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ORIGINAL ARTICLE

Early detection of anastomotic leakage after pancreatoduodenectomy with microdialysis catheters: an observational Study

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Abstract

Background: Microdialysis catheters can detect focal inflammation and ischemia, and thereby have a potential for early detection of anastomotic leakages after pancreatoduodenectomy. The aim was to investigate whether microdialysis catheters placed near the pancreaticojejunostomy can detect leakage earlier than the current standard of care.

Methods: Thirty-five patients with a median age 69 years were included. Two microdialysis catheters were placed at the end of surgery; one at the pancreaticojejunostomy, and one at the hepaticojejunostomy. Concentrations of glucose, lactate, pyruvate, and glycerol were analyzed hourly in the microdialysate during the first 24 h, and every 2–4 h thereafter.

Results: Seven patients with postoperative pancreatic fistulae (POPF) had significantly higher glycerol levels ($P < 0.01$) in the microdialysate already in the first postoperative samples. Glycerol concentrations >400 μmol/L during the first 12 postoperative hours detected patients with POPF with a sensitivity of 100% and a specificity of 93% ($P < 0.001$). After 24 h, lactate and lactate-to-pyruvate ratio were significantly higher ($P < 0.05$) and glucose was significantly lower ($P < 0.05$) in patients with POPF.

Conclusion: High levels of glycerol in microdialysate was an early detector of POPF. The subsequent inflammation was detected as increase in lactate and lactate-to-pyruvate ratio and a decrease in glucose (NCT03627559).

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Introduction

Pancreatoduodenectomy (PD) offers the only potential cure for patients with pancreatic and periampullary cancer. Historically, the procedure has been associated with high perioperative and postoperative mortality and morbidity, but over the past few decades the results have gradually improved along with advances in radiological and surgical techniques, as well as in anesthesiological and postoperative management. Today, the perioperative mortality is less than 5% in high volume centers.[1,2] However, patients undergoing PD are still at risk of postoperative complications such as anastomotic leaks, postoperative pancreatic fistulae (POPF), delayed gastric emptying, hemorrhage and infections. Between 20 and 65% of patients experience at least one complication requiring readmission and/or prolonged hospital stay.[3–5]

POPF is the most feared complication, and often discovered diagnosed with a significant delay, resulting in the development of peritonitis, and potentially with secondary organ dysfunction

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and sepsis.[3,6] The current standard of care for detection of POPF include measurement of pancreatic amylase and bilirubin in fluids from surgical drain, blood samples revealing increased white blood cell count, C-reactive protein, and procalcitonin, abdominal computed tomography scan and clinical signs of peritonitis. However, none of these are specific for POPF in the early postoperative period. Prompt detection of POPF is essential in enabling early intervention, and improving the outcome for patients undergoing PD.

Microdialysis catheters placed in or in close proximity to organs or tissues allow repeated bedside measurements of parameters of metabolism such as lactate, pyruvate, glucose, and glycerol within a microenvironment. The method is clinically being used for detecting complications in e.g. liver grafts,[7,8] large intestinal anastomoses,[9–11] and brain tissue.[12–15] Ischemia is typically detected as increased lactate and lactate-to-pyruvate ratio,[7,8] and with concurrent cell damage, glycerol level in the microdialysate is also increased. Ansorge and colleagues[16] have shown that patients who developed POPF after PD had higher levels of glycerol and lactate-to-pyruvate ratio in microdialysate collected near the pancreaticojejunostomy on the first postoperative day (POD) after surgery compared to patients with other complications and those with an uneventful postoperative recovery.

The aim of the present study was to explore if monitoring the pancreaticojejunostomy and the hepaticojejunostomy with microdialysis catheters could detect anastomotic leakages earlier than the current standard of care. We hypothesized that reduced tissue perfusion/ischemia in the anastomoses can cause the development of pancreatic and biliary fistulae. Consequently, we hypothesized that any patient developing a fistula would present with an initial increase in lactate and lactate-to-pyruvate ratio, reflecting ischemia, followed by increments of glycerol, reflecting cellular degradation and necrosis of fatty tissue.

Methods

Study design

The study was carried out at Oslo University Hospital – Rikshospitalet, a tertiary referral hospital for patients with pancreatic and periampullary tumors eligible for surgery in the South-Eastern Health Region in Norway (population of approximately 3.0 million). It was designed as a prospective, observational, one-armed open-label study with no defined interventions or treatments based on the results of microdialysis. The study protocol was approved by the regional ethical committee in southeastern Norway (reference number: 2012/143) and conducted according to the Helsinki declaration. We adhered to the guidelines and checklists in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cohort studies (www.strobe-statement.org). The study was registered in www.clinicaltrials.gov (NCT03627559).

