ORIGINAL

Post-meal endogenous insulin secretion was significantly lower in head than in body/tail cancer of the pancreas

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Abstract : The aim : Pancreatic cancer, a rapidly progressive malignancy, is often diagnosed in patients with diabetes. The incidence of pancreatic cancer has risen dramatically over recent decades. Early diagnosis of this malignancy is generally difficult because the symptoms do not become apparent until the disease has progressed, generally leading to a poor outcome. To achieve earlier diagnosis, we analyzed the clinical characteristics of pancreatic cancer patients showing deterioration of plasma glucose levels while hospitalized. Method : Thirty-six cases were divided into 2 groups ; those diagnosed with diabetes more than a year prior to identification of pancreatic cancer and diabetes secondary to pancreatic cancer. These 2 groups were further subdivided according to the tumor site (head or body/tail), allowing analysis of 4 subgroups. Anthropometric measurements, laboratory values were determined. Results : Both groups with diabetes lost at least 4 kg and showed HbA1c deterioration of at least 1% within 5 months of the pancreatic cancer diagnosis. The post-meal elevation of serum C-peptide immunoreactivity (CPR) was significantly decreased in the group with cancer of the pancreatic head, and this was unrelated to tumor size. Conclusion : Characteristically, pancreatic head cancer was associated with decreased endogenous insulin secretion as compared to body/tail cancer. J. Med. Invest. 70 : 350-354, August, 2023

Keywords **:** *pancreatic cancer, postprandial CPR, diabetes*

INTRODUCTION

The incidence of pancreatic cancer is estimated to be 35 per 100,000 people. Pancreatic cancer rates have been rising dramatically for several decades. This malignancy is known to have a poor prognosis. Because early diagnosis of pancreatic cancer is often difficult, due to symptoms being absent until the disease is advanced, outcomes are generally poor. Early diagnosis is thus considered to have a major prognostic impact.

Chari *et al*. examined 2,122 patients newly diagnosed with diabetes and found that 0.85% developed pancreatic cancers within 3 years after the diabetes had been diagnosed. Pancreatic cancer is reportedly detected in one of every 100 to 150 people with diabetes. In addition, half of pancreatic cancers are associated with diabetes and the percentage of new-onset diabetes with rapidly progressing morbidity is high (1). According to past reports, the risk of pancreatic cancer development in patients with diabetes is 1.82-fold greater than that in non-diabetic individuals (95% confidence interval (CI) : 1.66-1.89) (2). Early screening for pancreatic cancer is important for comprehensively managing patients with diabetes (3).

Various factors possibly underlying the blood glucose increases associated with pancreatic cancer are broadly attributed to either pancreatic β cell dysfunction or impaired insulin sensitivity. Possible causes of pancreatic β-cell dysfunction include direct infiltration of tumor cells into pancreatic islets, increased intraductal pressure due to occlusion of the main pancreatic duct and concomitant inflammation-induced disorders. Causes of increased insulin resistance include decreased glucose uptake and decreased phosphoinositol-3-kinase activity in muscle (4, 5).

Herein, we retrospectively examined the clinical backgrounds of pancreatic cancer patients with diabetes mellitus by focusing on the potential for diabetes to serve as a factor allowing early detection or progression of pancreatic cancer.

METHOD

Patients

Fifty-two diabetic patients, who had not yet received pancreatic cancer treatment, were admitted to Kyorin University Hospital during the period from April 2007 to September 2016 (Figure1). Diabetes was diagnosed based on the established criteria (6). Thirty-six patients with diabetes (24 males, 12 females) were analyzed after excluding 16 who rejected pancreatic cancer treatment and could not undergo detailed examinations, such as CPR measurement, or were lost to follow-up. The patients included in this analysis had relatively well-maintained insulin secretion, although some required insulin treatment and had neither renal dysfunction nor metastasis involving other organs. Though the precise onset time of pancreatic cancer was unknown, those with pancreatic cancer were divided into two groups ; Group A subjects had been diagnosed with diabetes more than a year prior to identification of pancreatic cancer, such that no patients developing pancreatic cancer within one year after the diagnosis of diabetes mellitus were included in this group, while in group B subjects the diabetes had developed after or been diagnosed concurrently with the detection of pancreatic cancer (diabetes secondary to pancreatic cancer).

