Anorexia nervosa and pancreatitis

Abstract

Acute pancreatitis is a condition whereby erroneous activation of trypsin and zymogen results in pancreatic autodigestion. There are many aetiologies, with alcohol intake and gallstones being the most common. Anorexia nervosa is an eating disorder in which patients' reduced food intake and psychological aversion of weight gain can result in low body weight and malnourishment. The link between pancreatitis and anorexia nervosa is not well understood; this article explores the theorised pathophysiology connecting the two conditions, as well as the optimal management of patients when the conditions co-exist based on current literature.

A literature search was performed using MEDLINE, EMBASE and CINAHL databases for all journal articles on the topic of presentations of acute or chronic pancreatitis in adults with anorexia nervosa.

The literature proposes various links between anorexia nervosa and pancreatitis. It is theorised that pancreatitis may arise as a result of malnourishment itself or secondary to the refeeding process. Some explanations focus on the histopathological changes to the pancreas that malnourishment induces, while others focus on the enzymatic changes and oxidative damage that arise in the malnourished state. More mechanical mechanisms such as gastric dilatation, gastrointestinal ileus and compartmental fluid shift during refeeding have also been proposed as explanations for the link between the conditions. Some medications used in the management of anorexia nervosa have also been linked to pancreatitis.

Key words: Anorexia; Anorexia nervosa; Acute pancreatitis; Chronic pancreatitis; Eating disorders; Pancreatitis

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Introduction

Acute pancreatitis is an inflammatory process in which erroneous activation of trypsin with consequent activation of zymogen results in a process of autodigestion within the pancreas (Wang et al, 2009). This can progress to severe pancreatitis in which an episode of acute pancreatitis is associated with a systemic inflammatory response syndrome, pancreatic necrosis and/or multiple organ failure. Pancreatitis resolves without major complication in the majority of examples but can also result in prolonged hospital stays, with critical care involvement in 20–30% of cases (Portelli and Jones, 2017).

There are many possible causative factors for acute pancreatitis, with alcohol use (36%) and gallstones resulting in obstruction of the common bile duct or pancreatic duct (38%) some of the most common causes in developed countries (Spanier et al, 2008). Less common causes include endoscopic retrograde cholangiopancreatography, certain medications, hypercalcaemia, elevated triglyceride levels, autoimmune damage and trauma (Van Dijk et al, 2017). In approximately 20% of cases, no cause is found. The aetiology in these instances is believed to be from occult biliary sludge or microlithiasis (Portelli and Jones, 2017).

Clinical presentation is varied but typically involves a sudden onset of epigastric pain which radiates to the back. Patients may also present with abdominal distension, nausea, vomiting or diarrhoea. Clinical signs include tachycardia, tachypnoea, fever, abdominal tenderness and guarding on examination. In some cases, patients may also be haemodynamically unstable and jaundiced. Respiratory compromise can be driven by systemic inflammatory response syndrome, resulting in acute respiratory distress syndrome (Shah et al, 2018).

Diagnosis is based upon a history consistent with the abdominal pain typical of pancreatitis, serum lipase or amylase levels, which are elevated by a factor of three above the upper limit of normal as well as imaging (ultrasound, computed tomography or magnetic

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resonance imaging) that is consistent with pancreatitis (Shah et al, 2018). It is important to note that baseline levels of amylase and lipase can be elevated in some forms of anorexia.

Histologically, pancreatitis is characterised by a necro-inflammatory reaction to the damage of the acinar cells (functional or structural). Necrosis of fatty tissue can also be seen. If the damage of the exocrine cells of the pancreas progresses to necrosis, this delineates the severe subcategory from the more mild forms of pancreatitis, which are typically associated with interstitial oedema (Trepte et al, 2013).

Anorexia nervosa is defined as an eating disorder characterised by a low body weight as a result of restricted food intake or persistent behaviours that affect weight gain, as well as an intense fear of gaining weight that ultimately leads to malnutrition. The cause of anorexia nervosa is not fully understood, although a variety of factors are thought to be involved including genetics, environmental and social influences. Anorexia nervosa is significantly more prevalent in women and primarily affects 15–19-year-olds. The lifetime prevalence of anorexia nervosa in women is between 2 and 4%. Complications can include psychological and emotional disturbances, social and relationship difficulties and a wide variety of physical abnormalities. This review focuses on the link between anorexia nervosa and pancreatitis (National Institute for Health and Care Excellence, 2017).

