Smoking as a Risk Factor for Complications in Chronic Pancreatitis

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Margarita Castiñeira-Alvariño, MS,* Laura Nieto-García, RN,* José Lariño-Noia, MD,*†
and J. Enrique Domínguez-Muñoz, MD, PhD*†

Objectives: Several recent studies have demonstrated the association between smoking and chronic pancreatitis (CP). However, less is known about the role of smoking in the development of CP-related complications. Our aim was to investigate the impact of smoking and alcohol consumption on age of onset and complications at CP diagnosis.

Methods: A cross-sectional case-case study was performed within a prospectively collected cohort of patients with CP. Alcohol consumption and smoking habits were assessed using a standardized questionnaire. Morphologic severity was defined based on endoscopic ultrasound criteria for CP and classified as mild (3–4 criteria), moderate (5–6 criteria), and severe (≥7 criteria or calcifications). Pancreatic exocrine insufficiency (PEI) was diagnosed using the 11C-mixed triglyceride breath test. Odds ratios (OR) with 95% confidence intervals (CI) for CP-related complications were calculated using a case-case design.

Results: A total of 241 patients were included. Smoking was associated with PEI (OR [95% CI], 2.4 [1.17–5.16]), calcifications (OR [95% CI], 2.33 [1.10–4.95]), and severe morphologic changes (OR [95% CI], 3.41 [1.31–8.85]) but not with pseudocysts or diabetes. Neither smoking nor alcohol consumption was associated with age of onset.

Conclusions: Tobacco, but not alcohol, is associated with PEI, calcifications, and severe morphologic (≥7 criteria or calcifications) CP at diagnosis. Smoking cessation should be encouraged in patients with CP.

Key Words: chronic pancreatitis, alcohol, breath test, pancreatic exocrine insufficiency, pancreatic disease

Abbreviations: CI - confidence interval, CP - chronic pancreatitis, EUS - endoscopic ultrasonography, MRCP - magnetic resonance cholangiopancreatography, MRI - magnetic resonance imaging, OR - odds ratio, PEI - pancreatic exocrine insufficiency, TIGAR-O - toxic, idiopathic, genetic, autoimmune, recurrent acute pancreatitis, and obstructive

Chronic pancreatitis (CP) is a complex inflammatory disease associated with progressive fibrosis and destruction of the normal secretory parenchyma of the pancreas.1 Disabling abdominal pain, exocrine and endocrine insufficiency, parenchymal calcifications, and pseudocysts are common symptoms and complications during the natural course of the disease.2,3 The molecular events leading to CP are still not fully understood. Established etiologic factors can be classified according to the TIGAR-O (toxic, idiopathic, genetic, autoimmune, recurrent acute pancreatitis, and obstructive) classification.1 Alcohol abuse is the most common cause of CP.

In recent years, several studies on the association between smoking and the risk of acute and CP have been published, and smoking is now considered as an established and independent risk factor for CP.4–10 However, less is known about factors associated with complications in patients with CP. Smoking was associated with calcifications, diabetes, and younger age at diagnosis in a multinational cohort of patients with alcohol-related CP.11 In addition, an association between smoking and an abnormal exocrine pancreatic secretion of bicarbonate has been reported in a series of 79 patients with CP.9 To the best of our knowledge, there are no studies to date investigating the impact of smoking on the complete spectra of complications in CP of any etiology at diagnosis, including functional (pancreatic exocrine insufficiency [PEI] and diabetes) and morphologic complications.

The aim of the present study was to investigate the association between smoking and alcohol consumption and major functional and morphologic complications of CP at the time of diagnosis. In addition, we also aimed at testing the hypothesis that smoking and/or alcohol consumption is associated with a younger age at disease onset.

(Pancreas 2014;43: 275–280)
Does tobacco influence the natural history of autoimmune pancreatitis?

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Author information

Abstract
Tobacco recently appeared as a major independent factor adversely influencing the natural course of alcoholic chronic pancreatitis. However, the role of tobacco in patients with autoimmune pancreatitis (AIP) has never been studied. Type 2 AIP is associated with inflammatory bowel disease, especially ulcerative colitis in which smoking is protective. The aim of our study was to evaluate the influence of smoking on course of AIP.

PATIENTS AND METHODS: All consecutive patients followed in our centre for AIP according to ICDC were studied. Tobacco consumption was recorded. A relation between smoking and all event related to AIP was searched for.

RESULTS: 96 patients with type 1 (73%) or type 2 (27%) AIP were included; 76% of patients were low smokers (never, ex- or smokers <10 p.y.) and 24% were high smokers (≥10 p.y.). The mean follow-up was 60 months [5-188]. AIP relapse was observed in 26% of patients. At the end-point, smokers ≥10 p.y. presented more frequently diabetes (50% vs 27%, p = 0.04) and imaging pancreatic damages (59% vs 34%, p = 0.02) than low smokers. There was also a non significant tendency to observe more frequently exocrine insufficiency and relapse in smokers ≥10 pack-year. No protective effect of smoking was observed in the subgroup of patients with type 2 AIP and ulcerative colitis.

CONCLUSIONS: In patients with AIP, high tobacco intake is associated with the risk of imaging pancreatic damages and with the occurrence of diabetes. Smoking cessation should be recommended.

KEYWORDS: Autoimmune pancreatitis; Diabetes; Exocrine insufficiency; Relapse; Smoking; Ulcerative colitis
Drug-induced acute pancreatitis: results from the hospital-based Berlin case–control surveillance study of 102 cases

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SUMMARY

Background
Drug toxicity is a well-known cause of acute pancreatitis (AP). Although many drugs have been associated with AP, the magnitude of the risk of most of them remains largely unknown.

Aim
To determine the pancreatotoxic risk of a wide range of drugs.

Methods
The hospital-based Berlin case–control surveillance study, including all 51 Berlin hospitals in a hospital network, ascertained 102 cases with idiopathic AP (IAP) and 750 controls between 2002 and 2011. Patients with IAP were thoroughly validated using anamnestic, clinical or laboratory data. Drug exposure was obtained in a face-to-face interview. Possible drug aetiology was assessed in individual patients through a standardised causality assessment applying the criteria of the World Health Organization. Drug risks were further quantified [odds ratios (OR) with 95% confidence intervals (CI)] in a case–control design with unconditional logistic regression analysis.

