A consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines

Supplemental material

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METHODOLOGY

Literature search details

Systematic literature search details are outlined in **table S1**. The initial literature searches were performed between October and December 2018. Prior to submission, literature searches were updated to include additional articles published up to and including 22 May 2020.

Table S1. Literature search strategy (PubMed)

Search	Literature search terms[a–c]
1	Diagnosis, definition, faecal elastase, fecal elastase, steatorrhoea, nutritional deficiencies, micronutrient, magnesium, trace elements, fat soluble vitamins, faecal fat, fecal fat, coefficient of fat absorption, endoscopic ultrasound, secretin, MRCP, Magnetic resonance cholangiopancreatography, s-MRCP, CT, Computerised tomography, triglyceride breath test, duodenal juice collection
2	Survival, quality of life, pancreatic cancer, pancreatic adenocarcinoma, pancreatic ductal adenocarcinoma, periampullary cancer, pancreatoduodenectomy, pancreaticoduodenectomy, whipples, distal pancreatectomy, progression, natural history, natural course
3	Bone density, absorptiometry, photon, bone diseases, metabolic, osteoporosis, osteopenia, osteomalacia, osteopathy
4	Acute pancreatitis, severe pancreatitis, necrotising pancreatitis
5	SIBO, SBBO, small intestinal bacterial overgrowth, small bowel bacterial overgrown, BAM, bile acid malabsorption, coeliac, celiac, TTG, tissue, transglutaminase, PPI, proton pump inhibitor, laxatives, chemotherapy, lactase deficiency, lactose intolerance, colorectal cancer, pancreatic cancer, IBD, inflammatory bowel disease, irritable bowel syndrome, IBS
6	Management, treatment, guidance, dose, timing, time, frequency, administration, capsule, microspheres, minitabs, increase, efficacy, side effects
7	Long term, follow up, monitoring, review
8	Quality of life, performance status, PROMS, patient reported outcome measures, outcome measures
9[d,e]	Pancreatin AND (pregnancy, breastfeeding, gout, fibrosing colonopathy, safety) AND Pancreatic exocrine insufficiency AND therapy AND safety

[a]Searches 1–8 used core search criteria (PERT OR Pancreatin OR Pancreatic Exocrine Insufficiency OR Exocrine Pancreatic Insufficiency OR Pancreas Insufficiency OR Pancreatic Insufficiency AND ≥1980) with specific literature search terms for each section as indicated; [b]search filters: terms appear in the abstract/title; human participants; English-language; randomised controlled trials, meta-analyses and observational studies; [c]screening: adults >18 years of age were included; [d]core search terms or filters were not used; [e]publication date: >1998

BAM, bile acid malabsorption; CT, computed tomography; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; PERT, pancreatic enzyme replacement therapy; PPI, proton-pump inhibitor; PROMS, patient-reported outcome measures; QoL, quality of life; SIBO, small intestinal bacterial overgrowth; SBBO, small bowel bacterial overgrowth; sMRCP, secretin injection at magnetic resonance cholangiopancreatography; TTG, tissue transglutaminase

Bone health literature searches

Only one paper was retrieved on the effect of pancreatic exocrine insufficiency (PEI) on bone health. However, this meta-analysis of nine studies did not examine the association between PEI and vitamin D deficiency or bone health and was, therefore, excluded. Prior to applying the search filters (specifically: terms appear in abstract/title, human, English language, abstract, meta-analysis/observational study/randomised controlled trial), 63 papers were retrieved, and these were reviewed to ensure that they had not been incorrectly excluded. Of the 63 papers, four were potentially relevant. The remaining papers were further excluded (reviews: n=20; not relevant: n=24; studies on children: n=7; non-English language: n=7). The search was repeated to ensure that papers had not been inappropriately excluded.

