381
Distal pancreatectomy	3 (12.5)	6 (26.1)		3 (13.6)	3 (20.0)	
Total pancreatectomy	3 (12.5)	0 (0)		2(9.1)	0 (0)	
Partial pancreatectomy	0 (0)	2 (8.6)		0 (0)	1 (6.7)	
Preoperative data						
Insulin user, *n* (%)	11 (23.4)	7 (29.2)	0.543	7 (31.8)	4 (26.7)	1.00
Sulfonylurea user, *n* (%)	10 (41.7)	2 (8.7)	0.024	10 (45.5)	2 (13.3)	0.073
DPP-4 inhibitor user, *n* (%)	16 (66.7)	8 (34.8)	0.058	16 (72.7)	8 (53.3)	0.388
GLP-1 receptor agonist user, *n* (%)	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND
SGLT-2 inhibitor user, *n* (%)	2 (8.3)	0 (0)	0.489	2 (9.1)	0 (0)	0.505
Drug categories† used for diabetes treatment (mean ± SD)	1.9 ± 1.1	0.8 ± 0.8	<0.001	2.0 ± 1.0	1.2 ± 0.7	0.003
Fasting plasma glucose, mg/dL (mean ± SD)	170.6 ± 62.7	150.2 ± 56.5	0.113	175.2 ± 63.4	159.2 ± 53.9	0.197
Fasting C-peptide, ng/mL (mean ± SD)	1.8 ± 0.8	2.8 ± 1.9	0.026	1.7 ± 0.8	2.9 ± 2.3	0.108
Fasting CPI (mean ± SD)	1.1 ± 0.6	2.0 ± 1.3	0.008	1.0 ± 0.5	1.8 ± 1.3	0.046
HbA1c, % (mean ± SD)	7.9 ± 1.0	7.4 ± 1.4	0.088	8.0 ± 0.9	7.9 ± 1.3	0.420

†Drug categories included sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, glinide, biguanide, thiazolidinedione, α-glucosidase inhibitor, sodium–glucose transporter 2 (SGLT-2) inhibitor and glucagon-like peptide-1 (GLP-1) receptor agonist. BMI, body mass index; CPI, C-peptide index; HbA1c, glycosylated hemoglobin; ND, not determined; SD, standard deviation.

who underwent pancreaticoduodenectomy. Similarly, in the 34 patients who were preoperatively diagnosed with diabetes, preoperative and postoperative CPI values were not significantly different between those who underwent pancreaticoduodenectomy and those who underwent distal pancreatectomy (Figure S1c,d).

Taken together, the history and duration of diabetes, preoperative CPI and the number of drug categories used for diabetes treatment might affect residual β-cell function after pancreatectomy.

Association with glycemic control 6 months after pancreatectomy

To identify the clinical factors contributing to glycemic control after pancreatectomy, we compared metabolic parameters and surgical procedures between the groups with low (HbA1c <7.0) and high HbA1c (HbA1c ≥7.0) levels 1 month and 6 months after surgery (Table 3). Interestingly, whereas preoperative CPI was significantly higher in the group with low HbA1c at 1 month after pancreatectomy (2.0 ± 1.3 vs 1.1 ± 0.6, *P* = 0.019), postoperative CPI was significantly higher in the group with low HbA1c at 6 months after the surgery (1.4 ± 1.2 vs 0.7 ± 0.6, *P* = 0.039). Although the number of drug categories used for diabetes treatment before pancreatectomy was significantly higher in patients with high HbA1c at 1 month after surgery (1.8 ± 1.1 vs 0.7 ± 0.8, *P* = 0.003), no significant differences were observed at 6 months postoperatively. Surgical procedures were not associated with HbA1c levels at either 1 month or 6 months after pancreatectomy. Among patients with preoperative diabetes, preoperative CPI was significantly higher in the group with low HbA1c at 1 month after pancreatectomy (1.8 ± 1.3 vs 1.1 ± 0.5, *P* = 0.026), whereas postoperative CPI tended to be higher in the group with low HbA1c at 6 months after the surgery (1.2 ± 1.2 vs 0.6 ± 0.4, *P* = 0.06). The number of drug categories used for diabetes treatment before pancreatectomy was significantly higher in patients with high HbA1c at 1 month after surgery (2.1 ± 0.9 vs 1.1 ± 0.8, *P* = 0.01), and tended to

