

Potential risk factors for nonalcoholic steatohepatitis related to pancreatic secretions following pancreaticoduodenectomy

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Abstract

AIM: To identify risk factors for nonalcoholic steatohepatitis following pancreaticoduodenectomy, with a focus on factors related to pancreatic secretions.

METHODS: The medical records of 228 patients who had a pancreaticoduodenectomy over a 16-mo period were reviewed retrospectively. The 193 patients who did not have fatty liver disease preoperatively were included in the final analysis. Hepatic steatosis was diagnosed using the differences between splenic and hepatic attenuation and liver-to-spleen attenuation as measured by non-enhanced computed tomography.

RESULTS: Fifteen patients (7.8%) who showed post-operative hepatic fatty changes were assigned to Group A, and the remaining patients were assigned to Group B. Patient demographics, preoperative laboratory findings (including levels of C-peptide, glucagon, insulin and glucose tolerance test results), operation types, and final pathological findings did not differ sig-

nificantly between the two groups; however, the frequency of pancreatic fistula ($P = 0.020$) and the method of pancreatic duct stenting ($P = 0.005$) showed significant differences between the groups. A multivariate analysis identified pancreatic fistula ($HR = 3.332$, $P = 0.037$) and external pancreatic duct stenting ($HR = 4.530$, $P = 0.017$) as independent risk factors for the development of postoperative steatohepatitis.

CONCLUSION: Pancreatic fistula and external pancreatic duct stenting were identified as independent risk factors for the development of steatohepatitis following pancreaticoduodenectomy.

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Key words: Nonalcoholic fatty liver diseases; Nonalcoholic steatohepatitis; Pancreatic duct stenting; Pancreatic fistula; Pancreatic surgery

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INTRODUCTION

Steatohepatitis refers to a spectrum of nonalcoholic fatty liver diseases (NAFLD) ranging from simple triglyceride

deposition and accumulation with or without fibrosis to the development of cirrhosis, end-stage liver failure, and even hepatocellular carcinoma^[1-6]. Nonalcoholic steatohepatitis (NASH), first described by Ludwig *et al*^[7] at the Mayo Clinic in 1980, refers to hepatic lobular or portal inflammation and focal necrosis with fatty changes in patients without a history of alcohol abuse^[4,8-12]. Steatohepatitis is associated with lipodystrophy, metabolic syndrome (dyslipidemia, insulin resistance, and diabetes mellitus), genetic susceptibility, environmental factors, and hepatocyte apoptosis associated with mitochondrial dysfunction and the production of reactive oxygen species, which can lead to hepatic fibrogenesis and inflammation^[10,13-15].

Fatty liver disease refers to either the accumulation of fat in hepatocytes in excess of 5% of the total liver weight or the fatty degeneration of more than one-third of the total number of cells in the liver^[16]. In the general population, the prevalence of NAFLD is 6%-40% among asymptomatic patients, and the incidence of fatty liver disease is 60%-75% in obese patients and 84%-96% in morbidly obese patients who undergo bariatric surgery, with 25%-55% of these patients also having NASH^[1,3-5,9,17].

Glucose intolerance in response to insulin resistance induces an elevation in blood levels of glucose and insulin and results in increased synthesis of hepatic free fatty acids^[5]. The oxidation of free fatty acids can lead to the production of reactive oxygen free radicals that can be cytotoxic to DNA, mitochondria, and other cellular structures and can lead to the production of pro-inflammatory cytokines. Steatohepatitis reportedly develops after a "first hit" involving triglyceride accumulation and a "second hit" involving oxidative stress, lipid peroxidation, pro-inflammatory cytokines, and mitochondrial dysfunction^[4,18].

Previous studies in humans or murine models have identified independent risk factors for hepatic fibrosis, including advanced age, obesity, hypertension, Type II diabetes, insulin resistance, dyslipidemia, an aspartate transaminase (AST)/alanine transaminase (ALT) ratio greater than 1, hyperinsulinemia, altered lipid homeostasis, and pancreatic steatosis^[4,7-9,17-20]. Additional risk factors that might contribute to disease progression include increased transferrin saturation, long-term total parenteral nutrition leading to choline deficiency, jejunoileal bypass surgery for morbid obesity, environmental toxins, and drugs such as chemotherapeutic agents or glucocorticoids^[3,5,18].

