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LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on the 13th of February 2026 at 09.00 in Segerfalksalen, BMC, Sölvegatan 17, Lund

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Abstract:

Background Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related death, and only a minority of patients with PDAC are resectable at diagnosis. Pancreatoduodenectomy (PD) is the standard surgical treatment of PDAC and other lesions located in the pancreatic head or in the periampullary region, and the morbidity rate is high. Overweight, hyperglycemia, and diabetes mellitus (DM) are risk factors for both PDAC and general postoperative complications.

The overall aim of this thesis is to identify risk factors for postoperative complications associated with overweight, hyperglycemia, and DM, and to investigate the impact of DM2 on survival in PDAC after PD. **Method** Paper I is a retrospective cohort study including 328 patients undergoing PD at Skåne University Hospital 2000-2015, investigating the impact of body constitution on postoperative complications. Body constitution was measured and defined by body mass index (BMI), body surface area (BSA), and body fat percentage (BF%). Paper II is a prospective cohort study evaluating the implementation of a continuous insulin infusion regimen and its effects on blood glucose and postoperative complications in one hundred patients undergoing PD at Skåne University Hospital from January 2017. Paper III and IV are register-based studies of patients undergoing PD from 2010 to 2020. Patients were identified in the Swedish National Pancreatic and Periampullary Cancer Registry and cross-linked with the Swedish National Diabetes Register. In paper III, the influence of DM on postoperative complications and mortality after PD was analysed in 2 939 patients, and in paper IV, the impact of DM type 2 (DM2) on long-term survival was assessed in 1 454 patients with PDAC undergoing PD. **Results** In paper I, the risk of postoperative complications was increased in overweight patients but not in overweight patients with concurrent DM. BMI, BSA, and BF% could all be used to identify patients at risk. In paper II, the insulin infusion regimen was feasible and significantly affected postoperative blood glucose. The effect on postoperative complications was limited. In paper III, patients with DM had a lower risk of major surgical complications and pancreatic anastomotic leakage. DM did not impact 30- or 90-day mortality after PD. In paper IV, the median overall survival in the cohort was 2.09 years. DM2 was correlated to worse survival, specifically in patients with long-standing DM2, but not in patients with new-onset DM2. Over 70% of tumours were stage 3 or 4. **Conclusion** Overweight and hyperglycemia are risk factors for postoperative complications, indicating a need for close monitoring of these high-risk patients postoperatively, whereas DM seems to be a protective factor. New-onset DM is favourable for long-term survival in patients with DM. The advanced tumour stages and poor survival in patients undergoing PD for PDAC suggest a necessity for earlier detection.

Key words: pancreatoduodenectomy, pancreatic cancer, overweight, hyperglycemia, diabetes mellitus, morbidity, mortality

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Outcome after pancreatoduodenectomy

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Per aspera ad astra

Table of Contents

Original papers

This thesis is based on the following original papers, which will be referenced to by their Roman numerals I-IV:

I. Ekström E, Ansari D, Williamsson C, Andersson R, Tingstedt B, Aronsson L, Nilsson J, Andersson B. Impact of body constitution on complications following pancreaticoduodenectomy: A retrospective cohort study. Int J Surg. 2017;48:116-121.

II. Ekström E, Fagher K, Tingstedt B, Rystedt J, Nilsson J, Löndahl M, Andersson B. Hyperglycemia and insulin infusion in pancreatoduodenectomy: a prospective cohort study on feasibility and impact on complications. Int J Surg. 2023;109: 3770–3777.

III. Ekström E, Bergenfeldt H, Fagher K, Tingstedt B, Nilsson J, Andersson B. Diabetes mellitus does not increase postoperative complications or mortality in pancreatoduodenectomy – A Swedish National register-based study. *Submitted*.

IV. Ekström E, Bergenfeldt H, Fagher K, Tingstedt B, Nilsson J, Andersson B. Diabetes and long-term survival after pancreatoduodenectomy for pancreatic cancer – A Swedish National register-based study. *Submitted*.

Abbreviations

ASA	American Society of Anesthesiologists
BF%	body fat percentage
BMI	body mass index
BSA	body surface area
CD	Clavien-Dindo
CGM	continuous glucose monitoring
DGE	delayed gastric emptying
DOS	day of surgery
ERP	Enhanced Recovery Program
ISGPS	International Study Group of Pancreatic Surgery
LOS	length-of-stay
NDR	National Diabetes Register
PD	pancreatoduodenectomy
PDAC	pancreatic ductal adenocarcinoma
PG	pancreaticogastric
PJ	pancreaticojejunal
POC	point-of-care
POD	postoperative day
POPF	postoperative pancreatic fistula
PPD	postpancreatectomy diabetes
PPH	postpancreatectomy hemorrhage
R	microscopic resection margin
SNPPCR	Swedish National Pancreatic and Periampullary Cancer Registry
TAR	time above range
TIR	time in range
TPN	total parental nutrition

Thesis at a glance

	AIM	METHOD	RESULTS AND CONCLUSION
I	To assess the impact of body constitution on complications after PD.	Retrospective cohort study on 328 patients undergoing PD 2000-2015 at Skåne University Hospital. Body constitution was measured by BMI, BSA and BF%.	The risk of major complications and POPF B and C was higher in overweight and large patients. The risk of POPF B and C was not increased in overweight patients with concurrent DM. BMI, BSA and BF% can be used to identify patients at risk.
II	To evaluate the feasibility of continuous insulin infusion and the effect on blood glucose and complications after PD.	Prospective cohort study on 100 patients subjected to a novel regimen of perioperative insulin infusion after PD at Skåne University Hospital 2017-2019. A historic cohort of 100 patients was included retrospectively.	The regimen was feasible in a non-ICU setting and significantly decreased median glucose levels. The impact on complications was limited. Patients with DM had a trend towards a lower incidence of POPF and PPH B and C.
III	To investigate the influence of DM on postoperative complications after PD.	A Swedish National register-based study including 2 939 patients undergoing PD 2010-2020. Data from the Swedish National Pancreatic and Periampullary Cancer Registry (SNPPCR) was cross-link with the National Diabetes Register (NDR).	Patients with DM had a lower risk of major surgical complications and pancreatic leakage. There were no differences in 30- and 90-day mortality compared to patients without DM.
IV	To analyse long-term survival in patients with DM2 and PDAC undergoing PD.	A Swedish National register-based study including 1 454 patients with PDAC undergoing PD 2010-2020. Data from the SNPPCR was cross-linked with the NDR.	Median overall survival was significantly worse in patients with DM2, specifically in patients with long-standing DM2 but not in patients with new-onset DM2.

Introduction

Wisdom begins in wonder.

– Socrates

Pancreatic ductal adenocarcinoma

The incidence of pancreatic ductal adenocarcinoma (PDAC) is low but rising.[1] Despite the low incidence of PDAC, it constitutes the third leading cause of cancer-related death in Western countries. (Fig.1)[1, 2] The only cure for PDAC is pancreatic resection, but merely 12-20% of patients are resectable at diagnosis, mainly due to the lack of symptoms until advanced disease occurs.[3, 4] The 5-year survival rate in PDAC is approximately 20% in patients undergoing pancreatic resection.[4-6] In patients not eligible for surgery, the 5-year survival is 0.9%.[6]

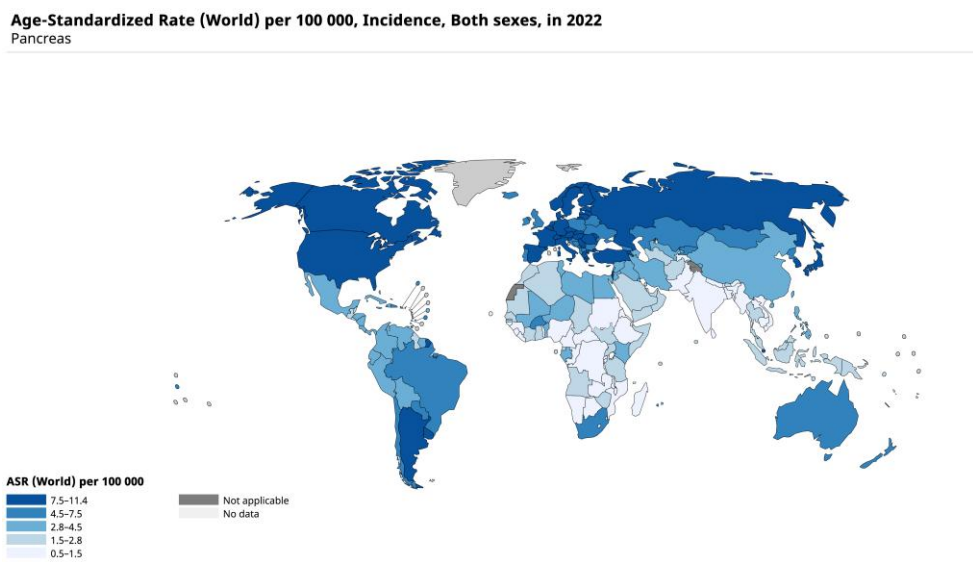

Figure 1. Incidence of pancreatic cancer in 2022. GLOBOCAN, World Health Organization.[2]

Risk factors, screening and diagnostics in PDAC

Smoking, high fasting blood glucose and obesity are the main known modifiable risk factors of PDAC.[7, 8] In contrast to other malignancies such as breast and colon cancer, screening of PDAC is not yet implemented in the overall population.

In patients with seemingly sporadic PDAC, approximately 4% have germline mutations.[9] Two genes (PRSS1 and STK11) correlated to a high risk of PDAC, are also associated with hereditary pancreatitis and Peutz-Jaegers syndrome, respectively. In both examples, the lifetime risk of PDAC is up to 40%.[10, 11] In Sweden, screening programs are initiated for these patients from the age of 40.[12] An elevated risk of PDAC is also seen in patients with mutations in BRCA1 and BRCA2, usually causing hereditary breast- and ovarian cancer, and mutations common in Lynch syndrome, most commonly causing colorectal cancers. The lifetime risk of PDAC in patients with a BRCA mutation or Lynch syndrome is up to 4%.[13, 14]

Heritability is estimated to represent approximately 20% of PDAC cases.[15] In patients with known hereditary risk factors, up to 13% have genetic mutations.[16] Instead, most of these patients only have a family history of PDAC, so called familial pancreatic cancer (FPC). Criteria for the definition FPC are two or more cases of PDAC in first-degree relatives without any detectable hereditary syndrome. In patients with FPC and three or more first-degree relatives with PDAC, screening programs are offered from the age of 50 in Sweden. This also applies to patients with a BRCA1 mutation and to patients with Lynch syndrome. In patients with a BRCA2 mutation and one first-degree relative or two relatives in the same family line, screening is likewise offered from the age of 50.[12]

The screening program in Sweden is in line with the international consensus regarding control programs, and includes a yearly Magnetic Resonance Imaging (MRI) scan and routine testing of blood glucose or HbA1c (glycated hemoglobin). Inconclusive findings are controlled with Endoscopic Ultra Sound (EUS) in addition to testing with the tumour marker Cancer Antigen (CA) 19-9.[12, 17]

Patients with PDAC, who are ultimately eligible for resection, usually present with nonspecific symptoms such as abdominal pain, jaundice or weight loss, leading to further investigation including diagnostic imaging. The suspected diagnosis is commonly derived from findings on Computed Tomography (CT). Imaging with a chest and abdominal CT is mandatory for staging and for evaluating resectability, and imaging is a basis for further treatment planning. In addition to the initial standard CT, a three-phase CT including a pancreatic phase, can be executed for higher accuracy. [18] MRI has a higher sensitivity for characterising lesions such as liver metastases than CT, and can be performed as a complement in cases with inconclusive findings or indeterminate lesions in the liver. [19] Positron emission tomography (PET)/CT is not used routinely in Sweden but might be used for metastatic screening. [12]

CA 19-9 is the tumour marker used as a supplement in the diagnosis of PDAC. The sensitivity of CA 19-9 in PDAC is low (78%), and CA 19-9 can be elevated by both benign (e.g. jaundice and pancreatitis) and malignant causes other than PDAC.[20-22] Additionally, CA 19-9 is not secreted normally or at all in patients with a certain antigen phenotype, the so-called Lewis phenotype, involved in the secretion of CA 19-9.[23] Other tumour markers are under development but are not yet available in clinical practice. Pancreas-specific circulating free DNA (cfDNA) has been evaluated as a diagnostic marker of PDAC, but has inferior sensitivity compared to cfDNA in colorectal cancer (CRC).[24, 25] In PDAC, the sensitivity has been shown to be 57% and the specificity 95%, with an increase in sensitivity with more advanced stages.[24] In CRC the sensitivity is 83-88%.[25]

Patients with findings leading to a suspect diagnosis of PDAC, are in Sweden referred to a Hepato-Pancreato-Biliary (HPB) unit for treatment planning. After referral to a HPB unit, most cases are discussed at a multidisciplinary conference and evaluated regarding resectability, based on tumour grading. Operability is evaluated based on the patient's performance status and comorbidities.

Criteria for upfront resectability are absence of metastatic disease and regional lymphadenopathy, as well as lack of tumour involvement of the celiac artery, the superior mesenteric artery, the common hepatic artery and no or ≤180° involvement of the portal vein or the superior mesenteric vein, without contour irregularity.[26] A margin-negative (R0) resection, with no microscopically residual tumour cells in the resection margin, is one of the strongest prognostic factors of survival after pancreatic cancer surgery.[27, 28] If the tumour is regarded as borderline resectable or locally advanced, neoadjuvant chemotherapy is frequently initiated to improve the possibility of R0 resection.[26] In Sweden, a minimum of 2 months' treatment is recommended and the effect is evaluated by repeated imaging and response on CA 19-9.[12]

The American Joint Committee on Cancer (AJCC) Cancer Staging Manual and tumour, node, metastasis (TNM) classification is used for grading PDAC. It was revised in 2016 with changes as shown in figure 2.[29, 30]

Category	7th edition	8th edition
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension	Tumor ≤2 cm in greatest dimension
T1a	-	Tumor ≤0.5 cm in greatest dimension
T1b	-	Tumor >0.5 cm and <1 in greatest dimension
T1c	-	Tumor 1-2 cm in greatest dimension
T2	Tumor limited to the pancreas >2 cm in greatest dimension	Tumor >2 and ≤4 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of CA or SMA	Tumor >4 cm in greatest dimension
T4	Tumor involves CA or SMA (unresectable primary tumor)	Tumor involves CA, SMA, and/or CHA, regardless of size
N1	Regional lymph node metastasis	Metastasis in 1-3 regional lymph nodes
N2	-	Metastasis in ≥4 regional lymph nodes

CA, denotes celiac axis

SMA, denotes superior mesenteric artery

CHA, denotes common hepatic artery

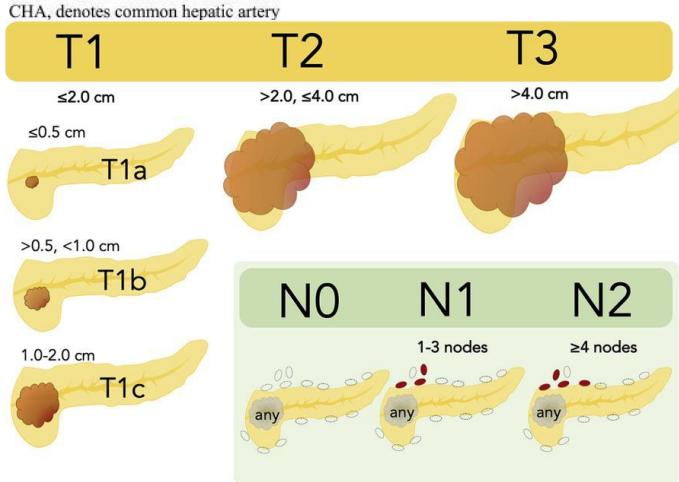

Figure 2. TNM classification for PDAC. Copyright M. Roalsø et al. Published by Elsevier. Reproduced under Creative Commons CC-BY licence. DOI: 10.1016/j.ejso.2020.02.014.

