

# Effects of Zinc on Non-alcoholic Fatty Liver Disease After Pancreatoduodenectomy

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**Abstract:** Background: The etiology, treatment and prevention of Nonalcoholic fatty liver disease (NAFLD) after pancreatoduodenectomy (PD) remain largely unknown. We aimed to elucidate the risk factors for NAFLD after PD and investigate the nutritional effects of zinc medication. Methods: We retrospectively examined 109 patients who underwent PD between 2013 and 2017. We diagnosed the postoperative NAFLD using CT attenuation at six months later. We identified the risk factors for postoperative NAFLD among perioperative factors and analyzed the nutritional effect of zinc medication at six months after surgery. Results: We diagnosed 27 patients with NAFLD after PD. A univariate analysis showed that pancreas cancer ( $p = 0.029$ ), operative time ( $p = 0.008$ ), blood loss ( $p = 0.034$ ), postoperative diarrhea ( $p < 0.001$ ) and zinc medication ( $p < 0.001$ ) were associated with postoperative NAFLD. A multivariate analysis demonstrated that zinc medication was the most important factor for the prevention of NAFLD after PD. All patients who received zinc also took pancreatic enzyme simultaneously and showed a significantly lower rate of body weight loss than in patients without zinc at six months after PD ( $p = 0.041$ ). These patients showed a significantly higher total cholesterol level ( $p = 0.006$ ) and higher serum zinc level ( $p < 0.001$ ). Furthermore, significantly fewer cases of postoperative NAFLD were noted among the patients who received zinc than among those who did not receive it (5.7% vs 33.8%;  $p = 0.001$ ). Conclusion: These results suggest that zinc administration might improve the postoperative nutritional status and prevent NAFLD after PD.

**Keywords:** Pancreatoduodenectomy, Nonalcoholic Fatty Liver Disease, Zinc

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## 1. Introduction

Pancreatoduodenectomy (PD) has become the standard operation for patients with peri-ampullary disease. The long-term survival after PD has gradually increased due to recent improvements in surgical techniques and perioperative management [1]. However, the extensive resection of organs and complicated reconstruction of the alimentary tract associated with PD lead to the inhibition of the pancreatic function and malnutrition in most patients [2]. Therefore, postoperative nutritional management is extremely important for patients undergoing PD.

Recently, reports of nonalcoholic fatty liver disease (NAFLD) after PD with malnutrition has become increasingly problematic and few reports documented some cases of hepatic failure after pancreatic resection [3-7]. However, the clinicopathological and etiological findings of NAFLD after PD are largely unknown. A few reports have suggested that NAFLD after PD was associated with postoperative malnutrition caused by pancreatic exocrine sufficiency [8, 9]. Other reports have suggested that the supplementation of pancreatic enzyme, such as pancrealipase, was effective for the treatment and prevention of NAFLD after PD [10, 11].

In addition, zinc deficiency has been occasionally reported

in patients who have undergone PD and is said to be closely correlated with the pancreatic exocrine function [12, 13]. Polaprezinc consists of zinc and has been reported to attenuate liver fibrosis in non-alcoholic steatohepatitis [14, 15].

In this study, we examined the risk factors for NAFLD after PD and investigated the nutritional effect of the supplementation of zinc.

## 2. Methods

### 2.1. Patients

This retrospective study included 109 consecutive patients who underwent pancreatoduodenectomy between April 2013 and December 2017 at the Department of Surgery, Saga-Ken Medical Centre Koseikan, Japan. Table 1 shows the patient characteristics of this study. The mean age was 68.5 years old, and 64 males and 45 females were included. The mean body weight and body mass index (BMI) were 56.4 kg and 22.2 kg/m<sup>2</sup>, respectively. The histological diagnosis was pancreatic carcinoma in 45 (41.3%), distal bile duct carcinoma in 27 (24.8%), ampulla of Vater carcinoma in 16 (14.7%), Intraductal papillary mucinous neoplasm (IPMN) in 12 (11.0%), pancreatic neuroendocrine tumor in 4 (3.7%), and others in 5 (4.5%). Regarding the surgical procedures, subtotal stomach-preserving PD and conventional PD were performed in 102 (93.5%), and 7 (6.5%) patients, respectively. Portal vein resection was performed in 30 (29.4%) patients who were suspected of having direct invasion to the vein.