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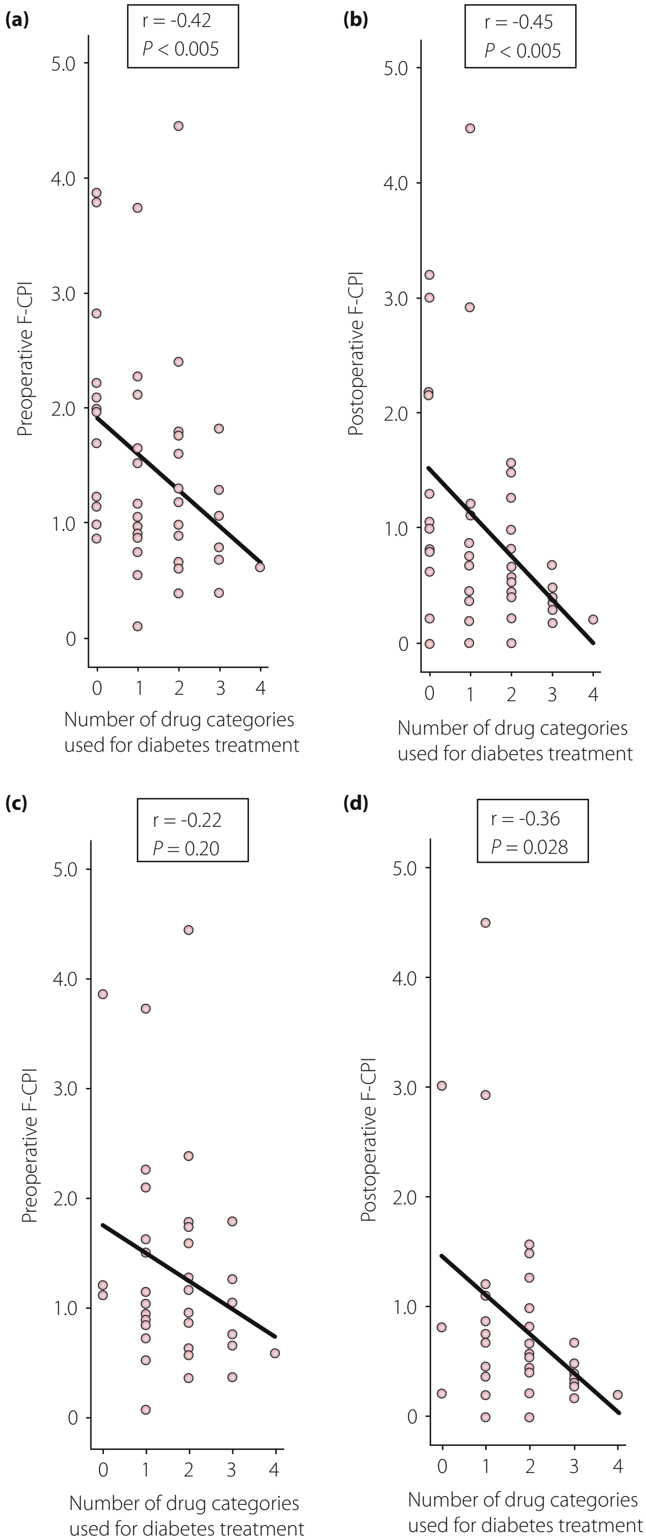

Figure 1 | Correlations between the number of drug categories used for diabetes treatment and (a) preoperative or (b) postoperative C-peptide index. The correlation between the number of drug categories used for diabetes treatment and (c) preoperative or (d) postoperative C-peptide index in patients with preoperative diabetes. Spearman's rank correlation coefficients were used for the analyses. F-CPI, fasting C-peptide index.

be higher at 6 months after surgery (2.0 ± 1.2 vs 1.4 ± 0.7, $P = 0.06$). These data show that postoperative CPI might predict glycemic control in the chronic phase after pancreatectomy.