In PDAC, tumours tend to metastasise early, with distant metastasis found in up to 30.6% of patients with tumours measuring 0.5 cm or less.[31] Hence, the resectability is not strictly correlated to tumour size. The chance of R0 resection however, improves with a smaller tumour size and vastly impacts median survival and the 5-year survival rate.[32, 33] In R1 resections, a margin <1 mm still provide a more favourable outcome than R1 resections with zero margin, with a 5-year survival rate of 30.1% compared to 20.3%.[32] The reported rates of R1 resections have previously co-varied with the accuracy in histopathological assessment. [34] After the implementation of a standardised protocol for histopathological examination in Sweden, the R1 resection rate increased significantly.[35]

The presence of metastatic lymph nodes is also a major prognostic factor of survival, with increasing numbers of affected lymph nodes leading to a corresponding decrease in survival.[36, 37]

Adjuvant chemotherapy is of great importance in improving survival after PD for PDAC, and is recommended to all patients considered able to tolerate treatment.[38-40] Treatment is initiated within 12 weeks after surgery and administered for 6 months.[12] Postoperative complications might delay the start-up of adjuvant chemotherapy or jeopardise the chance of receiving treatment at all. Hence, potentially avoidable complications and risk factors thereof must be identified and, if possible, prevented.

Pancreatoduodenectomy

Pancreatoduodenectomy (PD), also known as Whipple's procedure, is the standard surgical treatment of PDAC and other malignant or benign lesions of the head of the pancreas. PD is also performed for lesions in the periampullary region and duodenum, including distal cholangiocarcinoma, ampullary and duodenal cancer. (Fig.3) The procedure is named after Allen O Whipple, a surgeon active at Columbia Presbyterian Hospital in New York from 1921 to 1946. Whipple published his case report in 1935 describing the resection performed in two stages.[41, 42] The case report included three patients of which two survived. At the end of his career, Whipple had performed 37 pancreatoduodenectomies and the technique had been refined into a one-step procedure, using silk thread instead of cat-gut, with the latter more prone to dissolvement by pancreatic enzymes.[43] The first successful regional pancreatic resection however, was performed in 1909, when the German surgeon Walter Kausch successfully resected a periampullary tumour en bloc with a larger part of the duodenum.[42, 44]

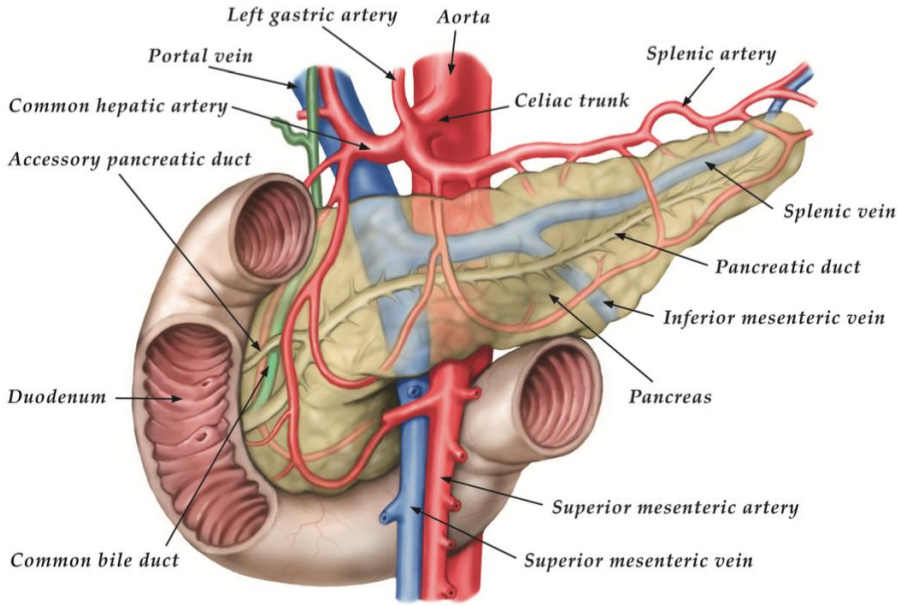

Figure 3. Anatomy of the pancreas and periampullary region. Reprinted with permission by Dr Daniel Ansari, ©Anders Flood.

A standard PD today includes resection of the pancreatic head, a distal gastrectomy, duodenectomy, cholecystectomy, resection of the distal common bile duct and lymphadenectomy. (Fig.4) Resection surfaces most prone to R1 resection are the vascular, the posterior and the circumferential margin.[27, 28] Recurrence commonly occurs within 12 months postoperatively, and most cases present with metastatic disease with only a minority of recurrence occurring solely locoregionally.[45-47]

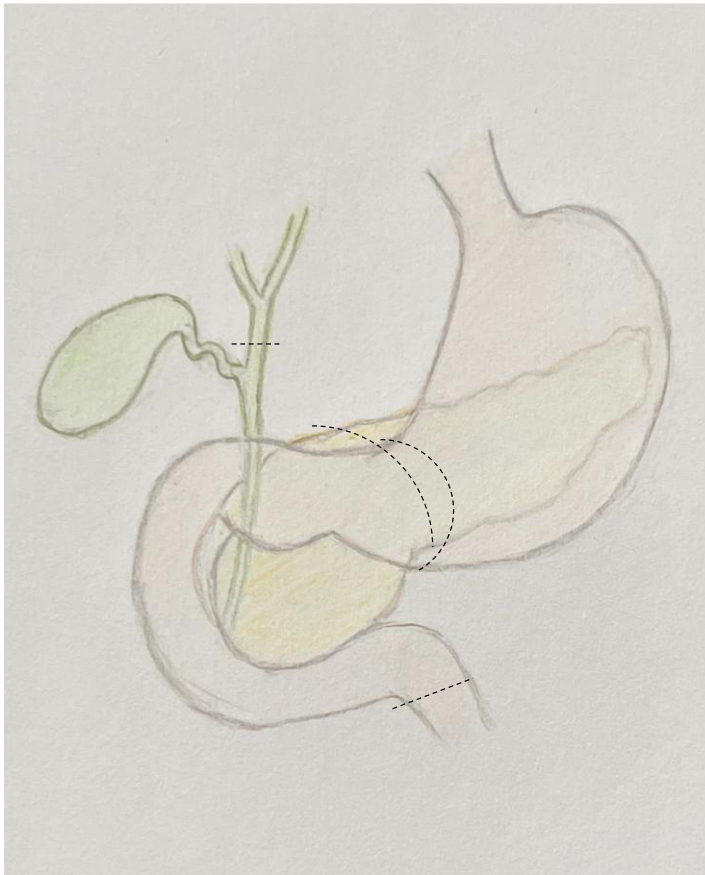

Figure 4. Resection lines in PD. Illustration by the author.

Pancreatoduodenectomy at Skåne University Hospital

At Skåne University Hospital, open PD is performed with a partial pancreatectomy, limited distal gastrectomy and standard lymphadenectomy. (Fig.5 and Fig.6) Reconstruction of the anatomy is performed by pancreaticogastric anastomosis as well as a gastrojejunostomy and hepaticojejunostomy on the same jejunal loop.

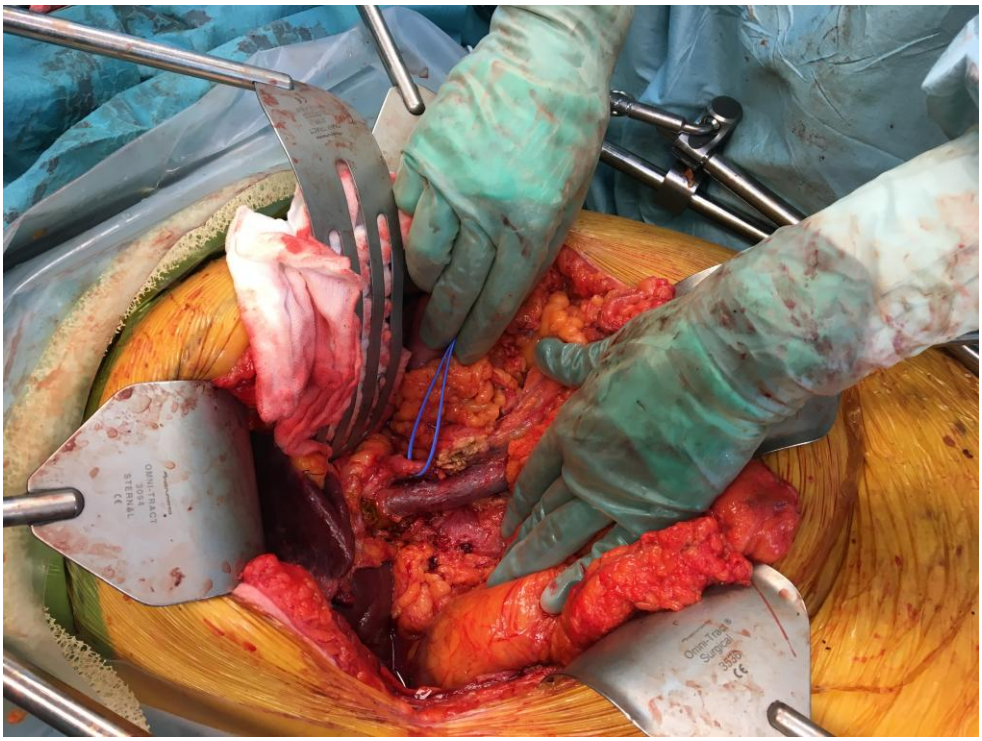

Figure 5. Picture of the surgical field during pancreatoduodenectomy. Photo by the author.

Four centres in Sweden prefer reconstruction with a pancreaticojejunal (PJ) anastomosis and the other two centres routinely use a pancreaticogastric (PG) anastomosis in open PD. All centres use a PJ in robot-assisted PD. The hypothetical advantage of PG is the lower risk of ischemia related to high gastric vascularisation. In addition, the lower pH-levels might counteract the activation of pancreatic enzymes. These factors could, in theory, reduce the risk of pancreatic anastomotic leakage.[48]

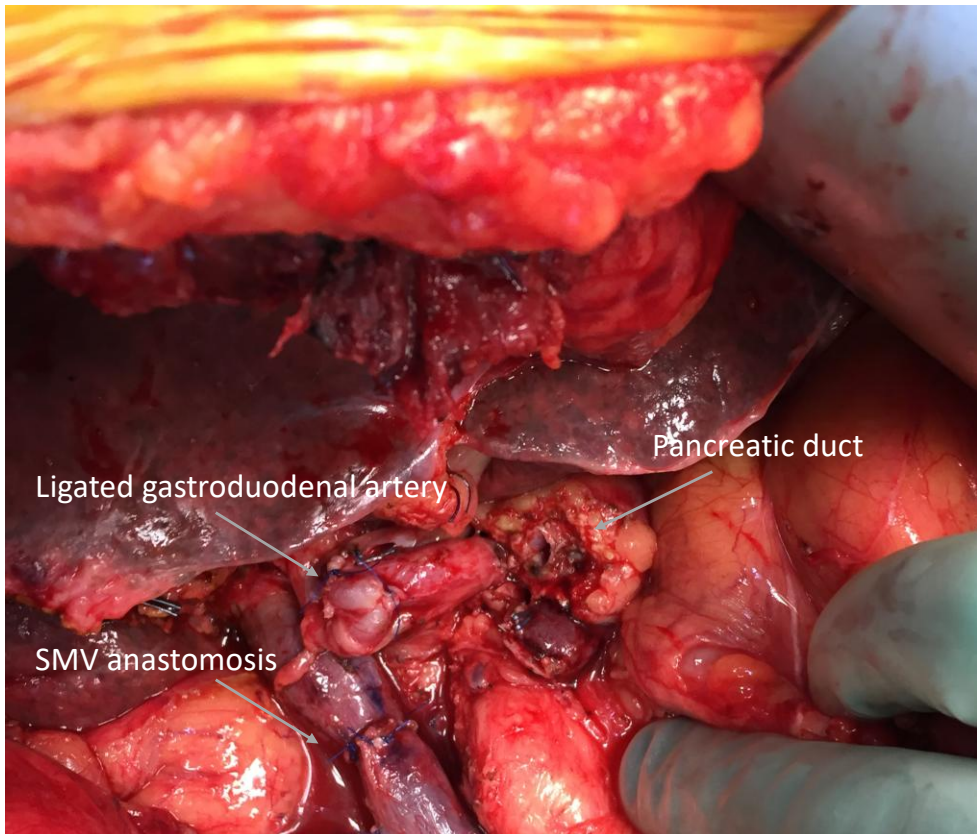

Figure 6. Anatomy after resection in pancreatoduodenectomy. Photo by Dr Bodil Andersson.

In the last decade, minimally invasive techniques have emerged with laparoscopic and robot-assisted PD. Despite these substantial technical improvements, the morbidity rates are still high, with complication and mortality rates equal to open PD.[49-51] Long-term survival does not seem to differ between minimally invasive and open PD.[52] A large impact on outcome, however, stems from the centralisation of pancreatic surgery to high-volume centres worldwide, which has led to positive effects with improved results, both regarding morbidity rates and mortality.[53, 54] In Sweden, pancreatic resections have since 2016 been centralised to six regional centres.[5] At Skåne University Hospital, both length-of-stay (LOS) and total hospital cost decreased with increased operation volumes after centralisation of PD.[55]

Complications after pancreatoduodenectomy

As noted, the surgical procedure in PD is complex and requires extensive resections. This makes it one of the most complication-prone procedures currently performed. Thankfully, the perioperative morbidity and mortality rate has improved since Whipples' case report in 1935.

The most common and PD-specific complications are postoperative pancreatic fistula (POPF), postpancreatectomy hemorrhage (PPH) and delayed gastric emptying (DGE), affecting approximately 20-30%, 4-8% and 16-19%, respectively.[56-61] POPF is defined as a pancreatic leakage with complications as classified and graded by the International Study Group of Pancreatic Surgery (ISGPS) as shown in table 1.[62] The definition "POPF grade A" was changed to biochemical leak (BL) in 2016. PPH and DGE are similarly classified from grade A to C based on severity and clinical impact.[63, 64] (Tab.1)

Table 1. Classification of POPF, PPH and DGE.