Results
The pancreatotoxic risk of several drugs, including azathioprine (OR 5.1; 95% CI 1.9–13.5), fenofibrate (OR 12.2; 95% CI 2.3–69.1), mesalazine (OR 3.3; 95% CI 1.1–9.5) or angiotensin-converting enzyme inhibitors, was corroborated by case–control analysis and causality assessment. Causality assessment suggested a pancreatotoxic potential, among others, for mercaptopurine or the seldom reported leflunomide, and alluded to a novel risk for tocilizumab. Case–control analysis showed an increased risk for two phytotherapeutics: harpagophytum and valerian radix.
### Summary of drug-induced acute pancreatitis based on drug class

<table>
<thead>
<tr>
<th>Class Ia</th>
<th>Class Ib</th>
<th>Class II</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-methyldopa</td>
<td>All-trans-retinoic acid</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Azodisalicylate</td>
<td>Amiodarone</td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>Azathioprine</td>
<td>Clozapine</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Clomiphene</td>
<td>Didanosine</td>
</tr>
<tr>
<td>Carbimazole</td>
<td>Dexamethasone</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Codeine</td>
<td>Ifosfamide</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Cytosine</td>
<td>Lamivudine</td>
<td>L-asparaginase</td>
</tr>
<tr>
<td>Arabinoside</td>
<td>Losartan</td>
<td>Pegaspargase</td>
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<tr>
<td>Dapsone</td>
<td>Lynestrenol/methoxyethinylestradiol</td>
<td>Propofol</td>
</tr>
<tr>
<td>Enalapril</td>
<td>6-mercaptopurine</td>
<td>Tamoxifen</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Meglumine</td>
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<tr>
<td>Isoniazid</td>
<td>Methimazole</td>
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<tr>
<td>Mesalamine</td>
<td>Nelfinavir</td>
<td></td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Norethindronate/mestranol</td>
<td>Irl</td>
</tr>
<tr>
<td>Pentamidime</td>
<td>Omeprazole</td>
<td>Is</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Premarin</td>
<td>Kα</td>
</tr>
<tr>
<td>Procainamide</td>
<td>TrimethoprimSulfamethazole</td>
<td>Ll</td>
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<td>Pyritonol</td>
<td></td>
<td>Mβ</td>
</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td>Mβ</td>
</tr>
<tr>
<td>Stibogluconate</td>
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<td>Mβ</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td></td>
<td>Mβ</td>
</tr>
<tr>
<td>Sulindac</td>
<td></td>
<td>Nα</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>Pα</td>
</tr>
<tr>
<td>Valproic acid</td>
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<td>Pβ</td>
</tr>
</tbody>
</table>
PANCREAS, BILIARY TRACT, AND LIVER

High Dietary Glycemic Load Increases the Risk of Non–Gallstone-Related Acute Pancreatitis: A Prospective Cohort Study

Viktor Oskarsson,* Omid Sadr–Azodi,*† Nicola Orsini,* Åke Andrén–Sandberg,§ and Alicja Wolk*

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BACKGROUND & AIMS: Obesity and type 2 diabetes—diseases linked to glucose intolerance and insulin resistance—have been positively associated with the risk of acute pancreatitis. However, it is unclear...
Vegetables, fruit and risk of non-gallstone-related acute pancreatitis: a population-based prospective cohort study

Viktor Oskarsson,1 Omid Sadr-Azodi,1,2 Nicola Orsini,1 Åke Andrén-Sandberg,2 Alicja Wolk1

ABSTRACT

Objective To examine the association of vegetable and fruit consumption with the risk of non-gallstone-related acute pancreatitis.

Design A population-based prospective cohort of 80,019 women and men, aged 46–84 years, completed a food-frequency questionnaire at baseline and was followed up for incidence of non-gallstone-related acute pancreatitis from 1 January 1998 to 31 December 2009. Participants were categorised into quintiles according to consumption of vegetables and consumption of fruit. Cox proportional hazards models were used to estimate RRs and 95% CIs.

Results In total, 320 incident cases (216 men and 104 women) with non-gallstone-related acute pancreatitis were identified during 12 years of follow-up (89,136 person-years). After adjustment for potential confounders, the authors observed a significant inverse linear dose–response association between vegetable consumption and risk of non-gallstone-related acute pancreatitis; every two additional servings per day were associated with 17% risk reduction (RR=0.83; 95% CI 0.70 to 0.98; p=0.03). Among participants consuming >1 drink of alcohol per day and among those with body mass index ≥25 kg/m², the RR for the highest compared with the lowest quintile of vegetable consumption was 0.29 (95% CI 0.13 to 0.67) and 0.49 (95% CI 0.29 to 0.85), respectively. Fruit consumption was not significantly associated with the risk of non-gallstone-related acute pancreatitis; the RR comparing extreme quintiles of consumption was 1.20 (95% CI 0.81 to 1.78).

Conclusions Vegetable consumption, but not fruit consumption, may play a role in the prevention of non-gallstone-related acute pancreatitis.

Significance of this study

What is already known on this subject?

► Oxidative stress and reactive species are associated with the pathogenesis of acute pancreatitis.
► The effect and possible benefit of antioxidant-rich food on the risk of acute pancreatitis have been scarcely investigated.

What are the new findings?

► This large population-based prospective cohort study is the first cohort study to examine the association of vegetable and fruit consumption with the risk of non-gallstone-related acute pancreatitis.
► A significant inverse association between vegetable consumption and risk of non-gallstone-related acute pancreatitis was observed; the risk declined in a linear dose–response fashion for every additional serving per day.
► There was no significant association between fruit consumption and risk of non-gallstone-related acute pancreatitis.

How might it impact on clinical practice in the foreseeable future?

► Recommendation of increased vegetable consumption may be beneficial for the prevention of non-gallstone-related acute pancreatitis.
The Role of Organ Failure and Infection in Necrotizing Pancreatitis

A Prospective Study

Qiang Guo, MD,* Ang Li, MD,* Qing Xia, MD,† Xubao Liu, MD,* Bole Tian, MD,* Gang Mai, MD,* Zongwen Huang, MD, † Guangyuan Chen, MD, † Wenfu Tang, MD, † Xiaodong Jin, MD, † Weixia Chen, MD, § Huimin Lu, MD,* Nengwen KE, MD,* Zhaoda Zhang, MD,* and Weiming HU, MD*

Objective: To clarify the roles of organ failure and infection in the outcome of necrotizing pancreatitis.

Background: Results of previous cohort studies that focused on the roles of infection and organ failure in acute pancreatitis are controversial.

Methods: In this study, we collected the medical records of 447 patients with necrotizing pancreatitis from January 2009 to June 2012. Data associated with organ failure and infection were analyzed.