The subjects consumed almost all daily meals, calculated on the basis of standard body weight. The study protocol was approved by the ethics committee of Kyorin University School of Medicine (No. 1545). Consent for this study was obtained by the opt-out method, allowing the content to be presented on the hospital homepage or in outpatient settings. All procedures followed

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were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2021.

Parameters

Age, sex, height, body mass index (BMI), family history of diabetes mellitus, history of smoking, alcohol consumption, family history of malignant disease, duration of diabetes, HbA1c, fasting plasma glucose, the serum and urinary C-peptide immunoreactivity (CPR) levels, CPR index, weight loss amount and duration, treatments (oral hypoglycemic agent/insulin/both), tumor marker (CA19-9), tumor diameter (long diameter of tumor as measured by computed tomography), pancreatic cancer development site and cancer treatments were examined. We determined ΔHbA1c, indicating HbA1c elevation at the time of pancreatic cancer diagnosis as compared to the most recent prior measurement, and weight loss within 5 months before the cancer diagnosis at a clinic or hospital.

Statistical analyses

Fisher's test, Spearman's rank correlation coefficient, the t test, or the Wilcoxon test was used for all statistical analyses. $p<0.05$ was considered to indicate a statistically significant difference. Statistical analysis and data management were conducted using statistical software ; JMP® version 11.1.1 (SAS Institute Inc. Cary NC USA).

RESULTS

There were 23 group A cases (16 males, 7 females) and 13 group B cases (8 males, 5 females) (Figure 1 and Table 1). The characteristics and comparisons of these patients are shown in Table 1. ΔHbA1c was more than 2% in both groups and weight loss exceeded 4kg in both groups. There was no difference in insulin secretion between the groups according to measurements

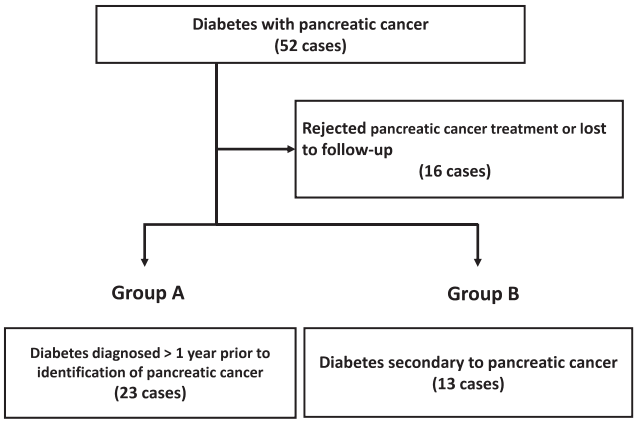


Figure 1. Flow chart showing inclusion and exclusion criteria
We obtained informed consent from 52 patients enrolled in the study. However, 16 cases could not be followed up and were thus excluded.

