Exocrine Pancreatic Insufficiency and Pancreatitis Associated with Celiac Disease

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Abstract

Background/Objectives: The aim of this review is to provide a valuable and focused source of information for understanding and evaluating pancreatic manifestations of patients with celiac disease (CD). Methods: The review encompasses the current diagnostic criteria of CD and disease related prevalence and mechanisms of secondary exocrine pancreatic insufficiency (EPI) and the risk and mechanisms of pancreatitis. Topics also include the prevalence of CD in idiopathic pancreatitis, when to investigate and treat other causes of steatorrhea, particularly EPI with pancreatic enzyme replacement therapy (PERT). Conclusions: In “classical” CD the prevalence of EPI ranges 0-77.8%, on the basis of secretagogue and test meal evoked direct pancreatic function tests. Severe EPI (sufficient to cause steatorrhea) is uncommon, ranging in prevalence from 0-18%, and is usually reversible. Major mechanisms of EPI in CD include disruption of enteric mediated hormone secretion, luminal dilution of digestive enzymes and bile acids, malnutrition and immune mediated inflammation. CD associates with an increased risk of developing acute pancreatitis and chronic pancreatitis. Conversely, there is likely an unrecognized incidence of CD in idiopathic pancreatitis. In patients with CD and persistent malabsorption or weight loss despite a gluten free diet (GFD), EPI should be one of several considerations and a trial of PERT offered to patients.

1. Introduction

Celiac disease (CD) is an autoimmune condition induced by gluten exposure in genetically predisposed individuals. The estimated prevalence is approximately 1% (20, 23, 53, 60). CD manifestations include gastrointestinal (GI), extra-intestinal with or without GI disease, or asymptomatic disease. To improve consensus with CD terminology, the 2011 Oslo multidisciplinary task force (29) defined and recommended use of 9 terms. The two major CD terms are “classical” (signs and symptoms of malabsorption) and “non-classical” (symptoms present but malabsorption signs/symptoms are absent) disease. Seven additional CD terms include subclinical, symptomatic, refractory, potential, autoimmunity, genetically at risk and non-celiac gluten sensitivity. This report and other reviews (23, 53) lack a discussion of pancreatic disease associations. The aim of this review is to address this gap in clinical information by reviewing secondary exocrine pancreatic insufficiency (EPI) and pancreatitis associated with CD.

2. Exocrine pancreatic insufficiency (EPI) in Celiac Disease
Table 1. EPI common in classical CD but frequency varies by test

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>% abnormal</th>
<th>Comments (diagnosis/testing)</th>
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<tbody>
<tr>
<td><strong>Secretin (i.v.) evoked pancreatic secretion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comfort</td>
<td>1949</td>
<td>0</td>
<td>(0/13) “Nontropical sprue” with steatorrhea. Juice outputs; and concentrations.</td>
</tr>
<tr>
<td>Dreiling</td>
<td>1957</td>
<td>9.2</td>
<td>(3/36) <strong>Sprue syndrome</strong> with steatorrhea. Juice outputs and concentrations.</td>
</tr>
<tr>
<td>Pink</td>
<td>1967</td>
<td>15.4</td>
<td>(2/13) <strong>Celiac syndrome</strong> with steatorrhea. Studied 16 of 54 patients failing to respond to GFD. Low juice output in 2 of 13. Severe pancreatic morphology in 1 of 3 autopsies (acinar atrophy, ductal dilation).</td>
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<tr>
<td><strong>CCK (i.v.) evoked pancreatic secretion</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Zieve</td>
<td>1966</td>
<td>50</td>
<td>(3/6) <strong>Idiopathic steatorrhea</strong> with jejunal mucosal atrophy and steatorrhea. Secretin &amp; pancreozymin juice outputs.</td>
</tr>
<tr>
<td>DiMagno</td>
<td>1972</td>
<td>NA</td>
<td>(n=14) “Nontropical sprue” with steatorrhea. Studied 14 of 16 with high CFA. Reported mean juice outputs and comparison to outputs evoked by duodenal perfusion of essential amino acids.</td>
</tr>
<tr>
<td>Novis</td>
<td>1972</td>
<td>77.8</td>
<td>(7/9) <strong>Idiopathic steatorrhea</strong> with jejunal mucosal atrophy and symptoms responsive to GFD. Secretin &amp; pancreozymin juice concentrations.</td>
</tr>
<tr>
<td>Regan</td>
<td>1980</td>
<td>42</td>
<td>(13/31) <strong>Celiac sprue</strong> with steatorrhea. CCK evoked juice outputs.</td>
</tr>
<tr>
<td>Carroccio</td>
<td>1991</td>
<td>22.7</td>
<td>(10/44) <strong>Celiac sprue</strong> with steatorrhea and active duodenal disease. Secretin-caerulein evoked juice outputs.</td>
</tr>
<tr>
<td><strong>Test meal evoked pancreatic secretion</strong></td>
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<tr>
<td>Thaysen</td>
<td>1964</td>
<td>58</td>
<td>(7/12) <strong>Idiopathic steatorrhea (gluten-induced enteropathy)</strong>. Juice concentration.</td>
</tr>
<tr>
<td>Worning</td>
<td>1965</td>
<td>42.9</td>
<td>(see text) <strong>Gluten-induced enteropathy</strong>. Juice concentration. Low values varied by enzyme: 5.6% (1/18), 20% (1/5), 24% (6/25), 42.9% (3/7).</td>
</tr>
<tr>
<td>Ihse</td>
<td>1977</td>
<td>NA</td>
<td>(n=10) <strong>Celiac disease</strong>, with untreated, active mucosal disease. Reported mean juice concentrations.</td>
</tr>
<tr>
<td><strong>Duodenal infusion of amino acids evoked pancreatic secretion</strong></td>
<td>1972</td>
<td>NA</td>
<td>(n=14) “Nontropical sprue” with steatorrhea. Studied 14 of 16 with high CFA. Reported mean juice outputs and comparison to outputs evoked by CCK.</td>
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CD, celiac disease; CCK, cholecystokinin; CFA, coefficient of fat absorption; EPI, exocrine pancreatic insufficiency; GFD, gluten free diet; i.v., intravenous; PERT, pancreatic enzyme replacement therapy; PFT, pancreatic function testing.