Ductal adenocarcinoma of the pancreatic head is the most predominant tumor in the pancreas, and pancreaticoduodenectomy is the treatment of choice^[11]. Pancreaticoduodenectomy is also used to treat various other malignancies of the periampullary region, the bile duct, and the duodenum or the borderline diseases of the pancreas^[21]. Side-effects associated with pancreaticoduodenectomy include weight loss, abdominal pain, fatigue, and exocrine and endocrine insufficiencies. Pancreaticoduodenectomy also has a high rate of morbidity

and mortality, including the postoperative development of steatohepatitis. Only a few reports have explored the relationship between pancreaticoduodenectomy and the development of steatohepatitis^[22]. Therefore, we aimed to identify the risk factors for steatohepatitis after pancreaticoduodenectomy, with a particular focus on factors related to pancreatic secretions.

MATERIALS AND METHODS

Patient demographics and clinical variables

All study procedures were approved by the Institutional Review Board (No. 2010-09-082, Samsung Medical Center). The study included 228 patients who had pylorus-preserving pancreaticoduodenectomy (PPPD), Whipple's procedure, or hepato-pancreato-duodenectomy (HPD) between January 2009 and April 2010. Electronic medical records and data were retrospectively reviewed. Exclusion criteria were: (1) patients without non-enhanced computed tomography (CT) findings ($n = 12$); (2) a preoperative diagnosis of fatty liver disease by non-enhanced CT ($n = 19$); and (3) mortalities resulting from postoperative pseudoaneurysm ($n = 4$). Thirty-five patients who consumed more than 150 g of alcohol per week were not excluded from the study because they did not have a diagnosis of preoperative fatty liver disease by non-enhanced CT. The final study group therefore consisted of 193 patients that were divided into two groups: Group A consisted of 15 patients who developed postoperative steatohepatitis, and Group B consisted of 178 patients who did not develop postoperative steatohepatitis.

Data were collected on patient demographics, operative procedures, pathologies, and perioperative clinical variables, including levels of insulin, C-peptide, and glucagon, and results from an oral glucose tolerance test conducted preoperatively. Data were also collected on postoperative liver function and the postoperative attenuation ratios for the liver and spleen.

Data on pancreatic enzyme levels in serum on postoperative day 7, pancreatic duct size, pancreatic fistula, pancreatic duct stenting, and type of stenting were collected and considered as potential parameters associated with pancreatic secretions. Pancreatic fistula was diagnosed according to the International study group pancreatic fistula (ISGPF) definition^[23]. External pancreatic duct stenting was usually placed during the first postoperative month. Post-discharge pancreatic enzyme supplementation was administered routinely to all patients who had a pancreaticoduodenectomy.

Evaluation of steatohepatitis

Fatty liver disease was defined according to the difference between the splenic and hepatic attenuation ratios (CT_{S-L}) and the liver-to-spleen attenuation ratio ($CT_{L/S}$). To minimize sampling error, we used two CT images from the liver, one from the right lobe and one from the left lobe, and we excluded images from the periphery of the liver. Perioperative steatohepatitis was presumed when CT_{S-L}

