Challenging dogmas in pancreatic surgery: biliary drainage, outcome and beyond
van der Gaag, N.A.

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Systematic Review of Pancreatic Function Following Surgery for Painful Chronic Pancreatitis

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Submitted
ABSTRACT

Background
The occurrence of pancreatic insufficiency in patients undergoing surgery for painful chronic pancreatitis was evaluated.

Methods
We performed a systematic literature search. Inclusion criteria were: chronic pancreatitis with pain as leading indication to decide for operation; surgical procedures including (organ-sparing) pancreatic head resection (Beger, Frey, pancreaticoduodenectomy), surgical drainage (pancreaticojejunostomy) or distal resection; and pre- and postoperative essential outcomes reported. Exclusion criteria were procedures other than described under inclusion criteria; cohort included acute pancreatitis; experimental or animal studies; auto-immune pancreatitis; tropical chronic pancreatitis; patients operated under suspicion of malignancy with pathological specimen of chronic pancreatitis.

Results
28 mostly descriptive cohort studies with a total of 1831 patients fulfilled inclusion criteria. Follow-up interval to evaluate pancreatic function differed dramatically between studies (6 months to 14 years). Preoperative endocrine insufficiency rate varied from 22.2 per cent (distal resection), 23.0 per cent (surgical drainage), to 36.7 per cent (head resection). Postoperative rates were 55.6 per cent, 41.9 per cent, and 51.9 per cent respectively. New-onset diabetes following surgery was mainly described in studies with follow-up length of more than 2 years. Largest increase in exocrine insufficiency following surgery was reported following distal resection (35.4 per cent). Head resection was characterized by highest presence of exocrine insufficiency (preoperative 56.8 per cent, postoperative 65.3 per cent).

Conclusion
Pancreatic insufficiency comprises significant and progressive comorbidity in patients with surgically treated painful chronic pancreatitis. Heterogeneous follow-up lengths preclude firm conclusions over attributed risk for insufficiency due to surgery, or as a consequence of progressive disease over time.
INTRODUCTION

Chronic pancreatitis is a progressive, inflammatory condition causing irreversible damage of pancreatic parenchymal tissue. Continuous or (superimposed) acute attacks of severe abdominal pain are the main complaint. Development of chronic pancreatitis is probably due to a complex interrelationship of etiological factors, the most important being toxic-metabolic (alcohol), genetic predisposition and recurrent and severe acute pancreatitis. Besides abdominal pain prolonged disease ultimately results in impaired pancreatic function.

Pain in patients with chronic pancreatitis is longstanding and often insufficiently controlled by medical interventions. Despite progressive destruction of the gland the complaints of pain frequently persist, especially in alcoholic and early-onset idiopathic pancreatitis. Pain is the principle indication to intervene surgically in patients. It is well-conceived that the increasing amount of evidence is showing clear benefits of surgery over endoscopic therapy in terms of longstanding pain relief and number of procedures. Different surgical options in the management of chronic pancreatitis for treatment of pain exist with choice of procedure mainly depending on the morphological features of the pancreas. With respect to the presence of an inflammatory mass a recent review suggests that more organ-sparing procedures are preferred over pure resectional procedures such as the pylorus preserving pancreateoduodenectomy, both in terms of clinical outcomes as intraoperative blood replacement, and hospital stay, as for medical outcomes as weight gain, and exocrine insufficiency.

Endocrine insufficiency in chronic pancreatitis results in pancreatogenic diabetes and is manifested by a spectrum of abnormal glucose regulation that ranges from mild hyperglycemia to secondary organ dysfunction to lethal hypoglycemia unawareness. In patients with alcoholic chronic pancreatitis and insulin dependent diabetes mellitus hypoglycemic complications are the main limitations of life expectancy. Exocrine pancreatic insufficiency is a serious condition, occurring frequently in chronic pancreatitis, and is characterized by an impaired enzyme secretion. The lack or absence of pancreatic enzymes leads to an inadequate absorption of fat, proteins, and carbohydrates, causing steatorrhea and creathorrhea, which results in abdominal discomfort, weight loss, and nutritional deficiencies.