Classification of POPF

Grade	Definition
A/BL*	Amylase >3 times the upper limit of normal serum amylase.
B	Clinically relevant change in management, e.g. persistent drainage >3 weeks, a need for terapeutic drainage, angiographic treatment of bleeding or signs of infection (related to POPF).
C	Reoperation, organ failure or death (related to POPF).

*Grade A was redefined as biochemical leak (BL) in 2016.

Classification of PPH

Grade	Definition
A	Mild. Early onset. Noninvasive treatment.
B	Severe early onset/mild late onset. Invasive treatment, e.g. transfusion, therapeutic endsocopy or surgery.
C	Severe. Late onset. Invasive treatment, e.g. embolization or surgery.

Classification of DGE

Grade	Definition
A	NGT 4-7 days or reinsertion >POD3 or unable of solid intake POD7.
B	NGT 8-14 days or reinsertion >POD7 or unable of solid intake POD14.
C	NGT >14 days or reinsertion >POD14 or unable of solid intake POD21.

NGT, nasogastric tube; POD, postoperative day.

Risk factors of POPF are soft pancreatic tissue, a small pancreatic duct diameter and pancreaticojejunal anastomoses (PJ).[56, 65, 66] PJ has been correlated to a higher incidence of POPF, but no consensus on the preferred anastomosis type has been reached in the ISGPS.[48, 65] PPH includes all types of postoperative abdominal bleeding, both intra- and extraluminal, early and late bleeding, following pancreatic surgery.[63] Most commonly, bleeding occurs from areas of resections, the gastroduodenal, pancreaticoduodenal, or superior mesenteric artery, or the hepatic arteries, and the suture lines of one of the anastomoses.[67, 68]

There is a strong correlation between PPH and POPF, where POPF is a common predisposing factor of late PPH due to the corrosive effect of pancreatic enzymes on adjacent vessels.[68] Other precursors of PPH are complications such as bile leaks and intraabdominal abscesses. Even though the incidence of PPH is rather low, the mortality rate is approximately 10-20%.[58, 68, 69]

DGE is not unique for PD and is seen in many other extensive intraabdominal procedures. In PD, however, DGE is more common and most commonly caused by POPF and surgical site infection, besides the resection itself.[61]

Management of complications

Enhanced Recovery Programmes (ERP) are used in many different surgical settings. The overall aim with ERPs is to optimise the peri- and postoperative care in order to prevent postoperative complications and to identify complications at an early stage. The introduction of ERP in PD has led to improvements with reduction of overall morbidity and LOS without an increase in readmission. [70, 71] ERP following pancreatic surgery at Skåne University Hospital includes early oral intake and physical mobilisation. Medically, postoperative administration of a somatostatin analogue (octreotide) until postoperative day (POD) 5 was included in the regimen until 2024. Somatostatin, and its analogues, inhibits pancreatic exocrine secretion which, in theory, could reduce the risk of pancreatic anastomotic leakage. However, studies on its effectiveness are inconclusive.[72, 73]

Except for invasive treatment of POPF, including drainage and reoperation, conservative and non-invasive treatment of POPF may include the use of somatostatin analogues (octreotide or sandostatin), with the same rational as previously mentioned.

Body constitution

Data from the World Health Organization (WHO) show that 44% of adults were overweight and 16% were obese in 2022, and the incidence has been increasing over time.[74] In Sweden, the corresponding ratio the same year was 51% and 15%, respectively.[75, 76]

Overweight and obesity are risk factors of PDAC and PDAC-related death, and are also correlated to worse postoperative outcome with regards to complications following many different surgical procedures.[8, 77-80] In PD, overweight and obesity particularly elevate the risk of POPF, likely due to a softer pancreatic texture caused by intrapancreatic fat.[81, 82]

Obesity has been correlated to the upregulation of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), causing oxidative stress and tissue destruction.[83] In colorectal surgery, preoperatively high levels of TNF-α is correlated to postoperative complications, and high levels of cytokines could be one explanatory factor of complications in PD as well.[84]

Anthropometric measurements

Body constitution can be estimated by many anthropometric measurements. The most common measurement used is body mass index (BMI), with its limitations in discriminating for body fat, since BMI only take total weight into account and does not discriminate between muscle mass and fat mass.[85] BMI is used in validated prediction models for POPF, including the prediction model used at Skåne University Hospital.[56] Body surface area (BSA), has been used as an alternative anthropometric measurement in studies aiming to identify patients at risk of postoperative complications related to overweight and obesity, and BSA has also been used to predict POPF and mortality in patients undergoing PD.[86] Body fat percentage (BF%) is hypothetically a more sensitive measurement for obesity than BMI, but is less commonly used.[85]

BMI is classified by the WHO, where overweight is defined as a BMI 25-29.99 and obesity is defined as a BMI ≥30.[87] Corresponding absolute numbers for overweight and obesity does not exist for BSA or BF%. Instead, a median value is most commonly used in BSA for the corresponding definition "large".[86, 88] Data from the US National Health and Nutrition Examination Survey (NHANES) showed that a BMI ≥25 corresponded to a BF% between 22.6% and 28.0% in males and 35.0% and 40.2% in females.[89] Neither one of these measurements are substitutes for a true risk factor of intrapancreatic fat, but they are cost-effective ways of estimating overall risk secondary to overweight and obesity.

Diabetes mellitus and hyperglycemia

In line with the incidence of overweight and obesity, the incidence of DM is also rising and the worldwide prevalence of DM in 2022 was 14% in adults.[90]

The prevalence of DM in PDAC, as well as in patients undergoing PD independent of diagnose is high, both in comparison to age-matched controls and other malignancies, ranging up to 51%, and the prevalence of DM in patients with PDAC is up to 68%.[91-94] New-onset DM (DM diagnosed within 2 years previous of PDAC diagnosis) is the predominant type of DM in patients with PDAC, constituting 40-74% of patients with DM in this population.[91, 92, 95, 96]

In terms of PDAC, DM might be both a factor that induces cancer and a paraneoplastic phenomenon. Given the short median survival in patients with PDAC it is unlikely that long-standing DM (diagnosis of DM longer than 2 years) is caused by PDAC. A more likely theory is the effect of long-standing DM on pancreatic cancer, where the insulin-resistance and the following hyperinsulinemia stimulate insulin-like growth-factor (IGF) 1 that in turn stimulates growth in pancreatic cancer cells.[97, 98] The high prevalence of small tumours and early-stage PDAC at diagnosis in patients with DM contradicts the hypothesis that glandular destruction, caused by the tumour, is the aetiology of DM. Instead, DM, and specifically new-onset DM, might be a paraneoplastic phenomenon.[99, 100] In patients with new-onset DM and PDAC undergoing PD, the DM remission rate is 57-65%, further supporting this theory.[91, 96]

Survival in PDAC is worse in patients with DM compared to patients without DM.[96, 101] However, in patients with new-onset DM, both disease-free survival and overall survival are longer than in patients with long-standing DM, and tumours in patients with new-onset DM seem to be more well-differentiated.[96]

As previously mentioned, no screening programs are implemented in the general population. However, in an ongoing randomized controlled trial, the Early Detection Initiative (EDI), patients with new-onset DM without a known hereditary risk are included. The aim is to evaluate if the intervention, including CT imaging, identifies PDAC at earlier stages in these patients.[102] The trial is using an algorithm-based screening of patients with new-onset DM. The algorithm used is based on the algorithm presented by Sharma et al. in the Enriching New-Onset Diabetes for Pancreatic Cancer (ENDPAC) study.[103] The ENDPAC algorithm includes age at onset of DM, and changes in weight and blood glucose, and was used to stratify patients older than 50 years into high-, intermediate-, or low-risk groups for PDAC. (Fig.7) The ENDPAC algorithm was applied to patients with new-onset DM within 3 years of PDAC diagnosis. In patients with ENDPAC scores of at least 3, correlating to high-risk of PDAC, the sensitivity and specificity for identifying patients with PDAC were 80%.

In the EDI study, patients with ENDPAC scores >0 undergo a CT or MRI scan and blood sampling at baseline and are thereafter followed with repeated imaging in 3-9 months if the initial radiology is negative. All patients are thereafter passively followed for 5 years. No results from the EDI study are yet published.

Blood Glucose (BG) Categories		**Δ BG Category Score (NOD-1y) (A)**
BG range (mg/dl)	**Score**	**Score Range**
BG category at −1 years		1–4
<100	1	
100–109	2	
110–125	3	
BG category at glycemically-defined new-onset diabetes		
126–160	4	
>160	5	
Δ Weight Categories		**Δ Weight score (B)**
Δ Weight (kg)	Score	Score Range
≤ −6.0	+6	−6 to +6
−5.9 to −4.0	+4	
−3.9 to −2.0	+2	
−1.9 to +1.9	0	
+2.0 to +3.9	−2	
+4.0 to +5.9	−4	
≥ +6.0	−6	
Age (years) at glycemically-defined new-onset diabetes		**Age score (C)**
Age range	Score	Score Range
≤59	−1	−1 to +1
60 to 69	0	
≥70	+1	
Total Score		**A + B + C**

Figure 7. The ENDPAC model and scoring algorithm. Copyright A.Sharma et al. Published by Elsevier. Reused under licence number 6146720872964 by Elsevier. DOI: 10.1053/j.gastro.2018.05.023.

DM and complications

Postoperative complications more commonly seen in patients with than without DM, undergoing colorectal and general surgery, are primarily surgical site infections, wound healing disorders and anastomotic leaks.[104, 105] However, DM is a preventive factor in the development of POPF. This preventive effect is correlated with a firmer texture of the pancreas caused by fibrosis in patients with DM.[106-108]

Hyperglycemia itself is a risk factor for mortality and postoperative complications such as infection and reoperation, with or without coexisting DM.[109] Interestingly, patients without DM seem to have a greater risk of complications correlated to hyperglycemia compared to patients with DM, with the risk increasing relative to higher levels of hyperglycemia in a dose-response relationship.[110] The elevated risk seen in hyperglycemia is reduced to levels corresponding to normoglycemic patients by insulin treatment on the day of surgery (DOS).[109, 110] The hypothesis behind the adverse effects of hyperglycemia are changes in inflammatory response and immune functions, in the same way as seen in obesity, where glucose elevates TNF-α and IL-6.[111, 112] DM and long-term hyperglycemia further leads to the accumulation of Advanced Glycation End products (AGEs), involved in inflammation and carcinogenesis, by stimulating cell proliferation and angiogenesis in the latter.[113] AGEs are also correlated with the development of PDAC.[114]

In PD, both the resection of the insulin producing organ itself and the surgical trauma, causing physiological stress, as well as the use of total parental nutrition (TPN), elevate blood glucose and cause hyperglycemia to a high extent in this group of patients. Further, TPN-induced hyperglycemia itself is associated with in-hospital complications such as acute renal failure and mortality.[115]

Given the aforementioned associations to both PDAC and complications after PD, body constitution, hyperglycemia and DM are important areas to study in an attempt to identify patients at risk of PDAC as well as patients at risk of postoperative complications after PD.

Continuous glucose monitoring (CGM)

As part of the ERP in patients undergoing PD at Skåne University Hospital, blood glucose is measured at least four times daily initially until POD4, usually by point-of-care (POC) capillary testing, and hyperglycemia is generally treated by subcutaneously administered bolus of insulin.

As previously mentioned, patients undergoing PD are at high risk of postoperative hyperglycemia, requiring repeated administration of insulin with sometimes short intervals. Intravenous insulin infusion is efficient in normalising hyperglycemia, but the regimen requires frequent blood glucose monitoring, increasing both the demands on the patient and staff.

Continuous glucose monitoring (CGM), using intermittently scanned continuous glucose monitoring (isCGM) systems, is an effective way of avoiding repeated POC capillary testing. (Fig.8) The method was approved for use in hospital settings by the U.S. Food and Drug Administration (FDA) in 2020. As of 2017, isCGM had not been used in a hospital setting in Sweden or in any other country, nor to regulate intravenous insulin treatment. Instead, the use of POC has been, and still is, the standard of care.

Figure 8. FreeStyle Libre 2 Plus. Photo by Dr Oscar Åkesson.

Aims

The general aim of this thesis is to identify risk factors of postoperative complications correlated to overweight, hyperglycemia and diabetes mellitus as well as to study the impact of diabetes mellitus on survival in PDAC after pancreatoduodenectomy.

Specific aims:

◊ Paper I

To assess how body constitution and diabetes mellitus effects postoperative complications in PD.

◊ Paper II

To evaluate the implementation of continuous insulin infusion and its effect on blood glucose and the impact of hyperglycemia on complications in PD.

◊ Paper III

To analyse the impact of diabetes mellitus and metabolic control on complications and diabetes mellitus' correlation to mortality following PD.

◊ Paper IV

To investigate long-term survival in patients with PDAC, with and without diabetes mellitus type 2, undergoing PD, and the incidence of diabetes remission and PPD.

Material and Methods

Study population and definitions

Pancreatoduodenectomy at Skåne University Hospital

At Skåne University Hospital, open PD is performed by partial pancreatectomy, limited distal gastrectomy and standard lymphadenectomy. Reconstruction of the anatomy is performed by a pancreaticogastric anastomosis as well as a gastrojejunostomy and hepaticojejunostomy on the same jejunal loop. An intra-abdominal drain was routine procedure during the study periods of paper I and II. In an overlapping clinical trial, ongoing from 2016, patients with a predicted low risk of POPF were randomised to receive a drainage or not.[56]

Classification of postoperative complications

Postoperative complications occurring within 30 days postoperatively were categorised according to the Clavien-Dindo (CD) classification of surgical complications.[116] A complication classified as CD≥3a was defined as a major complication.

POPF, PPH, DGE were classified as biochemical leak (BL, for pancreatic leakage) or grades A to C, as defined by The International Study Group of Pancreatic Surgery (ISGPS).[62-64] Grade B and C were considered clinically significant.

Paper I

Patients undergoing PD between 2000 and 2015 at Skåne University Hospital were identified from a local database consisting of patients undergoing pancreatic resections. The database was validated and missing data were supplemented when feasible. Exclusion criteria were multivisceral surgery in the same session as the PD.

Body constitution was measured by BMI, BSA, and BF%.

Formula for calculating BMI

$$\frac{\text{weight (kg)}}{\text{height (m)}^2}$$

Formula for calculating BSA

$$((\text{height (cm)} \times \text{weight (kg)}) / 3600)^{(1/2)}$$

Formula for calculating BF%

$$(1.20 \times \text{BMI}) + (0.23 \times \text{age}) - (10.8 \times \text{gender*}) - 5.4$$

*Gender: female=0, male=1

WHO's definitions were used for BMI (<18.5 underweight, 18.5-24.99 normal weight, 25-29.99 overweight and ≥30 obesity). [87] Cut-off for BSA and the definition large was determined as the median value, and the gender-specific median value defined overweight and obesity in BF%, in line with previous studies.[86, 88, 89]

Outcome in complications, including the PD-specific complications POPF, PPH and DGE, were compared between under- or normal weight patients and overweight or obese patients defined by BMI and BF%. Corresponding analysis was performed between non-large and large patients defined by BSA. A subgroup analysis on complications was performed in patients with and without DM.