Study population

All patients scheduled for PD during a six month period were asked to participate in the study. The inclusion criteria were tumor in the head of the pancreas, bile duct, ampulla Vateri or the duodenum detected on a computed tomography scan or magnetic resonance imaging, and deemed by a multidisciplinary team to be resectable with a PD. Written, informed consent was obtained before study enrollment.

The pancreatic anastomosis was performed in a two-layer fashion, end-to-side pancreaticojejunostomy in all patients. An internal row of sutures, duct-to-mucosa, was performed between the pancreatic duct and jejunal mucosa. The external row of sutures was performed as a single running suture between the remnant pancreatic capsule, parenchyma, and jejunal seromuscular layer. A baby feeding tube (Unomedical feeding tube, Convatec, Berkshire, United Kingdom), size 3, 5 or 8 Fr was inserted as a pancreatic-duct-to-mucosa-stent in all patients. Hepaticojejunostomy was performed in an end-to-side fashion, approximately 15–20 cm distally to the pancreaticojejunostomy. An antecolic end-to side gastro- or duodenojejunostomy was then carried out 40–50 cm downstream. Starting intraoperatively, intravenous pantoprazole 40 mg daily and subcutaneous octreotide 100 μg every 8 h was administered for 7 days. An active 19 Fr Blake drain (Ethicon – Johnson & Johnson, New Jersey, USA) was placed near the pancreatic and biliary anastomosis. Measurements of amylase and bilirubin in the surgical drain fluid were performed in all patients at POD 2 and 3, and on indication thereafter. The drain was removed on POD 3, unless the effluent was bile-, enteric stained, turbid, or had high levels of amylase or triglycerides (chylous effusion).

Definitions

Patients were retrospectively classified into low-, intermediate- and high-risk for POPF according to the alternative fistula risk score for PD developed by Mungroop et al.[17] Because of the retrospective nature of the classification, we were unable to do this in a blinded fashion. In 2016 an update of the International Study Group on Pancreatic Fistula (ISGPF) redefined POPF as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper institutional normal serum amylase level, associated with a clinically relevant development or condition related directly to the POPF.[18] POPF was graded for severity into B or C and formerly grade A was no longer considered a true POPF and with no clinical impact. In this study we define POPF in line with the 2016 criteria and data are presented accordingly. Postoperative bile leakage was defined according to the definition of the International Study Group of Liver Surgery.[19] Other intra-abdominal surgical complications were defined as the need for a re-operation (Clavien–Dindo IIIb) or percutaneous drainage of any reason other than pancreatic or biliary fistula (Clavien–Dindo IIIa).

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Microdialysis

The microdialysis system is illustrated in Fig. 1.

At the end of the surgical procedure, before closing the abdominal wall, two custom made microdialysis catheters with 300 mm shaft length and a 30 mm long microdialysis membrane with molecular weight cutoff of 100 kDa and with a diameter of <1 mm (CMA 65; MDialysis AB, Stockholm, Sweden) were inserted percutaneously through a hypodermic needle (14G X 3 $^1/_2$ ", Sterican, B. Braun AG, Melsungen, Germany) and anchored with a 5-0 absorbable suture to surrounding tissue in close vicinity (<1 cm) to the pancreaticojejunostomy and the hepaticojejunostomy respectively. The microdialysis catheters were perfused with 60 mg/ml hydroxyethyl starch (Voluven®; Fresenius Kabi AS, Halden, Norway) at a rate of 1 μL/min (CMA 107; MDialysis AB, Stockholm, Sweden) starting immediately after skin closure. The samples were analyzed bedside, every hour for the first 24 h and every 2–4 h thereafter for glucose, glycerol, lactate, and pyruvate (Iscus; M Dialysis AB, Stockholm, Sweden). The catheters were kept in situ until the patient was discharged or we were unable to retrieve measurable samples from the catheters. Arterial and venous blood gases were analyzed on indication (Radiometer® ABL 90; Copenhagen, Denmark) and blood samples for routine biochemical tests including C-reactive protein were obtained at least once daily for the entire postoperative stay.

Statistical analysis

Microdialysis parameters are presented as median with interquartile range. A linear mixed model for the analysis of repeated measurements was used to search for potential time dependencies and differences dependent on group or patient. The measured metabolic mediators were dependent variables. A random effects model was used, and model selection was performed for each variable by selecting the model achieving the lowest Akaike's information criteria. The random effects of patients and groups were included in the model. For laboratory values other than those collected with microdialysis catheters, the Wilcoxon signed-rank test was performed for repeated measurements, and the Mann–Whitney U test was used for group comparisons. Receiver operating characteristic (ROC) curves were created to explore the ability of the investigated variables to discriminate patients with postoperative complications, such as POPF and bile leakage, from patients with uneventful postoperative recovery. The area under the curve was calculated for multiple postoperative periods. The optimal cutoff value for each variable was defined as the value closest to the top left corner, and these values were used for contingency table analyses to determine sensitivity and specificity. A 2-tailed *P*-value <0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics version 22 (IBM, Armonk NY, USA).