Association with the requirement for insulin therapy after pancreatectomy

In all participants, both the preoperative (2.5 ± 1.4 vs 1.4 ± 1.1, $P = 0.020$) and postoperative CPI (2.0 ± 1.5 vs 0.7 ± 0.5, $P = 0.012$) levels were significantly higher in patients who did not require insulin therapy (non-insulin users) than in those who required insulin therapy (insulin users) at 6 months after surgery (Table 4). The numbers of drug categories used for diabetes treatment before pancreatectomy were significantly higher in insulin users at 1 month after the surgery (1.6 ± 1.1 vs 0.6 ± 0.7, $P = 0.002$). Among patients with preoperative diabetes, both the preoperative (2.3 ± 1.3 vs 1.2 ± 1.0, $P = 0.058$) and postoperative (1.7 ± 1.7 vs 0.6 ± 0.4, $P = 0.098$) CPI levels tended to be higher in those who did not require insulin therapy (non-insulin users) than in those who required insulin therapy (insulin users) at 6 months after surgery. The number of drug categories used for diabetes treatment before pancreatectomy was significantly higher in insulin users at 1 month after the surgery (1.9 ± 1.0 vs 1.0 ± 0.6, $P = 0.008$). These data show that both preoperative and postoperative CPI might predict the requirement for insulin therapy after pancreatectomy.

DISCUSSION

In the present study, we identified the clinical parameters contributing to residual pancreatic β-cell function in patients who underwent pancreatectomy. Furthermore, we showed the associations between preoperative or postoperative CPI, a useful index to evaluate β-cell function in patients with type 2 diabetes[7], and glycemic control 6 months after pancreatectomy. This is the first study to investigate the usefulness of CPI in predicting glycemic control after pancreatectomy.

We found that patients with a lower postoperative CPI had a higher prevalence and a longer duration of preoperative diabetes. Okuno *et al.*[13] similarly reported that a longer type 2 diabetes duration is associated with a lower CPI. In addition, longer disease duration was associated with higher HbA1c levels in type 2 diabetes patients[14] and in those who underwent pancreatectomy[15]. According to these findings, the duration of preoperative diabetes might affect residual β-cell function after pancreatectomy.

Notably, patients with a lower postoperative CPI had a higher rate of sulfonylurea use before pancreatectomy. Arai *et al.*[16] found that the prevalence of sulfonylurea pretreatment is significantly lower in type 2 diabetes patients who were able to stop insulin therapy after transient insulin therapy than in those who were not able to stop insulin administration. Additionally, a longer duration of sulfonylurea treatment was associated with a decline in endogenous insulin secretion[17]. The mechanism underlying insulin secretion reduction after long-

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Table 3 | Characteristics of patients stratified by low and high glycosylated hemoglobin at 1 month and 6 months after pancreatectomy