Results: The overall mortality rate was 13% (58/447). Intervention was performed in 223 of 447 patients. Among these 223 patients, 134 were confirmed to be with infected necrosis by a positive culture. The mortality rate was 15% (13/89) in the sterile necrosis group and 18% (24/134) in the infected necrosis group (P = 0.52). A multivariate analysis of death predictors indicated that bacteremia (odds ratio [OR] = 2.76, 95% confidence interval [CI], 1.23–5.46, P < 0.001), age (OR = 1.07, 95% CI, 1.03–1.11, P < 0.001), American Society of Anesthesiologists class (OR = 3.56, 95% CI, 1.65–7.18, P = 0.001), persistent organ failure in the first week (OR = 16.72, 95% CI, 7.04–32.56, P < 0.001), and pancreatic necrosis (OR = 1.73, 95% CI, 1.14–2.98, P = 0.008) were significant factors.

Conclusions: Among patients with necrotizing pancreatitis, the effects of organ failure on mortality are more critical than those of infection. Bacteremia, age, American Society of Anesthesiologists class, persistent organ failure in the first week, and pancreatic necrosis were identified as the predictors of mortality.

Keywords: acute pancreatitis, infection, organ failure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survived</th>
<th>Died</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>389/447 (87)</td>
<td>58/447 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age &gt; 60, yr</td>
<td>39/60 (65)</td>
<td>21/60 (35)</td>
<td>0.61</td>
</tr>
<tr>
<td>Male</td>
<td>235/268 (88)</td>
<td>33/268 (12)</td>
<td>0.61</td>
</tr>
<tr>
<td>Biliary cause</td>
<td>197/228 (86)</td>
<td>31/228 (14)</td>
<td>0.56</td>
</tr>
<tr>
<td>BMI &gt; 30 on admission</td>
<td>61/72 (85)</td>
<td>11/72 (15)</td>
<td>0.53</td>
</tr>
<tr>
<td>ASA class II or III on admission</td>
<td>241/286 (84)</td>
<td>45/286 (16)</td>
<td>0.023</td>
</tr>
<tr>
<td>APACHE II score &gt; 8 on admission</td>
<td>153/177 (86)</td>
<td>34/177 (14)</td>
<td>0.047</td>
</tr>
<tr>
<td>Persistent SIRS in the first week of onset</td>
<td>201/248 (81)</td>
<td>47/248 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Organ failure</td>
<td>68/107 (64)</td>
<td>39/107 (36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Persistent organ failure in the first week of onset</td>
<td>26/59 (44)</td>
<td>33/59 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Persistent MOF in the first week of onset</td>
<td>26/59 (44)</td>
<td>33/59 (56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Highest modified Marshall score &gt; 3 in the first week of onset</td>
<td>42/78 (54)</td>
<td>36/78 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>62/91 (68)</td>
<td>29/91 (32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT severity index &gt; 8</td>
<td>179/214 (84)</td>
<td>35/214 (16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pancreatic necrosis</td>
<td>179/214 (84)</td>
<td>35/214 (16)</td>
<td>0.04</td>
</tr>
<tr>
<td>Laboratory tests within 72 h of onset</td>
<td>131/152 (86)</td>
<td>21/152 (14)</td>
<td>0.70</td>
</tr>
<tr>
<td>White blood cell count &gt; 15, 10³/L</td>
<td>114/136 (84)</td>
<td>22/136 (16)</td>
<td>0.68</td>
</tr>
<tr>
<td>C-reactive protein &gt; 200, mg/L</td>
<td>28/56 (50)</td>
<td>28/56 (50)</td>
<td>0.006</td>
</tr>
<tr>
<td>Procalcitonin &gt; 1, ng/mL</td>
<td>31/53 (58)</td>
<td>22/53 (42)</td>
<td>0.43</td>
</tr>
<tr>
<td>IL-6 &gt;100, pg/mL</td>
<td>106/134 (79)</td>
<td>24/134 (21)</td>
<td>0.04</td>
</tr>
<tr>
<td>Infected necrosis</td>
<td>106/134 (79)</td>
<td>24/134 (21)</td>
<td>0.04</td>
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<tr>
<td>Extrapancreatic infectious complications</td>
<td>60/80 (75)</td>
<td>20/80 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>144/168 (86)</td>
<td>24/168 (14)</td>
<td>0.52</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>144/168 (86)</td>
<td>24/168 (14)</td>
<td>0.52</td>
</tr>
<tr>
<td>Time from onset to intervention &gt;28, days</td>
<td>80/96 (83)</td>
<td>16/96 (17)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

APACHE indicates Acute Physiology and Chronic Health Examination; ASA, American Society of Anesthesiologists; BMI, body mass index; CT, computed tomography; IL, interleukin; MOF, multiple organ failure; SIRS, systemic inflammatory response syndrome.
Early Factors Associated With Fluid Sequestration and Outcomes of Patients With Acute Pancreatitis

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BACKGROUND & AIMS: Predicting level of fluid sequestration could help identify patients with acute pancreatitis (AP) who need more or less aggressive fluid resuscitation. We investigated factors associated with level of fluid sequestration in the first 48 hours after hospital admission in patients with AP and effects on outcome.

METHODS: We analyzed data from consecutive adult patients with AP admitted to the Brigham and Women’s Hospital in Boston, Massachusetts, from June 2005 to December 2007 (n = 266) or the Alicante University General Hospital in Spain from September 2010 to December 2012 (n = 137). Level of fluid sequestration in the first 48 hours after hospital admission was calculated by subtracting the total amount of fluid administered and lost in the first 48 hours of hospitalization. Demographic and clinical variables obtained in the emergency department were analyzed to identify factors associated with level of fluid sequestration in the first 48 hours after hospital admission. Outcome assessed included length of hospital stay, acute fluid collection(s), pancreatic necrosis, persistent organ failure, and mortality.

RESULTS: The median level of fluid sequestration in the first 48 hours after hospital admission was 3.2 L (1.4–5 L). The simple and multiple linear regression models showed that younger age, alcohol etiology, hematocrit, glucose, and systemic inflammatory response syndrome were significantly associated with increased levels of fluid sequestration in the first 48 hours after hospital admission. Increased level of fluid sequestration in the first 48 hours was significantly associated with longer hospital stays and higher rates of acute fluid collection, pancreatic necrosis, and persistent organ failure. There was a nonsignificant trend toward a higher level of fluid sequestration in the first 48 hours among patients who died.

CONCLUSION: Age, alcoholic etiology of AP, hematocrit, glucose, and presence of systemic inflammatory response syndrome in the emergency department were independent predictors of increased levels of fluid sequestration in the first 48 hours after hospital admission. These patients have higher risks of local and systemic complications and longer hospital stays.