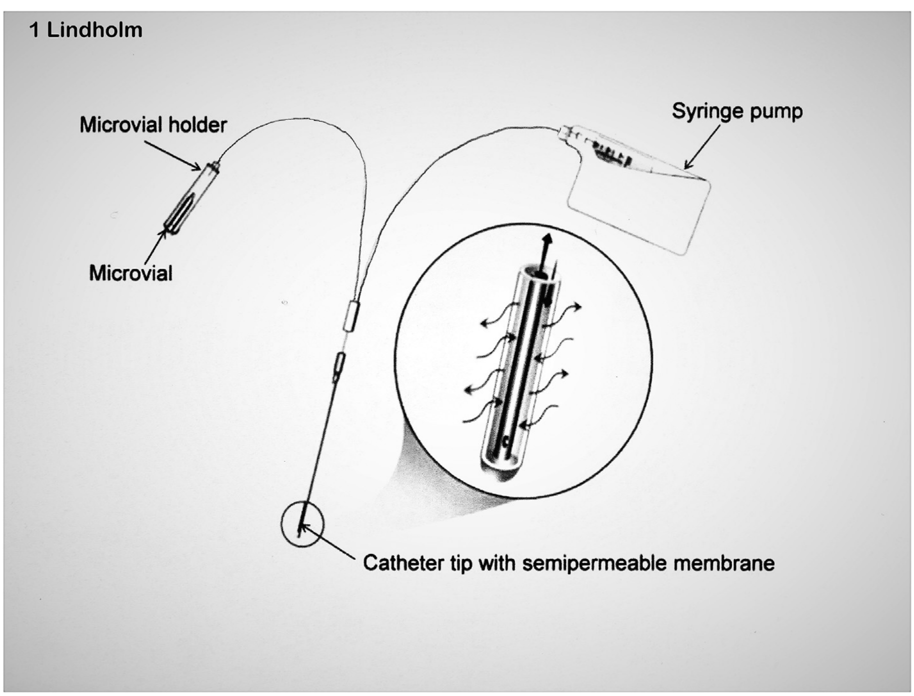

Figure 1 Microdialysis system. The double-lumen microdialysis catheter is perfused with a fluid containing hydroxyethyl starch 60 mg/ml and electrolytes by a small syringe pump at a velocity of 1 μL/min. The semipermeable membrane at the tip allows metabolic substances and inflammatory mediators to pass along their pressure gradient and mix with the fluid inside the catheter. The fluid (ie, the microdialysate) is collected in microvials, which can be analyzed at the bedside with a microdialysis analyzer (not depicted). Reprinted with permission from M Dialysis AB (Stockholm, Sweden)

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Results

Study population

Thirty-five patients (20 female, 15 male) with a median age of 69 years (range, 44–88 years) were included. Baseline demographics and intra- and postoperative characteristics for patients are given in Table 1. Screening of the patients with alternative fistula risk score for PD classified the patients as shown in Table 2. Eight patients (23%) had a risk score ≥15% and six (75%) of these developed POPF. Two patients, with a risk score of 10%, experienced a biochemical leakage and POPF grade C. Seventeen patients (49%) had one or more surgical complication, while 18 (51%) had an uneventful clinical and biochemical postoperative course, and served as a reference cohort (Fig. 2).

Table 2 Screening of the patients with alternative fistula risk score for PD

	Number of patients (%)	Observed number of patients with leakage (%)	Grade B	Grade C
Low risk	18 (51.4)	0 (0)	0	0
Intermediate risk	13 (37.1)	3 (23.1)	1	2
High risk	4 (11.4)	4 (100)	2	2

Table 1 Baseline demographics and intra- and postoperative characteristics for patients undergoing pancreatoduodenectomy (n = 35)

Variable	Value
Number of patients included (men/women)	35 (15/20)
Age (years)	68 ± 10
Body Mass Index (kg/m^2)	24 ± 4
Current or former smoker (n = 33)	15 (45)
Previous pancreatitis	3 (9)
Intraoperative findings	
Fluid balance (ml) (n = 33)	4580 ± 2337
Blood loss (ml) (n = 28)	609 ± 784
Patients receiving transfusion	9 (26)
Median amount transfused (ml) (n = 9)	250 (250)
Gland texture (hard/soft)	23 (66)/12 (34)
Pancreatic duct diameter (mm)	5.6 ± 3.2
Postoperative findings	
Histopathology	
Pancreatic adenocarcinoma	15
Cholangiocarcinoma	8
Ampullary adenocarcinoma of intestinal origin	2
Duodenal neuroendocrine carcinoma	1
Intraductal papillary mucinous neoplasm with development of adenocarcinoma	2
Pancreatic mucinous cystic neoplasm	1
Chronic pancreatitis	1
Type 1 autoimmune pancreatitis	1
Chronic duodenitis	1
Adenoma of the ampulla of Vater	1
Duodenal tubulovillous adenoma	1
Median length of stay at hospital (days)	8 (10)
With POPF	24 (38)
Without POPF	7 (3)

Values are mean ± SD or median with IQR or numbers of patients (men/women) or number (% of group). POPF: Postoperative pancreatic fistula.