Characteristics	Overall						With preoperative diabetes					
	1 month			6 months			1 month			6 months		
	Low HbA1c (<7.0%) (*n* = 17)	High HbA1c (≥7.0%) (*n* = 16)	*P*	Low HbA1c (<7.0%) (*n* = 18)	High HbA1c (≥7.0%) (*n* = 15)	*P*	Low HbA1c (<7.0%) (*n* = 11)	High HbA1c (≥7.0%) (*n* = 2)	*P*	Low HbA1c (<7.0%) (*n* = 4)	High HbA1c (≥7.0%) (*n* = 5)	*P*
Age, years (mean ± SD)	72.8 ± 8.6	72.1 ± 7.0	0.816	70.5 ± 8.8	67.2 ± 14.4	0.446	74.9 ± 6.3	71.6 ± 6.9	0.119	70.5 ± 8.2	72.3 ± 8.3	0.319
Male, *n* (%)	10 (58.8)	13 (81.2)	0.259	10 (55.6)	12 (80.0)	0.266	7 (63.6)	12 (85.7)	0.350	9 (64.3)	9 (90.0)	0.341
BMI, kg/m^2 (mean ± SD)	22.2 ± 2.5	22.7 ± 4.1	0.701	23.9 ± 6.4	24.4 ± 5.4	0.827	22.5 ± 2.7	21.8 ± 2.6	0.156	24.7 ± 7.1	21.8 ± 2.5	0.153
Duration of diabetes, years (mean ± SD)	4.0 ± 5.5	16.5 ± 15.7	0.007	8.5 ± 9.2	9.1 ± 15.2	0.899	6.4 ± 5.8	18.9 ± 15.4	0.013	11.5 ± 8.9	14.1 ± 17.1	0.395
Surgical procedure, *n* (%)												
Pancreaticoduodenectomy	12 (70.6)	13 (81.2)	0.360	13 (72.2)	10 (66.7)	0.590	8 (72.7)	12 (85.7)	0.482	10 (71.4)	9 (90.0)	0.622
Distal pancreatectomy	2 (11.8)	3 (18.8)		2 (11.1)	4 (26.7)		2 (18.2)	2 (14.3)		2 (14.3)	1 (10.0)	
Total pancreatectomy	2 (11.8)	0 (0)		1 (5.6)	1 (6.7)		1 (9.1)	0 (0)		1 (7.1)	0 (0)	
Partial pancreatectomy	1 (5.9)	0 (0)		1 (5.6)	0 (0)		0 (0)	0 (0)		1 (7.1)	0 (0)	
Preoperative data												
Insulin user, *n* (%)	2 (11.8)	4 (25.0)	0.398	4 (22.2)	3 (20.0)	1.000	2 (18.2)	4 (28.6)	0.661	4 (28.6)	3 (30.0)	1.000
Sulfonylurea user, *n* (%)	4 (23.5)	4 (25.0)	1.000	4 (22.2)	5 (33.3)	0.697	4 (36.4)	4 (28.6)	1.000	4 (28.6)	5 (50.0)	0.403
DPP-4 inhibitor user, *n* (%)	4 (23.5)	12 (75.0)	0.009	9 (50.0)	5 (33.3)	0.541	4 (36.4)	12 (85.7)	0.017	9 (64.3)	5 (50.0)	0.678
GLP-1 receptor agonist user, *n* (%)	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND
SGLT-2 inhibitor user, *n* (%)	0 (0)	2 (12.5)	0.227	0 (0)	1 (6.7)	0.455	0 (0)	2 (14.3)	0.487	0 (0)	1 (10.0)	0.417
Drug categories† used for diabetes treatment (mean ± SD)	0.7 ± 0.8	1.8 ± 1.1	0.003	1.1 ± 0.9	1.3 ± 1.3	0.346	1.1 ± 0.8	2.1 ± 0.9	0.010	1.4 ± 0.7	2.0 ± 1.2	0.060
Fasting plasma glucose, mg/dL (mean ± SD)	150.6 ± 59.7	170.5 ± 69.1	0170	143.6 ± 50.5	172.3 ± 77.9	0.160	158.5 ± 55.6	174.4 ± 73.3	0.292	141.0 ± 41.4	198.7 ± 82.5	0.017
Fasting C-peptide, ng/mL (mean ± SD)	3.0 ± 2.1	1.7 ± 0.7	0.023	2.7 ± 2.2	2.2 ± 0.9	0.493	3.1 ± 2.5	1.7 ± 0.6	0.059	2.7 ± 2.5	2.0 ± 0.9	0.500
Fasting CPI (mean ± SD)	2.0 ± 1.3	1.1 ± 0.6	0.009	1.9 ± 1.5	1.5 ± 0.9	0.313	1.8 ± 1.3	1.1 ± 0.5	0.026	1.8 ± 1.4	1.1 ± 0.5	0.232
Postoperative data‡												
Fasting plasma glucose, mg/dL (mean ± SD)	140.9 ± 53.9	143.1 ± 36.2	0.152	150.4 ± 53.6	135.2 ± 27.8	0.486	151.6 ± 62.6	144.4 ± 38.6	0.351	161.6 ± 55.1	128.1 ± 30.5	0.146
Fasting C-peptide, ng/mL (mean ± SD)	1.5 ± 1.4	1.1 ± 1.2	0.225	1.9 ± 1.5	1.0 ± 0.9	0.024	1.3 ± 1.3	1.1 ± 1.2	0.371	1.7 ± 1.5	0.7 ± 0.4	0.025
Fasting CPI (mean ± SD)	1.2 ± 1.1	0.7 ± 0.7	0.128	1.4 ± 1.2	0.7 ± 0.6	0.038	0.9 ± 0.8	0.7 ± 0.7	0.283	1.2 ± 1.2	0.6 ± 0.4	0.060

†Drug categories included sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, glinide, biguanide, thiazolidinedione, α-glucosidase inhibitor, sodium–glucose transporter 2 (SGLT-2 inhibitor) and glucagon-like peptide-1 (GLP-1) receptor agonist. ‡Data collected within 4 weeks after pancreatectomy. BMI, body mass index; CPI, C-peptide index; HbA1c, glycosylated hemoglobin; SD, standard deviation.