Paper II

In this single-centre cohort study at Skåne University Hospital, 100 patients who underwent PD from January 2017 to June 2019 were prospectively included in the intervention group and subjected to a regimen of perioperative continuous insulin infusion. A cohort of 100 patients were retrospectively included from January 2015 until December 2016, hereafter referred to as the historic cohort. Exclusion criteria were previous biliary reconstruction or cases were multivisceral resections or extensive vascular reconstructions were performed. Venous resections were not excluded.

Insulin infusion regimen

Patients included in the intervention group received a FreeStyle Libre isCGM sensor (Abbott Diabetes Care Inc.) preoperatively. The sensor was removed at discharge or 14 days postoperatively. Blood glucose was monitored by both capillary point-of-care (POC) testing and by isCGM with FreeStyle Libre 1. The continuous insulin infusion was initiated intraoperatively when blood glucose was >7 mmol/l. POC testing was performed every 3 hrs during the first 24 hrs to confirm the value given by the isCGM. After 24 hrs, POC testing was performed at least every 4 hrs, and additional POC testing was performed if values given by the isCGM were above or below our target range of 7-10 mmol/mol (125-180 mg/dl). Hereafter, the intervals between POC testing-points were gradually longer. The insulin dose was initially adjusted based on the values of the POC testing, but from POD2 the values given by the isCGM were used. The insulin infusion was terminated when TPN was discontinued.

HbA1c was registered preoperatively and at 6-8 weeks postoperatively in the intervention group. Only patients with a documented diagnosis of DM were defined as having DM independent of preoperative HbA1c-values. Data on capillary blood glucose retrieved from the POC testing during the in-hospital stay up to 30 days postoperatively, were collected and the corresponding sampling time were registered for all 200 patients. Adequate glucose control was defined as a blood glucose 3.9-10.0 mmol/l. Median glucose was calculated per individual until discharge, up to 30 days postoperatively, and compared between the intervention group and the historic cohort. Median glucose was further analysed in the entire cohort (n=200) by two time periods; DOS through POD3 and DOS through POD5, and hyperglycemia was defined as median glucose >10 mmol/l during these time periods.

Time in range (TIR) is defined as the percentage of time the patient spends within a predefined range. We used the target range 3.9-10.0 mmol/l, corresponding to the commonly used range in outpatient settings. Time above range (TAR) is the corresponding percentage of time the patient spend above the predefined range (>10

mmol/l). [117, 118] Data on TIR and TAR were extracted from the isCGM for the two time periods DOS through POD3 and DOS through POD5, in the intervention group.

Postoperative complication rates were analysed and compared between the intervention group and the historic cohort. Corresponding rates were also analysed and compared between normo- and hyperglycemic patients based on values obtained by POC testing. In the intervention group, complication rates were evaluated in correlation to TIR and TAR. A subgroup analysis on complication rates and hyperglycemia were analysed and compared between patients with and without DM.

The 90-day mortality rate was compared between the intervention group and the historic cohort.

Paper III and IV

The National Diabetes Register

In Sweden, caregivers in primary and in-hospital medical departments register data on patients with DM in the National Diabetes Register (NDR). The NDR was founded in 1996, and the rate of coverage is 85%.[119] The register contains, among many other parameters, data on DM type, time of diagnosis, diabetes-related complications, medical treatment, and data on metabolic control measured as HbA1c.

The Swedish National Pancreatic and Periampullary Cancer Registry

In the Swedish National Pancreatic and Periampullary Cancer registry (SNPPCR), patients with pancreatic and periampullary cancer and patients undergoing pancreatic surgery have been registered since 2010.[5] The SNPPCR was founded in 2009 and has a high rate of coverage over 90%.[120] Pancreatic resections have been centralised over the last decade and are now performed at only six centres.

Reliability in registry data is evaluated based on four main quality measures. Timeliness is assessed by comparing time of diagnosis and time of registration in the registry. Completeness measures the rate of coverage by comparing and controlling data in the registry with registered cases in national and regional mandatory registries. Comparability encompasses registration routines to ensure that these are homogeneous nationally. Validity is defined by the ratio of a data set that correlates to a true value. Validation of these quality measures is generally performed through an audit of data from a sample of patients.[121] Both the NDR and the SNPPCR are well-validated registries comprising verified high-quality data.

In paper III and IV, patients in the SNPPCR were cross-matched with the NDR for the years 2010 through 2020 to obtain the relevant cohort of patients undergoing PD. Only patients registered with DM in the NDR were included in the DM group. Hence, patients registered as having DM according to the SNPPCR but not according to the NDR, were excluded. Data on DM type, duration, treatment and HbA1c-levels were extracted from the NDR. All other data were retrieved from the SNPPCR.

In paper III, all patients undergoing PD with open resection, independent of histopathological diagnose, were included. Cases with concurrent multivisceral surgery and arterial resections were excluded. Venous resections were included.

Until May of 2018, the parameters POPF, PPH and DGE were not classified in the SNPPCR as biochemical leak (BL, for pancreatic leakage) or grades A to C, and hence, only data on whether a complication was present or absent were available. To compensate for this, a subgroup analysis on complications was executed on patients undergoing PD from May 2018 until December 2020, where data on specified classifications of these complications were registered. Analyses on the whole cohort of patients undergoing surgery between 2010 and 2020 are thus based on all grades of pancreatic leakage, PPH and DGE.

DM duration was divided into three subgroups; <5 years, 5-10 years and >10 years. HbA1c levels were subdivided into four groups; <53 mmol/mol (<7% (DCCT, Diabetes Control and Complications Trial)), 53-59 mmol/mol (7-7.5%), 60-69 mmol/mol (7.6-8.5%) and ≥70 mmol/mol (>8.5%). All available data on preoperative HbA1c levels in the NDR were merged to calculate a mean HbA1c.

Outcome in postoperative complications and 30- and 90-day mortality was compared between patients with and without DM, and the impact of DM duration and HbA1c was studied in patients with DM. The multivariable analyses were adjusted for age, sex, BMI, smoking and pancreatic anastomosis type.

In paper IV, solely patients with PDAC undergoing PD were included, with both open and minimally invasive resections. Only patients with DM2 were included in the DM group. Date of diagnosis of DM or the first DM related visit registered in the NDR was defined as time of diagnosis. Registered time of referral to an HPB surgical unit in the SNPPCR was set as time of diagnosis of PDAC. New-onset DM was defined as a diagnosis of DM within 24 months prior to the diagnosis of PDAC.

A HbA1c <48 mmol/mol without ongoing anti-diabetic treatment postoperatively, was defined as remission of DM. In patients without preoperative DM, a newly registered diagnosis of DM in the NDR postoperatively defined post-pancreatectomy DM (PPD).

TNM-classification was registered according to the 7th edition of the AJCC Cancer Staging Manual until December 1st 2020, and according to the 8th edition thereafter. (Fig.2)

The impact of DM and DM duration on long-term survival was analysed and the incidence of DM remission and PPD was investigated.

Statistical methods

In all four papers, continuous variables are presented as mean +/- standard deviation (SD) or median with an interquartile range (IQR). Categorical variables are presented as absolute numbers and frequencies in percentages n (%). All tests were two-sided and a p-value of <0.05 was considered statistically significant. Analyses are based on available data except in paper IV, as described below.

In paper I, uni- and multivariable logistic regression analyses, presented as odds ratios (OR) with a 95% confidence interval (CI), were conducted to evaluate the association between body constitution and POFP grade B and C, PPH grade B and C, DGE grades A-C, and major complications (CD≥3). Multivariable analyses were adjusted for clinically significant variables and potential confounders (age, gender, the American Society of Anesthesiologists physical status (ASA) score, operative time, intraoperative blood loss, preoperative bilirubin and C-reactive protein (CRP)). Corresponding analyses were performed comparing normal weight, overweight and obese patients without DM and outcome in POPF grade B and C as well as in corresponding patients with DM.

In paper II, a power calculation was executed. At the time of the study initiation, the morbidity rate was 65%. Approximately 45-55 PDs were performed annually. To detect a decrease from 65% to 45% with an α-value of 5% and a β-value of 80%, we calculated that 75 patients would be needed in each group. To compensate for loss during follow-up, 100 patients were included in each group. Demographic data and differences in outcome and intra- and postoperative complication rates between the historic and intervention group and between hyperglycemic and normoglycemic patients were analysed using a t-test, a Mann-Whitney U-test or a Pearson's chi-2 test. For categorical variables with frequencies less than 5, the Fisher's test was used.

In paper III, comparison of demographic and histopathological data and intra- and postoperative complications was performed using the Pearson's chi-2 test and a Mann-Whitney U-test as appropriate. To investigate the possible correlation between DM and outcome in medical, surgical and major surgical (CD≥3a) complications and anastomotic leak, a univariable analysis was performed. To adjust for confounding factors, a multivariable analysis was performed adjusting for age, sex, BMI (categorised according to the WHO definitions), smoking, and anastomosis type. The influence of DM, HbA1c, and DM duration on major surgical complications and pancreatic anastomotic leakage was analysed through multivariable logistic regression, where a separate multivariable logistic regression model was developed for each of the three variables (DM, HbA1c, and DM

duration). Each model was adjusted for age, sex, BMI (categorised according to the WHO definitions), smoking, and anastomosis type.

In paper IV, demographic and histopathological data were analysed using a Mann-Whitney U-test for continuous variables and Pearson's chi-squared test for categorical variables. To estimate overall 5-year survival in patients without DM, with long-standing DM, and new-onset DM, the Kaplan-Meier method was used with an associated log-rank test for statistical comparison between the three groups. To compare the risk between the groups, univariable and multivariable Cox proportional hazard regression analyses were further performed. The multivariable model was adjusted for age, gender, BMI, TN(M)-classification and tumour radicality (R0/1 resection). Missing data were handled by using multiple imputations by chained equations, where ten imputations were created with ten iterations for each imputation. A sensitivity analysis was conducted by a complete case analysis multivariable regression. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. Changes in DM medication over time was visualized through a Sankey plot.

All analyses were performed with Stata MP statistical package version 14.2, 2016 in paper I and II, and version 17.0, 2021 in paper III and IV (Stata Corporation, College Station, Texas, USA).

Ethics

All papers were conducted in accordance with the ethical principles in the Declaration of Helsinki. Ethical approval was obtained by the Regional Human Ethics Committee in Lund, Sweden, prior to all studies in this thesis (Paper I: Dnr 2010/298. Paper II: Dnr 2016/909. Paper III and IV: Dnr 2015/393 and Dnr 2015/846). In paper II, patients were enquired about participation, and a written informed consent was obtained from all participants.

Results

To really know is science; to merely believe you know is ignorance.

– Hippocrates

Paper I

A total of 328 patients were included, of which 24% (n=78) had DM. The prevalence of DM did not differ between under- or normal weight and overweight or obese patients, nor between non-large and large patients. Pancreatic or periampullary adenocarcinoma constituted approximately 80% of diagnoses in the study population.

Defined by BMI, 47% were overweight and 11% were obese. In overweight patients, the median operative time was significantly longer (478 vs. 447 min, p = 0.006) and the median intraoperative blood loss was greater (500 ml vs. 450 ml, p = 0.003). Postoperative complications were more common and the incidence of POPF grade B and C was more than threefold (18% vs. 5.2%, p<0.001) in overweight patients compared to under- or normal weight patients. In obese patients, the incidence was almost fivefold (25% vs. 5.2%, p < 0.001) and the incidence of PPH grade C was also significantly higher (11.1% vs. 2.3%, p=0.031), compared to under- or normal weight patients.

In patients defined as large (BSA ≥1.87), median intraoperative blood loss was greater (550 ml vs. 450 ml, p=0.014) and the incidence of POPF grade B and C was significantly higher than in non-large patients (16% vs. 6.7%, p=0.009).

A BF% ≥30% for males and ≥39% for females corresponded to overweight or obesity. The risk of several complications was significantly higher including the risk of POPF grade B and C (17% vs. 5.5%, p=0.001), compared to under- or normal weight patients.

In both unadjusted and adjusted multivariable regression analysis, the risk of POPF grade B and C was significantly higher in overweight patients defined by both BMI and BF% as well as in large patients. (Tab.2) The risk of PPH grade C was higher in patients defined by BMI as obese (OR 4.81, CI 1.01-22.8, p=0.048).

Table 2. Multivariable analysis on events of POPF grade B or C, PPH grade B or C, Clavien grade ≥3 and DGE in overweight and large patients.

	Events/N		Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value	ROC area
POPF B/C	a	b					
BMI	9/173	28/155	4.02 (1.83-8.82)	0.001	4.16 (1.83-9.47)	0.001	0.719
BSA	11/164	26/164	2.62 (1.25-5.50)	0.011	2.88 (1.19-6.96)	0.018	0.695
BF%	9/165	28/163	3.60 (1.64-7.89)	0.001	3.94 (1.76-8.83)	0.001	0.723
PPH B/C							
BMI	4/174	10/155	1.62 (0.76-3.42)	0.208	1.79 (0.78-4.12)	0.170	0.581
BSA	5/164	9/164	0.93 (0.44-1.95)	0.850	0.85 (0.34-2.09)	0.179	0.695
BF%	4/165	10/163	1.26 (0.60-2.64))	0.550	1.32 (0.59-2.91)	0.498	0.547
DGE							
BMI	62/172	76/153	1.75 (1.12-2.73)	0.013	1.72 (1.07-2-76)	0.024	0.628
BSA	62/163	76/162	1.44 (0.93-2.24)	0.106	1.72 (0.99-2.97)	0.054	0.574
BF%	55/164	83/161	2.11 (1.35-3.30)	0.001	2.13 (1.34-3.39)	0.001	0.644
CD ≥3							
BMI	18/173	37/154	2.72 (1.48-5.02)	0.001	2.63 (1.39-5.00)	0.003	0.642
BSA	24/164	31/163	1.37 (0.76-2.46)	0.290	1.11 (0.55-2.22)	0.778	0.513
BF%	18/165	37/162	2.42 (1.31-4-46)	0.005	2.31 (1.24-4.32)	0.009	0.638

N, number of non-missing values. ROC, receiver operating characteristics; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemmorhage; DGE, delayed gastric emptying; CD, Clavien-DIndo; BMI, body mass index; BSA, body surface area; BF%, body fat percentage.

a BMI < 25, BSA < 1.87, BF% < 29.6 male and < 38.9 female.

b BMI ≥ 25, BSA ≥ 1.87, BF% ≥ 29.6 male and ≥ 38.9 female.

* Adjusted for age, gender, American Society of Anesthesiologists (ASA)-score, operative time, intraoperative blood loss, bilirubin and C-reactive protein (CRP).