Keywords: Pancreatic Inflammation; Treatment; Morbidity; Intravenous Fluid Therapy; Management.
Fluid Sequestration in Acute Pancreatitis

Number of patients

Fluid sequestration in the first 48 h after admission (L)
Table 3. Outcome and FS in the First 48 Hours From Admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>FS (L)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Necrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.4 (3.6–9.5)</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>4.7 (2.9–7.3)</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>30%–50%</td>
<td>8.6 (5.4–12.3)</td>
<td></td>
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<tr>
<td>&gt;50%</td>
<td>7.8 (6.8–13.4)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>3 (1.5–5)</td>
<td></td>
</tr>
<tr>
<td>Acute collections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.3 (3.3–7.2)</td>
<td>&lt;.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Balthazar D</td>
<td>3.9 (2.8–5.8)</td>
<td>&lt;.001&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Balthazar E</td>
<td>6.2 (3.4–8.1)</td>
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</tr>
<tr>
<td>No</td>
<td>2.5 (1–3.9)</td>
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<td>Balthazar A</td>
<td>2.7 (0.9–3.6)</td>
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</tr>
<tr>
<td>Balthazar B</td>
<td>1.9 (0.7–3.59)</td>
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<tr>
<td>Balthazar C</td>
<td>2.5 (1.3–4.6)</td>
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<tr>
<td>Persistent organ failure</td>
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<tr>
<td>Yes</td>
<td>7.5 (4.4–12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No</td>
<td>3.1 (1.5–5.3)</td>
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<tr>
<td>Mortality</td>
<td></td>
<td>NS</td>
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<tr>
<td>Yes</td>
<td>4.2 (0.9–7.8)</td>
<td></td>
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<tr>
<td>No</td>
<td>3.3 (1.7–5.7)</td>
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<tr>
<td>Length of stay (days)</td>
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<td></td>
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<tr>
<td>&lt;10</td>
<td>2.9 (1.5–5)</td>
<td>.01</td>
</tr>
<tr>
<td>10–20</td>
<td>3.8 (2.2–5.8)</td>
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<tr>
<td>&gt;20</td>
<td>5.8 (2.9–7.6)</td>
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</table>
Original article

IAP/APA evidence-based guidelines for the management of acute pancreatitis

Working Group IAP/APA Acute Pancreatitis Guidelines\textsuperscript{a,b,*,1}

\textsuperscript{a} International Association of Pancreatology, UNSW Clinical School Locked Bag 7103, Liverpool, BC NSW 1871, Australia
\textsuperscript{b} American Pancreatic Association, PO Box 14906, Minneapolis, MN 55414, USA
High Prevalence of Osteoporosis in Patients With Chronic Pancreatitis: A Systematic Review and Meta-analysis

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BACKGROUND & AIMS: Patients with chronic pancreatitis may be at high risk for osteoporosis and osteopenia. We performed a systematic review and meta-analysis to determine the prevalence of osteoporosis and osteopenia in patients with chronic pancreatitis.

METHODS: Articles were identified from MEDLINE, EMBASE, and SCOPUS databases (through October 2012) and a manual search of the literature. The primary outcome measure was bone density, measured by dual-energy X-ray absorptiometry (T-score or Z-score). When available, data on the prevalence of osteopenia, bone mineral density, and bone mineral content also were recorded.

RESULTS: Ten studies including 513 patients were eligible for inclusion. Based on a random-effects model, the pooled prevalence rate for osteoporosis among patients with chronic pancreatitis was 23.4% (95% confidence interval, 16.6–32.0). The pooled prevalence for osteopenia was 39.8% (95% confidence interval, 29.1–51.6). The pooled prevalence rate for either osteoporosis or osteopenia was 65% (95% confidence interval, 54.7–74.0).

CONCLUSIONS: Based on meta-analysis, almost 1 of 4 patients with chronic pancreatitis have osteoporosis, and almost two-thirds of patients have either osteoporosis or osteopenia. Osteoporosis and osteopenia are underappreciated sources of morbidity in patients with chronic pancreatitis. Bone health management guidelines are urgently required in patients with chronic pancreatitis.

Keywords: Bone Disease, Metabolic; Demineralization; Risk Factor.
The Risk of Fractures Among Patients With Cirrhosis or Chronic Pancreatitis

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BACKGROUND & AIMS: Cirrhosis and chronic pancreatitis (CP) are accompanied by inflammation and malnutrition. Both conditions can have negative effects on bone metabolism and promote fractures. We evaluated the risk of fractures among patients with CP or cirrhosis and determined the effect of fat malabsorption on fracture risk among patients with CP.

METHODS: We performed a retrospective cohort study using the Danish National Patient Register to identify patients diagnosed with CP or cirrhosis. We analyzed data collected from January 1, 1995, to December 31, 2010, on 20,769 patients (35.5% women with cirrhosis and 11,972 patients (33.5% women) with CP. Each patient was compared with 10 age- and sex-matched controls. We also assessed the risk of fractures among patients with CP who received pancreatic enzyme substitution (PES) for fat malabsorption.

RESULTS: During the study period, bone fractures occurred in 3954 patients with cirrhosis and 2594 patients with CP. The adjusted hazard ratio (HR) for any fracture was 2.4 in patients with cirrhosis (95% confidence interval [CI], 2.2-2.5) and 1.7 in patients with CP (95% CI, 1.6-1.8). The relative risk of low-trauma fractures was highest among individuals younger than 50 years old. Alcohol as an etiology was associated with an increased risk of fracture compared with patients with nonalcoholic cirrhosis (HR, 2.4 vs 1.5; P < .0001) and CP (HR, 2.0 vs 1.5; P < .0001). Patients with CP receiving PES for fat malabsorption had a lower risk of fractures than other CP patients (HR, 0.8; 95% CI, 0.7-0.9). However, increasing the duration of treatment with PES was associated with an increased risk of fracture.

CONCLUSIONS: Patients, especially younger patients, with cirrhosis or CP have an increased risk of fractures of all types.

Keywords: Liver Disease; Fibrosis; Orthopedic; Database Analysis.
PORTOSPLENOMESENTERIC VENOUS THROMBOSIS IN PATIENTS WITH ACUTE PANCREATITIS IS ASSOCIATED WITH Pancreatic Necrosis and Usually Has a Benign Course

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BACKGROUND &AIMS: Although there are some data on prevalence of portosplenomesenteric venous thrombosis (PSMVT) in patients with acute pancreatitis (AP), the progression of PSMVT in patients who have and have not received anticoagulants has not been studied systematically. We evaluated the prevalence and natural history of PSMVT in a well-defined cohort of individuals with AP.