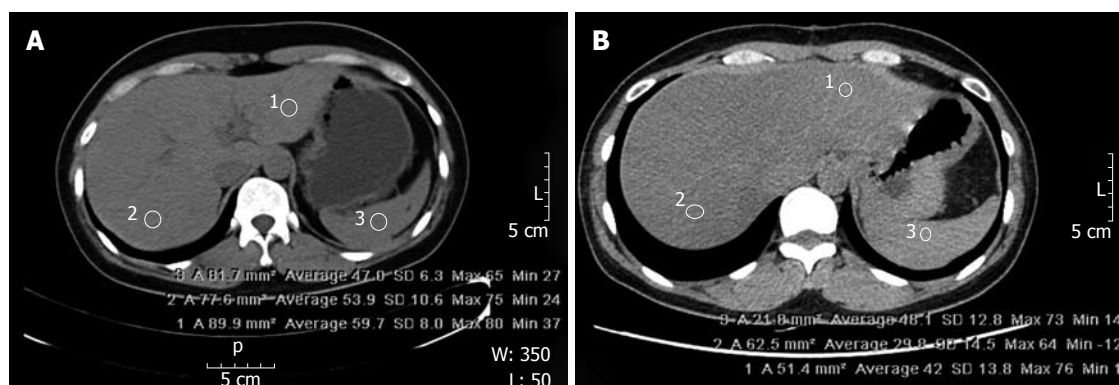


Figure 1 Preoperative and postoperative non-enhanced computed tomography images of a representative patient demonstrating different attenuation values for the spleen and liver. The inclusion criteria were: (1) $CT_{S-L} \geq 10$ Housefield unit (HU); or (2) $CT_{L/S} \leq 0.9$ HU [L: Mean attenuation value for two random points (1, 2) of the liver; S: Attenuation value for one random point (3) of the spleen]. A: Preoperative; B: Postoperative.

Table 1 Preoperative characteristics and laboratory findings for the two groups

| | Group A (n = 15) | Group B (n = 178) | P |
|---|------------------|-------------------|-------|
| Gender (M:F), n | 7:8 | 112:66 | 0.270 |
| Age in years, mean (range) | 58.7 (40-74) | 61.8 (15-81) | 0.295 |
| BMI (kg/m^2) \pm SD | 20.6 \pm 2.9 | 22.0 \pm 3.3 | 0.082 |
| Hepatitis B viral infection (+), n (%) | 0 (0) | 6 (3.4) | 1.000 |
| Type II diabetes, n (%) | 2 (13.3) | 34 (19.1) | 0.582 |
| Alcohol consumption > 150 g/wk, n (%) | 3 (20.0) | 32 (18.0) | 0.738 |
| Biliary drainage, n (%) | 4 (26.7) | 74 (41.6) | 0.245 |
| Albumin/globulin ratio (range) | 1.79 (1.2-4.1) | 1.53 (0.8-2.4) | 0.234 |
| Total cholesterol (mg/dL), mean (range) | 209.3 (136-309) | 200.6 (73-470) | 0.641 |
| Serum amylase (U/L), mean (range) | 91.3 (22-263) | 129.8 (15-1361) | 0.388 |
| Serum lipase (U/L), mean (range) | 170.4 (24-707) | 336.7 (7-13562) | 0.593 |
| AST (U/L), mean (range) | 134.3 (11-547) | 111.7 (12-1230) | 0.621 |
| ALT (U/L), mean (range) | 156.1 (11-551) | 144.0 (9-1371) | 0.826 |
| ALP (U/L), mean (range) | 315.9 (64-913) | 267.3 (34-2236) | 0.518 |
| INR, mean (range) | 0.99 (0.85-1.11) | 1.07 (0.81-8.78) | 0.585 |
| Total bilirubin (mg/dL), mean (range) | 5.7 (0.3-18.8) | 6.2 (0.2-44.3) | 0.799 |
| Fasting glucose (mg/dL), mean (range) | 140 (93-150) | 135 (47-458) | 0.735 |

BMI: Body mass index; SD: Standard deviation; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; INR: International normalized ratio.

was equal to or greater than 10 Housefield Units (HU) or when $CT_{L/S}$ was equal to or less than 0.9 HU (Figure 1).

CT images were obtained with a 64-channel, 4-multi-detector, CT scanner (General Electric®, NY, United States). The parameters for non-enhanced CT were: 100-300 mAs; rotation speed of 0.6 s; table speed of 3 mm; noise index of 11.57; detector coverage of 40 mm; pitch-to-speed ratio (mm/rot) of 0.984:1; and helical thickness of 5 mm. CT images were reviewed on a Picture Archiving Communication System workstation (General Electric®).