This systematic review focused on the incidence of endocrine and exocrine insufficiency in patients who underwent surgery for painful chronic pancreatitis. The primary aim was to determine the proportion of patients that were confronted with new-onset insufficiency following surgery.
METHODS

Study Selection

A systematic literature search from 1 January 1975 to 31 December 2010 was performed in Embase, MEDLINE and the Cochrane Library. We focused on the most regularly performed primary surgical procedures for painful chronic pancreatitis, i.e. longitudinal pancreaticojejunostomy (PJ) according to Partington-Rochelle or modified Puestow, duodenum-preserving pancreatic head resection according to Beger (DPPHR-B) or according to Frey (DPPHR-F; pancreatic head coring with longitudinal pancreaticojejunostomy), pancreatoduodenectomy (PD) or its pylorus-preserving modification (PPPD), and distal pancreatectomy (DP).

The MEDLINE and Embase search terms were ‘chronic pancreatitis AND (endocrine OR exocrine) AND (pancreaticojejunostomy OR pancreatoduodenectomy OR frey OR beger OR distal pancreatectomy OR duodenum preserving head resection OR surgical drainage)’. Search terms for the Cochrane Library were: ‘pancreatic (endocrine OR exocrine) (function OR insufficiency)) AND surgery AND chronic pancreatitis’, restricted to title, abstract, and keywords. All titles and abstracts of studies identified by the initial search were screened to select those reporting on endocrine or exocrine function of patients undergoing any of the mentioned surgical procedures. Subsequently, full-text papers of the selected studies were screened independently by three authors to assess eligibility.

Inclusion criteria were: cohort of adult patients with chronic pancreatitis with pain as the leading indication to decide for surgical intervention (>90% of patients); surgical procedures including (PP)PD, PJ, DPPHR-B or -F, or DP; and pre- and postoperative essential outcomes (either exocrine or endocrine function or both) reported. Exclusion criteria were procedures other than described under inclusion criteria (e.g. splanchnicectomy, pseudocyst alleviation, total pancreatectomy); different indication than pain to operate; cohort included acute pancreatitis; experimental or animal studies; auto-immune pancreatitis; tropical chronic pancreatitis; patients operated under suspicion of malignancy with pathological specimen of chronic pancreatitis; duplicate studies or different studies from a single center with clear overlap in analyzed cohort. In the latter case preferably the study with longest follow-up was included, on the condition of complete outcome reporting, including (the possibility to extract) preoperative values, of included individuals.

All cross-references were screened for potentially relevant studies not identified by the initial literature search. The final decision on eligibility was reached by consensus.

Data Extraction

The following variables were extracted, where available, from the included studies: number of patients with chronic pancreatitis who underwent either head resection, surgical drainage or distal pancreatectomy, type of test of endocrine and/or exocrine pancreatic function, study follow-up length, percentage of patients with preopera-
tive and postoperative endocrine or exocrine insufficiency, percentage of patients
whose pancreatic function improved after surgery or who developed new-onset insuf-
ficiency, and pre- and postoperative percentage of patients with endocrine insuffi-
ciency who used insulin.

RESULTS

The results of the literature search are summarized in Fig. 1. Of 58 papers that met
inclusion criteria based on title and abstract, 30 were excluded after reviewing full-
text for the following reasons: significant overlap of study cohorts with included
publication from same institution (10 studies), incomplete follow-up (10), lack
of or insufficient preoperative values (6), pain as principle indication to operate
less than 90% (3), and summarized outcome reporting, precluding calculation of
results per surgical procedure (2). The remaining 27 studies were included in the
present systematic review. Characteristics of the 28 included studies including
our own series are summarized in Table 1.