LESS COMMON CAUSES OF PEI: STATEMENTS AND SUPPORTING EVIDENCE

Statement 2.5.1: Ageing populations may have an increased prevalence of PEI and, therefore, should be considered for testing, particularly if presenting with unexplained weight loss or diarrhoea (good practice point [GPP]; 88% agreement)

Comments

Several studies have investigated the prevalence of PEI in the elderly using the FEL-1 diagnostic test. One study in individuals aged 50–75 years of age found that 105/914 (11.5%) had a FEL-1 level <200 µg/g stool.[1] Other studies have shown that PEI increases with increasing age.[2 3]

Statement 2.5.2: Patients with renal disease and rheumatological conditions may have an increased prevalence of PEI, but further studies are needed before routine testing can be recommended (GPP; 95% agreement)

Comments

Several other conditions have been associated with PEI, but high-quality studies examining prevalence, or the value of PERT are lacking. Sjögren's syndrome has been associated with PEI, although a recent study only showed a prevalence of 4%.[4] Similarly, patients with advanced renal disease are commonly malnourished and PEI has been implicated in the pathogenesis. Two small studies measured FEL-1 levels (using different cut-offs) in patients undergoing dialysis and found FEL-1 levels <100 µg/g stool in 12/25 (48%) and FEL-1 levels of 1–200 µg/g in 5/50 (10%).[5 6] However, there were no clinical correlations between FEL-1 level and the symptoms of steatorrhoea described by 20% of the patients.[5 6] Larger studies are required to determine the true prevalence of PEI and the value of PERT in patients with these conditions.

Statement 2.5.3: Patients with coeliac disease on a gluten-free diet, but still experiencing diarrhoeal symptoms, should be investigated for PEI and treated

with PERT if positive results are obtained. This should be reviewed at least annually as treatment may not need to be long term (Grade 1B; 100% agreement)

Comments

Studies suggest that approximately one-third of patients with coeliac disease who experience persistent symptoms (particularly diarrhoea) may have PEI.[7 8] PERT may be of benefit for these patients;[8] however, one study found that many had stopped taking PERT within 4 years of commencing treatment, suggesting that PEI is not permanent in patients with coeliac disease.[9] Therefore, patients with coeliac disease established on a gluten-free diet but still experiencing diarrhoeal symptoms should be tested for PEI with FEL-1 and treated with PERT if positive. The test should be repeated at least annually as long-term treatment may not be required.

Statement 2.5.4: PEI should be considered in patients with IBS-D. The role of PERT in this group is not fully understood (Grade 2C; 95% agreement)

Comments

Two studies screened patients with functional bowel disorders for PEI using the FEL-1 test. In the first study, of 314 patients with diarrhoea-predominant irritable bowel syndrome (IBS-D), 19/314 (6.1%) had a FEL-1 level <100 µg/g stool, indicative of severe PEI. Following open-label treatment with PERT, there were significant improvements in abdominal pain ($p<0.003$), stool frequency ($p<0.001$) and stool consistency ($p<0.001$).[10] A subsequent study screened 218 patients with a range of functional gut symptoms and found that 10/218 (4.6%) had a FEL-1 level <200 µg/g stool and 2.3% had a FEL-1 <100 µg/g stool, with CP identified in two patients.[11] However, if those with IBS-D were considered alone, then 3/35 (8.6%) of patients had a low FEL-1 level, which is similar to the findings of Leeds, et al. [10]. No information was given regarding treatment in this study.[11] Given the high prevalence of IBS-D, routine FEL-1 testing of

these patients for PEI seems sensible, but more studies in this area are needed to strengthen this recommendation.

Statement 2.5.5: Patients with IBD and continued diarrhoeal symptoms should be investigated for PEI (Grade 2B; 100% agreement)

Comments

There appears to be an increased risk of developing CP in patients with inflammatory bowel disease (IBD) that increases over time.[12] The true frequency of PEI in patients with IBD is unknown, as clinically symptomatic PEI may be unrecognised and treated as a disease flare. Two studies reported a 14–22% prevalence of PEI in patients with IBD using the FEL-1 diagnostic test.[13 14] However, this was possibly an underestimation, as FEL-1 levels may have been falsely reduced by watery stools caused by active disease, previous pancreatic damage or degradation of elastase by bacteria. Neither of these studies looked at the benefit of PERT in patients with abnormal FEL-1 levels. Some patients have continued diarrhoea despite mucosal improvement and improved inflammatory markers following standard treatment for IBD. In these circumstances, PEI should be considered.