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Table 4 | Characteristics of insulin users and non-insulin users at 1 month and 6 months after pancreatectomy

Characteristics	Overall						With preoperative diabetes					
	1 month			6 months			1 month			6 months		
	Insulin users (*n* = 32)	Non-insulin users (*n* = 12)	*P*	Insulin users (*n* = 23)	Non-insulin users (*n* = 9)	*P*	Insulin users (*n* = 28)	Non-insulin users (*n* = 7)	*P*	Insulin users (*n* = 17)	Non-insulin users (*n* = 6)	*P*
Age, years (mean ± SD)	73.9 ± 7.5	65.5 ± 14.0	0.070	69.4 ± 12.2	68.3 ± 11.4	0.820	74.1 ± 6.8	68.1 ± 10.6	0.090	72.4 ± 6.8	69.0 ± 12.2	0.472
Male, *n* (%)	24 (75.0)	7 (58.3)	0.295	16 (69.6)	5 (55.6)	0.681	22 (78.6)	5 (71.4)	0.648	13 (76.5)	4 (66.7)	0.632
BMI, kg/m^2 (mean ± SD)	22.8 ± 3.7	24.1 ± 7.5	0.565	24.0 ± 4.8	24.9 ± 8.5	0.763	22.3 ± 3.1	24.9 ± 9.2	0.475	22.4 ± 3.2	27.1 ± 9.8	0.210
Duration of diabetes, years (mean ± SD)	15.6 ± 15.2	1.5 ± 2.6	<0.001	10.0 ± 13.4	7.2 ± 10.4	0.551	18.1 ± 14.9	2.8 ± 3.1	<0.001	13.7 ± 14.1	10.8 ± 11.3	0.632
Surgical procedure, *n* (%)												
Pancreaticoduodenectomy	24 (75.0)	9 (75.0)	0.154	15 (65.2)	7 (77.8)	0.078	22 (78.6)	6 (85.7)	0.137	13 (76.5)	5 (83.3)	0.234
Distal pancreatectomy	6 (18.8)	1 (8.3)		6 (26.1)	0 (0)		5 (17.9)	0 (0)		3 (17.6)	0 (0)	
Total pancreatectomy	2 (6.2)	0 (0)		2 (8.7)	0 (0)		1 (3.6)	0 (0)		1 (5.9)	0 (0)	
Partial pancreatectomy	0 (0)	2 (16.6)		0 (0)	2 (22.2)		0 (0)	1 (14.3)		0 (0)	1 (33.3)	
Preoperative data												
Insulin user, *n* (%)	8 (25.0)	2 (16.7)	0.702	6 (26.1)	1 (11.1)	0.640	8 (28.6)	2 (28.6)	1.000	6 (35.3)	1 (16.7)	0.621
Sulfonylurea user, *n* (%)	11 (34.4)	1 (8.3)	0.132	6 (26.1)	1 (11.1)	0.640	11 (39.3)	1 (14.3)	0.38	6 (35.3)	1 (16.7)	0.621
DPP-4 inhibitor user *n* (%)	19 (59.4)	3 (25.0)	0.091	10 (43.5)	4 (44.4)	1.000	19 (67.9)	3 (42.9)	0.383	10 (58.8)	4 (66.7)	1.000
GLP-1 receptor agonist user, *n* (%)	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND	0 (0)	0 (0)	ND
SGLT-2 inhibitor user, *n* (%)	2 (6.25)	0 (0)	1.000	2 (8.70)	0 (0)	1.000	2 (7.14)	0 (0)	1.000	2 (8.7)	0 (0)	1.000
Drug categories[†] used for diabetes treatment (mean ± SD)	1.6 ± 1.1	0.6 ± 0.7	0.002	1.3 ± 1.1	0.8 ± 1.0	0.110	1.9 ± 1.0	1.0 ± 0.6	0.008	1.8 ± 1.0	1.2 ± 1.0	0.232
Fasting plasma glucose, mg/dL (mean ± SD)	167.4 ± 61.4	146.5 ± 61.8	0.118	157.3 ± 68.5	166.9 ± 63.5	0.245	170.6 ± 64.2	164.1 ± 50.0	0.443	166.6 ± 75.5	180.0 ± 44.9	0.163
Fasting C-peptide, ng/mL (mean ± SD)	2.0 ± 1.2	3.4 ± 2.1	0.004	2.0 ± 1.3	3.8 ± 2.2	0.005	2.0 ± 1.2	3.5 ± 2.7	0.058	1.9 ± 1.4	4.0 ± 2.6	0.014
Fasting CPI (mean ± SD)	1.2 ± 0.8	2.5 ± 1.4	0.003	1.4 ± 1.1	2.5 ± 1.4	0.020	1.2 ± 0.8	2.1 ± 1.3	0.077	1.2 ± 1.0	2.3 ± 1.3	0.058
Postoperative data[‡]												
Fasting plasma glucose, mg/dL (mean ± SD)	148.1 ± 51.6	127.8 ± 30.0	0.200	149.4 ± 49.3	121.2 ± 29.5	0.068	150.2 ± 54.3	131.1 ± 34.8	0.371	152.3 ± 55.9	124.5 ± 33.4	0.2
Fasting C-peptide, ng/mL (mean ± SD)	0.9 ± 0.7	2.8 ± 1.7	<0.001	1.0 ± 0.9	2.5 ± 1.9	0.016	0.9 ± 0.7	2.9 ± 2.0	0.007	0.8 ± 0.7	2.2 ± 2.2	0.124
Fasting CPI (mean ± SD)	0.6 ± 0.4	2.1 ± 1.2	<0.001	0.7 ± 0.5	2.0 ± 1.5	0.012	0.6 ± 0.4	2.1 ± 1.5	0.004	0.6 ± 0.4	1.7 ± 1.7	0.098