The scarcity of research into the presentation of pancreatitis in patients with anorexia nervosa limits the literature to fewer than 20 case reports, case series and published papers. The majority of the literature on these two conditions comprises case reports published over the last 60 years. This article reviews the literature and presents comparative aetiologies for a link between anorexia nervosa and acute pancreatitis, as well as discussing subsequent management options.

Method

A literature search was performed using MEDLINE, EMBASE and CINAHL databases for all journal articles on the topic of acute or chronic pancreatitis presentations in patients with anorexia nervosa or eating disorders. Key words used were anorexia, anorexia nervosa, pancreatitis, eating disorders. Case reports and case series with or without systematic reviews in adult human patients were eligible for inclusion. Exclusion criteria included articles not written in the English language that were unable to be translated. There was no limit in terms of publication date. No additional references were obtained by hand searching the literature. In total 103 articles were identified and screened for exclusion criteria and duplication, of which 10 were included within this review (four case reports, two systematic reviews and four literature reviews). **Figure 1** shows the identification, screening and inclusion process for the selection of studies.

Discussion

The link between anorexia nervosa and pancreatitis is currently not well understood, but a number of mechanisms have been proposed for the relationship. These are based around chronic starvation, malnutrition, the refeeding process and some of the pharmacotherapies used in the management of anorexia nervosa. In the absence of the more common aetiologies of pancreatitis (gallstones, alcohol, metabolic causes), eating disorders should be actively considered as an idiopathic cause.

Effects of chronic starvation on the gastrointestinal tract and pancreas

Chronic starvation and malnutrition, as seen in anorexia nervosa, causes a significant delay in gastric motility, gastric emptying and intestinal tract transit (Norris et al, 2016; Santonicola et al, 2019). In a malnourished state, the body is under an increased amount of oxidative stress which promotes inflammation. This increases the activation of trypsinogen, resulting in enzyme-mediated inflammation and cell damage within the pancreas (Morris et al, 2004). According to the literature, awareness of the association between anorexia nervosa and the development of pancreatitis can result in prompt diagnosis and management, despite the exact mechanism remaining unclear.

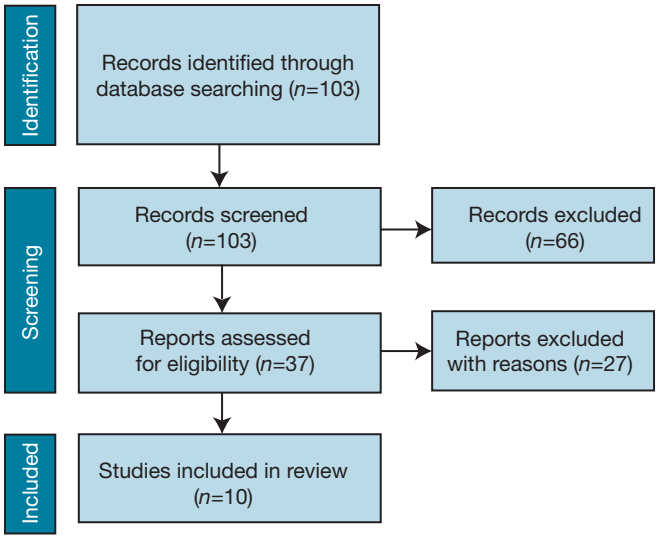

Figure 1. PRISMA flow diagram outlining selection of studies.

Proposed mechanisms for the development of pancreatitis in people with anorexia nervosa