Statistical analysis

For continuous variables, the paired-sample Student's *t* test was used to compare the two patient groups. For categorical variables, Chi Square analysis or Fisher's exact test was used to compare the two groups. Two-way Analysis of Variance was used to analyze group differences in repeated measures of the levels of glucose, insulin,

C-peptide, and glucagon. Pearson's correlation coefficient test was used to determine the correlation between the postoperative difference of CT_{S-L} and the postoperative liver function test results. Multivariate analysis of risk factors was conducted using multivariate Cox proportional hazards modeling. Statistical analyses were performed using SPSS, version 16.0 (SPSS Inc., Chicago, IL, United States), and *P* values < 0.05 were considered statistically significant.

RESULTS

Perioperative clinical characteristics

The mean period between the operation and the patient's postoperative follow-up appointment was 3.2 ± 2.0 mo (range: 1-11). For each group, the average period was 2.4 mo in Group A and 3.3 mo in Group B (*P* = 0.106). Fifteen patients (7.8%) who showed postoperative hepatic fatty changes were included in Group A,

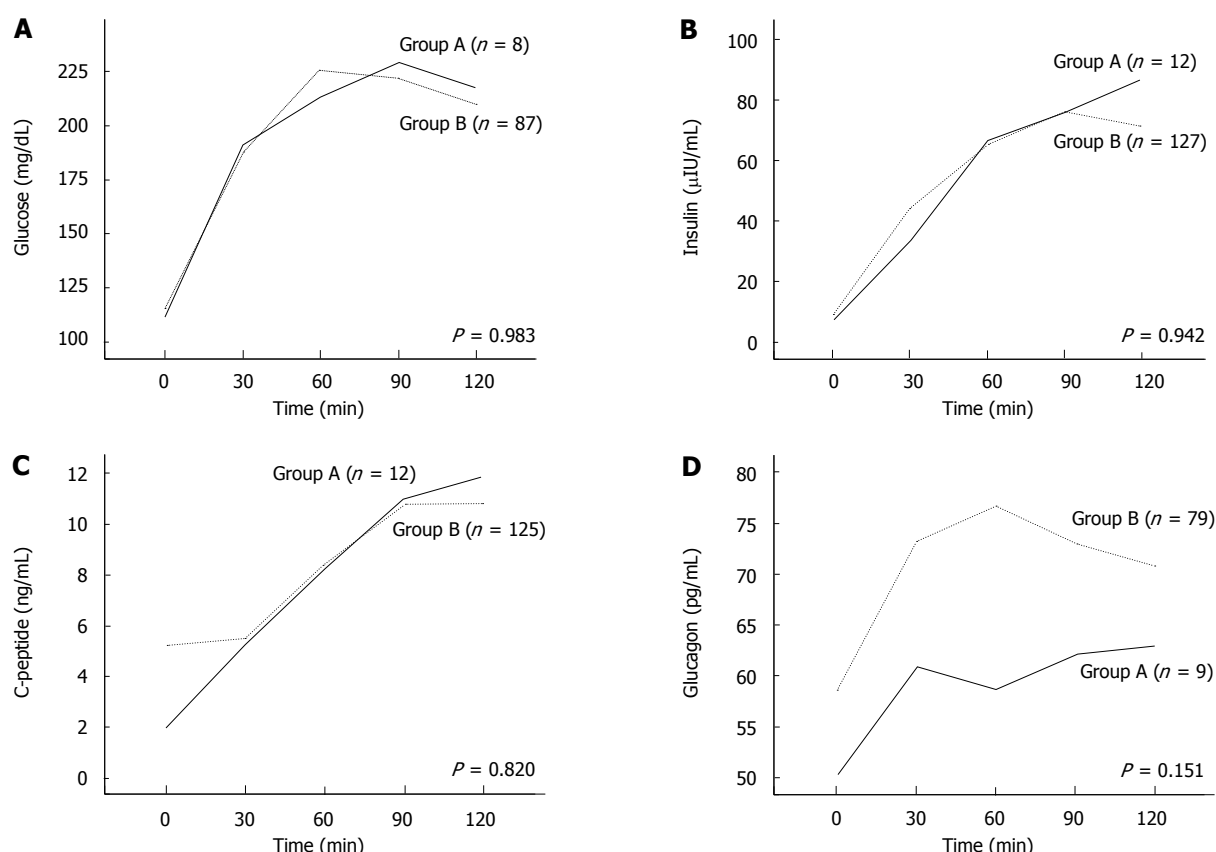


Figure 2 Preoperative oral glucose tolerance test results, continuous stimulation test results for insulin, C-peptide, and glucagon levels. A: Glucose levels; B: Insulin levels; C: C-peptide levels; D: Glucagon levels.