**Table 1.** Patient characteristics (n=109).

Age (years)	68.5±8.6
Gender (male/female)	64 / 45
Body weight (kg)	56.4±9.8
BMI (kg/m <sup>2</sup> )	22.2±3.0
<i>Diagnosis</i>	
Pancreas cancer	45 (41.3%)
Distal bile duct cancer	27 (24.8%)
Ampulla of Vater cancer	16 (14.7%)
IPMN	12 (11.0%)
PNET	4 (3.7%)
Others	5 (4.5%)
<i>Operation</i>	
SSPPD	102 (93.5%)
PD	7 (6.5%)
Operation time (min.)	394 ± 92
Blood loss (ml)	803 ± 658
Portal vein resection	30 (29.4%)
<i>Postoperative morbidity</i>	
DGE	4 (3.6%)
Pancreatic fistula (ISGPF ≥Grade B)	16 (14.8%)
Mortality	0 (0)

BMI: body mass index, IPMN: intraductal papillary mucinous neoplasm, PNET: pancreatic neuroendocrine tumor, SSPPD: subtotal stomach preserving pancreatoduodenectomy, PD: pancreatoduodenectomy, DGE: delayed gastric empty, ISGPF: international study group of pancreatic fistula

To prevent postoperative severe diarrhea, dissection of the nerve plexus around the superior mesenteric artery (SMA) was avoided and the cutting line of pancreas was on the

portal vein in most patients. The reconstruction procedure was a modified Child's method that involved end-to-side pancreaticojejunostomy plus Braun anastomosis with external drainage of the main pancreatic duct in most patients. Postoperative supplementation therapy including pancreatic enzyme (pancrealipase; Eisai Pharmaceutical Co., Japan), or zinc (polaprezinc; Zeria Pharmaceutical Co., Tokyo, Japan) was prescribed to patients at the surgeon's discretion. The dosages of Pancrealipase were 900mg-1800mg/day and those of polaprezinc were 75mg/day that contain 34mg of zinc. Postoperative adjuvant chemotherapy with S-1 (Taiho Pharmaceutical Co, Tokyo, Japan) was usually administered to patients with pancreas carcinoma and bile duct carcinoma for six months.

All patients underwent periodic abdominal computed tomography (CT) and were evaluated the postoperative nutritional status at the blood test. The routine follow-up interval was once every three to four months.

Informed consent was obtained from all individual participants included in the study.

This study was approved as project number 17-11-3-1 by the Ethics Committee of Saga-Ken Medical Centre Koseikan, and conducted in accordance with mandates of the Helsinki Declaration.

### 2.2. The Diagnosis of Postoperative NAFLD Using CT Attenuation

CT images were obtained with a 64-multidetector CT scanner, and the raw data set was reconstructed at 2-mm thickness. At six months after surgery, the average CT attenuation values in four sectors of the liver and in one region of the spleen were monitored to determine the hepatic fat content for each patient. We calculated the liver-to-spleen attenuation ratio (L/S ratio) on CT, and postoperative NAFLD was defined as an L/S ratio of <0.9 [16, 17]. Four patients with NAFLD after PD were underwent the liver biopsy and diagnosed by the pathological findings.

### 2.3. Analyses of the Risk Factors for NAFLD

We evaluated the pre-, intra-, and postoperative factors that might be associated with the development of NAFLD after PD. The preoperative factors were age, gender, BMI, preoperative jaundice, diabetes mellitus, and primary disease. The intraoperative factors were operative time, the volume of blood loss, pancreatic consistency, the resection of portal vein, and total pancreatectomy. The postoperative factors were postoperative enteral nutrition, the presence of pancreatic fistula based on the International Study Group on Pancreatic Fistula criteria [18], eating disorder, and diarrhea based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Other postoperative factors included the administration of adjuvant chemotherapy, pancrealipase, polaprezinc, and insulin.

### 2.4. Analyses of the Effect of Zinc in PD Patients

We analyzed the nutritional effect of zinc administration on

patients after PD. We evaluated the postoperative nutritional state, such as BMI loss, body weight (BM) loss, BM loss rate calculated by (preoperative BM- postoperative BM) / preoperative BM x 100, serum albumin, transaminase, total cholesterol, and serum zinc levels at six months after surgery.

### 2.5. Statistical Analyses

Continuous variables were expressed as the mean ( $\pm$ standard deviation) and compared using Student's *t*-test. Categorical variables were compared using the  $\chi^2$ -test. A P value of less than 0.05 was considered statistically significant.

Variables associated with the development of postoperative NAFLD were first assessed using a univariate analysis. The variables that were significant were then subjected to a multivariate logistic regression analysis to identify the independent risk factors for the development of postoperative NAFLD after PD.

All data were analyzed using the StatView software

program, version 5.0 (SAS Institute, Cary, NC, USA) and the SPSS 15.0 software program (SPSS Chicago, IL, USA).