METHODS: In a retrospective study, we analyzed data from the University of Pittsburgh Medical Center on 162 patients with a sentinel attack of AP from 2003–2010. Data were collected on patient demographics, clinical presentation, etiology, clinical course, and outcomes. One hundred twenty-two patients underwent contrast-enhanced computed tomography; the scans were reviewed to identify thromboses and/or narrowing of splanchnic veins (splenic, superior mesenteric, and portal).

RESULTS: PSMVT was detected in 22 patients overall (14%; 18% among patients who underwent contrast-enhanced computed tomography). Median time to detection of PSMVT was 17 days (interquartile range, 11–40 days). PSMVT formed most frequently in the splenic vein (19 of 22, 86%), followed by portal (8 of 22, 36%) and superior mesenteric (6/22, 27%) veins. Development of PSMVT was associated with presence (21 of 22, 95%), location, and extent of pancreatic necrosis. Fifty-three percent of patients (21 of 40) with necrosis developed PSMVT. Anticoagulants were administered infrequently (6 of 22, 27%) and always for indications unrelated to PSMVT. Most patients with PSMVT developed collateral veins (19 of 22, 86%), and 27% (6 of 22) were found to have varices during endoscopic evaluation, but clot resolution was infrequent (2 of 22, 9%). No patient developed complications directly related to PSMVT.
The role of routine fine-needle aspiration in the diagnosis of infected necrotizing pancreatitis

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Background. Diagnosing infected necrotizing pancreatitis (INP) may be challenging. The aim of this study was to determine the added value of routine fine-needle aspiration (FNA) in addition to clinical and imaging signs of infection in patients who underwent intervention for suspected INP.

Methods. We conducted a post hoc analysis of 208 consecutive patients from a prospective, multicenter database who underwent intervention because of suspected INP. In retrospect, 3 groups were constructed based on the patients preoperative characteristics: Clinical, imaging, and FNA. Patients in the clinical group had clinical signs of infection but no gas on preoperative computed tomography (CT) and no FNA performed before intervention. Patients in the imaging group had gas bubbles on the preoperative CT but no FNA performed, whereas patients in the FNA group had a positive FNA before intervention. The reference standard for infection was the culture taken during the first intervention (either catheter drainage or necrosectomy).

Results. The initial intervention for INP was performed a median of 27 days (interquartile range, 20–39) after admission without difference between the 3 groups (P = .15). Infection was confirmed in 80% of 92 patients of the clinical group, in 94% of 88 patients of the imaging group, and in 86% of 28 patients of the FNA group (P = .07). Mortality was 19% and was not different between groups (P = .39).

Conclusion. INP can generally be diagnosed based on clinical or imaging signs of infection. FNA may be useful in patients with unclear clinical signs and no imaging signs of INP. (Surgery 2014;155:442-8.)

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ORIGINAL ARTICLE

Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis

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ABSTRACT

Background Diabetes mellitus (DM) is common in the general population and it poses a heavy burden to society in the form of long-term disability, healthcare use and costs. The pancreas is a key player in glucose homeostasis, but the occurrence of newly diagnosed DM after acute pancreatitis (AP), the most frequent disease of the pancreas, has never been assessed systematically. The aim of this study was to conduct a systematic literature review to determine the prevalence and time course of DM and related conditions after the first attack of AP as well as the impact of covariates.

Methods Relevant literature cited in three electronic databases (Scopus, EMBASE and MEDLINE) was reviewed independently by two authors. The main outcome measures studied were newly diagnosed prediabetes, DM, or DM treated with insulin. Pooled prevalence and 95% CIs were calculated for all outcomes.

Results A total of 24 prospective clinical studies, involving 1102 patients with first episode of AP, met all the eligibility criteria. Prediabetes and/or DM was observed in 37% (95% CI 30% to 45%) individuals after AP. The pooled prevalence of prediabetes, DM and

Significance of this study

What is already known on this subject?
- Diabetes mellitus is a growing health problem worldwide.
- The pancreas plays an important role in regulation of blood glucose.
- Risk of diabetes mellitus and related conditions after first attack of acute pancreatitis has never been systematically evaluated.

What are the new findings?
- Prediabetes and diabetes are common after acute pancreatitis, and occur in nearly 40% of patients after hospital discharge.
- Prevalence of newly diagnosed diabetes is much higher after acute pancreatitis (23%) than the prevalence of diabetes in the general population (4–9%).
- Risk of diabetes increases by at least 2 times after 5 years as compared with 12 months.
- Severity of acute pancreatitis appears to have a minor effect on risk of diabetes and related
Early versus On-Demand Nasoenteric Tube Feeding in Acute Pancreatitis


ABSTRACT

BACKGROUND

Early enteral feeding through a nasoenteric feeding tube is often used in patients with severe acute pancreatitis to prevent gut-derived infections, but evidence to support this strategy is limited. We conducted a multicenter, randomized trial comparing early nasoenteric tube feeding with an oral diet at 72 hours after presentation to the emergency department in patients with acute pancreatitis.
IgG4-related disease is a protean condition that mimics many malignant, infectious, and inflammatory disorders. This multi-organ immune-mediated condition links many disorders previously regarded as isolated, single-organ diseases without any known underlying systemic condition. It was recognised as a unified entity only 10 years ago. Histopathology is the key to diagnosis. The three central pathology features of IgG4-related disease are lymphoplasmacytic infiltration, storiform fibrosis, and obliterator phlebitis. The extent of fibrosis is an important determinant of responsiveness to immunosuppressive therapies. IgG4-related disease generally responds to glucocorticoids in its inflammatory stage, but recurrent or refractory cases are common. Important mechanistic insights have been derived from studies of patients treated by B-cell depletion. Greater awareness of this disease is needed to ensure earlier diagnoses, which can prevent severe organ damage, disabling tissue fibrosis, and even death. Identification of specific antigens and T-cell clones that drive the disease will be the first steps to elucidate the pathogenesis of IgG4-related disease.