Table 2 Operative treatments and final pathological findings for the two groups

| | Group A (<i>n</i> = 15) | Group B (<i>n</i> = 178) | <i>P</i> |
|---|-----------------------------|------------------------------|----------|
| PPPD | 12 | 126 | 0.482 |
| Whipple's procedure | 3 | 47 | |
| HPD | 0 | 5 | |
| Pancreatic cancer | 7 | 50 | 0.665 |
| Common bile duct cancer | 3 | 45 | |
| Ampulla of Vater cancer | 5 | 27 | |
| Duodenal cancer | 0 | 11 | |
| IPMN of pancreas | 0 | 23 | |
| NET of pancreas or duodenum | 0 | 3 | |
| MCN or SPT of pancreas | 0 | 5 | |
| Duodenal GIST | 0 | 2 | |
| Hilar cholangiocarcinoma | 0 | 4 | |
| Colon cancer with duodenal invasion | 0 | 4 | |
| Gallbladder cancer with duodenal invasion | 0 | 1 | |
| Pancreatitis | 0 | 3 | |

PPPD: Pylorus-preserving pancreaticoduodenectomy; HPD: Hepato-pancreato-duodenectomy; IPMN: Intraductal papillary mucinous neoplasm; NET: Neuroendocrine tumor; MCN: Mucinous cystic neoplasm; SPT: Solid pseudopapillary tumor; GIST: Gastrointestinal stromal tumor.

and the remaining 178 patients (92.2%) were included in Group B (Table 1). Seventy-eight patients (40.4%) had preoperative biliary drainage, including percutaneous transhepatic biliary drainage, endoscopic retrograde biliary drainage, endoscopic nasobiliary drainage,

and biliary stenting. None of the patients had undergone bariatric surgery (data not shown).

Preoperative patient characteristics and laboratory findings, including liver function test results and levels of pancreatic enzymes, were similar in the two groups (Table 1). PPPD or Whipple's procedure was performed on 15 patients (100%) in Group A and 173 patients (97.2%) in Group B ($P = 0.842$) (Table 2). HPD was performed on 5 patients (2.8%) in Group B. Based on final pathologic reports, all patients (100%) in Group A were diagnosed with malignant disease, whereas patients in Group B were diagnosed with a variety of diseases (Table 2). Preoperative oral glucose tolerance test results, continuous stimulation test results for insulin, C-peptide and glucagon levels were not significantly different between the two groups (Figure 2). For patients with malignant disease, the two groups were similar in terms of cancer stage ($P = 0.190$), perineural invasion ($P = 0.259$), and vessel invasion ($P = 1.000$). The liver function test for all patients showed that postoperative $CT_{L/s}$ values correlated with postoperative ALT levels ($\gamma = -0.149$, $P = 0.039$) but not with postoperative AST or ALP levels (Table 3).

Factors associated with pancreatic secretions

Serum levels of pancreatic enzymes on postoperative day 7, pancreatic duct size, and the proportion of patients that received a pancreatic duct stent were similar in the two groups (Table 4); however, the proportion

Table 3 Pearson's correlation coefficients for the correlation between postoperative liver function and the difference in the postoperative attenuation values between the spleen and liver (CT_{S-L}) in all patients

| Postoperative liver function test result | γ | <i>P</i> |
|--|----------|----------|
| AST | -0.138 | 0.056 |
| ALT | -0.149 | 0.039 |
| ALP | -0.023 | 0.755 |