It has been postulated that either chronic malnutrition or refeeding after periods of prolonged malnutrition can lead to pancreatitis through several pathological mechanisms (Brooks and Golden, 1992; Morris et al, 2004). Histological studies looking at the effect of malnutrition on the pancreas have suggested an increase in pancreatic acinar cell atrophy and an increase in zymogen granule release, leading to pancreatic tissue damage (Pitchumoni, 1973; Brooks and Golden, 1992; Sandhyamani et al, 1999; El-Hodhod et al, 2005). Continually high trypsinogen levels seen in malnourished patients may trigger the inflammatory response through activation of protease enzymes, ultimately causing cell damage and pancreatic duct obstruction (Cleghorn et al, 1991; de Kolster et al, 1991; Briars et al, 1998). Furthermore, anorexia nervosa may lead to pancreatitis through mechanisms involving oxidative damage within a system of poor antioxidant reserves (Moyano et al, 1999), or through inflammatory damage as a result of elevated levels of cytokines interleukin-1, interleukin-6 and tumour necrosis factor-alpha (Allende et al, 1998; Dülger et al, 2002; Azevedo et al, 2005). These result in the activation of pancreatic stellate cells with persistent inflammation and fibrosis, leading to chronic pancreatitis (Mądro et al, 2004; Wesson et al, 2008).

Studies have also implied the involvement of more mechanical factors, suggesting that both chronic malnutrition and the process of refeeding after a period of prolonged starvation can cause gastrointestinal ileus and gastric dilatation. This is referred to as enteroptosis and causes an increase in retrograde pressure, forcing duodenal contents into the pancreatic duct. This prevents the release of pancreatic enzymes which leads to pancreatic autolysis (Keane et al, 1978; Backett, 1985; Winter et al, 2001).

Other studies have highlighted an alternate link between acute gastric dilatation and pancreatitis in patients with anorexia nervosa. It is speculated that superior mesenteric artery syndrome, which can develop secondary to anorexia nervosa (Verhoef and Rampal, 2009; Johnson and Paladugu, 2019), can link the two conditions as a result of duodenal compression by the enlarged superior mesenteric artery, causing gastric dilatation. This can result in increased duodenal pressures causing retrograde passage of duodenal contents into the pancreatic duct and thus pancreatitis (Keane et al, 1978; Backett, 1985). Bargiacchi et al (2019) suggested that, during the refeeding process, ischaemic injury to the pancreas may also occur with fluid shifts and cardiac compromise which may subsequently result in pancreatitis.

Pancreatitis in the course of anorexia nervosa may also be associated with pharmacotherapy, specifically tricyclic antidepressants. It has been suggested in previous literature that sertraline may be associated with the development of pancreatitis in patients with anorexia nervosa, but this was deemed not to be the case following a comprehensive review by the World Health Organization adverse events database (Spigset et al, 2003; Malbergier and De Oliveira, 2004).

Ultimately, the proposed pathogenesis of pancreatitis in anorexia nervosa remains speculative. It can be argued that anorexia may derange normal pancreatic function, either precipitating an episode of acute pancreatitis, or rendering these patients in a prolonged state of low grade chronic pancreatitis.

Typical manifestation of pancreatitis in people with anorexia nervosa

Typically, pancreatitis in people with anorexia nervosa manifests either during periods of malnutrition or during the early refeeding stages. It is characterised by epigastric pain which radiates posteriorly and is accompanied by nausea and vomiting. This is accompanied by elevated levels of the pancreatic enzymes, amylase and lipase, although baseline levels of these enzymes may already be elevated in people with anorexia nervosa. Starvation leads to the dysfunction of all body systems and organs, but patients with anorexia nervosa often complain of digestive ailments, such as abdominal pain, post-prandial fullness, nausea, bloating and constipation as part of the disease course. These common gastric complaints may hinder both the initial diagnosis of pancreatitis and the nutritional treatment of anorexia nervosa. Patients looking for an organic cause of their low body mass index may use these symptoms as justification for their aversion to eating (Malczyk and Oświęcimska, 2017). Patients who present with recurrent gastrointestinal symptoms, specifically recurrent epigastric pain, in conjunction with a low body mass index or evidence of malnutrition, should be investigated for pancreatic pathology.

Management of pancreatitis in people with anorexia nervosa

The nature of pancreatic insult in people with anorexia nervosa ranges from asymptomatic to life-threatening. Earlier recognition allows for earlier intervention, such as fluid rehydration which is associated with improved outcomes (Gardner et al, 2008; Wall et al, 2011). In acknowledging that the gastrointestinal complaints often associated with anorexia nervosa can overlap and potentially mask the symptoms of pancreatitis, it is important for clinicians to have a high index of suspicion when dealing with these patients. This vigilance can prevent poor patient outcomes, critical care admissions and prolonged hospital stays with associated morbidities.