Introduction

IgG4-related disease is a multi-organ immune-mediated condition that mimics many malignant, infectious, and inflammatory disorders. The diagnosis links many conditions once regarded as isolated, single-organ diseases without any known underlying systemic condition (panel 1). IgG4-related disease, unrecognised as a unified disease for well over a century, has been likened to a “black crow flying through the dark night”. The disease has many similarities to sarcoidosis and some forms of systemic vasculitis, other protean diseases in which the histopathological findings are consistent across a wide range of organ systems.
Atteintes d’organes au cours du syndrome d’hyper-IgG4

Syndrome de Mikulicz
- Dacryoadénite
- Sialadénite

Adénopathies profondes
- PTI hépatique
- Cholangite sclérosante
- Néphrite interstitielle

Infiltration hypophysaire
- PTI de l’orbite
- Thyroidite de Riedel
- PTI pulmonaire
- Pancréatite sclérosante
- Fibrose rétropéritonéale

Prostatite
- Aortite

PTI=pseudo-tumeur inflammatoire; les atteintes les plus fréquemment rapportées sont signalées en rouge

Fig. 1. Atteintes d’organes au cours du syndrome d’hyper-IgG4.
Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis


ABSTRACT
Objective Autoimmune pancreatitis (AIP) is a treatable form of chronic pancreatitis that has been increasingly recognised over the last decade. We set out to better understand the current burden of AIP at several academic institutions diagnosed using the International Consensus Diagnostic Criteria, and to describe long-term outcomes, including organs involved, treatments, relapse frequency and long-term sequelae.

Design 23 institutions from 10 different countries participated in this multinational analysis. A total of 1064 patients meeting the International Consensus Diagnostic Criteria for type 1 (n=978) or type 2 (n=86) AIP were included. Data regarding treatments, relapses and sequelae were obtained.

Results The majority of patients with type 1 (99%) and type 2 (92%) AIP who were treated with steroids went into clinical remission. Most patients with jaundice required biliary stent placement (71% of type 1 and 77% of type 2 AIP). Relapses were more common in patients with type 1 (31%) versus type 2 AIP (9%, p<0.001), especially those with IgG4-related sclerosing cholangitis (56% vs 26%, p<0.001). Relapses typically occurred in the pancreas or biliary tree. Retreatment with steroids remained effective at inducing remission with or without alternative treatment, such as azathioprine. Pancreatic duct stones and cancer were uncommon sequelae in type 1 AIP and did not occur in type 2 AIP during the study period.

Conclusions AIP is a global disease which uniformly displays a high response to steroid treatment and tendency to relapse in the pancreas and biliary tree. Potential long-term sequelae include pancreatic duct stones and malignancy, however they were uncommon during the study period and require additional follow-up.

Significance of this study

What is already known on this subject?
- Autoimmune pancreatitis (AIP) is a treatable form of chronic pancreatitis that is felt to be responsive to steroid treatment.
- There are few long-term data regarding response to treatment and subsequent disease sequelae.

What are the new findings?
- Disease relapses are common after steroid discontinuation, and typically occur in the pancreas and/or biliary tract.
- Pancreatic duct stones are relatively uncommon, but are seen more frequently in patients with at least one disease relapse.
- The occurrence of incidental cancers following AIP diagnosis appears to be uncommon.

How might it impact on clinical practice in the foreseeable future?
- Since disease relapses are common, additional studies are needed to compare different treatment strategies for maintaining disease remission.
- Further investigations are needed to understand if the risk of cancer is increased compared with the general population.

in 1995 by Yoshida et al, there was minimal progress in understanding this disease until a serum biomarker (IgG4 antibody) was identified by Shimosegawa et al.
Diagnosis and treatment of autoimmune pancreatitis types 1 and 2

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Background: Autoimmune pancreatitis (AIP) is characterized by diffuse or focal swelling of the pancreas. AIP has been divided into types 1 and 2. The aim of the study was to evaluate and compare the clinicopathological characteristics, therapy and outcome of patients with AIP.

Methods: The medical records of patients diagnosed with AIP between January 2003 and July 2011 were reviewed. Characteristics of patients with AIP types 1 and 2 were compared with those of patients with pancreatic ductal adenocarcinoma (PDAC).

Results: AIP was classified as type 1 in 40 patients and type 2 in 32 according to the HISORt (Histology, Imaging, Serology, Other organ involvement, Response to therapy) criteria. Patients with histologically confirmed AIP type 2 were younger than those with type 1 (P = 0.005). Some 30 of 32 patients with AIP type 2 were found to have a localized tumour-like pancreatic mass and underwent pancreatectomy, compared with only 16 of 40 with type 1 (P < 0.001). Three of 25 patients with AIP type 2 presented with raised serum levels of IgG4 compared with 21 of 38 with type 1 (P < 0.001). There was no difference in symptoms and involvement of other organs between AIP types 1 and 2. Presentation with weight loss was more common among patients with PDAC than those with AIP, but there was no difference in pain or jaundice between the groups. Raised serum carbohydrate antigen 19-9 levels were more prevalent in patients with PDAC.

Conclusion: Patients with AIP type 2 frequently present with abdominal pain and a tumour-like mass. Differentiating AIP from PDAC is difficult, so making the clinical decision regarding operative versus conservative management is challenging.

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Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience


ABSTRACT

Background There is a paucity of data on long-term management of type 1 autoimmune pancreatitis (AIP), a relapsing steroid-responsive disorder.

Objective We describe our experience with treatment of relapses and maintenance of remission using steroid-sparing immunomodulators (IMs) and induction of remission using rituximab (RTX).

Methods We obtained details of disease relapse and treatment in 116 type 1 AIP patients from clinic visits, medical records and telephone interviews. We compared relapse-free survival in those treated with IMs versus those treated with steroids alone, assessed patients’ response to RTX, and identified treatment-related complications.

Results During a median follow-up of 47 months, 52/116 AIP patients experienced 76 relapse episodes. The first relapse was treated with another course of steroids in 24 patients, and with steroids plus IM in another 27 patients; subsequent relapse-free survival until a second relapse was similar in the two groups (p=0.23). 38 patients received an IM for >2 months; failure or intolerance of IM therapy occurred in 17 (45%). 12 patients with steroid or IM intolerance/resistance were treated with RTX, an antiCD20 antibody; 10 (83%) experienced complete remission and had no relapses while on maintenance therapy. Treatment-limiting side effects related to RTX were uncommon.

Conclusions In type 1 AIP relapses are common. Relapse-free survival is similar in those treated with steroids plus IM compared to those treated with steroids alone. Nearly half the patients on IMs will relapse during treatment. RTX is effective in the treatment of both IM resistant and steroid intolerant patients.

Significance of this study

What is already known on this subject

► Although patients with type 1 autoimmune pancreatitis have a dramatic response to steroid treatment, disease relapses are common.
► There are limited studies describing treatment for relapses.

What are the new findings?