Juice (pancreatic) concentration or output: °amylase, °bicarbonate, °carboxypeptidase, °chymotrypsin, °lipase °phospholipase A2, °trypsin.

NOTE: Additional studies of secretin evoked pancreatic secretion in CD were identified but not included due to having fewer than 5 patients in the case series (18, 26, 36, 66).
In “classical” CD, numerous studies have reported an association with EPI, diagnosed by measurements of pancreatic enzyme or bicarbonate secretions (Tables 1 and 2) evoked by the intravenous (i.v.) administration of GI hormone analogues for secretin (5, 17, 43), cholecystokinin (CCK) (8, 14, 39, 51, 72), or cholinergic agonists (19), ingestion of test meals (22, 64, 70), and duodenal infusion of amino acids (14). In case series having at least 5 patients the overall prevalence of EPI in “classical” CD ranges 0-77.8% (Table 1) but varies considerably by the specific pancreatic function test (PFT); 0-15.4% with i.v. secretin, 22.7-77.8% with i.v. CCK analogues, and 42.9-58% with test meal. Severe EPI (<10% normal enzyme outputs evoked by CCK (51)) sufficient to contribute to steatorrhea is uncommon, ranging in prevalence from 0-18.8% in series with at least 5 patients with active CD (Table 2) (5, 8, 43, 51, 72), and described in only 10 cases confirmed by direct PFTs or clinical history and autopsy (5, 8, 18, 19, 43, 51, 72). Of these ten cases, 6 responded to pancreatin (5, 19, 51, 72), 1 responded to GFD alone (18), and 3 were resistant to both therapies (43).

Intestinal damage, a histological feature of “classical” CD, correlates with the degree of decline in exocrine pancreatic function (38). Following initiation of gluten free diet (GFD), EPI is typically reversible (18, 66); some patients slowly resolve EPI and malabsorption. Only 7 cases with

<table>
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<th>Table 2. Severe EPI is uncommon in classical CD</th>
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<tr>
<td><strong>Author</strong></td>
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<tr>
<td>Secretin (i.v.) evoked pancreatic secretion</td>
</tr>
<tr>
<td>Benson (5)</td>
</tr>
<tr>
<td>Pink (43)</td>
</tr>
<tr>
<td>CCK agonist (i.v.) evoked pancreatic secretion</td>
</tr>
<tr>
<td>Zieve (72)</td>
</tr>
<tr>
<td>Regan (51)</td>
</tr>
<tr>
<td>Carroccio (8)</td>
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</table>

**CD, celiac disease; CCK, cholecystokinin; CFA, coefficient of fat absorption; EPI, exocrine pancreatic insufficiency; GFD, gluten free diet; i.v., intravenous; PERT, pancreatic enzyme replacement therapy; PFT, pancreatic function testing. Juice (pancreatic) concentration or output: aamylase, bicarbonate, ccarboxypeptidase, chchymotrypsin, lipase, phospholipase A2, trypsin.**

**NOTE:** Additional studies of secretin (15) and carbachol (19) evoked pancreatic secretion in CD were identified but not included due to having fewer than 5 patients in the case series.
clinical follow-up have been reported to have irreversible EPI, including 5 confirmed by direct PFT (5, 19, 43, 51), one by clinical characteristics and autopsy (43), and one by low serum immunoreactive trypsin with steatorrhea improving with PERT (67).