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

of patients that developed a pancreatic fistula postoperatively ($P = 0.020$) or had an external pancreatic duct stent placed ($P = 0.005$) was higher in Group A than in Group B (Table 4). A multivariate analysis of risk factors identified the postoperative development of a pancreatic fistula ($HR = 3.332$, $P = 0.037$) and the postoperative placement of an external pancreatic duct stent ($HR = 4.530$, $P = 0.017$) as independent risk factors for postoperative steatohepatitis (Table 5). Among the 41 patients who showed postoperative pancreatic fistula in the two groups, 32 and 9 patients showed grade A and B fistulas guided by ISGPF definition, respectively. Grade A fistula was observed in 6 patients (85.7%) in group A, and in 26 patients (76.5%) in group B ($P = 1.000$).

DISCUSSION

Steatohepatitis associated with pancreatic secretions

Duct-to-mucosal anastomosis and pancreatic duct stenting are used to prevent pancreatic leakage. In our institution, pancreatic stenting is usually performed when the diameter of the pancreatic duct is 2-5 mm, although there is some variability according to the attending surgeon's preferences. The methods chosen for pancreatic duct stenting in association with steatohepatitis involve several considerations. The remnant pancreas secretes several enzymes that are associated with digestion, including enterokinase, trypsinogen, chymotrypsin, amylase, lipase, cellulase, phospholipase, and esterase^[24-26]. External pancreatic duct stenting induces an earlier impairment in the secretion of pancreatic enzymes into the bowel lumen. Phospholipases A1 and A2 cleave fatty acids from phospholipids, and esterase hydrolyzes cholesterol esters. We hypothesize that hepatic fibrosis can be prevented by inhibiting the entry of free fatty acids into hepatocytes. Furthermore, lipid absorption by bile acid denaturation, which can lead to fat accumulation in hepatocytes, might be prevented by impairing bicarbonate secretion within the acidic gastric environment.

Adipokines such as leptin, resistin, adiponectin, and tumor necrosis factor (TNF)- α are known to regulate hepatic and peripheral glucose levels and lipid metabolism^[27]. Decreased serum levels of adiponectin and increased serum levels of leptin or TNF- α are associated with NASH. Also, the hydrolysis of starches and glycogen into disaccharides or trisaccharides by amylolytic

pancreatic enzymes can be impaired by external pancreatic duct drainage. These endocrine abnormalities are accelerated by the loss of insulin and glucagon, and they can induce insulin insensitivity and abnormal glucose metabolism.

Reduced motilities of the stomach and duodenum after pancreaticoduodenectomy can lead to the development of diabetes (20%-40%) with hyperglycemia and delayed gastric emptying (15%-40%), and a reduction in the release of pancreas-stimulating hormones from the duodenum (100%)^[28]. These effects can aggravate insulin resistance. Moreover, motility dysfunction can be induced by intestinal bacterial overgrowth as well as anatomic alterations that may result from anastomotic procedures. Wu *et al.*^[29] found that decreased small intestinal motility was associated with delayed intestinal transit followed by bacterial overgrowth (*Escherichia coli*) in a rat model of NASH. Furthermore, patients who have undergone a pancreaticoduodenectomy are at increased risk of developing an ascending infection through hepaticojejunostomy and jejunojunctionostomy. The effectiveness of antibiotics for decreasing elevated liver enzymes in NASH needs to be further investigated, however.

A previous study^[23] identified the duration of untreated jaundice, malignancy, small pancreatic duct size, and soft pancreatic texture as risk factors for pancreatic fistula. The relationship between pancreatic fistula and steatohepatitis is still questionable, but the use of long-term total parenteral nutrition or the development of a secondary infection or sepsis after a pancreatic fistula might influence hepatic function.

Other factors related to steatohepatitis

High levels of low density lipoprotein-cholesterol (LDL-C) and low levels of high density lipoprotein-cholesterol (HDL-C) are established risk factors for atherogenesis in patients with diabetic dyslipidemia^[30]. Insulin resistance is a key factor in the development of metabolic syndrome involving dyslipidemia and Type II diabetes. Dyslipidemia is associated primarily with low levels of HDL-C, high levels of LDL-C, and hepatic overproduction of triglyceride-rich very low density lipoprotein-cholesterol (VLDL-C)^[31]. In the present study, LDL-C levels tended to be higher in Group A than in Group B, but this apparent difference was not significant (data not shown); therefore, the relationship between LDL-C and steatohepatitis remains to be determined.