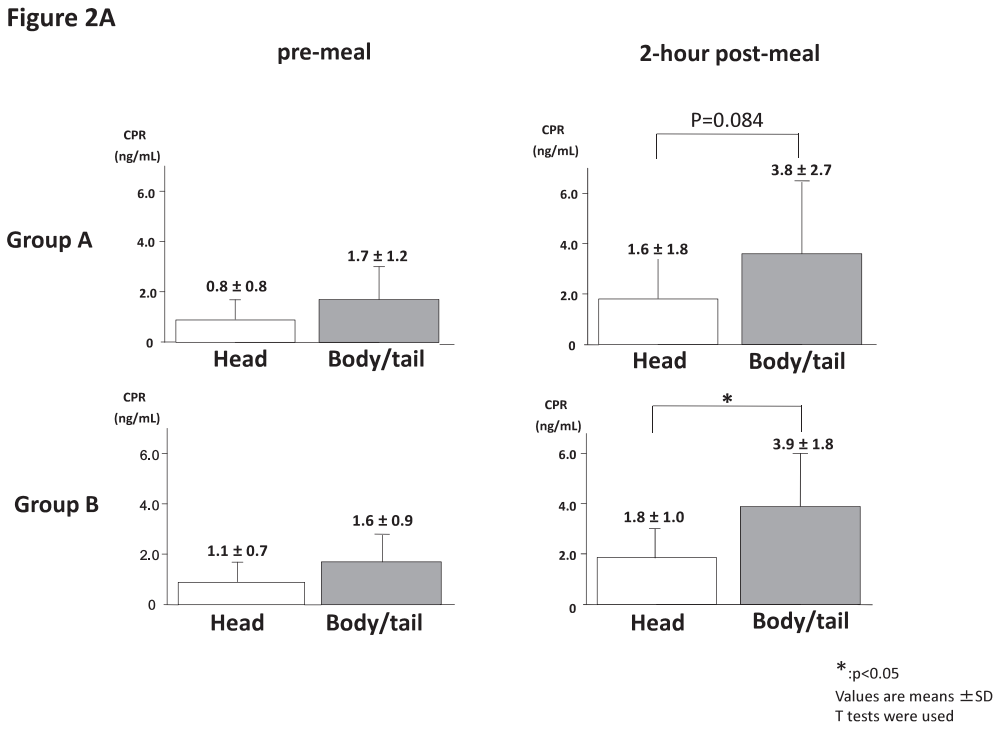
Table 1. Characteristics of patients with diabetes diagnosed more than a year prior to identification of pancreatic cancer (A) and diabetes secondary to pancreatic cancer (B)

	Group A (n = 23)	Group B (n = 13)	*P*
Sex (male/female)	15/8	9/4	1.00[#]
Age	68.5 ± 5.6	71.9 ± 4.3	0.07
Height (cm)	161 ± 9.0	162 ± 9.0	0.97
BMI (kg/m^2)	22.3 ± 4.3	20.9 ± 2.3	0.27
Family history of diabetes mellitus (%)	13(56.5%)	5 (38.5%)	0.49[#]
History of smoking (%)	12(52.2%)	6(46.2%)	1.00[#]
Alcohol (%)	15(65.2%)	8(61.5%)	1.00[#]
Family history of malignant disease (%)	9(39.1%)	5(38.5%)	1.00[#]
Duration of diabetes (year)	15.0 [8.0-19.5]	1.0 [1.0-1.0]	<0.001[$, &]
Fasting plasma glucose (mg/dL)	152 ± 17	160 ± 18	0.19
HbA1c (%)	9.8 ± 2.1	9.4 ± 2.1	0.56
ΔHbA1c (%)	2.2 ± 1.5	2.6 ± 2.0	0.45
HbA1c deterioration period (months)	4.0 [3.0-6.0]	3.0 [2.0-6.0]	0.67[$]
Pre-meal CPR (ng/mL)	1.5 ± 1.2	1.4 ± 0.8	0.77
CPR 2 hours after meal (ng/mL)	3.2 ± 2.6	3.0 ± 1.8	0.88
ΔCPR (ng/mL)	2.0 [0.1-2.5]	1.6 [0.52-2.24]	0.98[$]
CPR index (Pre-meal)	0.9 [0.31-1.41]	0.76 [0.51-1.14]	0.76[$]
Urine CPR (mg /day)	49.8 [15.4-68.4]	49.8 [26.6-83.0]	0.34[$]
Weight loss (kg)	3.0 [0.0-6.5]	4.0 [3.0-6.0]	0.55[$]
Weight loss duration (months)	3.0 [0.0-6.0]	3.5 [2.75-5.25]	0.67[$]
Treatment (Diet only/Oral hypoglycemic agent/Insulin/both) (n)	0/11/10/2	7/2/4/0	0.001[#, &]
Pancreatic tumor diameter (mm)	25.0 [20.0-35.0]	25.0 [20.0-35.0]	0.97[$]
Pancreatic cancer site (Head/Body/Tail) (n)	9/7/7	6/5/2	0.74[#]
CA19-9 (U/mL)	118.5 [13.7-742.7]	380 [73.8-2650]	0.13[$]
Cancer treatment (Surgery/chemotherapy)	15/8	9/4	1.00[#]