In accordance with the 2016 ISGPF definition, seven patients (20%) developed POPF of which four also had a biliary fistula (11%). Three patients (9%) experienced a biochemical leakage. One patient had an isolated biliary fistula. Four POPF were severe (Grade C), of which three patients also developed a biliary fistula. In two patients with combined fistulae, the hepatic artery eroded causing severe hemorrhage and liver necrosis. One patient with combined fistulae was successfully reoperated with resuturing of the hepaticojejunostomy and occlusion of the pancreatic duct with polychloroprene Faxan-Latex (Oslo University Hospital Pharmacy). One patient died on POD 7 (isolated POPF, grade C). The patient experienced fever, abdominal pain, delayed gastric emptying, altered mental state, an elevated C-reactive protein and white blood cell count. Systemic broad spectrum antimicrobial treatment was commenced, and an ultrasound-guided drain was inserted on POD 6 into a peripancreatic abscess. An autopsy revealed a peripancreatic abscess and an acute myocardial infarction.

One patient had an isolated biliary fistula and was successfully treated with an ultrasound-guided percutaneous drainage. Six patients experienced other complications such as superficial surgical wound infection (n = 5), abdominal infection (n = 1), colon perforation (n = 1), chylous leakage (n = 1), and intraabdominal hemorrhage (n = 1) (Fig. 2). There were no complications related to the insertion or removal of the microdialysis catheters.

The median length of stay was 24 (IQR 9–30) days in patients with POPF and 7 (IQR 6.5–8), ($p = 0.004$) days in patients without POPF.

Pancreaticojejunal anastomosis microdialysis catheter

In the microdialysate from patients that had an uneventful recovery, glycerol was typically between 50 and 100 μmol/L in the beginning and thereafter stabilized at values around 50 μmol/L from POD 1 (Fig. 3a). Lactate was stable in the range 2–4 mmol/L (Fig. 3b) throughout the postoperative period resulting in a lactate to pyruvate ratio in the range 10–20 (Fig. 3c). Glucose had a circadian physiological variation with higher values during the daytime hours and decreasing gradually during late evening and night (Fig. 3d). Those who fulfilled criteria for POPF on POD 3 or