[†] Drug categories included sulfonylurea, dipeptidyl peptidase-4 (DPP-4) inhibitor, glinide, biguanide, thiazolidinedione, α-glucosidase inhibitor, sodium–glucose transporter 2 (SGLT-2) inhibitor, and glucagon-like peptide-1 (GLP-1) receptor agonist. [‡]Data collected within 4 weeks after pancreatectomy. BMI, body mass index; CPI, C-peptide index; HbA1c, glycosylated hemoglobin; SD, standard deviation.

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term sulfonylurea treatment is speculated to involve a reduction in the number of adenosine triphosphate-sensitive potassium channels on the β-cell membrane and apoptosis of β-cells in the pancreas[18]. Based on these previous studies, the present findings suggest that preoperative sulfonylurea treatment affects residual β-cell function after pancreatectomy.

Furthermore, we found that the number of drug categories for diabetes treatment was inversely correlated with postoperative CPI. In a previous study, the number of oral hypoglycemic agents used for treatment was higher in type 2 diabetes patients with inadequate glycemic control than in those with good glycemic control[19]. The mechanism of the deterioration of β-cell function by multiple hypoglycemic agents remains unclear, as only a few reports have focused on diabetes treatment before pancreatectomy. In addition, multiple oral hypoglycemic agents, including drugs that stimulate insulin secretion, might burden pancreatic β-cell function, leading to a decrease in residual endogenous insulin secretion after pancreatectomy. We also considered the possibility that the number of drug categories used for diabetes treatment reflected the duration of hyperglycemia, resulting in a lower CPI. In our analysis, the number of drug categories was associated with the duration of diabetes, but not with the values of HbA1c and CPI. However, as the number of patients in each group with several drug categories was low, an analysis with a higher number of patients would be required to confirm those associations.

Regarding future glycemic control after pancreatectomy, we showed that postoperative CPI is associated with HbA1c values, and that both preoperative and postoperative CPI values are associated with the requirement for insulin therapy 6 months after surgery. Maxwell *et al.*[8] observed that preoperative hemoglobin HbA1c level, BMI (>30 kg/m^2), age (>65 years) and pancreatectomy are associated with the development of diabetes after pancreatectomy. However, to date, the effect of preoperative or postoperative CPI on future glycemic control and the requirement for insulin therapy after pancreatectomy has not been previously investigated, although low CPI was reported to correlate with the initiation of insulin therapy in type 2 diabetes patients[5]. The present results suggest that perioperative CPI can predict glycemic control and the initiation of insulin therapy in patients who underwent pancreatectomy. In the future, we consider it necessary to study CPI and postoperative insulin introduction, and the cutoff value of CPI.