3. Mechanisms of EPI in Celiac Disease

Four major mechanisms of EPI in CD have been proposed, including, disruption of enteric mediated hormone secretion, luminal dilution of bile acids and pancreatic enzymes, malnutrition and immune mediated inflammation (discussed under Pancreatitis).

Disruption of enteric mediated hormone secretion

Two methodologic approaches have been used to establish the disruption in enteric-mediated hormone secretion in untreated CD (Figure 1), causing reduced pancreatic secretion of digestive juice and gallbladder emptying: pancreatic function testing (in response to amino acids, diet and exogenous hormones) and measurement of enteric hormones secreted in blood.

In untreated CD, reduced release of enteric hormones has been postulated to cause secondary EPI (14, 22, 70). In these studies, EPI was diagnosed by direct pancreatic function testing, with measurement of enzyme and bicarbonate outputs or concentrations in duodenal juice following test meals (14, 22, 70) and duodenal infusion of amino acids (14). For example, the 1973 study by DiMagno and colleagues (Figure 2) showed that patients with untreated CD had evidence of reduced pancreatic enzyme outputs and gallbladder emptying in response to intraluminal amino acid infusion, which evokes endogenous cholecystokinin (CCK) secretion, but that exocrine pancreatic- and gallbladder functions normalized in response to exogenous intravenous infusion of CCK-pancreozymin (14).

In addition, these investigators fed two test meals four hours apart. As we summarized previously, “Postprandially these abnormalities resulted in maldigestion of fat due to asynchronization between transit of the meal and delayed and reduced secretion of pancreatic enzymes and bile into the small intestine that occurred during the first 30 minutes after eating. After the initial 30 postprandial minutes, dilution of intraluminal content secondary to abnormalities of fluid and electrolyte absorption/secretion contributed to impaired fat digestion. Fat maldigestion was worse after a second meal” (15). Restoration of pancreatic function is possible by introduction of a GFD with resultant enteric healing. Conversely, EPI is generally a manifestation of persistently active enteric disease (8, 43, 67), and as discussed above is uncommonly severe and usually reversible.

Figure 1. Schematic of enterocyte damage impairing cholecystokinin (CCK) signaling.

In health (A) the small intestine enterocytes (solid black) release into the lumen CCK releasing factor (CCK-RF), which has paracrine effects on I-cells, leading to CCK release into the circulation, which in turn acts via vagal cholinergic pathways to stimulate pancreatic secretion (41). Signaling is sensitive to luminal trypsin (from endogenous pancreatic juice or exogenously administered pancreatic enzymes), which degrades intraluminal CCK-RF. In active celiac disease (B) associated with enterocyte injury, CCK signaling is impaired (14) at the level of enterocyte release of CCK-RF into the small bowel lumen and enterocyte (I-cell) release of CCK into the circulation.
Small intestinal enterocytes synthesize, store and secrete the enteric hormones CCK and secretin (25). In untreated CD, associated with intestinal mucosal atrophy, blood levels of these hormones are reduced. Compared to controls, patients with untreated CD have lower blood CCK levels while fasting (6) and postprandially (6, 32) and have lower postprandial gallbladder emptying (32). Treatment with GFD normalized both postprandial CCK and gallbladder emptying (32). Similarly, reduced blood secretin levels are also present in untreated CD, measured following duodenal perfusion of hydrochloric acid (24, 40, 52, 69), but normalizes after GFD treatment (24). Data is conflicting whether secretin levels are low in the unstimulated/fasting state (24, 40, 52).

Figure 2. Impaired cholecystokinin-pancreozymin (CCK-PZ) secretion in celiac disease.
Mean (SE) pancreatic enzyme outputs per hour in health (n=12) and celiac disease with steatorrhea (n=14) in response to intravenous CCK-PZ stimulation (0.25 Crick-Harper-Raper units/kg/min), representing exogenous CCK, and intraduodenal essential amino acids (EAA, 78 mM), the latter stimulating endogenous CCK release. *P <0.01 vs. intraduodenal EAA treated normal. Adapted from Gastroenterology (14).