Fisher's test ([#]), the t-test, or the Wilcoxon test ([$]) was used
[&] denotes significant difference between groups A and B
Values are means ± SD or medians [interquartile range]

of pre-meal and post-meal CPR or post-meal elevation of CPR (ΔCPR), as an indicator of endogenous insulin secretion. Dietary intake amounts were not the same at each of the CPR determinations. The sites of pancreatic cancer occurrence, visualized on magnetic resonance images, were the head in 9, the body in 7 and the tail in 7 of the group A patients, and were the head in 6, the body in 5 and the tail in 2 of the group B patients. Then, groups A and B were each further divided into 2 subgroups according to the pancreatic cancer site (body/tail and head). ΔHbA1c did not differ between the subgroups in either group A or group B (data not shown). The 2-hour postprandial CPR level in group B and the ΔCPR level in both group A and group B were significantly lower for the head site than for the body/tail site of pancreatic cancer (Figures 2A, 2B).

On the other hand, tumor size was not related to all CPR conditions at all tumor sites (Figure 3). According to cancer stage classified by TNM, (I : 4 cases, II : 14 cases, III : 13 cases, IV : 6 cases), there were no significant differences in the timing of CPR



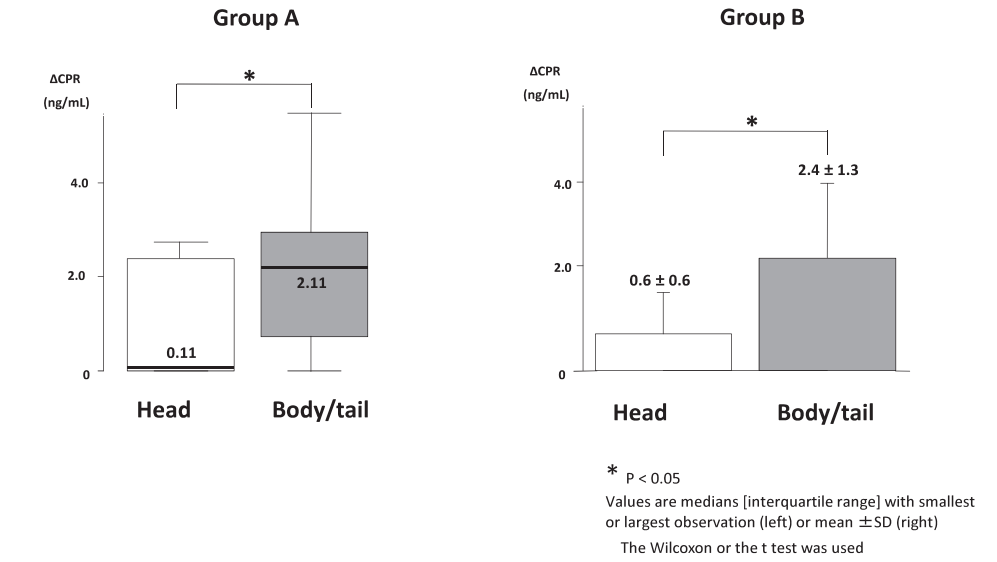


Figure 2. Comparison of pre-meal CPR, post-meal 2-hour CPR and ΔCPR between the two groups
2A Pre- and 2-hour post-meal CPR in each subgroup
2B ΔCPR in each subgroup
Data are expressed as means ± standard deviation (2A and group B in 2B) and as medians [interquartile range] with the smallest or largest observation (group A in 2B).
A : Diabetes diagnosed more than a year prior to identification of pancreatic cancer
B : Diabetes secondary to pancreatic cancer