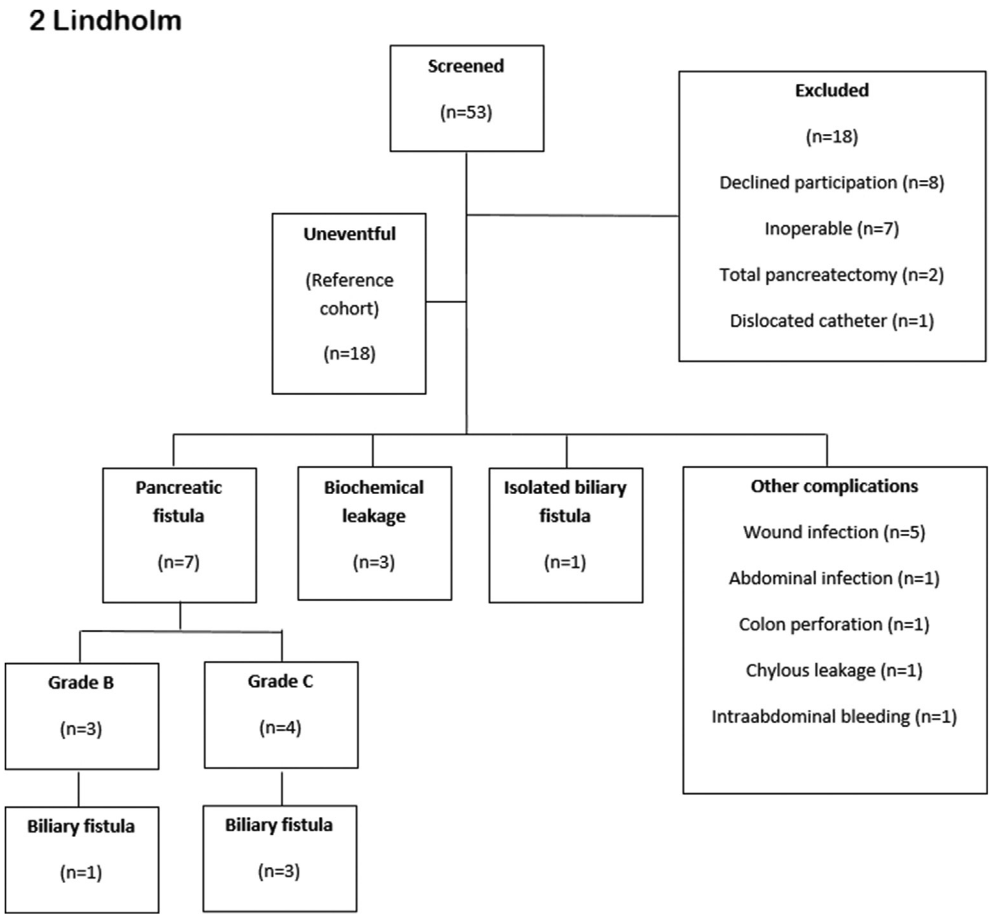

Figure 2 Flowchart. Flowchart of patients undergoing pancreatoduodenectomy monitored with microdialysis catheters postoperatively

later, had significantly higher glycerol concentrations already in the first postoperative sample obtained within 2 h postoperatively with a median of 854 µmol/L (range 347–2083) compared to the reference cohort (i.e. an uneventful recovery) with a median of 108 µmol/L (range 64–334) ($P < 0.001$), and the values remained elevated several hours with a median of 33 h (range 11–165) ($P < 0.001$) (Fig. 3a and Supplementary file 1). All values were higher than the pathological cut-off value of 400 µmol/L within the first 3.1 h in all patients with POPF.

During the first 12 h glycerol discriminated patients that were later diagnosed with POPF from the reference cohort with an area under the curve of 0.96 (95% confidence interval (CI) 0.91–1.00, $P < 0.001$), with an optimal cutoff value of 400 µmol/L. With three consecutive measurements of glycerol values higher than 400 µmol/L, POPF was detected with a sensitivity of 100% and a specificity of 93% and the positive predictive value was 78%. The negative predictive value for all patients with POPF was 100%.

Three patients fulfilled criteria for a biochemical leakage. The first patient had a high concentration of drain fluid amylase on POD 3 (5.3 times serum concentration), but glycerol concentrations in microdialysate below the cutoff level of 400 µmol/L (highest glycerol at 265 µmol/). The patient recovered uneventfully and was discharged on POD 7. The second patient had an amylase concentration in drain fluid on POD 3 of 3.6 times serum concentration. The microdialysis values showed glycerol concentrations above 400 µmol/L the first 22 h after surgery. Thereafter, a pathological rise in lactate and L/P-ratio occurred the next 30 h. An abdominal computed tomography was performed at POD 5 which revealed a fluid collection of probable infectious origin in close proximity to the pancreatic anastomosis. The surgical drain was kept for six days. No antibiotic or other POPF-related treatment was administered. The third patient had a drain fluid amylase concentration of 4.1 times serum concentration on POD 3. Initial glycerol value was 302 µmol/L 2 h after surgery. This increased steadily to 1376 µmol/L after 12 h where the values stabilized approximately at the same level until 30 h postoperatively. In addition this patient showed an increase in lactate and L/P- ratio on POD 2. The patient was reoperated on POD 7 due to a wound dehiscence. During the primary surgery some bile was collected for microbiological cultivation. Subsequent answer reported growth of *Enterococcus faecalis*, Klebisella pneumoniae and *Escherichia coli*. The patient was discharged to his local hospital at POD 9 were he received antibiotics and was treated for his wound infection for a further 4 weeks.