Luminal dilution of bile acids and pancreatic enzymes
As discussed above, CD disease associates with decreased luminal concentrations of pancreatic enzymes and bile acids due to disruption of enteric mediated hormone pancreatic secretion and gallbladder emptying. Decreased luminal concentrations of pancreatic enzymes and bile acids may be further diminished due to a luminal dilution from reduced absorption of fluid and electrolytes (21, 59). The latter has been attributed to small bowel injury with impaired absorption of nutrients resulting in an increased prandial luminal osmotic load (59), but also to reduced mucosal pore size in active CD (21), both of which are reversible.

Malnutrition
EPI, diagnosed by diminished pancreatic enzyme secretions evoked by administration of intravenous secretagogues, associates with a spectrum of protein-calorie malnutrition (PCM) disorders, including kwashiorkor (with features of muscle wasting, peripheral edema, skin lesions, growth retardation, hypoalbuminemia and deficiencies of essential amino acids) and marasmus (features of kwashiorkor but without edema or skin lesions) (3, 44, 57, 63). Because severe cases of “classical” CD can give rise to malnutrition, it has been postulated that EPI in CD may also be due in part to malnutrition (66, 70).

There are two postulated mechanisms for EPI with PCM but these have doubtful relevance to CD. First, deficiencies of essential amino acids are common in PCM (3) and would be expected to impair protein synthesis of digestive enzymes. Evidence to support this mechanism is that dietary therapy to replete these deficiencies quickly restores pancreatic exocrine function in most patients (3, 44, 57, 62, 63). Due to the typical prompt restoration of exocrine pancreatic function with dietary therapy, it seems unlikely that EPI in most patients with PCM is directly related to pancreatic morphological changes, described as pancreatic acinar atrophy which may progress to fibrosis (see reviews (44, 63)). These pancreatic morphologic abnormalities in PCM resemble those in CD described at autopsy (discussed in Pancreatitis section) (1), and perhaps could account for rare instances of irreversible EPI in CD,
described above. Despite these morphological similarities, PCM is unlikely to be a true independent primary cause of EPI in CD because EPI in CD is not dependent on nutritional status (10).

4. Pancreatitis and Celiac Disease

CD associates with an increased risk of developing acute pancreatitis (AP) and chronic pancreatitis (CP); the latter has a much stronger association (30, 42, 55). The overall risk of pancreatitis is approximately 3-fold higher than the general population (30, 55). The risks (Hazards ratios) of pancreatitis appear to be higher for CP compared to AP (3.3-19.8 vs. 1.9) (30, 55). As previously reviewed (15), the variability in the reported risk of pancreatitis is likely due to inaccurate diagnoses of AP and CP, which were based primarily on International Classification of Diseases-Clinical Modification (ICD-CM codes) (editions 7-10). These ICD-CM codes are only 83% accurate for definite AP in the Swedish Registry (48) and only 49% accurate for definite CP based on a study at the University of Michigan (50). Because hyperamylasemia without AP occurs in CD (7, 46) and diagnosis of AP did not necessarily require imaging evidence, it is possible there were misdiagnoses of AP, which most commonly would represent over diagnosis of AP in patients with nonspecific hyperamylasemia or macroamylasemia.

Pancreatic histological findings described for CD disease are based on an autopsy study of 6 patients without documentation of clinical pancreatitis (1). Abnormalities included acinar cell atrophy in one patient and fibrosis (fine, interlobular and intralobular fibrosis) in 4 other patients. Over time, progression of these features may give rise to evidence of clinical pancreatitis in a subset of patients.

Proposed mechanisms of pancreatitis include immune-mediated pancreatic inflammation and papillary stenosis. The mechanism of immune-mediated pancreatic inflammation is poorly understood. CD has an increased prevalence of autoimmune diseases (35), but only a single case of co-existent autoimmune pancreatitis and CD has been reported (31). It has also been proposed that chronic duodenal inflammation may give rise to papillary stenosis and recurrent pancreatitis (42). Data to support this supposition is that CD was diagnosed in 7.1% of patients (12 of 169) referred to tertiary institution with suspected sphincter of Oddi dysfunction, having either recurrent abdominal pain (2 of 12) or idiopathic pancreatitis (10 of 12) (42). Although no patient had recurrent pancreatitis during the mean 22 month follow-up period, it is unclear whether treatment aimed at sphincter of Oddi dysfunction (biliary and pancreatic sphincterotomy) is helpful because all 10 patients who received this therapy also received concomitant GFD. As a word of caution about endoscopic therapy, it should be noted that in idiopathic pancreatitis, recurrent attacks of pancreatitis commonly persist despite endoscopic therapy, as recently reviewed (68).