In the majority of cases, pancreatic exocrine function appears to resume with nutritional rehabilitation (Backett, 1985; Morris et al, 2004). Generally, there is significant evidence to support early enteral nutrition in all patients with acute pancreatitis to maintain the mucosal integrity of the gastrointestinal tract, prevent bacterial translocation and subsequent infection of sterile pancreatic necrosis, although the optimal timing of when to initiate refeeding remains unclear (Barbezat and Hansen, 1968; Zhao et al, 2015). Early tube enteral refeeding has also been proven to reduce short-term morbidity and mortality (Zhao et al, 2015). Owing to the reduction in levels of digestive enzymes, gastric complaints are common in patients with anorexia nervosa, including early satiety, nausea, dysphagia, bloating and constipation, which may hinder nutritional rehabilitation (Malczyk and Oświęcimska, 2017).

Refeeding too rapidly, both orally and parenterally, in malnourished patients can result in refeeding syndrome, characterised by severe fluid and electrolyte shifts and the resultand metabolic implications. It is important to note that ischaemic injury to the pancreas can also occur as a result of this, leading to pancreatitis caused by the refeeding process itself. Guidelines suggest that nutrition should be increased gradually to prevent refeeding syndrome. More recent publications have suggested that limiting the amount of energy supplied at the beginning of nutritional rehabilitation does not reduce the risk of refeeding syndrome, although specific guidelines with regards to refeeding are scarce (Allende et al, 1998; Kohn et al, 2011; Bargiacchi et al, 2019).

Effective care of patients with anorexia nervosa often requires involvement of a multidisciplinary team, such as psychiatry, psychology and nutritional teams (Malczyk and Oświęcimska, 2017). Timely involvement of gastroenterology, general surgery and critical care teams is also advisable in cases where pancreatitis is suspected. Despite early diagnosis and determination of aetiology, a successful outcome is heavily dependent on the patient's compliance with treatment, their resilience and physiological reserve.

Key points

- Pancreatitis is a life-threatening condition that requires early recognition, intervention and management.
- Gastrointestinal symptoms are common in patients with anorexia nervosa, so the warning signs for pancreatitis can be missed, resulting in delayed diagnosis and poor outcomes.
- The severity of pancreatitis in anorexia nervosa can be increased as a result of poor physiological reserve, malnutrition and chronic starvation which can result in critical care admission and prolonged hospital stays.
- Early enteral nutrition and monitoring for refeeding syndrome is key in this patient cohort.
- Early involvement of the multidisciplinary team is advised to ensure optimal patient outcomes.

Conclusions

Pancreatitis is a potentially life-threatening condition where patient outcomes are inextricably linked with early recognition and intervention. Various mechanisms to link pancreatitis with anorexia nervosa have been postulated but the pathophysiology remains speculative. In people with anorexia nervosa, gastrointestinal complaints are common so symptoms of pancreatitis may be masked, resulting in a delayed diagnosis and poor outcomes. This reinforces the importance of clinicians having a high index of suspicion in this patient group. The risk of delayed diagnosis coupled with a reduced physiological reserve, as a result of malnutrition and chronic starvation, can increase the severity of pancreatitis for patients with anorexia nervosa resulting in longer hospital stays and critical care admissions. Early enteral nutrition is key to preventing complications in patients with pancreatitis. This can be difficult in patients with anorexia because of their psychological aversion to eating and reduced levels of digestive enzymes leading to gastrointestinal complications during the refeeding process. Refeeding syndrome is a complication that occurs more readily in malnourished patients, so the input of a specialist nutritional team forms a key part of their care. Pancreatitis is more difficult to recognise, treat and manage in patients with anorexia nervosa, so early recognition, early refeeding and management under an experienced multidisciplinary team is needed to ensure optimal patient outcomes.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

References

Allende LM, Corell A, Manzanares J et al. Immunodeficiency associated with anorexia nervosa is secondary and improves after refeeding. Immunology. 1998;94(4):543–551. https://doi.org/10.1046/j.1365-2567.1998.00548.x

Azevedo ZMA, Luz RA, Victal SH et al. Increased production of tumor necrosis factor-α in whole blood cultures from children with primary malnutrition. Braz J Med Biol Res. 2005;38(2):171–183. https://doi.org/10.1590/S0100-879X2005000200005