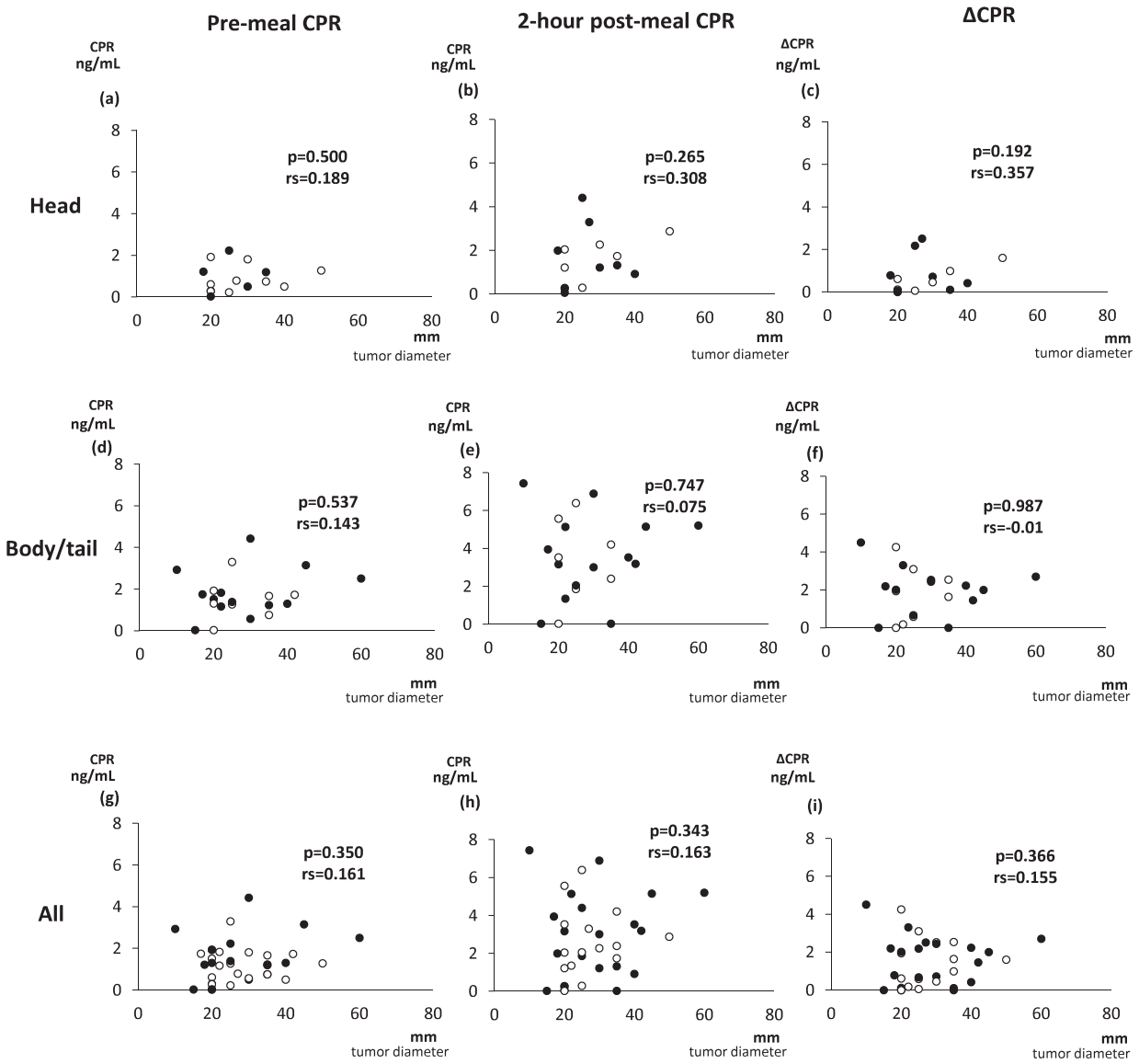


Figure 3. Correlations pancreatic tumor size with CPR and ΔCPR
(a), (b), and (c) show head site, (d), (e), and (f) show body/tail site, while (g), (h), and (i) show total pancreatic tumor sites.
Black circle : group A, unfilled circle : group B
X-axis : tumor diameter
Y-axis : Serum C-peptide levels

determination among the stages (data not shown), though the tumors had not been clinically classified as advanced or early-stage pancreatic cancer.