Additionally, we found no significant associations between the various surgical procedures of pancreatectomy and postoperative CPI. Previous reports have described glucose tolerance in each procedure of pancreatectomy[8,9]. Resection of the distal pancreas could also be a risk factor for long-term endocrine disorders after pancreatectomy[20,21]. However, the parameters related to endogenous insulin secretion, including CPI, have not been thoroughly assessed among the procedures in these studies. We also found no significant differences in postoperative CPI according to the pancreatectomy technique. As duodenal–jejunal bypass was carried out after pancreaticoduodenectomy, it is expected to increase the secretion of glucagon-like peptide-1[22]. A previous study of patients who had not been diagnosed with diabetes before pancreatectomy showed that the incidence of new-onset diabetes is lower in patients who underwent pancreaticoduodenectomy than in those who underwent distal pancreatectomy[23,24]. The reason that postoperative CPI was not different among each pancreatectomy procedure might be that nearly 80% of the patients with preoperative diabetes were included, and that patients who underwent pancreaticoduodenectomy tended to have a lower preoperative CPI than those who underwent distal pancreatectomy. Recently, the different plasticity between intestinal bacteria and pancreatic endocrine cells among various surgical techniques have been suggested to affect the incidence of newly developed diabetes[24]. Such mechanistic analyses and a longer observation period might show more details on the associations between various pancreatectomy surgical procedures and pancreatic β-cell function.

The present study had some limitations. First, it was a single-center study with a small sample size. Second, the observation period was only 6 months, because most of the study participants have returned to the clinics or hospitals where they regularly visit. Third, as this was a retrospective observational study, the effects of various concomitant medications on the present results could not be excluded. Finally, the percentage of patients without preoperative or postoperative diabetes was low. Thus, it is desirable to include a control group for comparison of CPI. Multicenter prospective studies with a larger sample size should be carried out in the future.

In conclusion, postoperative, and both preoperative and postoperative pancreatic β-cell function, as assessed by the CPI, were associated with glycemic control and the requirement for insulin therapy, respectively, at 6 months after pancreatectomy. The present results suggest that perioperative CPI is a useful parameter for predicting the status of diabetes management after pancreatectomy.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The ethics committee of the Toyama University Hospital approved the study protocol (approval number R2020207) and waived the requirement for informed consent owing to the retrospective nature of the study.