In patients without DM, the risk of POPF grades B and C was significantly higher in patients with coexisting overweight or obesity defined by BMI, with an up to eightfold OR compared to normal or underweight patients. This risk was not seen in patients with DM. (Tab.3)

Table 3. Events of POPF grade B or C in diabetic and nondiabetic normal weight, overweight and obese patients.

	Events/N	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
NO DM					
BMI <25	7/137	1		1	
BMI 25-29.99	17/85	4.64 (1.84-11.7)	0.001	4.45 (1.70-11.6)	0.002
BMI ≥30	8/28	7.43 (2.43-22.7)	<0.001	8.14 (2.48-26.7)	0.001
DM					
BMI <25	2/36	1		1	
BMI 25-29.99	2/34	1.06 (0.141-8.00)	0.953	0.85 (0.34-2.09)	0.977
BMI ≥30	1/8	2.43 (0.193-30.6)	0.493	2.88 (0.214-38.7)	0.425

N, number of non-missing values. DM, diabetes mellitus; No DM, patients without diabetes; DM, patients with diabetes; BMI, body mass index.

* Adjusted for age, gender, American Society of Anesthesiologists (ASA)-score, operative time, intraoperative blood loss, bilirubin and C-reactive protein (CRP).

Paper II

Among patients in the entire cohort (n=200) the prevalence of DM was 22% with no significant difference between the intervention group and the historic cohort. Adenocarcinoma located in the pancreas or the periampullary region was present in 83%. Fewer patients in the intervention group received an intraoperative drainage (82% vs. 92%, p=0.036).

In total (n=200), the incidence of POPF, PPH, and DGE grades B and C was 12%, 6% and 23%, respectively. In 27%, a major complication (CD≥3) occurred. There were no significant differences in complication rates between the intervention group and the historic cohort. The 90-day mortality was equal in the intervention group and the historic cohort (n=3 and n=2, respectively).

The median glucose within the first 30 postoperative days was significantly lower in the intervention group compared to the historic cohort. (Fig.9)

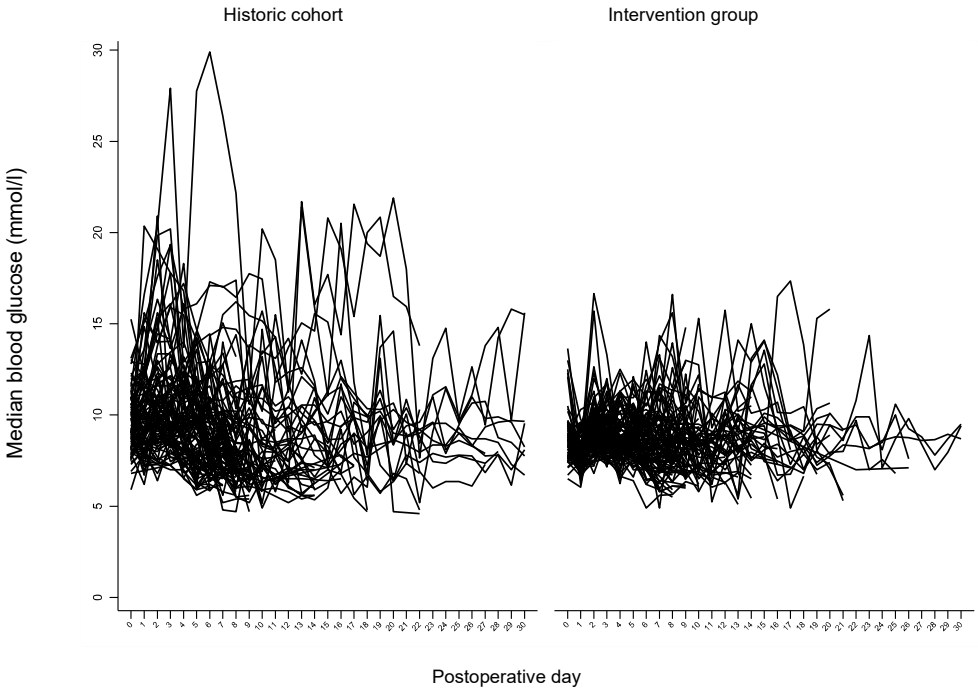

Figure 9. Median blood glucose per person per day within the first 30 postoperative days (capillary, point-of-care (POC) testing). Historic cohort vs. intervention group. Median blood glucose 9.1(IQR 6.8-17)[a] vs. 8.5 (IQR 6.4-11)[b], p=0.007 (Mann-Whitney U-test).

Hyperglycemia and complications

When comparing normo- and hyperglycemic patients in the entire cohort (n=198) during DOS-POD3 and DOS-POD5, there were no significant differences in complication rates. (Tab.4) Patients with DM constituted 46% of hyperglycemic patients compared to 14% in the normoglycemic group DOS-POD3 ($p<0.001$). During DOS-POD5, 52% of hyperglycemic patients had DM compared to 12% of normoglycemic patients ($p<0.001$).

Table 4. Complications among normoglycemic vs. hyperglycemic patients (n=198)

	DOS-POD3[a]			DOS-POD5[b]		
	Normoglycemic (n=148)	Hyperglycemic (n=50)	p-value	Normoglycemic (n=150)	Hyperglycemic (n=48)	p-value
POPF B or C	17 (12)	7 (14)	0.638	19 (13)	5 (10)	0.678
PPH B or C	10 (6.8)	1 (2.0)	0.296	10 (6.7)	1 (2.1)	0.302
DGE B or C	35 (24)	11 (22)	0.811	32 (21)	14 (29)	0.263
CD ≥3	38 (26)	14 (28)	0.853	38 (25)	14 (29)	0.599
Deep abscess	16 (11)	6 (12)	0.817	16 (11)	6 (13)	0.725

[a]Hyperglycemia defined as median blood glucose >10 mmol/l during the period DOS-POD3.

[b]Hyperglycemia defined as median blood glucose >10 mmol/l during the period DOS-POD5.

Data are presented as n (%). POPF, postoperative pancreatic fistula; PPH, post pancreatectomy hemorrhage; DGE, delayed gastric emptying. CD, Clavien-Dindo.

During DOS-POD3 and DOS-POD5 almost half of patients in the historic cohort were defined as hyperglycemic compared to 3-4% in the intervention group. The incidence of complications classified as CD≥3 in the intervention group was higher in patients with hyperglycemia DOS-POD3 and DOS-POD5 compared to normoglycemic patients. In the latter group, however, the difference was not significant. (Tab.5)

Table 5. Complications among normoglycemic vs. hyperglycemic patients.

A	Historic cohort			Intervention group		
	Normoglycemic (n=53)	Hyperglycemic (n=47)	p-value	Normoglycemic (n=95)	Hyperglycemic (n=3)	p-value
POPF B or C	5 (9.4)	7 (15)	0.540	12 (13)	0 (0)	1.000
PPH B or C	5 (9.6)	1 (2.1)	0.210	5 (5.3)	0 (0)	1.000
DGE B or C	11 (21)	11 (23)	0.750	24 (25)	0 (0)	1.000
CD ≥3	12 (23)	11 (23)	0.928	26 (27)	3 (100)	0.024
Deep abscess	3 (5.7)	5 (11)	0.469	13 (14)	1 (33)	0.374
B	**Historic cohort**			**Intervention group**		
	Normoglycemic (n=56)	Hyperglycemic (n=44)	p-value	Normoglycemic (n=94)	Hyperglycemic (n=4)	p-value
POPF B or C	7 (13)	5 (11)	0.862	12 (13)	0 (0)	1.000
PPH B or C	5 (8.9)	1 (2.3)	0.225	5 (5.3)	0 (0)	1.000
DGE B or C	10 (18)	12 (27)	0.259	22 (23)	2 (50)	0.251
CD ≥3	12 (21)	11 (25)	0.674	26 (28)	3 (75)	0.076
Deep abscess	3 (5.4)	5 (11)	0.272	13 (14)	1 (25)	0.466

A. Hyperglycemia defined as median blood glucose >10 mmol/l during the period DOS-POD3.

B. Hyperglycemia defined as median blood glucose >10 mmol/l during the period DOS-POD5.

Data are presented as n (%). POPF, postoperative pancreatic fistula; PPH, post pancreatectomy hemorrhage; DGE, delayed gastric emptying; CD, Clavien-Dindo.

The use of TIR and TAR could not detect differences in outcome. In 2 346 paired POC-CGM values hypoglycemia (<3.9 mmol/l) occurred in 4.5% but values were never <3.0 mmol/l and only six of these were confirmed by POC testing.

In patients with DM the TIR was significantly lower (78% vs. 91% DOS-POD3 and 78% vs. 92% DOS-POD5, both p<0.001). The incidence of POPF grade B and C and PPH grade B and C was lower in patients with DM compared to patients without DM, but not statistically significant (6.8% vs. 14%, p=ns and 2.3% vs. 7.0%, p=ns).

HbA1c was significantly higher preoperatively in patients with DM compared to patients without DM (55 and 38 mmol/mol, respectively, p<0.001). The HbA1c-levels were reduced 6-8 weeks postoperatively in patients with DM and elevated in patients without DM (51 and 40 mmol/mol, respectively, p<0.001).

Paper III

From 2010 through 2020, a total of 2 939 patients registered in the SNPPCR underwent PD and were included in the study. (Fig.10)

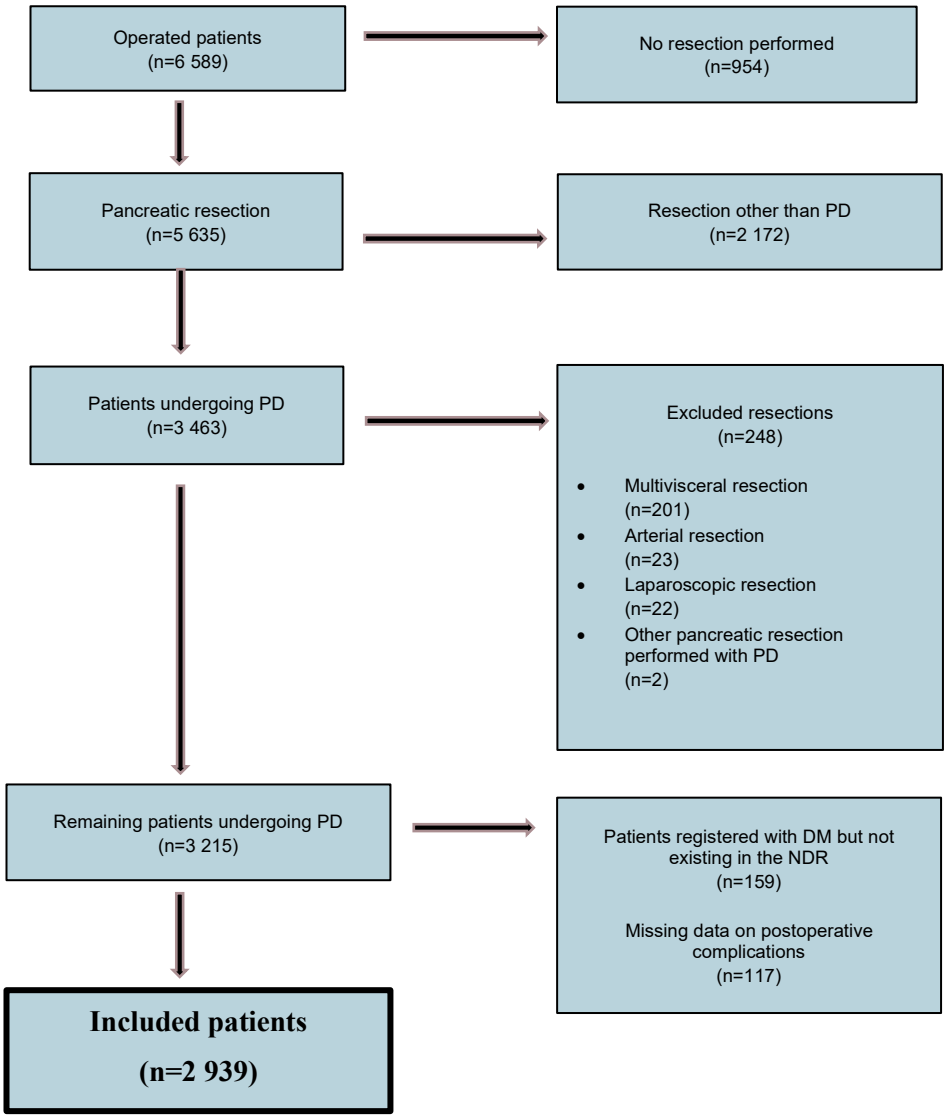

Figure 10. Flow chart of the exclusion process of patients in the Swedish National Pancreatic and Periampullary Cancer Registry. PD, pancreatoduodenectomy; DM, diabetes mellitus; NDR, The Swedish National Diabetes Register.

Of these, 78% (n=2 240 of 2 887) had pancreatic or periampullary adenocarcinoma, and 48% (n=1 394 of 2 887) had pancreatic adenocarcinoma. The prevalence of DM was 19% (n=558). In patients with DM, 87% (n=483) had DM2.

Most patients with DM (38%, n=189) had a DM-duration <5 years and 47% (n=263) had a mean HbA1c <53 mmol/mol.

More patients with DM were smokers (18% vs. 15%, p=0.032), had a higher ASA-classification (45% vs. 19% ASA 3, p<0.001), had heart failure (44% vs. 24%, p<0.001) and preoperative weight loss (61% vs. 48%, p<0.001) than patients without DM. The operative time was longer (400 [IQR 339-470] min vs. 383 [IQR 325-445] min, p=0.002) and the intraoperative blood loss was larger (500 [IQR 300-1000] ml vs. 500 [IQR 250-800] ml, p<0.001).

Postoperative complications

The incidence of surgical complications in the study population was 52% (n=1 530) and 20% (n=598) had a major surgical complication. Corresponding incidence for postoperative medical complications was 23% (n=675). In patients with DM, the incidence of pancreatic anastomotic leakage (including biochemical leak, POPF grade B and C), PPH grades A-C, and reoperation was significantly lower than in patients without DM. Thirty- and 90-day mortality were equal. (Tab.6)

Table 6. Data on postoperative complications by diabetes status.