DISCUSSION

There were no significant differences in characteristics, such as age and BMI, between groups A and B. Weight loss of 4 kg or more and HbA1c deterioration by more than 2% were observed within 5 months of the pancreatic cancer diagnosis in both groups. In order to avoid missing pancreatic cancers in patients without a diabetes history, Lee *et al*. advocated that pancreatic cancer be suspected in those with one or more of the following risk factors : a family history of diabetes, older than age 65 years, weight loss over 2kg, and BMI under 25 prior to cancer symptom onset (7). In addition, Yuan *et al*. reported that diabetes found in the wake of weight loss has a higher risk of being associated with pancreatic cancer development, and has a frequency 6.75 times higher in diabetic patients with a weight loss of 8 pounds than in those without weight loss (95% confidence interval : 4.55-10.00) (8). Consistent with their report, our present study also showed weight loss and deterioration of HbA1c, especially in those with weight loss of 4 kg or more and HbA1c deterioration of 1% or more, to generally be observed within 5 months of the diagnosis of pancreatic cancer.

The risk of pancreatic cancer approximately doubled when the fasting blood glucose level before the onset was 140 mg/dL and was more than 2.15-fold at 200 mg/dL or higher (9). However, to our knowledge, there have been no studies comparing CPR just before versus after the diagnosis of pancreatic cancer.

Contrary to our speculations regarding β-cell function, this

study clearly demonstrated the body and tail site of pancreatic cancer to be associated with significantly preserved endogenous insulin secretion as compared to the head site, based on postprandial blood CPR and Δ CPR, regardless of diabetes history and tumor size (Figure 3). This observation might be explained by reports describing secondary effects of pancreatic duct obstruction due to pancreatic head cancer as strongly impairing pancreatic β-cell function (4, 5), though body and tail cancer also show partial direct invasion into β-cells.

As a limitation of this study, we acknowledge that while it might be possible to diagnose pancreatic head cancer at an early stage by testing CPR before and after a meal, it is somewhat difficult to perform pre- and post-meal CPR measurements in all patients in an outpatient setting. However, the major limitation of this study is that neither historical nor imaging analyses such as cholangiopancreatography were performed to confirm pancreatic duct obstruction, which is related to impaired pancreatic β-cell function. Moreover, we did not examine whether endogenous insulin secretion shows any association with the progression of pancreatic cancer or reflects postoperative changes.

Adrenomedullin has been suggested as a possible mediator of pancreatic β-cell dysfunction and was reportedly detected at higher levels in pancreatic cancer patients than in healthy controls (10). Islet amyloid polypeptide was also suggested to be a mediator of insulin resistance and its elevation was observed in patients with pancreatic cancer complicated by diabetes (11). Further analysis, including cytokine measurements, might be needed to confirm the evidence obtained herein suggesting reduced residual insulin secretion associated with pancreatic cancer-related diabetes.

IN CONCLUSION

Pancreatic cancer patients experienced not only marked weight loss, but also HbA1c elevation within 5 months of diagnosis. Notably, we demonstrated for the first time that a poor postprandial CPR response, after the pancreatic cancer diagnosis, might suggest the tumor to be in the head of the pancreas.

ACKNOWLEDGMENTS

Not applicable

COMPLIANCE WITH ETHICAL STANDARDS

Ethics approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Kyorin University School of Medicine (approval number : 1545, 2020/7/20) ; the protocol was registered at the University Hospital Medical Information Network Centre clinical trial registry (Registry No. UMIN000047330, 2020/8/3). Informed consent was obtained by the opt-out method in all subjects.

Conflicts of interest / Competing interests : HS, TH, FT, YS, HI and KY have no conflicts of interest to declare.

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