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Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis

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ABSTRACT

Objectives: This study systematically explores the prevalence of pancreatic exocrine insufficiency (PEI) after acute pancreatitis in different subgroups of etiology (biliary/alcoholic/other), disease severity and follow-up time (<12, 12–36 and > 36 months after index admission).
Methods: PubMed and EMBASE databases were searched, 32 studies were included in this study level meta-analysis.
Results: In a total of 1495 patients with acute pancreatitis, tested at a mean of 36 months after index admission, the pooled prevalence of PEI was 27.1% (95%-confidence interval [CI]: 20.3%–35.1%). Patients from seven studies (n = 194) underwent direct tests with pooled prevalence of 41.7% [18.5%–69.2%]. Patients from 26 studies (n = 1305) underwent indirect tests with pooled prevalence of 24.4% [18.3% –31.8%]. In subgroup analyses on patients that underwent fecal elastase-1 tests, PEI occurred more often in alcoholic pancreatitis (22.7% [16.6%–30.1%]) than in biliary pancreatitis (10.2% [6.2%–16.4%]) or other etiology (13.4% [7.7%–22.4%]; $P = 0.02$). Pooled prevalence of PEI after mild and severe pancreatitis was 19.4% [8.6%–38.2%] and 33.4% [22.6%–46.3%] respectively in studies using fecal elaste-1 tests ($P = 0.049$). Similar results were seen in patients without (18.9% [9.3%–34.6%]) and with necrotizing pancreatitis (32.0% [18.2%–49.8%]; $P = 0.053$). Over time, the prevalence of PEI decreased in patients who underwent the fecal elastase-1 test and increased in patients who underwent the fecal fat analysis.
Conclusions: After acute pancreatitis, a quarter of all patients develop PEI during follow-up. Alcoholic etiology and severe and necrotizing pancreatitis are associated with higher risk of PEI. The prevalence of PEI may change as time of follow-up increases.

Introduction

Acute pancreatitis may be complicated by loss of exocrine pancreatic function. This is typically depicted by a loss of pancreatic cell mass and functional capacity because of pancreatic necrosis, which occurs in around 20% of patients [1,2]. Around 30% of patients with necrotizing pancreatitis need catheter drainage and/or pancreatic necrosectomy as treatment of infected necrosis [3,4]. During removal of infected necrosis, adjacent vital pancreatic tissue may also be damaged which reduces the functional reserve capacity of the remnant pancreas even further. Other explanations for functional loss after acute pancreatitis include secondary impairment of hormonal mediators or neural stimuli, damaged receptors that control enzyme releasing acinar cells or obstructions in the exocrine ductal system through altered anatomy caused by the

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inflammation [5].

The pancreatic gland has two main functions; synthesis and endocrine secretion of insulin for glycemic control, and synthesis and exocrine secretion of enzymes for digestion of fat, protein and carbohydrate in the gut. Impaired function of the endocrine pancreas causes diabetes mellitus, which is a well-known complication and reported to be newly diagnosed in around a quarter of all patients after acute pancreatitis [6]. Pancreatic exocrine insufficiency causes insufficient digestion and uptake of foods, which may lead to indigestion, flatulence, diarrhea and, in severe form, steatorrhea and malnutrition. Consequences are weight loss, vitamin and mineral deficiencies and metabolic bone disease [7]. Therapy of pancreatic exocrine insufficiency consists of supplemental pancreatic enzymes to be taken with every meal or snack to substitute the deficient endogenous pancreatic enzyme production [8].

Pancreatic exocrine insufficiency is a common complication of pancreatic cancer and chronic pancreatitis [9,10]. Several, mainly small clinical studies, report on pancreatic exocrine insufficiency in the follow-up of acute pancreatitis [11]. Between these studies, etiology of pancreatitis, severity of disease, diagnostic tests for pancreatic exocrine insufficiency and follow-up time differs substantially, which severely impedes comparability of results. Published reviews on exocrine insufficiency after acute pancreatitis are narrative or focus on specific subgroups of patients [11–13]. We conducted a systematic review of studies reporting on exocrine insufficiency in the follow-up of acute pancreatitis and performed a study level meta-analyses to explore the prevalence of pancreatic exocrine insufficiency in different subgroups of etiology, severity of disease and follow-up time.