Study design comprised retrospective non-controlled case series, prospective non-controlled series or series employing prospectively maintained databases, prospectively controlled case series, prospectively comparative case series, and RCT. For randomized studies sample size calculations were not based on expected differences of pancreatic function outcome between different treatments. Pancreatic function was generally not a primary outcome measure.
Table 1 Characteristics of included studies.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Study Interval</th>
<th>Type of operation*</th>
<th>Endocrine function test†</th>
<th>Exocrine function test†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warshaw et al.</td>
<td>1980</td>
<td>USA</td>
<td>Prospective non-controlled case series</td>
<td>1974-1978</td>
<td>PJ</td>
<td>OGT</td>
<td>NR</td>
</tr>
<tr>
<td>Prinz et al.</td>
<td>1981</td>
<td>USA</td>
<td>Retrospective non-controlled case series</td>
<td>1954-1980</td>
<td>PJ</td>
<td>FBG</td>
<td>NR</td>
</tr>
<tr>
<td>Bradley et al.</td>
<td>1984</td>
<td>USA</td>
<td>Prospective non-controlled case series</td>
<td>NR</td>
<td>PJ</td>
<td>N/A</td>
<td>Fecal fat</td>
</tr>
<tr>
<td>Pap et al.</td>
<td>1987</td>
<td>Hungary</td>
<td>Retrospective non-controlled case series</td>
<td>NR</td>
<td>PJ</td>
<td>OGT</td>
<td>Secretin pancreozymin, Lundh test</td>
</tr>
<tr>
<td>Kerremans et al.</td>
<td>1987</td>
<td>Belgium</td>
<td>Prospective non-controlled case series</td>
<td>NR</td>
<td>DPPHR(B)</td>
<td>OGT</td>
<td>N/A</td>
</tr>
<tr>
<td>Nealon et al.</td>
<td>1988</td>
<td>USA</td>
<td>Prospective non-controlled case series</td>
<td>1984-1988</td>
<td>PJ</td>
<td>OGT</td>
<td>Bentinromide PABA, fecal fat</td>
</tr>
<tr>
<td>Izbicki II et al.</td>
<td>1995</td>
<td>Germany</td>
<td>RCT</td>
<td>1992-1994</td>
<td>DPPHR(F,B)</td>
<td>OGT</td>
<td>Chymotrypsin, pancreolauryl</td>
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<tr>
<td>Ikenaga et al.</td>
<td>1995</td>
<td>Japan</td>
<td>Retrospective non-controlled case series</td>
<td>1985-1994</td>
<td>DPPHR(M)</td>
<td>OGT</td>
<td>NR</td>
</tr>
<tr>
<td>Izbicki III et al.</td>
<td>1998</td>
<td>Germany</td>
<td>RCT</td>
<td>1995-1997</td>
<td>PPPD, DPPHR(F,T)</td>
<td>OGT</td>
<td>Fecal chymotrypsin</td>
</tr>
<tr>
<td>Kovács et al.</td>
<td>1999</td>
<td>Hungary</td>
<td>Prospective non-controlled case series</td>
<td>1992-1997</td>
<td>PJ, PD</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Schoenberg et al.</td>
<td>1999</td>
<td>Germany</td>
<td>Prospective non-controlled case series</td>
<td>1982-1995</td>
<td>DP</td>
<td>OGT</td>
<td>N/A</td>
</tr>
<tr>
<td>Beger et al.</td>
<td>1999</td>
<td>Germany</td>
<td>Retrospective non-controlled case series</td>
<td>1972-1998</td>
<td>DPPHR(B)</td>
<td>OGT</td>
<td>Pancreolauryl</td>
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<tr>