## 3. Results

### 3.1. Risk Factors for NAFLD After PD

We diagnosed 27 (24.8%) patients with NAFLD in this series. Table 2 shows the results of the univariate analysis for identifying the risk factors associated with the NAFLD after PD. Among pre- and intraoperative factors, a primary disease of pancreas cancer ( $p = 0.029$ ), the operative time >400 minutes ( $p = 0.008$ ), and blood loss > 500 ml ( $p = 0.034$ ) were found to be significantly correlated with NAFLD after PD. Postoperative NAFLD was not associated with the administration of pancrealipase. However, postoperative diarrhea ( $p < 0.001$ ) and the administration of polaprezinc ( $p < 0.001$ ) were correlated with NAFLD after PD.

**Table 2.** Univariate analysis of the risk factors for NAFLD after PD.

	NAFLD (+) (n=27)	NAFLD (-) (n=82)	P values
<i>Preoperative factors</i>			
Age (years)	66.8 $\pm$ 8.3	69.0 $\pm$ 9.0	0.253
Gender (male/female)	17/ 10	47 /35	0.605
BMI (kg/m <sup>2</sup> )	22.2 $\pm$ 3.4	22.2 $\pm$ 2.8	0.969
DM (+/-)	11 / 16	28 /54	0.663
Jaundice (+/-)	17 / 10	47 /35	0.664
Primary disease (pancreas cancer/other)	16 /11	29 /53	0.029
<i>Intraoperative factors</i>			
Operative time >400 min (+/-)	17/10	28 /54	0.008
Blood loss >500 ml (+/-)	21 / 6	45 / 37	0.034
Blood transfusion (+/-)	5 / 22	14 / 68	0.864
Pancreatic consistency (soft/ hard)	10 /17	48 / 34	0.051
Resection of PV (+/-)	10/17	20 /62	0.228
<i>Postoperative factors</i>			
Enteral nutrition (+/-)	2/23	11/57	0.502
Pancreatic fistula (+/-)	4/22	10/58	0.735
Eating disorder (+/-)	4/23	8/74	0.466
diarrhea (+/-)	7 /20	2/80	<0.001
Adjuvant chemotherapy (+/-)	18/9	40/42	0.153
Pancrealipase (+/-)	17 /10	62 /20	0.210
Polaprezinc (+/-)	2/25	33 /49	<0.001
Insulin (+/-)	6 /21	15 /67	0.677

NAFLD: nonalcoholic fatty liver disease, BMI: body mass index, DM: diabetes mellitus, PV: portal vein

Table 3 shows the results of the multivariate analysis for identifying the independent risk factors for NAFLD after PD. Postoperative diarrhea and polaprezinc were independent predictors of postoperative NAFLD.

**Table 3.** Multivariate analysis of the risk factors for NAFLD after PD.

Factor	Hazard ratio	95% CI	P value
Pancreas cancer	2.260	0.784 – 6.510	0.131
Operating time >400 min	2.028	0.642 – 6.399	0.228
Blood loss > 500ml	1.733	0.480 – 6.258	0.8401
Diarrhea	14.962	2.099 – 106.634	0.006
Polaprezinc	10.416	0.016 – 0.561	0.009

CI: confidence interval

### 3.2. Effects of Zinc Administration on PD Patients

Table 4 shows the analysis of the nutritional effect of zinc on patients at 6 months after PD. In the background of patients, all patients who received polaprezinc also took pancrealipase simultaneously ( $p < 0.001$ ). However, there was no significant differences in the other background factors. In the nutritional evaluation, BMI and BM loss in patients with polaprezinc were less than in patients without polaprezinc. BM loss rate in patients with polaprezinc was significantly lower than in patients without polaprezinc (0.041). Patients who received polaprezinc had significantly lower ALT levels ( $p = 0.014$ ), higher total cholesterol levels ( $p = 0.004$ ), and higher serum zinc levels ( $p <$

0.001). Furthermore, significantly fewer cases of postoperative NAFLD were noted among the patients who received polaprezinc than among those who did not receive it (5.7% vs 33.8%;  $p = 0.001$ ).

**Table 4.** An analysis of the nutritional effect of zinc.

Factor	Polaprezinc (+) (n=35)	Polaprezinc (-) (n=74)	P value
<i>Background</i>			
Gender (male/female)	19 /16	45/ 29	0.519
Age	68.8±7.9	68.3±9.0	0.772
Primary disease (pancreas ca/other)	15 /20	30 /44	0.818
Portal vein resection (+/-)	9/26	21 /53	0.901
Adjuvant chemotherapy (+/-)	19 /16	39/35	0.575
Pancrealipase (+/-)	35/0	44/30	<0.001
Insulin (+/-)	5 /30	16 /57	0.338
<i>Nutrition</i>			
BMI loss (kg/m <sup>2</sup> )	-1.6 ±1.6	-2.2±1.9	0.114
Body weight loss (kg)	-4.2±3.5	-5.7±4.3	0.094
Rate of Body weight loss (%)	6.4 ±7.0	9.4 ±7.3	0.041
Diarrhea (+/-)	2/33	7/67	0.507
Eating disorder (+/-)	5/30	7 /67	0.452
AST (U/L)	26.1±10.8	38.4±46.3	0.123
ALT (U/L)	19.8±8.8	36.5±39.2	0.014
Albumin (g/dL)	3.8±0.4	3.6±0.6	0.166
Cholinesterase (U/L)	241.8±86.1	218.2±89.5	0.229
Total cholesterol (mg/dL)	163.2±44.7	138.6±32.8	0.004
Zinc (µg/dL)	102.8±41.2	66.4±16.0	<0.001
Postoperative NAFLD	2 (5.7%)	25 (33.8%)	0.001

BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, NAFLD: nonalcoholic fatty liver disease

## 4. Discussion

Recently, NAFLD after PD with malnutrition has become increasingly problematic. Studies exploring the mechanism of postoperative NAFLD have reported several risk factors, including pancreas cancer, postoperative diarrhea, blood loss, small remnant pancreatic volume, and a long operative time [5, 6, 19].

Several reports have suggested that NAFLD after PD is mainly associated with pancreatic exocrine dysfunction [5, 6, 9]. Nakagawa et al showed that postoperative pancreatic exocrine sufficiency was an independent risk factor for NAFLD [8]. Nagai et al and Kishi et al demonstrated that the administration of pancrealipase was useful for the treatment of NAFLD after PD [10, 11]. However, Satoi et al failed to show a significant preventive effect of pancrealipase for NAFLD development after PD on randomized control trial [20].

In the current study, we analyzed the risk factors for NAFLD after PD. The univariate analysis revealed that postoperative NAFLD was associated with pancreas cancer, the operative time, blood loss, postoperative diarrhea, and the administration of polaprezinc but not pancrealipase. The multivariate analysis identified postoperative diarrhea and polaprezinc as independent predictive factors for NAFLD after PD. These analyses demonstrated that administration of zinc was the most important crucial factor for the prevention of NAFLD after PD.

Zinc is the most abundant intracellular trace element and is strongly implicated in cell turnover and repair systems. Indeed, zinc deficiency has been reported to increase the inflammatory conditions and disrupt the barrier function of

endothelial cells [21, 22]. PD with massive resection of the pancreas causes a zinc deficiency, as zinc is absorbed mainly in the distal duodenum and proximal jejunum. In addition, zinc deficiency after PD has been reported to impair the pancreatic exocrine functions and cause maldigestion, malabsorption, and malnutrition [23, 24]. Kato et al reported that a high-zinc diet after major pancreatectomy enhanced cell proliferation in the remnant pancreas and improved the pancreatic exocrine function in a dog model [12]. However, the usefulness of zinc for NAFLD after PD has not been elucidated in the clinical data.

Polaprezinc consists of zinc and carnosine and is used for the treatment of gastric ulcers. Zinc and carnosine are reactive oxygen species (ROS) scavengers and have antioxidant activities [25, 26]. Polaprezinc was reported to attenuate liver fibrosis in conventional non-alcoholic steatohepatitis by reducing inflammation and lipid peroxidation in a mouse model [14]. However, no study has investigated the effect of polaprezinc on NAFLD after PD in a clinical setting.

In the present study, most patients with zinc had a well-controlled nutritional status after PD and showed a significantly lower BM loss rate and higher serum zinc level and total cholesterol level than those without zinc. Furthermore, almost no patients with zinc presented with postoperative NAFLD. These results suggested that zinc administration might improve the postoperative nutritional status and prevent NAFLD after PD. In addition, all patients with zinc simultaneously took pancrealipase. Therefore, both zinc and pancreatic enzymes might be important for preventing postoperative NAFLD. Oxidative stress has also

been reported to play a central role in the pathogenesis of NAFLD [27, 28]. The effect of polaprezinc as an ROS scavenger might help prevent NAFLD development.

This retrospective analysis was informative but had some limitations. First, postoperative supplementation therapy including pancreatic enzyme or zinc was prescribed to patients at each surgeon's discretion. Second, the postoperative pancreatic exocrine function, which was associated with zinc, was not examined. Therefore, a prospective randomized control study including an analysis of the pancreatic exocrine function should be considered to elucidate the prevention effect of zinc for NAFLD after PD.

## 5. Conclusion

The postoperative diarrhea and the zinc administration are independent predictors of postoperative NAFLD. Zinc administration might improve the postoperative nutritional status and prevent NAFLD after PD.

This is the first study to demonstrate the prevention effect of zinc for NAFLD after PD using clinical data. To prevent NAFLD after PD, the administration of zinc, pancreatic enzyme usage, and provision of adequate nutritional support are recommended.

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