Methods

This systematic review and study level meta analyses was performed according to the MOOSE guidelines for reporting meta-analysis of observational studies [14]. The protocol for this study was registered in the PROSPERO international prospective register of systematic reviews (CRD42015029733).

Search strategy

We searched for studies reporting on pancreatic exocrine insufficiency following acute pancreatitis in PubMed and EMBASE databases. No restrictions on publication date were set. The search was performed on November 16, 2017 with the following items in both Mesh terms and plain text: 1; (exocrine pancreas) OR (exocrine) OR (pancreatic funct*) OR (pancreas funct*) OR (pancreatic dysfunct*) OR (pancreas dysfunct*) OR (pancreatic insufficien*) OR (pancreas insufficien*) AND 2; (Pancreatitis) AND (acute OR necro*). Detailed searches for both databases are available online at the PROSPERO website (CRD42015029733) and in the supplementary appendix (p 2).

Study selection

Included were studies 1) including patients with acute pancreatitis; 2) that reported on diagnostic laboratory testing for pancreatic exocrine insufficiency; 3) during follow-up, i.e. at least three months after discharge of index admission. Excluded were 1) studies that reported on patients with chronic pancreatitis only or studies that reported on patients with chronic and acute pancreatitis, but data of these two groups were not reported separately; 2) studies including fewer than 10 patients; 3) animal studies; 4) studies reporting in other than English language and 5) unpublished studies and conference abstracts. Two investigators (RAH, DJM) screened titles and abstracts for eligibility and included studies by consensus in collaboration with a third investigator (NDH). Reference lists of included publications were screened for relevant studies that were not identified by the initial search, primarily by title and if eligible, by abstract and full text.

Data extraction

Using a predefined data extraction file, three investigators (RAH, NDH and DJM) extracted the following variables from the included studies: first author and country, study period and year of publication, study design and inclusion criteria, number of patients included, sex, age, etiology of acute pancreatitis, severity of disease, number of patients with pancreatic necrosis, number of patients that underwent pancreatic necrosectomy, test method to diagnose pancreatic exocrine insufficiency, timing and reference values of pancreatic exocrine insufficiency tests, number of patients with pancreatic exocrine insufficiency according to performed test, etiology of pancreatitis of patients with exocrine insufficiency and number of patients that used supplemental pancreatic enzymes. Extracted data were checked for consistency and plausibility. Any discrepancies were resolved by consensus. If studies reported on pancreatic exocrine insufficiency for subgroups of severity of disease (e.g. non-necrotizing and necrotizing pancreatitis) separately, then data were extracted as such for pooling and meta-analysis. For quality assessment of included studies the Newcastle-Ottawa Scale for non-randomized studies in meta-analyses was used, in which the maximum score is nine points for high quality studies [15]. No attempt was made to complete missing data through communication with corresponding authors. Missing data is reported as ‘not reported’ and left unhandled in further analyses.

Severity of disease

To compare the prevalence of pancreatic exocrine insufficiency in different subgroups of disease severity, the Atlanta Classification from 1992 was used [16]. Most included studies classified severity of disease by the Atlanta 1992 classification as this was the general standard before the classification was updated in 2012. The classification defines mild acute pancreatitis by an uneventful recovery without organ failure or necrosis and severe acute pancreatitis by organ failure and/or local complications such as necrosis [16]. The Atlanta 2012 classification of acute pancreatitis includes a third category of moderate severe acute pancreatitis in addition to mild and severe acute pancreatitis [17]. Studies not reporting severity according to Atlanta 1992 were reclassified, if possible, to the Atlanta 1992 classification of mild or severe acute pancreatitis. For example, studies including only patients with necrosis were classified as ‘severe’. Studies reporting only that a subgroup of patients did not have necrosis were not re-classified as ‘mild’ because no data of possible organ failure was presented and thus, uncertainty remains for the classification ‘mild’ or ‘severe’. It was not deemed possible to re-classify severity of disease from the Atlanta 1992 to the Atlanta 2012 classification based on the available data.

Data processing and statistical analysis

Weighted means were estimated for the variables age and follow-up time to pancreatic exocrine insufficiency test through methods described by Hozo et al. [18] Using a random effects model, pooled prevalence and associated 95% confidence intervals (CI) were calculated for pancreatic exocrine insufficiency for direct and indirect test method separately because of fundamental differences between both test types. During direct tests (e.g. secretine testing), pancreatic secretory content is collected and analyzed by duodenal intubation which is a highly specialized procedure

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