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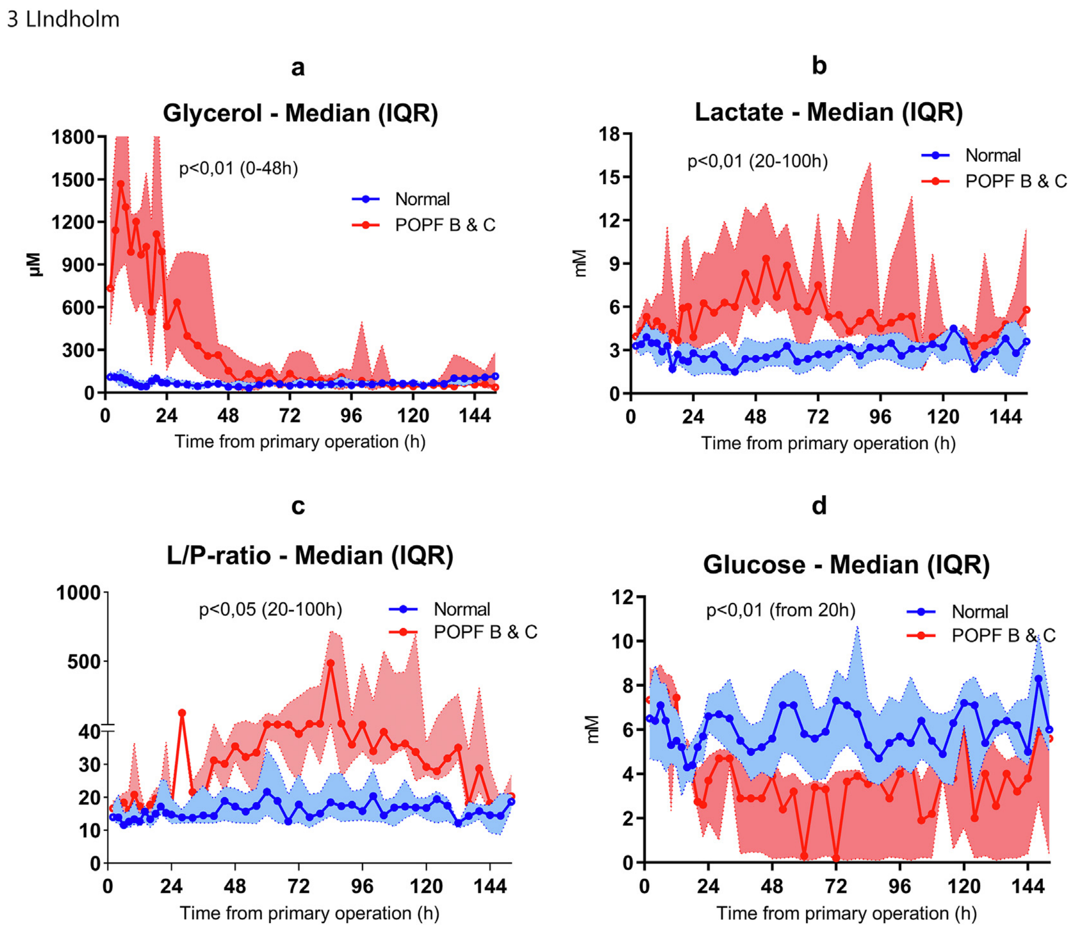

Figure 3 a, b, c, d - Postoperative microdialysis measurements from the pancreaticojejunal anastomosis. Postoperative microdialysis measurements in samples catheter in patients with pancreatic fistula after pancreatoduodenectomy (n = 7, red) and in patients with no complications (reference cohort, n = 18, blue). Glycerol (Fig. 3a), lactate (Fig. 3b), lactate-pyruvate ratio (Fig. 3c), and glucose (Fig. 3d) values during the postoperative course. Data are presented as median (line) and interquartile range (shadow)

The lactate values (Fig. 3b) were similar in the POPF and reference groups during the first 12–16 h postoperatively ($P > 0.05$). Thereafter, lactate increased significantly in patients with POPF ($P < 0.001$). The only exceptions appeared in the two previously mentioned biochemical leakage patients with an intraabdominal collection of probable infectious fluid and the patient with wound and bile infection. In these two patients, the lactate concentration increased gradually during the first 24 h after surgery. With lactate increase in the POPF group and no pyruvate increase ($P > 0.05$), the lactate-to-pyruvate ratio (Fig. 3c) increased significantly ($P = 0.02$). The glucose concentrations were similar in the two groups during the first 20–24 h ($P > 0.05$), but were thereafter significantly lower in the POPF group as compared to patients in the reference group ($P < 0.001$) (Fig. 3d).

Hepaticojejunal anastomosis microdialysis catheter

Five patients had a leakage from the hepaticojejunal anastomosis or bile duct of which four also had a pancreaticojejunal anastomotic leakage (Fig. 2). Fig. 4 shows a typical example of a patient with an initial pancreaticojejunal anastomosis leakage only. Interestingly, lactate increased 24–48 h later in samples from the hepaticojejunal anastomosis catheter compared to the pancreaticojejunal anastomosis catheter indicating a spread of leakage, erosion and inflammation from the pancreaticojejunal anastomosis to the hepaticojejunostomy.