<td>Sakorafas et al.</td>
<td>2000</td>
<td>USA</td>
<td>Retrospective non-controlled case series</td>
<td>1976-1997</td>
<td>PJ, DP, PD</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>Madura et al.</td>
<td>2003</td>
<td>USA</td>
<td>Retrospective non-controlled case series</td>
<td>1994-2001</td>
<td>PJ</td>
<td>N/R</td>
<td>NR</td>
</tr>
<tr>
<td>Witzigmann et al.</td>
<td>2003</td>
<td>Germany</td>
<td>Prospective controlled case series</td>
<td>1996-2000</td>
<td>DPPHR(B), PD</td>
<td>OGT</td>
<td>Fecal elastase</td>
</tr>
<tr>
<td>Maartense et al.</td>
<td>2004</td>
<td>The Netherlands</td>
<td>Prospective controlled case series</td>
<td>1990-1999</td>
<td>PJ, DPPHR(B)</td>
<td>OGT, OAT</td>
<td>Fecal fat estimation, C-peptide level</td>
</tr>
<tr>
<td>Farkas et al.</td>
<td>2004</td>
<td>Hungary</td>
<td>Prospective non-controlled case series</td>
<td>1999-2004</td>
<td>DPPHR(M)</td>
<td>OGT, OAT</td>
<td>Fecal elastase</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>Country</td>
<td>Study Design</td>
<td>Study Interval</td>
<td>Type of operation*</td>
<td>Endocrine function test†</td>
<td>Exocrine function test†</td>
</tr>
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<tr>
<td>Yekebas et al.</td>
<td>2006</td>
<td>Germany</td>
<td>Prospective non-controlled case series</td>
<td>1992-2004</td>
<td>DPPHR(M)</td>
<td>FBG, OGT</td>
<td>Chymotrypsin, Pancreoburol</td>
</tr>
<tr>
<td>Pessaux et al.</td>
<td>2006</td>
<td>France</td>
<td>Prospective non-controlled case series</td>
<td>2000-2005</td>
<td>DPPHR(F)</td>
<td>FBG</td>
<td>Fecal elastase</td>
</tr>
<tr>
<td>Cahen et al.</td>
<td>2007</td>
<td>The Netherlands</td>
<td>RCT</td>
<td>2000-2004</td>
<td>PJ</td>
<td>FBG, HbA1c</td>
<td>Fecal elastase</td>
</tr>
<tr>
<td>Chiang et al.</td>
<td>2007</td>
<td>Taiwan</td>
<td>Prospective, comparative case series</td>
<td>1996-2003</td>
<td>PD, DPPHR(F)</td>
<td>C-peptide level, HbA1c</td>
<td>Fecal elastase, BT-PABA</td>
</tr>
<tr>
<td>Riediger et al.</td>
<td>2007</td>
<td>Germany</td>
<td>Prospective non-controlled case series</td>
<td>1994-2005</td>
<td>(PP)PD, DPPHR(F,B), DP</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Muller et al.</td>
<td>2008</td>
<td>Germany</td>
<td>RCT</td>
<td>1991-1993</td>
<td>PPPD, DPPHR(B)</td>
<td>FBG, HbA1c</td>
<td>NR</td>
</tr>
<tr>
<td>Litwin et al.</td>
<td>2008</td>
<td>Poland</td>
<td>Prospective non-controlled case series</td>
<td>2005-2006</td>
<td>PD</td>
<td>FBG, OGT</td>
<td>N/A</td>
</tr>
<tr>
<td>Hildebrand et al.</td>
<td>2010</td>
<td>Germany</td>
<td>Retrospective non-controlled case series</td>
<td>2000-2005</td>
<td>PPPD, DPPHR(F)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Van der Gaag et al.</td>
<td>2010</td>
<td>The Netherlands</td>
<td>Own the series, Netherlands</td>
<td>1992-2006</td>
<td>(PP)PD, DPPHR(F,B), PJ, DP</td>
<td>FBG, HbA1c</td>
<td>Fecal elastase</td>
</tr>
</tbody>
</table>