► Relapse-free survival is similar in patients treated with steroids alone versus steroids plus immunomodulator (IM) maintenance treatment.
► Nearly half of patients treated with IMs relapse during treatment.
► Rituximab treatment is highly effective for induction and maintenance of remission in patients with autoimmune pancreatitis with or without IgG4-related sclerosing cholangitis, including those who are resistant to IM treatment.

How might it impact on clinical practice in the foreseeable future?

► Although over half (55%) of the patients might benefit from IM treatment, a significant group is resistant to IMs, so additional approaches are needed for patients with relapsing autoimmune pancreatitis.
► Rituximab treatment can be considered for such patients with difficult-to-treat relapsing disease.
A Randomized Trial of Rectal Indomethacin and Sublingual Nitrates to Prevent Post-ERCP Pancreatitis

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OBJECTIVES: Acute pancreatitis is the most common adverse event of endoscopic retrograde cholangiopancreatography (ERCP). Recent data suggest that indomethacin can reduce the risk of post-ERCP pancreatitis (PEP) in high-risk individuals. However, whether the combination of indomethacin and sublingual nitrates is superior to indomethacin alone is unknown. Therefore, we aimed to evaluate the efficacy of rectally administered indomethacin plus sublingual nitrate compared with indomethacin alone to prevent PEP.

METHODS: During a 17-month period, all eligible patients who underwent ERCP were enrolled in this study. We excluded patients who had undergone a prior endoscopic sphincterotomy. In a double-blind controlled randomized trial, patients received a suppository containing 100 mg of indomethacin, plus 5 mg of sublingual nitrate (group A), or a suppository containing 100 mg of indomethacin, plus sublingual placebo (group B), before ERCP. Serum amylase levels and clinically pertinent evaluations were measured in all patients after ERCP.

RESULTS: Of the 300 enrolled patients, 150 received indomethacin plus nitrate. Thirty-three patients developed pancreatitis: 10 (6.7%) in group A and 23 (15.3%) in group B (P=0.016, risk ratio=0.39, 95% confidence intervals (CI): 0.18–0.86). More than 80% of the patients were at high risk of developing pancreatitis after ERCP. Absolute risk reduction, relative risk reduction, and number needed to treat for the prevention of PEP were 8.6% (95% CI: 4.7–14.5), 56.2% (95% CI: 50.6–60.8), and 12 (95% CI: 7–22), respectively.

CONCLUSIONS: Combination of rectal indomethacin and sublingual nitrate given before ERCP was significantly more likely to reduce the incidence of PEP than indomethacin suppository alone. Multicenter trials to confirm these promising findings are needed.

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Original article

Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function

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Background: Exocrine insufficiency frequently develops in patients with pancreatic cancer owing to tumour ingrowth and pancreatic duct obstruction. Surgery might restore this function by removing the primary disease and restoring duct patency, but it may also have the opposite effect, as a result of resection of functional parenchyma and anatomical changes. This study evaluated the course of pancreatic function, before and after pancreatic resection.

Methods: This prospective cohort study included patients with tumours in the pancreatic region requiring pancreatic resection in a tertiary referral centre between March 2010 and August 2012. Starting before surgery, exocrine function was determined monthly by measuring faecal elastase 1 levels (normal value over 0-200μg per g faeces). Endocrine function, steatorrhoea-related symptoms and bodyweight were also evaluated before and after surgery. Subjects were followed from diagnosis until 6 months after surgery, or until death.

Results: Twenty-nine patients were included, 12 with pancreatic cancer, 14 with ampullary carcinoma and three with bile duct carcinoma (median tumour size 2-6cm). Twenty-six patients underwent pancreaticoduodenectomy and three distal pancreatectomy. Thirteen patients had exocrine insufficiency at preoperative diagnosis. After a median follow-up of 6 months, this had increased to 24 patients. Diabetes was present in seven patients at diagnosis, and developed in one additional patient within 1 month after surgery.

Conclusion: Most patients with tumours in the pancreatic region requiring pancreatic resection either had exocrine insufficiency at diagnosis or became exocrine-insufficient soon after surgical resection.

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A Prospective Assessment of the Natural Course of the Exocrine Pancreatic Function in Patients With a Pancreatic Head Tumor

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Introduction: In cancer of the pancreatic head region, exocrine insufficiency is a well-known complication, leading to steatorrhea, weight loss, and malnutrition. Its presence is frequently overlooked, however, because the primary attention is focused on cancer treatment. To date, the risk of developing exocrine insufficiency is unspecified. Therefore, we assessed this function in patients with tumors of the pancreatic head, distal common bile duct, or ampulla of Vater.

Methods: Between March 2010 and August 2012, we prospectively included patients diagnosed with cancer of the pancreatic head region at our tertiary center. To preclude the effect of a resection, we excluded operated patients. Each month, the exocrine function was determined with a fecal elastase test. Furthermore, endocrine function, steatorrhea-related symptoms, and body weight were evaluated. Patients were followed for 6 months, or until death.

Results: Thirty-two patients were included. The tumor was located in the pancreas in 75%, in the bile duct in 16%, and in the ampullary region in 9%, with a median size of 2.5 cm. At diagnosis, the prevalence of exocrine insufficiency was 66%, which increased to 92% after a median follow-up of 2 months (interquartile range, 1 to 4 mo).

Discussion: Most patients with cancer of the pancreatic head region were already exocrine insufficient at diagnosis, and within several months, this function was impaired in almost all cases. Given this high prevalence, physicians should be focused on diagnosing and treating exocrine insufficiency, to optimize the nutritional status and physical condition, especially for those patients undergoing palliative chemotherapy and/or radiotherapy.

Key Words: pancreatic cancer, biliary carcinoma, ampullary carcinoma, exocrine pancreatic insufficiency, steatorrhea, weight loss, enzyme replacement therapy

including palliative chemotherapy and (neo)adjuvant chemoradiation.

In patients with a tumor of the pancreatic head region, weight loss is a major problem that affects 90% of patients already at diagnosis. For this, both primary and secondary tumor effects (eg, mechanical and intestinal obstruction or side effects of treatment) are responsible. In addition, exocrine insufficiency may play a role, which develops as a result of tumor invasion and/or obstruction of the pancreatic duct. The subsequent malabsorption of fat results in steatorrhea, with typical symptoms of voluminous and greasy stools, abdominal cramps, and bloating. This malabsorption not only negatively affects the clinical condition and quality of life of these patients, but may also lead to a delayed recovery, or even interruption of tumor therapy.