Discussion

In this observational cohort of 35 patients undergoing PD, leakage from the pancreaticojejunostomy was detected as a high concentration of glycerol in samples from microdialysis catheters positioned close to the pancreaticojejunal anastomosis. All seven POPFs were identified by microdialysis during the first postoperative hours suggesting that POPF can be predicted with high accuracy almost immediately postoperatively. Two patients with biochemical leakage had high glycerol values above the calculated cut-off limit of 400 µmol/L, but both patients underwent other

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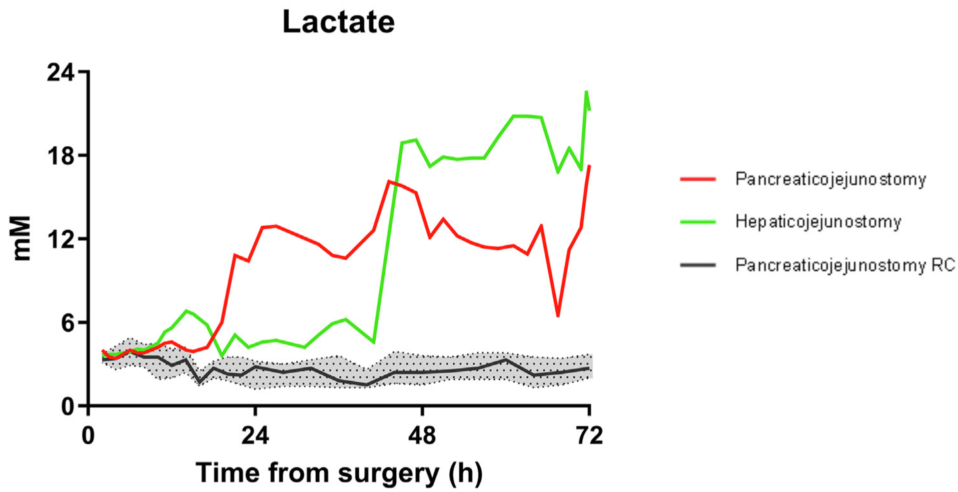

Figure 4 Lactate concentrations. Lactate concentrations in microdialysate at the pancreaticojejunostomy (red line) and hepaticojejunostomy (green line) from a patient with a pancreatic fistula after pancreatoduodenectomy. Lactate at the pancreaticojejunostomy in the reference cohort is presented as median (line) and interquartile range (shadow)

infectious complications which may explain the later increase in lactate and L/P-ratio as a sign of an inflammatory state. Interestingly, the first postoperative glycerol value obtained within 2 h after arrival in the postoperative care unit was higher than the pathological cut-off value of 400 μmol/L in all patients with POPF. Furthermore, with exception of the two above-mentioned biochemical leakage patients, no patients without POPF had three consecutive measurements of glycerol >400 μmol/L during the first 12 postoperative hours. Our data strongly suggest that the anastomotic leakage leading to a later clinically detectable POPF can be diagnosed rapidly, within hours, postoperatively with microdialysis. Earlier detection allows for intervention before clinical signs become apparent.

In contrast to a previous study where measurements of microdialysate were done on POD 1,[16] our data demonstrate that POPF can be detected already within the first 3 h postoperatively. Furthermore, measuring frequently from the time of arrival at the postoperative ward, we demonstrate the dynamic picture of a pathophysiological processes leading to, and following a POPF. The findings in our study may have important clinical implications. Firstly, our data suggest that anastomotic leakages can be detected early and thereby open for studies exploring the utility of early interventions. Secondly, during the first 12 h postoperatively, the sensitivity for the diagnosis of POPF grade B and C were 100% and specificity 93%. The high negative predictive value (100%) of low glycerol values for the development of POPF may guide early drain removal in patients who are not at risk of complications and thereby facilitate enhanced recovery.[20] This is a higher sensitivity and specificity than what has been reported in several systematic reviews and meta-analysis using the measurement of drain fluid amylase on POD 1−3 for the diagnosis of a POPF.[21−24] Moreover, measuring amylase activity in pancreatic fluid is associated with some methodological issues. Firstly, it is difficult to compare amylase levels measurement between different institutions due to variations in methods utilized.[25] Secondly, the optimal cut-off level of drain fluid amylase for making the diagnosis of a pancreatic leak is somewhat equivocal, as the cutoff values reported differs significantly and also varies between different types of pancreatic resections.[22,25] For these reasons, the authors in a recent Cochrane review expressed a level of skepticism whether drain fluid amylase activity should be used for diagnosing a pancreatic leak in an unselected population after pancreatic resection.[22]

An elevated glycerol level most likely reflects an ongoing leakage. Glycerol forms the backbone of triglycerides in adipocytes and phospholipids in cell membranes. A leakage of pancreatic lipase into the area surrounding the anastomosis most likely leads to cellular degradation of peripancreatic fat causing a release of glycerol to the peritoneal fluid.[26] Lactate and lactate-to-pyruvate ratio increased later than glycerol in patients with POPF and these increases most likely reflect inflammation and tissue ischemia following tissue break-down by pancreatic lipases and proteases. Inflammatory cells like neutrophils produce lactate when they are activated (oxidative burst).[27,28] This increased glycolysis requires a lot of glucose resulting in decreased tissue glucose, which was indeed observed. The decrease in glycerol on POD 2 may be due to increased consumption of glycerol by peritoneal and inflammatory cells and consumption by gram-negative (e.g. *E. coli*) and gram-positive (e.g. Enterococcus species) bacteria from the intestine.[29] Glucose levels fell to almost