* specific operation included when >5 procedures were performed per series.
† Other than prescribed medication for insufficiency.
NR, not reported; N/A, not applicable; RCT, randomized controlled trial; PJ, pancreateojunostomy; PG, pancreaticogastrostomy; (E)DP, (extended) distal pancreatectomy; (PPP)(PP, pylorus-preserving) pancreatoduodenectomy; DPPHR, duodenum preserving pancreatic head resection; (F) according to Frey, (B) according to Beger, (M) modified; OGT, oral glucose tolerance; OAT, oral amyloglucosidase tolerance; FBG, fasting blood glucose; FABA, para-aminobenzoic acid; HbA1c, glycated hemoglobin; BT-PABA, N-benzoyl-L-tryosyl para-aminobenzoic acid.

1 Only procedures with complete follow-up included.
in study publications, but reported as concomitant finding. Oral glucose tolerance test (OGT) and fasting blood glucose (FBG) levels were the most commonly used tests to determine whether endocrine insufficiency was present. The spectrum of laboratory tests for exocrine function was even more heterogeneous, and in some cases only clinical signs of possible insufficiency (steatorrhea) were considered confirmative.

**Patient Characteristics**

The 28 studies included a total of 1,831 patients who underwent surgery for painful chronic pancreatitis; the number of included patients per study ranged from 7 to 303. Of the 28 studies 19 reported both endocrine and exocrine function, 8 only endocrine function, and 1 only exocrine function. Follow-up ranged from 6 months to 14 years between studies (weighted mean 4.8 years, median 5.0 years). Head resection prevailed as surgical procedure (1,155 patients) with the technique according to Beger mostly performed (461 patients\(^{49,52,53,56,58,61,62,67}\)), followed by pancreateoduodenectomy (309 patients\(^{59,58,62,65-67}\)), the technique according to Frey (254 patients\(^{53,54,58,64-66,69}\)), and a modified organ-sparing or V-shaped technique (311 patients\(^{50,51}\)). Surgical drainage by pancreaticojunostomy was performed in 452 patients\(^{8,44-47,51,55,58,59,61}\), distal pancreatectomy or left-sided resection in 234 patients\(^{46,48,60,66}\).

**Endocrine Function Outcome**

Overall preoperative prevalence of endocrine insufficiency was 31.6 per cent (578 of 1,831 patients). The proportion of patients with endocrine insufficiency who underwent distal resection was 22.2 per cent (52 of 234 patients), 23.0 per cent (102 of 442 patients) for surgical drainage, and 36.7 per cent (424 of 1,155 patients) for head resection. Table 2, 3 and 4 display the endocrine function outcomes for these surgical categories separately. Overall postoperative insufficiency prevalence, unadjusted for length of follow-up, was 50.0 per cent (915 of 1,831 patients). Rates for the separate procedures were 55.6 per cent (130 patients) for distal resection (relative increase compared to preoperative situation 33.3 per cent), 41.9 per cent (185 patients) for surgical drainage (relative increase 18.8 per cent), and 51.9 per cent (600 patients) for head resection (relative increase 15 per cent). Concerning the latter category patients who underwent pancreatectoduodenectomy showed the largest increase in insufficiency rate postoperatively, 26.9 per cent, whereas organ-sparing procedures had lower rates: Beger procedure 10.4 per cent, Frey procedure 16.1 per cent, and modified organ-sparing head resection 3.1 per cent.

Lowest rates or even absence\(^{64,60,61}\) of new onset diabetes following surgery were generally reported in studies with short follow-up (2 years or less), and not reported after (Figure 2). Improvement in (severity of) preoperatively present endocrine insufficiency as a consequence of surgery, variably defined as decreased insulin use, change from insulin to oral anti-diabetic medication or based on improved laboratory tests, was sporadically reported following distal resection and surgical drainage, respectively 1.9 per cent (1 of 52 patients) and 2.9 per cent (3 of 102 patients). For head
### Table 2
Characteristics and endocrine function of patients who underwent distal resection.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. Of Patients</th>
<th>Follow-up (yrs)</th>
<th>Endocrine Insufficiency Preoperatively*</th>
<th>Endocrine Insufficiency Postoperatively*</th>
<th>Improvement†</th>
<th>New Onset Diabetes‡</th>
<th>Insulin Use Postoperatively ¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morrow et al.14</td>
<td>21</td>
<td>5</td>
<td>6(29)</td>
<td>10(48)</td>
<td>0</td>
<td>4(27)</td>
<td>10(100)</td>
</tr>
<tr>
<td>Pap et al.16</td>
<td>11</td>
<td>2</td>
<td>9(82)</td>
<td>9(82)</td>
<td>0</td>
<td>0</td>
<td>4(44)</td>
</tr>
<tr>
<td>Schoenberg et al.15</td>
<td>58</td>
<td>4,8</td>
<td>20(34)</td>
<td>28(48)</td>
<td>0</td>
<td>8(21)</td>
<td>NR</td>
</tr>
<tr>
<td>Sakorafas et al.18</td>
<td>101</td>
<td>7,9</td>
<td>9(9)</td>
<td>57(56)</td>
<td>0</td>
<td>48(52)</td>
<td>NR</td>
</tr>
<tr>
<td>Riediger et al.19</td>
<td>21</td>
<td>4,7</td>
<td>4(19)</td>
<td>12(57)</td>
<td>1(25)</td>
<td>9(53)</td>
<td>NR</td>
</tr>
<tr>
<td>Van Der Gaag et al.</td>
<td>22</td>
<td>5,8</td>
<td>4(18)</td>
<td>14(64)</td>
<td>0</td>
<td>10(56)</td>
<td>10(71)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages of *total number of patients, of †preoperative insufficient patients, of ‡preoperative sufficient patients, and of ¶postoperative insufficient patients.
NR, not reported; NA, not applicable.