Bariatric surgery is often considered for patients who are morbidly obese. Roux-en-Y gastric bypass, gastropasty, or adjustable gastric banding are commonly performed, and jejunioileal or ileoileal bypass surgeries are no longer preferred^[4,3]. Biliopancreatic diversion that involves a small bowel bypass procedure to form a short common channel from the ileocecal valve can induce metabolic derangement and is associated with a high incidence of postoperative hepatic steatosis^[3,32]. This is caused by a combination of malnutrition and malabsorption of vitamins, iron, ferritin, and calcium. Pancreaticoduodenectomy involving a Roux-en-Y jejunojunctional bypass appears

Table 4 Perioperative clinical variables related to pancreatic secretions

| | Group A (n = 15) | Group B (n = 178) | P |
|---|------------------|-------------------|-------|
| Serum amylase ¹ , mean (range) | 44.5 (9.0-119.0) | 51.4 (6.0-266.0) | 0.558 |
| Serum lipase ¹ , mean (range) | 31.9 (6.0-266.0) | 30.0 (1.0-215.0) | 0.793 |
| Pancreatic duct size, mean (range) (mm) | 4.5 (2-18) | 3.5 (1-11) | 0.401 |
| Pancreatic fistula ² , n | 7 | 34 | 0.020 |
| Placement of pancreatic duct stent, n | 13 | 131 | 0.363 |
| Internal, n | 4 | 95 | 0.005 |
| External, n | 9 | 36 | |

¹Postoperative day 7; ²Diagnosed according to International study group pancreatic fistula criteria^[23].

Table 5 Multivariate analysis of risk factors for the development of steatohepatitis after pancreaticoduodenectomy¹

| Variables | HR | 95% confidence interval | P |
|-------------------------------------|-------|-------------------------|-------|
| Serum amylase ² | 0.990 | 0.973-1.007 | 0.262 |
| Serum lipase ² | 1.014 | 0.986-1.041 | 0.332 |
| Pancreatic duct size ³ | 0.882 | 0.635-1.224 | 0.452 |
| Pancreatic fistula ⁴ (-) | 1.000 | - | - |
| Pancreatic fistula ⁴ (+) | 3.332 | 1.075-10.321 | 0.037 |
| Internal pancreatic duct stenting | 1.000 | - | - |
| External pancreatic duct stenting | 4.530 | 1.312-15.643 | 0.017 |

¹Analyzed by logistic regression; ²Postoperative day 7; ³Dichotomized for categorical variables using a median split; ⁴Diagnosed according to International study group pancreatic fistula criteria^[23]. HR: Hazard ratio.

to be associated with the same side-effects as small bowel bypass surgery. We also found that all patients with postoperative steatohepatitis had malignant pathological findings, but the pathogenesis remains uncertain.

Diagnostic methods to identify fatty liver disease

Histological evaluation through liver biopsy remains the gold-standard method for distinguishing NASH from simple fatty liver disease and for estimating intrahepatic fat content, the extent of necroinflammatory lesions and fibrosis. However, liver biopsy is associated with sampling errors and the risk of bleeding, infection, and biliary leakage^[1,6,8,20,33]. Kleiner *et al.*^[15] proposed a semi-quantitative scoring system (the NAFLD activity score) to assess the histological features of NAFLD and to discriminate between NASH and non-NASH fatty liver disease. Five features-steatosis, hepatocellular ballooning, lobular inflammation, fibrosis, and the absence of lipogranulomas-were independently associated with the accurate diagnosis of NASH using adult liver biopsies.