Although exocrine insufficiency can be easily corrected with enzyme supplementation, treatment is not always commenced. The presence of exocrine insufficiency is frequently overlooked, because physicians are mainly focused on cancer treatment. In addition, in case of incurable disease, some consider treatment of exocrine insufficiency to be futile. Yet, even in patients with a fatal prognosis, steatorrhea-related symptoms and the associated weight loss can be a tremendous burden.

So far, the natural course of the exocrine function in pancreatic cancer is unknown and the risk of patients developing exocrine insufficiency is not well established. Therefore, we assessed this function on a monthly basis, from the time of diagnosis. To preclude the confounding effects of a pancreatic resection, we only evaluated inoperable patients.

METHODS
Validation of international consensus guidelines for the resection of branch duct-type intraductal papillary mucinous neoplasms

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Background: Classifications of intraductal papillary mucinous neoplasm (IPMN) remain ambiguous, especially for the mixed type. Factors predicting malignancy remain unclear. The aim of this study was to evaluate the usefulness of factors predicting malignancy in the new international consensus guidelines for resection of branch duct-type (BD)-IPMN and to compare them with those in the previous version.

Methods: A prospectively collected database of patients with biopsy-proven BD-IPMN was analysed to compare factors between the first and second consensus guidelines, particularly as predictors of malignancy.

Results: Of 350 patients with BD-IPMN, sensitivity (0.724) and balanced accuracy (0.751) of the second guidelines were superior to those (0.639 and 0.730) in the first version at the expense of slightly reduced specificity (0.779 versus 0.822 for the first version) by random forest models. Multiple logistic regression analysis showed that main pancreatic duct dilatation greater than 5 mm (hazard ratio (HR) 4.54, 95 per cent confidence interval 2.45 to 8.41; P < 0.001), mural nodules (HR 6.27, 3.27 to 12.01; P < 0.001) and carbohydrate antigen 19–9 level above 37 units/ml (HR 4.03, 1.83 to 8.90; P = 0.001) were independent predictors of BD-IPMN malignancy.

Conclusion: The new consensus guidelines provide better sensitivity, performance of factors predicting malignancy, and balanced accuracy in the diagnosis of BD-IPMN malignancy. Size alone was limited in predicting malignancy. Variability in clinical significance of the individual factors associated with a risk of malignancy indicates the need for a tailored approach in the management of patients with BD-IPMN.

Paper accepted 10 February 2014
**Table 3**  Multiple logistic regression analysis of factors predicting malignancy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPD diameter &gt; 5 mm</td>
<td>4.54 (2.45, 8.41)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mural nodule</td>
<td>6.27 (3.27, 12.01)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Thickened cyst wall</td>
<td>1.55 (0.76, 3.17)</td>
<td>0.231</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>4.97 (0.48, 51.62)</td>
<td>0.180</td>
</tr>
<tr>
<td>CA19-9 &gt; 37 units/ml</td>
<td>4.03 (1.83, 8.90)</td>
<td>0.001</td>
</tr>
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Values in parentheses are 95 per cent confidence intervals. MPD, main pancreatic duct; CA, carbohydrate antigen.
Objective: As such, the natural history of MPD-involved IPMN is poorly understood.

Background: The high-risk of malignancy associated with main pancreatic duct (MPD)-involved intraductal papillary mucinous neoplasm (IPMN) has been established by surgical series. The International Consensus Guidelines recommend surgical resection of MPD-involved IPMN in fit patients.

Methods: A review of a prospectively collected database (1992–2012) of patients with IPMN undergoing primary surveillance was performed. Invasive progression was defined as invasive carcinoma on pathology and/or positive cytology. Analyses included univariate, logistic regression, and receiver operating characteristic curve analyses.

Results: A total of 503 patients with IPMN underwent primary surveillance, 70 for MPD-involved, mixed-type IPMN. Indications for intensive surveillance of these 70 high-risk patients were comorbidities, patient choice, and early/borderline MPD dilation (42%, 51%, and 7%, respectively). Mean follow-up was 4.7 years. Nine patients (13%) progressed at a mean of 3.5 (range, 1–9) years during follow-up. Univariate analyses yielded weight loss, interval (from isolated branch-duct IPMN) to MPD involvement, diffuse MPD dilation, increase of MPD diameter, absence of extra pancreatic cysts, elevated serum CA19-9 levels, and elevated serum alkaline phosphatase levels as significant. Maximum MPD and/or branch-duct diameter were not significant. In logistic regression, diffuse MPD dilation, serum CA19-9 and serum alkaline phosphatase levels, and absence of extra pancreatic cysts were predictors of invasiveness. The receiver operating characteristic curve indicated that the combination of these 4 factors achieved an accuracy of 98% in predicting progression.

Conclusions: Primary surveillance of mixed-type IPMN may be a reasonable strategy in select patients. Diffuse MPD dilation, serum CA19-9, serum alkaline phosphatase, and absence of extrapancreatic cysts predict patients likely to progress during primary surveillance.

Keywords: IPMN, mixed-type, natural history, predictors of invasive progression.
Abnormal serum pancreatic enzymes, but not pancreatitis, are associated with an increased risk of malignancy in patients with intraductal papillary mucinous neoplasms

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Introduction. Pancreatitis is associated with intraductal papillary mucinous neoplasm (IPMN). This association is in part due to inflammation from pancreatic ductal obstruction. Although the correlation between pancreatitis and the malignant potential of IPMN is unclear, the 2012 International Consensus Guidelines (ICG) consider pancreatitis a “worrisome feature.” We hypothesized that serum pancreatic enzymes, markers of inflammation, are a better predictor of malignancy than pancreatitis in patients with IPMN.

Methods. Between 1992 and 2012, 364 patients underwent resection for IPMN at a single university hospital. In the past decade, serum amylase and lipase were collected prospectively as an inflammatory marker in 203 patients with IPMN at initial surveillance and “cyst clinic” visits. The latest serum pancreatic enzyme values within 3 months preoperatively were studied. Pancreatitis was defined according to the 2012 revision of the Atlanta Consensus.

Results. Of the 203 eligible patients, there were 76 with pancreatitis. Pancreatitis was not associated with an increased rate of malignancy ($P = .51$) or invasiveness ($P = .08$). Serum pancreatic enzymes categorically outside of normal range (high or low) were also not associated with malignancy or invasiveness. In contrast, as a continuous variable, the higher the serum pancreatic enzymes were, the greater the rate of invasive IPMN. Of the 127 remaining patients without pancreatitis, serum pancreatic enzymes outside of normal range (low and high) were each associated with a greater rate of malignancy ($P < .0001$ and $P = .009$, respectively). Serum pancreatic enzyme levels above normal range (high) were associated with a greater rate of invasiveness ($P = .02$).
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