	N	No DM	DM	p-value
Any surgical complication	2 939	1 259 (53)	271 (49)	0.067
Major surgical complication (CD≥3a)	2 938	497 (21)	101 (18)	0.142
Pancreatic anastomotic leak*	2 938	552 (23)	92 (16)	0.001
Deep infection/abscess	2 926	276 (12)	56 (10)	0.299
Surgical site infection	2 938	464 (19)	104 (19)	0.644
Wound dehiscence	2 938	71 (3.0)	17 (3.0)	0.937
PPH grade A-C	2 938	235 (9.9)	36 (6.5)	0.012
Postoperative bile leakage	2 938	144 (6.1)	26 (4.7)	0.205
DGE grade A-C	2 938	502 (21)	118 (21)	0.977
Other surgical complication	2 937	241 (10)	61 (11)	0.575
Reoperation	2 929	249 (10)	42 (7.5)	0.037
Interventional treatment	2 939	98 (4.1)	31 (5.6)	0.135
Any medical compliaction	2 939	546 (23)	129 (23)	0.925
Medical infection	2 939	305 (13)	68 (12)	0.691
Pulmonary embolism	2 939	66 (2.8)	9 (1.6)	0.118
DVT	2 939	12 (0.5)	2 (0.4)	0.653
Cardiovascular complication	2 939	123 (5.2)	31 (5.6)	0.710
Other medical complication	2 939	169 (7.1)	51 (9.1)	0.099
30-day mortality	2 840	53 (2.3)	13 (2.4)	0.922
90-day mortality	2 939	79 (3.3)	18 (3.2)	0.900
Readmission (within 30 days)	2 939	81 (3.4)	22 (3.9)	0.532
Major complication (CD≥3a)	2 939	510 (21)	106 (19)	0.206

N, number of non-missing values. Data are expressed as n (%).

*Biochemical leak (BL) and POPF grade B and C. PPH, postpancreatectomy hemorrhage; POPF, postoperative pancreatic fistula; DGE, delayed gastric emptying; CD, Clavien-Dindo grade. (Pearson's chi-squared test).

In multivariable analysis, DM was correlated to a significantly lower risk of major surgical complications and pancreatic leakage but DM was not correlated to postoperative medical complications. (Tab.7)

Table 7. Univariable and multivariable analysis on risk of complications in patients with versus without DM.

	N	Univariable analysis OR (95% CI)	p-value	N	Multivariable analysis* OR (95% CI)	p-value
Any complication	2 939	0.88 (0.73-1.06)	0.167	2 841	0.81 (0.67-0.99)	0.037
Medical complication	2 939	1.01 (0.81-1.26)	0.925	2 841	0.95 (0.76-1.20)	0.681
Surgical complication	2 939	0.84 (0.70-1.01)	0.067	2 841	0.77 (0.64-0.94)	0.010
Major surgical complication (CD≥3)	2 938	0.84 (0.66-1.06)	0.142	2 840	0.76 (0.59-0.97)	0.030
Pancreatic anastomotic leak*	2 938	0.65 (0.51-0.83)	0.001	2 840	0.60 (0.47-0.78)	<0.001

N, number of non-missing values.

CD, Clavien-Dindo grade. *Biochemical leak (BL) and postoperative pancreatic fistula (POPF) grade B and C. Multivariable analysis adjusted for age, sex, BMI (categorised according to the WHO definitions), smoking and anastomosis type.

Neither DM duration nor HbA1c-levels were significantly associated with complications. The risk of pancreatic anastomotic leakage was lower but not statistically significant in patients with DM and HbA1c >70 mmol/mol. (Fig.11)

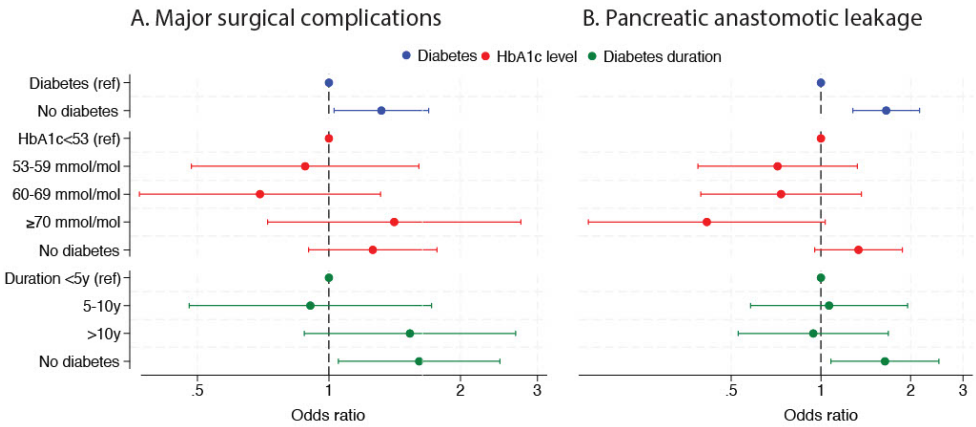

Figure 11. The influence of DM, HbA1c and DM duration on major surgical complications and pancreatic anastomotic leakage.

A separate multivariable logistic regression model was developed for each of the three variables (DM, HbA1c and DM duration), and each model was adjusted for age, sex, BMI (categorised according to the WHO definitions), smoking and anastomosis type. DM, diabetes mellitus.

In the subgroup of patients undergoing PD from May 2018 (n=769), in which POPF, PPH and DGE were recorded according to the ISGPS classification, no significant differences in outcome were found between patients with versus without DM.

A majority of patients (69%, n=2 028 of 2 927), were reconstructed with a PJ, with the same ratio in patients with and without DM. The incidence of pancreatic anastomotic leakage in patients with DM reconstructed with a PJ was significantly higher than in patients with DM reconstructed with a PG (21%, n=78 vs. 8%, n=14, $p<0.001$). In patients without DM, the results were similar (29%, n=483 in PJ vs. 9.5%, n=69 in PG, $p<0.001$). In the subgroup undergoing PD from May 2018, the incidence of POPF grade B and C in patients without DM was higher in patients reconstructed with a PJ (12%, n=45 vs. 5.8%, n=12, p=0.022). Similar but not statistically significant results were seen in patients with DM reconstructed with a PJ (13%, n=14 vs. 3.5%, n=2, p=0.051).

Paper IV

In total, 1 454 patients with PDAC undergoing PD were included, and patients with DM2 recorded in the NDR constituted 19% (n=274). (Fig.12)

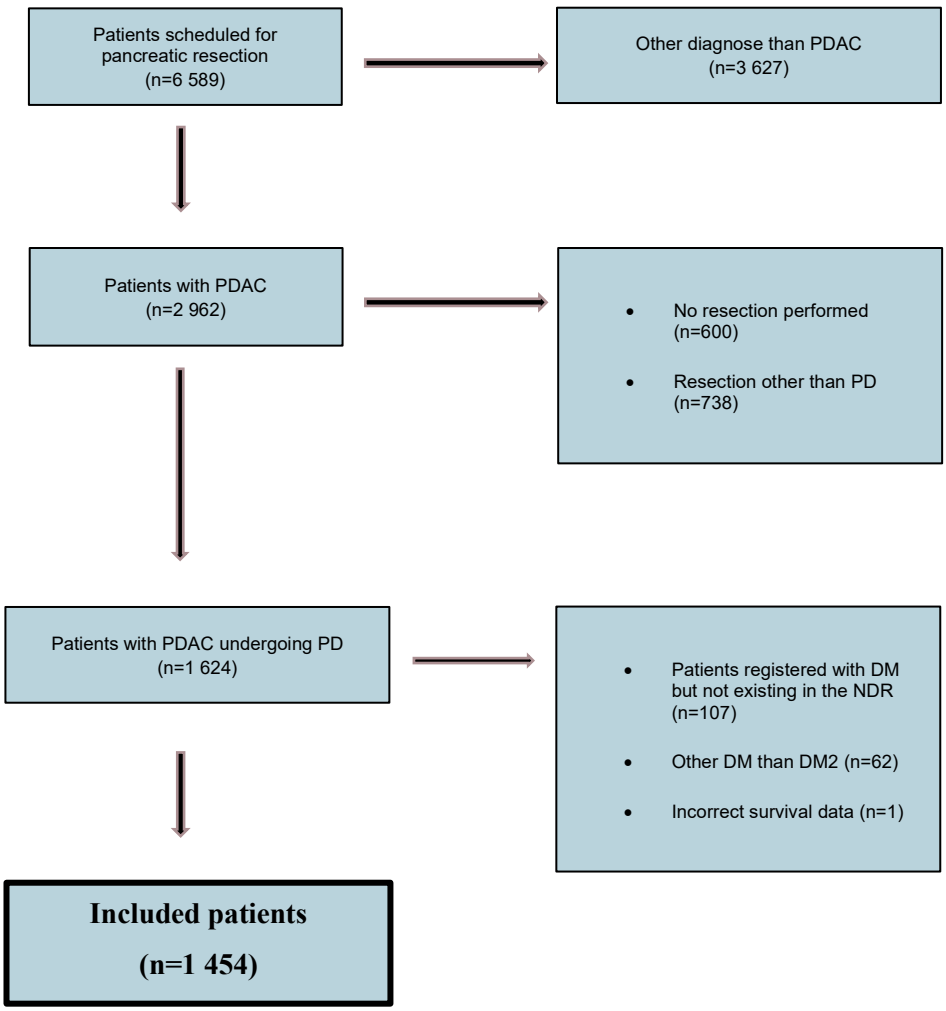

Figure 12. Flow chart of the exclusion process of patients in the Swedish National Pancreatic and Periampullary Cancer Registry. PDAC, pancreatic ductal adenocarcinoma; PD, pancreatoduodenectomy; DM, diabetes mellitus; NDR, The Swedish National Diabetes Register.

The duration of DM was only specified in 256 patients, of whom 24% (n=61) had new-onset DM. In patients with DM, 8 of 274 (3%) with DM at baseline went into remission postoperatively. PPD developed in 13% (n=155) of patients without a previous diagnosis of DM at baseline (n=1 180).

Preoperative insulin treatment was more common in patients with long-standing DM compared to patients with new-onset DM (43%, n=82 of 190, and 19%, n=11 of 59, p=0.007). The ratio of insulin-treated patients with DM was 36% (97 of 267 patients) preoperatively and 72% (137 of 190 patients) postoperatively.

Tumour characteristics

Over 70% of tumours were classified as stage T3 or T4 in the entire cohort (n=1 454). R1 resections constituted about 50% of all resections. Approximately 31-33% received adjuvant chemotherapy, with similar ratios in the subgroups. Neoadjuvant chemotherapy was given in 5-8% of patients. (Tab.8 and Tab.9)

In patients with DM, tumours were larger than in patients without DM (median 35 mm vs. 31 mm, p=0.002). Other tumour characteristics were similar between the groups. (Tab.8)

Patients with new-onset DM, had a lower ratio of undifferentiated or poorly differentiated tumours 34% (n=21) compared to patients with long-standing DM (43%, n=83), but the difference was not statistically significant. (Tab.9)

In patients developing PPD, the ratio of undifferentiated and poorly differentiated tumours was lower (32%, n=49 vs. 43%, n=435; p=0.038) and lymph node metastasis was less common (66%, n=102 vs. 78%, n=803; p=0.001) compared to patients who did not develop PPD. The tumour size was smaller and lymphovascular invasion was less common in patients with PPD, but not statistically significant.

Table 8. Demographic and histopathological data on patients without diabetes mellitus and with type 2 diabetes mellitus.

	N	No DM (n=1 180)	DM (n=274)	p-value
Age at operation (years)	1 454	69 (62-74)	72 (67-75)	<0.001
Sex	1 454			0.001
Male		583 (49)	171 (62)	
Female		597 (51)	103 (38)	
ASA-classification	1 452			<0.001
1		269 (23)	14 (5.1)	
2		657 (56)	128 (47)	
3		242 (21)	127 (46)	
4		12 (1.0)	3 (1.1)	
BMI	1 410	24.3 (22.1-26.9)	25.9 (23.2-28.4)	<0.001
Weight loss	1 439	651 (55)	195 (71)	0.001
Tumour size (mm)	1 384	31 (25-40)	35 (27-40)	0.002
Tumour location	1 454			0.602
Caput pancreatis		1 138 (96)	262 (96)	
Corpus pancreatis		18 (1.5)	3 (1.1)	
Cauda pancreatis		10 (0.8)	4 (1.5)	
Ductus pancreatis		14 (1.2)	5 (1.8)	
T-classification	1 434			0.043
Tx		5 (0.4)	1 (0.4)	
T1		68 (5.8)	7 (2.6)	
T2		233 (20)	52 (19)	
T3		824 (70)	208 (76)	
T4		34 (2.9)	2 (0.7)	
Microscopic radicality	1 448			0.627
R0		562 (48)	(130 (47)	
R1		602 (51)	140 (51)	
Differentiation level	1 397			0.610
Well		96 (8.1)	20 (7.3)	
Moderately		483 (41)	112 (41)	
Poorly		475 (40)	108 (39)	
Undifferentiated		9 (0.8)	4 (1.5)	
Lymph node metastasis	1 434	905 (77)	224 (82)	0.092
Lymphovascular invasion	1 437	730 (62)	172 (63)	0.427
Perineural invasion	1 438	930 (79)	226 (83)	0.314
Neoadjuvant chemotherapy	1 452	57 (4.8)	16 (5.8)	0.484
Adjuvant chemotherapy	671	394 (33)	87 (32)	0.234

N, number of non-missing values. Categorical variables are presented as n (%) and continuous variables as median (IQR). DM, diabetes mellitus; ASA, American Society of Anesthesiologists; BMI, body mass index; T, tumour; R0, microscopically no residual tumour cells in resection margin; R1, microscopically residual tumour cells in resection margin.

(Mann-Whitney U-test for continuous variables; Pearson's chi-squared test for categorical variables).

Table 9. Demographic and histopathological data on patients with long-standing and new-onset type 2 diabetes mellitus.

	N	Long-standing DM (n=195)	New-onset DM (n=61)	p-value
Age at operation (years)	256	72 (68-75)	71 (66-76)	0.427
Sex	256			0.053
Male		129 (66)	32 (53)	
Female		66 (34)	29 (48)	
ASA-classification	254			0.653
1		8 (4.1)	4 (6.6)	
2		91 (47)	31 (51)	
3		93 (48)	24 (39)	
4		2 (1.0)	1 (1.6)	
BMI	241	26.3 (23.5-28.7)	25.9 (23.1-28.1)	0.324
Weight loss	253	132 (68)	49 (80)	0.081
Tumour size (mm)	237	35 (27-40)	35 (28-42)	0.513
Tumour location	256			0.277
Caput pancreatis		188 (96)	56 (92)	
Corpus pancreatis		1 (0.5)	2 (3.3)	
Cauda pancreatis		3 (1.5)	1 (1.6)	
Ductus pancreatis		3 (1.5)	2 (3.3)	
T-classification	252			0.778
Tx		1 (0.5)	0 (0.0)	
T1		6 (3.1)	1 (1.6)	
T2		37 (19)	10 (16)	
T3		145 (74)	50 (82)	
T4		2 (1.0)	0 (0)	
Microscopic radicality	255			0.281
R0		90 (46)	35 (57)	
R1		102 (52)	25 (41)	
Differentiation level	229			0.288
Well		17 (8.7)	3 (4.9)	
Moderately		74 (38)	31 (51)	
Poorly		81 (42)	20 (33)	
Undifferentiated		2 (1.0)	1 (1.6)	
Lymph node metastasis	252	155 (80)	53 (87)	0.304
Lymphovascular invasion	215	115 (59)	43 (71)	0.516
Perineural invasion	234	158 (81)	52 (85)	0.980
Neoadjuvant chemotherapy	255	11 (5.6)	5 (8.2)	0.452
Adjuvant chemotherapy	121	63 (32)	19 (31)	0.182

N, number of non-missing values. Categorical variables are presented as n (%) and continuous variables as median (IQR). DM, diabetes mellitus; ASA, American Society of Anesthesiologists; BMI, body mass index; T, tumour; R0, microscopically no residual tumour cells in resection margin; R1, microscopically residual tumour cells in resection margin. (Mann-Whitney U-test for continuous variables; Pearson's chi-squared test for categorical variables).