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immeasurable levels during POD 2 in patients with POPF. Peritoneal and inflammatory cells as well as certain bacteria, will switch to glycerol as energy substrate by introducing it at the level of the glycolytic intermediate dihydroxyacetone-phosphate into the glycolysis metabolic pathway.[29] Consequently, the increased lactate and lactate-to-pyruvate ratio and decreased glucose reflect inflammation following pancreatic leakage and glucose depletion leads to glycerol consumption. This process is first detected by increased glycerol (Fig. 4). Accordingly, our hypothesis that anastomotic leakages are caused by tissue hypoperfusion or ischemia and detected as increased lactate and lactate-to-pyruvate ratio and that increases in glycerol would follow the increases in lactate and lactate-to-pyruvate ratio was not supported by our findings. Importantly, our data reveal that the leakage from the pancreaticojejunostomy is present immediately postoperatively and detected on the first sample, within 2–3 h after skin closure. Consequently, the leakage is due to an insufficient anastomosis present at the time of surgery and not caused by several days of erosion thereof.

The bile leak rate was 14.3% (5/35), in contrast to the previously reported average bile leak rate of about 5% at our institution.[30] In four patients both pancreaticojejunal and hepaticojejunal anastomotic leakage occurred. In these patients, the microdialysis catheter close to the pancreaticojejunal anastomosis showed high glycerol values immediately after surgery and within 24 h an inflammatory pattern appeared with high lactate, high lactate:pyruvate ratio with unchanged pyruvate and low glucose. This inflammatory pattern appeared in the microdialysis catheter at the hepaticojejunal anastomosis 1–2 days before a biliary leak was found as bilirubin in the drain or by imaging techniques. Three of the four bile leak patients had POPF-C and underwent reoperation showing large erosive area from POPF to the biliary anastomosis. The patient with isolated biliary leakage is the only patient where we observed a distinct increase in lactate and lactate-to-pyruvate ratio with normal glycerol and glucose values 24–36 h prior to increased bilirubin in drain fluid. In accordance with this, the increased glycerol associated with a pancreaticojejunal leakage is caused by pancreatic lipases, whereas a bile leak contains no lipases and hence glycerol is normal. Our data suggest that the leakages at the pancreatic anastomoses were present immediately postoperatively. Thereafter biliary leakages were probably caused secondarily by tissue erosion due to pancreatic enzymes from the POPF spreading to the hepaticojejunal anastomosis (Fig. 4). Thus, clinical intraoperative findings were in line with microdialysis findings at the pancreaticojejunal and the hepaticojejunal anastomosis.

Admittedly, the study has some limitations that need to be acknowledged. The number of patients who developed POPF was higher than the previously reported average POPF rate of 12.9% at our institution.[30] Alternative risk score was estimated retrospectively and we were unable to blind the observers that calculated the score. However, according to calculations, a relatively high percentages of the patients had a risk score (≥15%) and 75% of these developed POPF. In summary, seven patients had a clinically relevant POPF, but no patients with a low risk score had POPF. Presumably, there has been a cluster of patients with POPF in this cohort compared to our previously reported results.[30] Theoretically, one can question whether the increased incidence of POPF is linked to the microdialysis method itself. This seems very unlikely as the microdialysis catheter, which has a diameter of 0.6 mm at the distal tip, is highly elastic and soft without any sharp edges or cutting properties and is not located in the anastomosis itself but sutured in connective tissue in close vicinity to the anastomosis.

The microdialysis method has some limitations. Although minimally invasive, it has potential risks such as bleeding and infections. We did not observe any complications related to the microdialysis catheters in this study. Our research group has inserted more than 200 microdialysis catheters in transplanted livers without experiencing any clinical complications.[7,8] By placing the catheters in the vicinity of the anastomosis and not penetrating the intestinal wall, complications are very unlikely as shown also by other research groups.[11,31] The life span of the catheters is restricted due to biofouling of the semipermeable membrane.[32]

We conclude that POPF can be detected very early postoperatively with a microdialysis catheter positioned close to the pancreaticojejunostomy. Randomized controlled trials in larger patient populations are needed to verify our findings. Our research group is currently conducting a randomized controlled trial where high values of glycerol and lactate will trigger earlier interventions like percutaneous optimal drainage, administration of antibiotics, and an early removal of surgical drain if glycerol levels are <400 μmol/L in the microdialysate (NCT03631173).

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Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2021.10.020.

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