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

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REFERENCES

1. Hardt PD, Brendel MD, Kloer HU, *et al.* Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? *Diabetes Care* 2008; 31: S165–S169.
2. Cancer Statistics: Cancer Information Service, National Cancer Center, Japan (Vital Statistics of Japan, Ministry of Health, Labour and Welfare); 1958–2019.xls. Available from: https://ganjoho.jp/reg_stat/statistics/data/dl/excel/cancer_mortality Accessed January 7, 2022 (Japanese).
3. Ben Q, Xu M, Ning X, *et al.* Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer* 2011; 47: 1928–1937.
4. Draznin B, Aroda V, Bakris G, *et al.* 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2022. *Diabetes Care* 2022; 45: S17–S38.
5. Saisho Y, Kou K, Tanaka K, *et al.* Postprandial serum C-peptide to plasma glucose ratio as a predictor of subsequent insulin treatment in patients with type 2 diabetes. *Endocr J* 2011; 58: 315–322.
6. Suzuki T, Takahashi K, Fujiwara D, *et al.* A reliable serum C-peptide index for the selection of an insulin regimen to achieve good glycemic control in obese patients with type 2 diabetes: an analysis from a short-term study with intensive insulin therapy. *Diabetol Int* 2016; 7: 235–243.
7. Iwata M, Matsushita Y, Fukuda K, *et al.* Secretory units of islets in transplantation index is a useful predictor of insulin requirement in Japanese type 2 diabetic patients. *J Diabetes Investig* 2014; 5: 570–580.
8. Maxwell DW, Jajja MR, Galindo RJ, *et al.* Post-pancreatectomy diabetes index: a validated score predicting diabetes development after major pancreatectomy. *J Am Coll Surg* 2020; 230: 393–402.e3.
9. Wu L, Nahm CB, Jamieson NB, *et al.* Risk factors for development of diabetes mellitus (Type 3c) after partial pancreatectomy: a systematic review. *Clin Endocrinol* 2020; 92: 396–406.
10. Maxwell DW, Jajja MR, Tariq M, *et al.* Development of diabetes after pancreaticoduodenectomy: results of a 10-year series using prospective endocrine evaluation. *J Am Coll Surg* 2019; 228: 400–412.e2.
11. Van Rossum G, Drake FL. Python 3 Reference Manual. Scotts Valley, CA: CreateSpace, 2009.
12. Pollard TJ, Johnson AEW, Raffa JD, *et al.* tableone: an open source Python package for producing summary statistics for research papers. *JAMIA Open* 2018; 23: 26–31.
13. Okuno Y, Sakaguchi K, Komada H, *et al.* Correlation of serum CPR to plasma glucose ratio with various indices of insulin secretion and diseases duration in type 2 diabetes. *Kobe J Med Sci* 2013; 59: E44–E53.
14. Ostgren CJ, Lindblad U, Ranstam J, *et al.* Glycaemic control, disease duration and beta-cell function in patients with type 2 diabetes in a Swedish community. Skaraborg Hypertension and Diabetes Project. *Diabet Med* 2002; 19: 125–129.
15. Hirata K, Nakata B, Amano R, *et al.* Predictive factors for change of diabetes mellitus status after pancreatectomy in preoperative diabetic and nondiabetic patients. *J Gastrointest Surg* 2014; 18: 1597–1603.
16. Arai K, Hirao K, Yamauchi M, *et al.* Short duration of diabetes and disuse of sulfonylurea have any association with insulin cessation of the patients with type 2 diabetes in a clinical setting in Japan (JDDM 30). *Endocr J* 2013; 60: 305–310.
17. Shin MS, Yu JH, Jung CH, *et al.* The duration of sulfonylurea treatment is associated with β-cell dysfunction in patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 2012; 14: 1033–1042.
18. Takahashi A, Nagashima K, Hamasaki A, *et al.* Sulfonylurea and glinide reduce insulin content, functional expression of K(ATP) channels, and accelerate apoptotic beta-cell death in the chronic phase. *Diabetes Res Clin Pract* 2007; 77: 343–350.
19. Saisho Y, Kou K, Tanaka K, *et al.* Association between beta cell function and future glycemic control in patients with type 2 diabetes. *Endocr J* 2013; 60: 517–523.
20. Kusakabe J, Anderson B, Liu J, *et al.* Long-term endocrine and exocrine insufficiency after pancreatectomy. *J Gastrointest Surg* 2019; 23: 1604–1613.
21. Hwang HK, Park J, Choi SH, *et al.* Predicting new-onset diabetes after minimally invasive subtotal distal pancreatectomy in benign and borderline malignant lesions of the pancreas. *Medicine* 2017; 96: e9404.
22. Jirapinyo P, Haas AV, Thompson CC. Effect of the Duodenal-jejunal bypass liner on glycemic control in patients with type 2 diabetes with obesity: a meta-analysis with secondary analysis on weight loss and hormonal changes. *Diabetes Care* 2018; 41: 1106–1115.
23. Scholten L, Mungroop TH, Haijtink SAL, *et al.* New-onset diabetes after pancreatoduodenectomy: a systematic review and meta-analysis. *Surgery* 2018; 164: 6–16.
24. Fukuda T, Bouchi R, Takeuchi T, *et al.* Importance of intestinal environment and cellular plasticity of islets in the development of postpancreatectomy diabetes. *Diabetes Care* 2021; 44: 1002–1011.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Table S1 | Multivariate analysis to evaluate the correlations between drug categories used for diabetes treatment and pre- and post-operative C-peptide index adjusted by body mass index and age.

Table S2 | Comparison of clinical factors among the groups with various numbers of drug categories used for diabetes treatment in patients with preoperative diabetes (n = 37).

Figure S1 | (a, b) Comparison of (a) preoperative and (b) postoperative fasting C-peptide index (F-CPI) between patients who underwent distal pancreatectomy and those who underwent pancreaticoduodenectomy (PD). (c, d) Comparison of (c) preoperative and (d) postoperative fasting C-peptide index (F-CPI) between patients with preoperative diabetes who underwent distal pancreatectomy and those who underwent pancreaticoduodenectomy.

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