Survival

Median overall survival was 2.09 years in the study population (n=1 454) and 2.23 years in patients without DM (n=1 180). In patients with a known DM2 duration (n=256), median overall survival was 2.43 years in patients with new-onset DM (n=61) and 1.55 years in patients with long-standing DM (n=195).

In the Kaplan-Meier analysis, patients without DM and patients with new-onset DM had significantly better survival compared to patients with long-standing DM. (Fig.13)

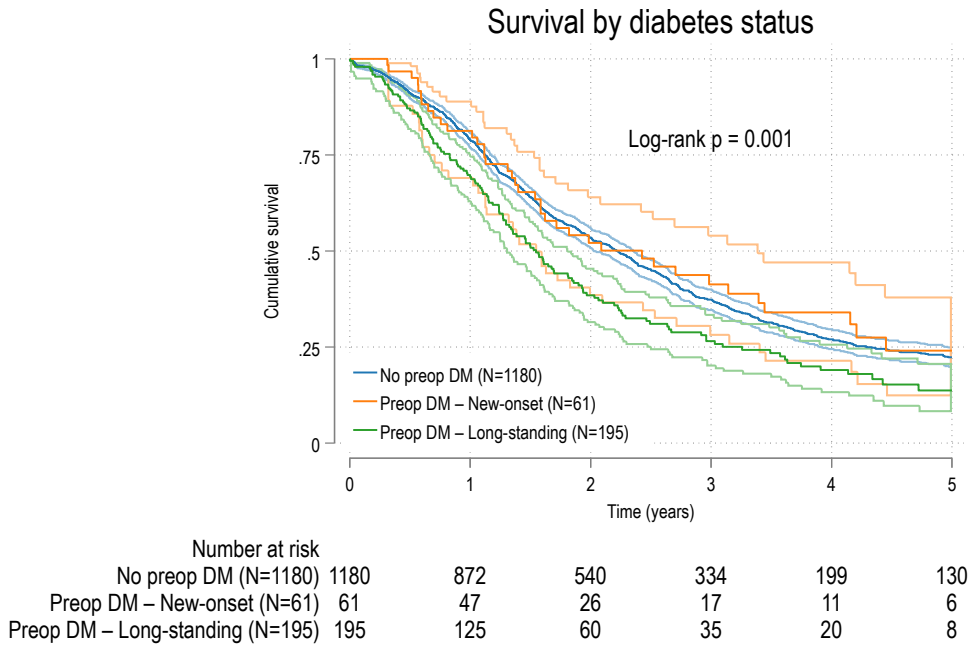

Figure 13. Kaplan-Meier curve on 5-year survival in patients without diabetes mellitus and in patients with long-standing and new onset diabetes mellitus. DM, diabetes mellitus.

Cox analysis including all three groups, showed worse long-term survival in long-standing DM, both adjusted an unadjusted, and more favourable long-term survival in new-onset DM (ns), compared to patients without DM (A). The long-term survival was also significantly worse in patients with DM2 compared to patients without DM, both adjusted and unadjusted (B). In subgroup analysis comparing new-onset DM to long-standing DM, patients with new-onset DM had a significantly favourable unadjusted long-term survival, compared to patients with long-standing DM (C). (Tab.10)

Table 10. Cox proportional hazard regression analysis on survival in patients without diabetes mellitus and in patients with long-standing and new onset type 2 diabetes mellitus.

	Unadjusted HR (95% CI)	p-value	Adjusted* HR (95% CI)	p-value
A				
No DM	1		1	
Long-standing DM	1.39 (1.16-1.66)	<0.001	1.27 (1.04-1.54)	0.016
New-onset DM	0.95 (0.69-1.31)	0.767	0.90 (0.65-1.24)	0.522
B				
No DM	1		1	
DM	1.30 (1.12-1.53)	0.001	1.19 (1.01-1.41)	0.038
C				
Long-standing DM	1		1	
New-onset DM	0.69 (0.49-0.99)	0.044	0.71 (0.49-1.00)	0.052

A. The analysis is a full-cohort contrasts with No DM as the reference.

B. The analysis is a linear contrast from the three-level model with No DM as the reference.

C. The analysis is restricted to patients with known diabetes duration (n=301) with long-standing DM as the reference.

Adjusted estimates are from the same covariate set across all contrasts.

*Adjusted for age, gender, BMI, TN(M)-classification and tumour resection radicality (R0/1).

HR, hazard ratio. DM, diabetes mellitus. BMI, body mass index; TNM, T: tumour, N: nodes, M: metastasis; R0, microscopically no residual tumour cells in resection margin; R1, microscopically residual tumour cells in resection margin.

Discussion

The only true wisdom is in knowing you know nothing.

– Socrates

PDAC is the third leading cause of cancer-related death in the Western world, and with an increasing incidence more patients will become subjects to surgery as well.[1] Despite exceptional technical progress with the introduction of minimally invasive PD, centralisation to high-volume centres and improvements in perioperative care, median overall survival is approximately two years in patients with PDAC undergoing PD, and the total morbidity rate in PD still exceeds 30%.[5, 49-54, 70] This is most likely attributed to advanced tumours even in patients available for surgery, and the extensive resection needed. Further improvements may, hence, be out of the hands of surgeons. Instead, the aim should be to identify patients at risk of PDAC and complications thereof.

As previously shown, both overweight and DM are risk factors for PDAC, as well as for complications after PD.[8, 77, 78, 81, 82, 91-93] Furthermore, the incidence of both overweight and DM is increasing.[74, 90] Consequently, patients with overweight or DM will presumably continue to constitute a large group of patients with PDAC and represent a significant proportion of patients at risk of complications after PD.

Aspects of complications

In papers I-III, the incidence of major complications ranged from 17% to 27%. For POPF B and C, the incidence was approximately 12%, and 22% for overall pancreatic anastomotic leakage. Overall DGE ranged from 21% to 43%, with an incidence of 23% for DGE B and C in paper II. The incidence of overall PPH was 11% in paper I, and PPH B and C were 6% and 9% in paper II and III, respectively. Hence, the overall complication rates in this thesis are in line with previous studies.[56-59, 61] The incidence of POPF B and C was somewhat lower, but in accordance with previous data from other Swedish population studies.[55, 65]

In paper I, we showed that overweight and obesity are risk factors of severe complications after PD and that BMI, BSA and BF% all can be applied to identify patients at risk of postoperative complications. These anthropometric measurements

could be used in risk scores predicting complications, in line with established predictive models of POPF.[56] BF% had not yet been evaluated as an anthropometric measure in identifying patients at risk of complications after pancreatic surgery, but was shown to correctly identify patients at risk of complications correlated to overweight in PD. Neither of the measurements used are specific for visceral or intrapancreatic fat, which are correlated to the risk of POPF, but they are accessible and cost effective ways of identifying patients at risk of overall complications in PD.[122, 123] Further, general risk factors such as prolonged operating time and the development of abscesses, were more prevalent in overweight patients, making these results relevant also in general surgery.

In paper II, we showed that the use of insulin infusion as well as the use of isCGM are feasible in a surgical ward and could be used to obtain normoglycemia in an efficient and safe way in the postoperative care following PD. To the best of our knowledge, this was the first study to evaluate insulin infusion in a non-ICU setting, as well as glucose monitoring with isCGM, after PD.

Our definition of hyperglycemia was a blood glucose >10 mmol/mol, which is rather high. Despite of this, hyperglycemia in the historic cohort was up to 15 times more prevalent than in the intervention group, and the median glucose within 30 days postoperatively was lowered with the intervention. Although we could not confirm any impact on postoperative complications with the studied regimen, an improved blood glucose level should improve outcome given the well-known risk factors correlated to hyperglycemia.[110, 124, 125]

As shown in previous studies, patients without DM tend to be more prone to complications correlated to hyperglycemia compared to patients with DM, which could indicate a need for a more aggressive treatment in patients without DM.[110] This is further strengthened by the reduction in risk of complications previously seen in patients with normalized blood glucose after administration of insulin, both in patients with and without DM.[110]

As emphasised by Kotagal et al., the correlation between hyperglycemia and complications in patients without DM could signify that hyperglycemia in patients without DM is a representation of a higher level of surgical stress or more severe illness, compared to patients with DM, who usually have higher blood glucose preoperatively.[110] In paper II, we did not compare hyperglycemic patients with and without DM regarding the incidence of complications, and we can therefore neither confirm nor disprove this theory. In paper III, however, we compared the incidence of complications in patients with and without DM, where the incidence of complications was equal, except for pancreatic leakage and PPH. Mortality rates were also equal between these groups. Hence, patients without DM were not found to be subjects of more severe illness. The results in paper III could presumably be extrapolated to the cohort in paper II, disproving the aforementioned theory presented by Kotagal et al. Independent of theories, hyperglycemia has previously

been correlated to adverse events and should be treated in all patients postoperatively, and the regimen in paper II could safely be used to obtain normoglycemia after PD.

In paper III, the incidence of pancreatic anastomotic leakage was threefold higher in PJ than in PG, both in patients with and without DM. A similar higher incidence ratio was found when comparing outcomes in POPF grade B and C. No consensus has been reached by the ISGPS on preferred anastomosis type.[48] Based on the findings in paper III and other studies, PG should be considered in high-risk patients.[65, 126] Given the outcome in overweight and obese patients in paper I, as well as high risk scores of POPF related to high BMI, overweight patients are at greater risk of POPF and should be included in the group of patients considered for PG.

The role of DM and complications

Despite the overrepresentation of hyperglycemia in patients with DM in paper II, both POPF and PPH grade B and C, seemed to be lower in patients with DM. Also in paper I and III, DM was found to be a protective factor of complications, primarily of POPF, despite more risk factors in patients with DM, such as smoking, higher ASA classification, heart failure, and preoperative weight loss, as seen in paper III. In addition to pancreatic anastomotic leakage, the incidence of PPH and reoperation was lower as well as the risk of major surgical complications, in patients with DM in paper III. These findings, including a lower incidence of PPH, as well as a lower incidence of composite complications classified as CD≥3 in patients with DM, are most likely an expression for, and a consequence of, the lower incidence of POPF in this group of patients.

The lower incidence of POPF, in turn, is presumably attributed to the firmer pancreatic texture in patients with DM, generated by fibrosis, as previously described.[106-108]

Given the advanced stages of PDAC most commonly seen at the time of diagnosis, the role of prehabilitation, with the intention of reducing risk factors of postoperative complications, might have a peripheral place in optimising patients preoperatively. However, adjusting preoperative hyperglycemia, independent of DM status, and obtaining well-regulated blood glucose in patients with DM, could be a means of reducing risk factors correlated to hyperglycemia.

The knowledge of risk factors of complications after PD, as shown in this thesis, could further facilitate the identification of patients at risk and possibly generate early detection of complications. Ideally, this could enable intervention before severe complications occur.

Impact of DM2 on survival

Individuals with DM have a higher all-cause mortality and the risk increases with a lower age at diagnosis of DM.[127-129] In paper IV, including only type 2 DM, no differences in comorbidity could be characterised, since only ASA classification was analysed between patients with and without DM. The DM diagnosis itself generates a higher ASA score and, hence, the ASA score alone can not determine actual differences in comorbidity. In paper III, however, the prevalence of heart failure was significantly higher among patients with DM. With a median overall survival of merely 1.5 years after PD in patients with long-standing DM and PDAC, the probable DM correlated comorbidity should not impact survival in PDAC, as shown by Yuan et al.[130]

Even small tumours metastasises to a high degree in PDAC, with 30.6% of patients with a tumour size of 0.5 cm or less presenting with distant metastasis.[31] Further, tumours >2 cm have a significantly higher incidence of risk factors of a worse prognosis, such as lymph node metastasis, poor differentiation, vascular and perineural invasion and R1 resections, compared to patients with tumours ≤2 cm.[33] In paper IV, patients with DM2 had significantly worse survival than patients without DM. Patients with DM2 had larger tumours than patients without DM, but the median tumour size was 30 mm or above in all subgroups. No other major differences in risk factors were found between patients with and without DM2.

Patients with long-standing DM undergoing PD for PDAC, however, had worse outcome than patients with new-onset DM and patients without DM. The longest median overall survival of 2.43 years was observed in patients with new-onset DM, and the shortest survival of 1.55 years was observed in patients with long-standing DM, but we could not show any significant differences in Cox analysis between patients with new-onset DM and patients without DM. This could indicate a similar risk in these two groups. Hypothetically, the better survival in patients with new-onset DM could be attributed to a more beneficial tumour biology. In paper IV, although not statistically significant, fewer patients with new-onset DM had R1 resections and fewer had tumours that were poorly differentiated or undifferentiated. Conversely, they had more risk factors such as lymph node metastases and lymphovascular and perineural invasion. The reason for the favourable survival in patients with new-onset DM, as seen in paper IV, is therefore not fully explained.

Only patients with a diagnosis of DM registered in the NDR were included in the DM groups in paper III and IV. In the group of patients with PPD in paper IV, undiagnosed or not yet registered patients with new-onset DM, could constitute a part of this group, thus contributing to the findings. Patients with PPD had smaller tumours, and fewer tumours which were poorly differentiated or undifferentiated, and had the lowest incidence of lymph node metastases and lymphovascular invasion and perineural invasion, than all other groups. If these results are applicable to patients with undiagnosed new-onset DM, this may explain the generally better

survival generally seen in patients with new-onset DM compared to patients with long-standing DM, but they are not explanatory factors in paper IV.

The possibility to evaluate the impact of adjuvant chemotherapy on survival is limited due to approximately 50% missing data for this parameter in paper IV. Based on available data, approximately 31-33% received adjuvant chemotherapy, except in the group with PPD, where 42% received treatment. Given comparable ratios, adjuvant chemotherapy is unlikely the cause of differences seen in survival between the groups. In patients with new-onset DM, 8% received neoadjuvant chemotherapy compared to 5% and 6% of patients without DM and long-standing DM, respectively. Since neoadjuvant chemotherapy is only recommended to borderline resectable patients, this finding should not explain the favourable outcome seen in patients with new-onset DM.