### Table 3
Characteristics and endocrine function of patients who underwent surgical drainage (pancreaticojejunostomy).

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. Of Patients</th>
<th>Follow-up (yrs)</th>
<th>Endocrine Insufficiency Preoperatively*</th>
<th>Endocrine Insufficiency Postoperatively*</th>
<th>Improvement†</th>
<th>New Onset Diabetes‡</th>
<th>Insulin Use Postoperatively ¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warshaw et al.14</td>
<td>10</td>
<td>1</td>
<td>3(30)</td>
<td>5(50)</td>
<td>0</td>
<td>2(29)</td>
<td>4(80)</td>
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<tr>
<td>Prinz et al.15</td>
<td>87</td>
<td>7,9</td>
<td>34(39)</td>
<td>45(52)</td>
<td>0</td>
<td>11(21)</td>
<td>24(53)</td>
</tr>
<tr>
<td>Morrow et al.14</td>
<td>46</td>
<td>5</td>
<td>11(24)</td>
<td>27(59)</td>
<td>0</td>
<td>16(44)</td>
<td>27(100)</td>
</tr>
<tr>
<td>Nealon et al.11</td>
<td>30</td>
<td>1,3</td>
<td>11(37)</td>
<td>14(47)</td>
<td>0</td>
<td>3(16)</td>
<td>NR</td>
</tr>
<tr>
<td>Kovács et al.15</td>
<td>20</td>
<td>1,8</td>
<td>4(20)</td>
<td>5(25)</td>
<td>0</td>
<td>1(6)</td>
<td>NR</td>
</tr>
<tr>
<td>Sakorafas et al.18</td>
<td>89</td>
<td>8</td>
<td>9(10)</td>
<td>29(33)</td>
<td>0</td>
<td>20(25)</td>
<td>NR</td>
</tr>
<tr>
<td>Madura et al.17</td>
<td>35</td>
<td>1</td>
<td>3(9)</td>
<td>4(11)</td>
<td>0</td>
<td>13(3)</td>
<td>2(50)</td>
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<td>Maarlense et al.11</td>
<td>12</td>
<td>1,3</td>
<td>5(42)</td>
<td>3(25)</td>
<td>2(40)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cahen et al.14</td>
<td>20</td>
<td>2</td>
<td>4(20)</td>
<td>5(25)</td>
<td>0</td>
<td>1(6)</td>
<td>NR</td>
</tr>
<tr>
<td>Van Der Gaag et al.</td>
<td>93</td>
<td>5,9</td>
<td>18(19)</td>
<td>48(52)</td>
<td>1(6)</td>
<td>31(41)</td>
<td>30(63)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages of *total number of patients, of †preoperative insufficient patients, of ‡preoperative sufficient patients, and of ¶postoperative insufficient patients.
NR, not reported; NA, not applicable.
### Table 4  Characteristics and endocrine function of patients who underwent head resection.

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. Of Patients</th>
<th>Procedure</th>
<th>Follow-up yr</th>
<th>Endocrine Insufficiency Preoperatively*</th>
<th>Endocrine Insufficiency Postoperatively</th>
<th>Improvement†</th>
<th>New Onset Diabetes‡</th>
<th>Insulin Use Postoperatively¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerremans et al.⁷⁷</td>
<td>12</td>
<td>dpphr-b</td>
<td>2,7</td>
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Values in parentheses are percentages of *total number of patients, of †preoperative insufficient patients, of ‡preoperative sufficient patients, and of ¶postoperative insufficient patients.

NR, not reported; NA, not applicable; (PP)PD, (pylorus-preserving) pancreatoduodenectomy; DPPHR, duodenum preserving pancreatic head resection; (F) according to Frey, (B) according to Beger, (M) modified.
resection the calculated improvement rate was 13.9 per cent (59 of 424 patients) with the connotation that the figure was largely determined by a single study\(^4\). From studies that reported on medication use for patients who suffered from diabetes at follow-up we derived percentages of insulin use. Proportions were 72.7 per cent (24 of 33 patients) for distal resection, 65.9 per cent (87 of 132 patients) for surgical drainage, and 61.1 per cent (274 of 448 patients) for head resection.