There is likely an unrecognized incidence of CD in idiopathic pancreatitis. Approximately 10-30% of patients with AP have idiopathic pancreatitis (27). Of these, pancreatic endoscopic ultrasonography (EUS) can identify an etiology in 30-55% of cases (61, 65, 71), but a subset of these patients may actually have unidentified CD. Pancreatic calcifications are absent in patients from most series of CD patients, except for two patients in studies highlighted in Table 1 and Table 2 (19, 43), and few additional and scattered examples of CD associated with non-alcoholic calcific chronic pancreatitis (2, 33, 45). In a preliminary retrospective study of patients undergoing EUS for idiopathic pancreatitis, who also had duodenal biopsy, 7.4% (5/68) of patients with definite chronic pancreatitis (by Mayo Criteria (49)) had CD (34), a 10-fold increase over the 0.71% prevalence of CD noted within the general U.S. population (54). These data mirror the 7.1 prevalence of CD in patients with suspected sphincter of Oddi dysfunction (42) and would support screening for
CP as part of the evaluation of patients with idiopathic pancreatitis.

5. Treatment of Pancreatic Component of Celiac Disease

In CD, the likelihood of coexisting EPI depends on the clinical context. In routine clinical practice, accurate testing for EPI can be challenging in CD, which can be mitigated in part by a trial of empiric treatment with pancreatic enzyme replacement therapy (PERT).

As a point of emphasis it is worth reiterating that EPI is common but variable in patients with CD, ranging 0-77.8% (Table 1) but severe EPI (<10% normal enzyme outputs evoked by CCK) sufficient to cause pancreatic steatorrhea is uncommon, ranging in prevalence from 0-18.8% in small series having a minimum of 5 patients (Table 2), with only 10 cases confirmed by direct PFTs or clinical history and autopsy. Strong clinical clues for severe EPI in CD include intractable malabsorption or weight loss despite adherence to a GFD. In patients with CD and milder symptomatology it is possible that PERT may be clinically useful, at least in children, but this is not standard of care. In a double blind randomized controlled trial PERT was useful in the first 30 days after diagnosis of CD in a pediatric population (9). For persistent malabsorption despite GFD and PERT, inadvertent gluten ingestion and refractory CD should be considered, which can be addressed with intensive counseling by an experienced registered dietician, serologic testing and repeat duodenal biopsies to exclude alterations in T lymphocyte morphology suggestive of enteropathy-associated T-cell lymphoma. An additional cause of malabsorption relevant to CD include decreased micellar concentration of bile acids because of delayed gallbladder contraction, precipitation of bile acids due to low luminal pH, deconjugation due to small intestinal bacterial overgrowth, and dilution (14, 21, 28, 32, 59). Other relevant causes include inadequate dosing or noncompliance with PERT; acid induced degradation or delayed release of PERT; biliary obstruction or ileal disease; other duodenal diseases (e.g. giardia); and a mixing disorder due to timing of PERT, gastroparesis or gastrointestinal surgery (16).

The most specific tests for detecting EPI in the contexts of CD are direct pancreatic function tests (PFT), performed by collecting and measuring pancreatic enzyme secretions into the duodenum evoked by administration of intravenous secretagogues or a standard test meal. Unfortunately, these tests are not widely available. Indirect tests of pancreatic exocrine function are more widely available and simpler to perform but less accurate. For example, 25-30% of patients with various small bowel enteropathies have a low pancreatic fecal elastase due to dilutional effects of diarrhea (4, 11, 37, 56, 58), such that fecal elastase has been considered a general marker of enteropathy (37). For this reason, use of fecal elastase to assess pancreatic digestive function in CD is problematic, as illustrated by a recent study which reported diarrhea in 80% of 36 patients with CD, of which 28% (10 of 36) had a modestly reduced fecal elastase (mean 141.6 μg/g of stool) (47). Quantitative fecal fat testing is cumbersome and does not distinguish among specific causes of steatorrhea, but documentation of steatorrhea (a summation of multiple digestive processes) may influence decisions to offer additional testing for active CD, small intestinal bacterial overgrowth or other causes and targeted or empiric therapy for these disorders, including secondary EPI.

PERT treatment of severe EPI in patients with CD is similar to treatment of EPI related to chronic pancreatitis (13). There is no primary data to suggest that either enteric coated or uncoated formulations of PERT have greater efficacy.

Financial Support
MJD receives research support from the National Institutes of Health (DK106647).
6. References