Statement 2.5.6: Patients with HIV presenting with steatorrhoea, diarrhoea or weight loss should be investigated for PEI and offered PERT if positive results are obtained (Grade 2B; 88% agreement)

Comments

Gastrointestinal (GI) symptoms are common in patients with human immunodeficiency virus (HIV) infection, and autopsy studies have shown histological changes suggestive of exocrine pancreatic disease.[15] The FEL-1 diagnostic test has indicated a prevalence of PEI of 23–54% in this patient population.[16 17] PERT has been shown to reduce fat malabsorption and improve GI symptoms in patients with HIV infection and low FEL-1 levels.[16-19] Most of these studies are small

and open-label and may have other confounders limiting their validity. Considering the impact and prevalence of fat malabsorption in patients with HIV, those with relevant symptoms should be tested for PEI and offered PERT if positive.

Statement 2.5.7: There may be an increased prevalence of PEI in patients with ALD, but the role of PERT in this group has not been examined (GPP; 89% agreement)

Comments

Identifying individuals with alcohol-related liver disease (ALD) and concomitant exocrine pancreatic disease is important, as nutrition in liver disease is crucial.[20] Despite this, there have only been a few small studies examining this relationship. Furthermore, the diagnostic tests used have varied between studies, resulting in a wide range of prevalence estimates. Two studies using direct intubation tests (involving endoscopic intubation of the pancreatic duct) showed that concomitant pancreatic disease occurred in 5/32 (15.6%) and 1/26 (3.8%) of patients with ALD, respectively.[21 22] A study of 60 patients with liver cirrhosis, of which 35 were due to alcohol, showed that 18/60 (30%) had imaging changes consistent with CP.[23] Another study examining FEL-1 levels in patients with ALD reported PEI in 7% of patients.[24]

None of these studies reported intervention with PERT and only two presented GI symptoms that might be relevant. This area is important, but there is a large gap in the data, meaning that the benefit of routine testing and treatment is unknown.

Table S2. Other causes of loose stools in patients with PEI despite PERT (see **table 5** in the main manuscript)

Cause	Investigation and treatment
SBBO	Investigated using a glucose hydrogen breath test. Ideally this should give values for both hydrogen and methane, but some centres only measure hydrogen. A rise of exhaled hydrogen of >20ppm is suggestive. This is not usually performed if the person has taken antibiotics in the last 4 weeks. Treatment for a positive result is antibiotics
BAM	Investigated using a SeHCAT scan, which requires two visits to the nuclear medicine department 7 days apart. Treatment for a positive result is with bile acid sequestrants
Infection	Investigated with a stool sample and usually treated with antibiotics
Coeliac disease	Consider a serum tissue transglutaminase and /or duodenal biopsy (biopsy not necessary if TTG > 10 x upper normal limit.[25] Patient must be eating adequate gluten (equivalent to 4 slices of bread a day) for the 4 weeks prior to their test for a negative result to be accurate. Treatment for a positive result consists of a strict gluten-free diet
Lactase deficiency	Investigated with a breath test. Treatment for a positive result consists of removing intake of lactose from foods, drinks and medication
Other food intolerances	Investigated with an exclusion diet under the guidance of a specialist dietitian. Treatment involves avoidance of trigger foods
IBS-D	Can be treated with a low FODMAP diet under the guidance of a specialist dietitian.
No other cause identified	Anecdotally, some patients have fewer side effects and increased efficacy with one brand of PERT than another. Therefore, it is helpful for a patient to trial another brand of PERT if no other cause of the symptoms can be identified

BAM, bile acid malabsorption; IBS-D, diarrhoea-predominant irritable bowel syndrome; PERT, pancreatic enzyme replacement therapy; SBBO, small bowel bacterial overgrowth; SeHCAT, selenium homocholic acid taurine

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