**Figure 2** Proportion of patients (with standard error) of each study designated with new-onset diabetes following pancreatic head resection (pancreatoduodenectomy, duodenum-preserving head resection), surgical drainage (pancreaticojejunostomy) or distal pancreatectomy for chronic pancreatitis. Studies are plotted by increasing follow-up length.

**Exocrine Function Outcome**

Definition of exocrine insufficiency was based on more heterogeneous laboratory tests compared to endocrine function, or frequently based even only on presence of clinical symptoms (steatorrhea, administration (in amount of) enzyme replacement therapy). Careful interpretation of given figures is therefore warranted. Figures of individual studies are provided in the online supplement. Overall prevalence of exocrine insufficiency prior to surgery was 45.2 per cent (665 of 1471 available patients). Surgical entity rates were 15.2 per cent (25 of 164 patients) for patients who underwent distal resection, 33.0 per cent (142 of 430 patients) for surgical drainage, and 56.8 per cent (498 of 877 patients) for head resection. Overall postoperative prevalence of exocrine insufficiency, unadjusted for length of follow-up, was 59.3 per cent (872 of 1471 patients). Postoperative rates were 50.6 per cent...
(83 patients) for distal resection (relative increase compared to preoperative situation 35.4 per cent), 50.2 per cent (216 patients) for surgical drainage (relative increase 17.2 per cent), and 65.1 per cent (577 patients) for head resection (relative increase 8.9 per cent). Only for the Beger procedure an improvement following surgery was reported, from 83.4 per cent preoperatively insufficient to 70.9 per cent postoperatively, albeit again largely determined by a single study. Insufficiency rate for patients who underwent a Frey procedure increased with 15.5 per cent, the only series who evaluated exocrine function after a modified head resection remained equal compared to preoperatively (29.7 per cent). Equal to endocrine function patients who underwent pancreateoduodenectomy showed the largest increase, 29.3 per cent.

**DISCUSSION**

This study reviewed available, largely descriptive literature that reported on pancreatic function before and after the most common surgical procedures for painful chronic pancreatitis. Up to a third of patients indicated to undergo surgery for pain already have been affected by endocrine insufficiency prior to surgery. Depending on type of surgical procedure and length of follow-up measurement figures rise to around 40 to 50 per cent after surgery. Improvement to some extent is reported but rare. The occurrence of new-onset diabetes seems lowest within two years after surgery, increasing rates are reported in studies with longer follow-up. Of patients who suffer from diabetes at follow-up the large majority, around two-third, is insulin dependent. Exocrine insufficiency is preoperatively present in around 15 per cent of patients who undergo distal resection, up to 50 per cent for head resection. Postoperative figures range from 50 to 65 per cent. However, overall reports, definitions of improvement and length of follow-up are highly variable between studies, which warrants careful interpretation of these figures.

The overall prevalence of endocrine insufficiency of 31.6 per cent prior to surgery is considerable. After surgery one out of every two patients with surgically treated chronic pancreatitis has become endocrine insufficient, of whom the majority is insulin dependent. Considering the fact that the spectrum of abnormal glucose regulation can range from mild hyperglycemia to secondary end-organ failure and to lethal hypoglycemia unawareness, this finding signifies major comorbidity and a potentially more severe risk than exocrine insufficiency. A recent review showed that, when some kind of resection procedure is indicated for pancreatic head disease in CP, the more organ-sparing variants like the Frey or Beger procedure, are preferred over pancreateoduodenectomy for their favorable effects on pancreatic function. Accordingly we found that patients who underwent pancreateoduodenectomy had the highest increase in both endocrine and exocrine pancreatic insufficiency. These descriptive results reconfirm that, whenever a resection procedure is indicated for painful pancreatic surgery, the more organ-sparing variants are preferred over pancreateoduodenectomy from the perspective of pancreatic function preservation.
Whether these observations will hold in a head-to-head prospective comparison is under investigation in a randomized controlled multicentre trial.\textsuperscript{73}