Ultrasonography, non-enhanced CT, magnetic resonance imaging, and proton magnetic resonance spectroscopy (¹H MRS) are radiological, non-invasive methods to diagnose hepatic steatosis^[1,4,16], but these methods cannot accurately distinguish NASH from simple fatty liver disease or objectively quantify fat content^[1,6]. Recently, fatty infiltration of the liver was detected using chemical-shift imaging and a selective fat-suppression technique, acquired by the percentage of relative signal intensity loss on magnetic resonance T1- or T2-weighted images, the ratio of peak lipid to water by ¹H MRS, dual-energy

multi-slice spiral CT, and non-enhanced CT measuring tissue density as a radiographic attenuation that can be objectively measured in Housefield units^[16,34]. In a study by Nomura *et al.*^[22], non-enhanced CT was found to be useful for diagnosing steatohepatitis with established accuracy and for evaluating CT_{L/S} and CT_{S-L}. Other studies identified a correlation between CT_{L/S} and CT_{S-L} and histological findings of steatohepatitis, and some reports defined steatohepatitis as CT_{L/S} < 0.9 HU or CT_{S-L} ≥ 10 HU^[16,35]. Unlike the study by Nomura *et al.*^[22], which identified a relationship between postoperative AST and CT_{S-L}, our study found that CT_{S-L} correlated significantly with postoperative ALT levels, not AST levels. Kato *et al.*^[36] proposed a NAFLD scoring system that was based on the development of pancreatic adenocarcinoma, the pancreatic resection line, and postoperative diarrhea. This group diagnosed NASH by percutaneous liver biopsy after pancreaticoduodenectomy and revealed a significant correlation between their scoring system and CT findings.

Limitations

The present study has several limitations that should be considered when interpreting the results. First, the study was retrospective, and the period between the operation and the postoperative follow-up CT was not uniform and averaged 3.2 mo, which is short. Nevertheless, if we consider the prevalent period for the development of steatohepatitis postoperatively, the results could present useful information.

Second, there were only 15 patients (7.8%) who developed steatohepatitis after surgery in our study, whereas in the study by Nomura *et al.*^[22] 33% of asymptomatic patients without severe obesity had decreased hepatic attenuation meeting the criteria for steatohepatitis after pancreaticoduodenectomy. The reason for the difference in the incidence between our study and that of Nomura *et al.* is not clear, but it might reflect differences in the rates of obesity and the timing between the operation and the follow-up CT scan. Our study had a very small number of obese patients (24 patients with a BMI ≥ 25 kg/m² and 2 patients with a BMI ≥ 30 kg/m²).

Third, we used a radiological method to diagnose steatohepatitis or NAFLD without histopathological evidence. Non-enhanced CT was reported to have a sensitivity of 73%-100% and a specificity of 95%-100% for the detection of moderate or severe steatohepatitis, al-

though hepatic iron overload might alter these rates^[1,37].

Finally, the location and the extent of the pancreatic resection and postoperative patient-related factors such as steroid use, weight loss, and exercise were not included in our statistical analyses. In addition, the effect of adjuvant chemoradiotherapy, which was administered to 7 patients (46.7%) in Group A and 80 patients (44.9%) in Group B, was not included in our analysis.

Future prospective controlled studies with a larger sample size based on histopathological findings are needed to verify the relationships identified in the present study. Postoperative steatohepatitis might not be a significant problem, especially in late-stage malignant patients. Nevertheless, this preliminary report provides evidence for operation-related causes of steatohepatitis following pancreaticoduodenectomy, ruling out other factors causing hepatic fatty change or injury.

COMMENTS

Background

Only a limited number of reports have examined operation-related causes of postoperative steatohepatitis following pancreaticoduodenectomy.

Research Frontiers

To identify the risk factors for steatohepatitis after pancreaticoduodenectomy, with a particular focus on factors related to pancreatic secretions.

Innovations and breakthroughs

This preliminary report helps to identify operation-related causes of steatohepatitis following pancreaticoduodenectomy, and it is the first study to identify potential risk factors related to pancreatic secretions.

Applications

In this study, pancreatic fistula and external pancreatic duct stenting significantly influenced the development of steatohepatitis following pancreaticoduodenectomy. These findings have clinical implications and could be used to design future clinical trials.

Peer review

This is very interesting clinical research about the mechanism of post-operative steatohepatitis development following pancreaticoduodenectomy.

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