Given the previously observed higher prevalence of DM in PDAC, both in comparison to the overall population and in comparison to other malignancies, it is debated whether DM in PDAC is a cause of cancer or a paraneoplastic phenomenon.[91, 92, 131] The strongest association between DM and PDAC is observed in patients with new-onset DM, in whom the rate of remission after resection exceeds 50%.[96] Furthermore, patients with DM have been shown to present with small tumours.[100] These findings strengthen the theory that DM in these cases is not a result of glandular destruction caused by the tumour, but rather constitutes a paraneoplastic phenomenon, resulting from impaired β-cell function and increased insulin resistance secondary to tumour-derived factors.[99, 132, 133] Additionally, the short survival in PDAC contradicts the possibility of PDAC causing long-standing DM. One explanation model proposed on the correlation between long-standing DM and PDAC, is the upregulating effect of hyperinsulinemia on insulin-like-growth-factor 1 (IGF-1), which has been shown to stimulate pancreatic cancer cell proliferation.[97, 98] Moreover, the accumulation of AGEs, as seen in DM and long-standing hyperglycemia, stimulates cell proliferation and angiogenesis.[113, 114] Thus, new-onset and long-standing DM present as two different entities, with the first as a clinical manifestation of PDAC and the latter as a driving factor in PDAC. The difference in survival between new-onset and long-standing DM emphasises the prognostic value of DM duration

If, in fact, PDAC is induced by modifiable risk factors such as obesity and DM2, with the latter being related to the metabolic syndrome, these conditions should be targeted and reduced through preventive health care. Furthermore, in order to detect PDAC at earlier stages in patients with DM, guidelines regarding screening should be implemented when feasible in a similar manner as in patients with a hereditary risk of PDAC. Considering the high prevalence of DM in relation to the low incidence of PDAC, further studies in line with the EDI study are needed to identify high-risk patients.[102]

With a median overall survival of approximately 2 years and approximately 50% R1 resections, with over 70% of tumours being stage T3 or T4 in paper IV, this indicates a late diagnosis and subsequently advanced stages also in our material. Considering the poor survival in this minority of patients with PDAC available for PD, this suggests that focus must be on early detection as a means of identifying patients with PDAC at an earlier stage, optimising survival. Given the advanced disease at diagnosis and the high grade of recurrence, PDAC could be regarded as a disseminated disease even without visible distant metastasis at diagnosis, and patients could hypothetically benefit from neoadjuvant chemotherapy. However, evidence of improved survival after neoadjuvant chemotherapy compared to upfront surgery in resectable pancreatic cancer is limited.[134-137]

Limitations

Paper I, III and IV are register-based studies with a retrospective design, which hypothetically might generate limitations in available data where missing data can not be supplemented. This limitation was somewhat compensated for in paper I, where missing data were supplemented as needed. Further, with many different users in the registries, data could be registered and classified heterogeneously, affecting the comparability and validity of registered data. The NDR and the SNPPCR are well-validated registries with confirmed high-quality data, reducing the impact of some of these limitations.

The power calculation in paper II was based on all grades of complications, but analyses were performed mainly on major complications. To obtain a larger study population from a single centre, with the aim to strengthen the power sufficiently, would take several years. Given the relatively low resection volume per HPB centre in Sweden, clinical studies such as the regime in paper II, should ideally be multicentre studies. As a consequence of an overlapping clinical trial, some patients were randomised to not receive an intraabdominal drainage, limiting one of the diagnostic criteria of POPF B in paper II.

In paper II, the time periods DOS-POD3 and DOS-POD5 were chosen based on the regimen where insulin infusion and TPN are usually ongoing until POD5. These first postoperative days are also when extreme glucose values have been previously noted, and when we chose to investigate the impact of insulin infusion. However, it is not yet established in which time periods hyperglycemia has its greatest impact on hyperglycemia-related complications. To evaluate optimal time periods, the use of artificial neural networks could be a way of identifying time periods and cut off-values for hyperglycemia significant for outcome, unbiased.

In paper III and IV, only patients registered in the NDR were defined as having DM. This could lead to smaller cohorts and the risk of undiagnosed or not yet registered patients with DM being defined as patients without DM in paper III. In paper IV,

the prevalence of DM2 was 19%, and merely 24% of patients with a known DM2 duration had new-onset DM, contradicting previous data on prevalence of DM in PDAC, most likely due to the inclusion criteria. Further, new-onset DM could be misclassified as PPD, and the results in the PPD group could instead be attributed by new-onset DM in paper IV. For certainty regarding the diagnosis of DM, screening of blood glucose or HbA1c would be needed in all patients preoperatively. This would require extensive testing, which is time consuming and costly in studies with corresponding cohort sizes as in paper III and IV.

A further limitation in paper III was the unspecified grades of POPF, PPH and DGE, according to the ISGPS, until May 2018. Consequently, the impact of DM on outcome in clinically significant grades of POPF, PPH and DGE could only be evaluated in a small study population where these variables were included in the registry.

Conclusions

◊ Paper I

BMI, BSA and BF% can be used to identify patients at risk of postoperative complications after PD. The risk of POPF grade B and C was elevated in overweight and obese patients without DM but not in corresponding patients with DM.

◊ Paper II

An insulin infusion regimen is feasible and significantly decrease blood glucose postoperatively after PD. The impact on complications was limited. The incidence of POPF grade B and C in patients with DM was lower, but not significantly, compared to patients without DM.

◊ Paper III

The risk of major surgical complications and pancreatic leakage after PD, as well as the incidence of PPH and reoperations, were lower in patients with DM. There were no differences in 30- and 90-day mortality in patients with and without DM. Postoperative complications were not correlated to DM duration or HbA1c levels.

◊ Paper IV

Patients with DM2 and PDAC undergoing PD have significantly worse survival than patients without DM, but new-onset DM2 is more favourable for survival than long-standing DM2. A minority of patients with DM2 went into remission, and the incidence of PPD in patients without DM was low, following PD for PDAC.

Future perspectives

Foolish the doctor who despises the knowledge acquired by the ancients.

– Hippocrates

As concluded in this thesis, PDAC is correlated to poor survival also in patients undergoing PD, with a median overall survival of approximately 2 years. The poor survival rate is presumably a consequence of advanced tumours seen even in patients undergoing surgery, with half of resections being R1 resections. This indicates that improvement in survival rates require early detection, preferably through screening with tumour biomarkers. As of yet, no biomarkers are in clinical practice as a means of screening for PDAC. When such biomarkers have been implemented, guidelines for screening, including screening of normal weight patients with a late debut of DM, should be implemented, preferably in combination with advanced imaging. Technologies such as artificial intelligence (AI) could potentially make way for enhanced imaging assessments, resulting in a higher sensitivity in existing imaging methods, where the human eye might fail to find early signs of tumours. To fully understand the difference in survival seen in patients with long-standing and new-onset DM, studies on tumour biology and the identification of mediators in DM-associated PDAC are needed, potentially identifying tumour markers in this group of patients. The oncological advancements in immunotherapy and targeted treatment based on patient specific tumour biology, might also be a link to a future cure in patients with PDAC. Further randomised controlled trials, examining the effect of established neoadjuvant chemotherapies versus upfront surgery on survival, should be evaluated in patients with resectable PDAC.

The resection performed in PD is, as noted, extensive, making it one of the most complication-prone surgical procedures performed today. A prospective study, using novel biomarkers such as TNF-α, to predict postoperative complications, would be a valuable addition in identifying patients at risk. The insulin infusion regimen and its effect on postoperative complications, as evaluated in this thesis, could be further investigated through a national multicentre study, potentially identifying a beneficial outcome of the regimen.

Populärvetenskaplig sammanfattning

Cancer i bukspottkörteln är en ovanlig cancerform men är trots detta den tredje vanligaste orsaken till cancerrelaterad död i västvärlden. Förekomsten av bukspottkörtelcancer verkar nu öka över tid. Orsaken till detta är sannolikt livsstilsrelaterade faktorer såsom övervikt och diabetes. Operation är enda möjligheten till bot men endast 20% av de som drabbas av bukspottkörtelcancer har möjlighet att genomgå kirurgi på grund av att cancern spridit sig eller att tumören växer på ett sätt som gör att den inte går att operera bort. Operationen som står till buds för cancer i bukspottkörtelns huvud, i sista delen av huvudgallgången eller dess mynning till tolvfingertarmen, eller vid cancer i tolvfingertarmen, kallas pankreatoduodenektomi och innebär att huvudet på bukspottkörteln, sista delen av magsäcken, tolvfingertarmen, gallblåsan och sista delen av huvudgallgången opereras bort. Härefter kopplas kvarvarande delar samman för att rekonstruera anatomin. Magsäcken och gallgången kopplas till tunntarmen och bukspottkörteln kopplas till tunntarm eller magsäck. Operationen är behäftad med en hög andel komplikationer där över 30% av patienterna drabbas. För att förbättra överlevnaden genom att förebygga återfall efter operationen ges cellgifter en tid efter operationen. Om den opererade patienten drabbas av en komplikation riskerar cellgiftsbehandlingen att fördröjas eller helt utebli. Det är därför viktigt att försöka hitta riskfaktorer för att drabbas av komplikationer och, om möjligt, förebygga komplikationer.

Man vet att det finns ett samband mellan övervikt respektive diabetes mellitus och cancer i bukspottkörteln. Dessa två grupper har också en generellt ökad risk att drabbas av komplikationer efter många olika typer av operationer i bukhålan. Diabetes har dock visat sig vara skyddande för en av de vanligaste komplikationerna vid pankreatoduodenektomi, så kallad bukspottkörtelfistel, där det uppstår ett läckage från bukspottkörteln. Nedbrytande ämnen, så kallade enzymer, läcker då ut i bukhålan och kan orsaka infektion och blödning genom vävnadsnedbrytning i området. Skyddet som diabetiker verkar ha tror man beror på att bukspottkörteln blir fastare vid diabetes till följd av att mer bindväv utvecklas i bukspottkörteln. Risken för läckage vet man minskar om bukspottkörteln har fast konsistens.

I denna avhandling var målet att studera utfallet hos överviktiga patienter, hos patienter med högt blodsocker efter pankreatoduodenektomi samt hos patienter med diabetes, gällande komplikationer och risk för död efter pankreatoduodenektomi.

I delarbete I, som var en retrospektiv registerstudie, studerades utfallet för komplikationer efter pankreatoduodenektomi kopplat till övervikt hos 328 patienter som genomgick pankreatoduodenektomi åren 2000–2015 vid Skånes universitetssjukhus. Vi utvärderade olika mätmetoder för kroppskonstitution, där BMI är den mest välkända och använda. Utöver BMI använde vi även body surface area (BSA) och body fat percentage (BF%). Patienter som definierades som överviktiga eller obesa, baserat på BMI och BF%, samt patienter som definierades som ”stora”, baserat på BSA, hade en ökad risk att drabbas av svåra komplikationer. Överviktiga och obesa patienter hade också en ökad risk att drabbas av allvarliga bukspottkörtelfistlar jämfört med normal- och underviktiga. Denna risk för allvarliga fistlar sågs inte hos överviktiga och obesa med diabetes.

Delarbete II var en prospektiv interventionsstudie där 100 patienter som genomgick pankreatoduodenektomi vid Skånes universitetssjukhus från januari 2017 inkluderades. För jämförelse inkluderades även 100 patienter i en historisk grupp. Patienterna i interventionsgruppen erhöll insulindropp efter operationen och blodsockervärdena uppmättes med hjälp av en mätare som avläser blodsocker kontinuerligt. Målet var att se om man genom tillförsel av insulin via dropp kunde sänka blodsockervärdena och minska risken för komplikationer samt att studera hur högt blodsocker påverkar risken för komplikationer. Blodsockervärdena var signifikant lägre under uppföljningstiden i interventionsgruppen men vi såg ingen skillnad i andelen patienter med komplikationer i denna grupp jämfört med den historiska gruppen. Det var vanligare med svåra komplikationer i interventionsgruppen bland patienter med högt blodsocker jämfört med patienter med normalt blodsocker.

I delarbete III och IV samkörde vi data för åren 2010-2020 från två olika register, Nationella diabetesregistret och Nationella kvalitetsregistret för tumörer i pankreas och periampullärt. I dessa registreras uppgifter om patienter med diabetes respektive patienter med tumörer i bukspottkörteln, nedre delen av huvudgallgången och dess mynning samt i tolvfingertarmen. I sistnämnda registreras även patienter som inte genomgår operation.

I delarbete III var målet att studera skillnader i komplikationer efter pankreatoduodenektomi mellan diabetiker och icke-diabetiker. Totalt inkluderades 2939 patienter. Av dessa hade 19% diabetes. Diabetiker hade en lägre risk att drabbas av allvarliga komplikationer och bukspottkörtelfistlar.

I delarbete IV undersöktes hur diabetes inverkade på överlevnad i bukspottkörtelcancer efter pankreatoduodenektomi. I hela gruppen av patienter (n=1454) var medianöverlevnaden drygt 2 år. Längst medianöverlevnad sågs för diabetiker som haft diabetes kortare tid än 2 år (medianöverlevnad 2,43 år). Patienter som haft diabetes längre tid än 2 år hade sämre långtidsöverlevnad än diabetiker som haft diabetes kortare tid än 2 år och de hade också sämre långtidsöverlevnad än icke-diabetiker.

Sammantaget visar resultaten i denna avhandling att övervikt ökar risken för komplikationer efter pankreatoduodenektomi men att diabetes verkar vara skyddande för fistlar och andra allvarliga komplikationer som vanligen är en följd av utvecklingen av fistlar. Ur sistnämnda perspektiv verkar inte diabetiker utgöra en riskgrupp vad gäller komplikationer efter pankreatoduodenektomi, trots deras generellt sett högre sjuklighet och fler rökare i denna grupp. För att identifiera riskpatienter relaterat till kroppskonstitution, kan såväl BMI som BSA och BF% användas och skulle förslagsvis kunna användas i modeller för att förutsäga och bedöma risken för komplikationer efter pankreatoduodenektomi. Interventionsstudien i denna avhandling visar att det är genomförbart och säkert att använda insulindropp för att framgångsrikt sänka blodsocker efter pankreatoduodenektomi. Givet kännedomen om att högt blodsocker ökar risken för komplikationer bör blodsockernivåer efter pankreatoduodenektomi hållas välkontrollerade, både hos diabetiker och icke-diabetiker, vilket skulle kunna möjliggöras genom den utvärderade regimen med insulindropp. Den studerade överlevnaden i bukspottkörtelcancer efter pankreatoduodenektomi var låg och de flesta tumörer var avancerade. Detta talar för upptäckt av cancern sent i förloppet vilket sannolikt bidrar till den generellt sett dåliga överlevnaden. Eftersom diabetiker har en ökad risk för bukspottkörtelcancer bör screeningprogram tas fram på sikt för dessa patienter för att försöka möjliggöra upptäckt av cancer i tidigare stadier. Ett sådant screeningprogram förutsätter dock lämpliga metoder att diagnosticera dessa patienter med, vilket kräver ytterligare forskning inom området.

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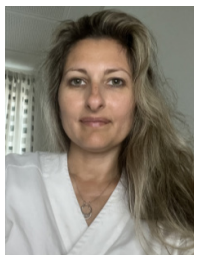

Eva Ekström is a surgeon at the Department of Surgery, Ystad Hospital, Sweden.

This thesis explores the effect of body constitution, hyperglycemia and diabetes on postoperative complications after pancreatoduodenectomy, and investigates the impact of diabetes on survival in patients with pancreatic adenocarcinoma undergoing pancreatoduodenectomy.

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