In chronic pancreatitis patients with exocrine dysfunction maldigestion of dietary macronutrients (fat, proteins and carbohydrates) leads to malnutrition, which is associated with various health problems. Maldigestion of fat results in steatorrhoea, which causes symptoms such as greyish, fatty stools, abdominal cramps, bloating and chronic abdominal pain. Furthermore, steatorrhoea may cause weight loss. In this review overall prevalence of exocrine insufficiency before and after surgery was higher than endocrine insufficiency, but the figures as we could extract from the included studies are to be interpreted with caution. A number of studies did not report the method of laboratory testing of pancreatic exocrine function, if employed at all. Frequently this diagnosis was established based on clinical markers steatorrhoea or need for or response to pancreatic enzyme supplementation therapy with respect to abdominal pain or malabsorption. Non-invasive tests such as fecal fat and fecal chymotrypsin test are known to be less reliable to evaluate insufficiency, while fecal elastase measurement is thought to be only reliable in severe insufficiency.\textsuperscript{74} Better tests such as the \textsuperscript{13}C-MTG breath test was not used, the more invasive Lund test meal only in one study.\textsuperscript{48,74} Therefore, the reported insufficiency numbers in this review should be considered only indicative for this health problem.

Long-term exocrine or endocrine insufficiency in chronic pancreatitis patients treated surgically is thought to be due to the surgical intervention as well as the progression of the underlying disease.\textsuperscript{75} The timing of intervention may be another factor that determines the extent of pancreatic insufficiency. In an experimental study using a porcine model it was found that early surgical drainage resulted in a marked improvement in histopathology grades and pancreatic exocrine function as opposed to the late surgical drainage group.\textsuperscript{76} A group from Texas proposed a policy of early surgery before development of irreversible functional impairment leading to endocrine or exocrine insufficiency occurs.\textsuperscript{77} The authors found that surgery in their clinical series of surgical drainage could halt progression of disease. Time interval from initial complaints to surgery could not be extracted from included studies in this review. Moreover, the highly variable follow-up length obscures observations to what extent insufficiency is due to surgery, or whether insufficiency is merely the inherent result of progressive, chronic disease. These confounders limit drawing firm conclusions. In our opinion this finding underlines the necessity that these factors are addressed in future publications for transparent interpretation of the consequences of surgical intervention for chronic pancreatitis. Proper nationwide (new case) disease registration, as has been initiated in The Netherlands, is mandatory to monitor these parameters. A randomized trial that is evaluating the result of early surgical intervention versus a conservative step-up approach is currently recruiting.\textsuperscript{78}

Development of endoscopic techniques such as endoscopic shockwave lithotripsy for pancreatic duct stones and advanced stenting techniques have led to widespread use of endoscopy as first-line treatment for pain due to chronic pancreatitis not responding to medication. Theoretically this minimal-invasive therapy, compared
to invasive surgical procedures, could have less side-effects in terms of induction of new-onset pancreatic insufficiency or aggravation of existing insufficiency. However, the initial enthusiasm over endoscopy has been dampened down, because of disappointing long-lasting results in achieving pain relief, the prime indication to intervene in the course of disease of chronic pancreatitis. A review on surgical versus endoscopic pancreatic duct drainage for painful chronic pancreatitis, as well as a randomized controlled trial, that directly compared endoscopy versus surgery, demonstrated less pain relief of shorter endurance in patients who underwent endoscopy. Recently published long-term results of the randomized trial were not any different, and, moreover, almost half of the patients in the endoscopy group eventually underwent surgery. An analysis of the series from the Academic Medical Center demonstrated that poor response to surgical treatment for chronic pancreatitis in terms of pain relief and good quality of life was related to increasing numbers of stenting procedures prior to surgery. Therefore, endoscopy cannot any longer be considered a comparative alternative to treat painful chronic pancreatitis, and, thus not an option to prevent or limit pancreatic insufficiency.

A limitation of the present systematic review is that many of the included studies were descriptive and retrospective in which pancreatic function was generally reported as coincidental outcome. Extensive variation in employed laboratory tests to measure function, different definitions of insufficiency and highly variable follow-up length precludes definite conclusions to be drawn. A formal assessment of methodological quality could not be performed because many papers did not provide enough detailed information for such an assessment.

Nevertheless, this review presents the most extensive evaluation of the heavy disease burden of pancreatic insufficiency that coincides with pain in patients with advanced chronic pancreatitis, who undergo surgery as a salvage procedure.

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