Backett SA. Acute pancreatitis and gastric dilatation in a patient with anorexia nervosa. Postgrad Med J. 1985;61(711):39–40. https://doi.org/10.1136/pgmj.61.711.39

Barbezat GO, Hansen JDL. The exocrine pancreas and protein-calorie malnutrition. Pediatrics. 1968;42(1):77–92

Bargiacchi A, Clarke J, Paulsen A, Leger J. Refeeding in anorexia nervosa. Eur J Pediatr. 2019;178(3):413–422. https://doi.org/10.1007/s00431-018-3295-7

Briars GL, Thornton SJ, Forrest Y et al. Malnutrition, gastroenteritis and trypsinogen concentration in hospitalised aboriginal children. J Paediatr Child Health. 1998;34(1):69–73. https://doi.org/10.1046/j.1440-1754.1998.00157.x

Brooks SE, Golden MH. The exocrine pancreas in kwashiorkor and marasmus. Light and electron microscopy. West Indian Med J. 1992;41(2):56–60

Cleghorn GJ, Greer R, Holt TL et al. Exocrine pancreatic dysfunction in malnourished Australian Aboriginal children. Med J Aust. 1991;154(1):45–48. https://doi.org/10.5694/j.1326-5377.1991.tb112850.x

de Kolster CC, Kolster JG, Rached I et al. Serum cationic trypsinogen: marker of exocrine pancreatic dysfunction in children with protein-calorie malnutrition. GEN. 1991;45(2):92–97

Dülger H, Arik M, Şekeroğlu MR et al. Pro-inflammatory cytokines in Turkish children with protein-energy malnutrition. Mediators Inflamm. 2002;11(6):363–365. https://doi.org/10.1080/0962935021000051566

El-Hodhod MA, Nassar MF, Hetta OA, Gomaa SM. Pancreatic size in protein energy malnutrition: a predictor of nutritional recovery. Eur J Clin Nutr. 2005;59(4):467–473. https://doi.org/10.1038/sj.ejcn.1602053

Gardner TB, Vege SS, Pearson RK, Chari ST. Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol. 2008;6(10):1070–1076. https://doi.org/10.1016/j.cgh.2008.05.005

Johnson BM, Paladugu G. Superior mesenteric artery syndrome secondary to anorexia nervosa and methamphetamine use. Cureus. 2019;11(11):e6121. https://doi.org/10.7759/cureus.6121

Keane FBV, Fennell JS, Tomkin GH. Acute pancreatitis, acute gastric dilation and duodenal ileus following refeeding in anorexia nervosa. Irish J Med Sci. 1978;147(1):191–192. https://doi.org/10.1007/BF02939399

Kohn MR, Madden S, Clarke SD. Refeeding in anorexia nervosa: increased safety and efficiency through understanding the pathophysiology of protein calorie malnutrition. Curr Opin Pediatr. 2011;23(4):390–394. https://doi.org/10.1097/MOP.0b013e3283487591

Mądro A, Celiński K, Stomka M. The role of pancreatic stellate cells and cytokines in the development of chronic pancreatitis. Med Sci Monit. 2004;10(7):166–171

Malbergier A, De Oliveira HP. Sertraline and acute pancreatitis: a case-report. Rev Bras Psiquiatr. 2004;26(1):39–40. https://doi.org/10.1590/s1516-44462004000100011

Malczyk Ż, Oświęcimska J. Gastrointestinal complications and refeeding guidelines in patients with anorexia nervosa. Psychiatr Pol. 2017;51(2):219–229. https://doi.org/10.12740/PP/65274

Morris LG, Stephenson KE, Herring S, Marti JL. Recurrent acute pancreatitis in anorexia and bulimia. JOP. 2004;5(4):231–234

Moyano D, Sierra C, Brandi N et al. Antioxidant status in anorexia nervosa. Int J Eat Disord. 1999;25(1):99–103. https://doi.org/10.1002/(SICI)1098-108X(199901)25:1<99::AID-EAT12>3.0.CO;2-N

National Institute for Health and Care Excellence. Eating disorders: recognition and treatment. 2017. www.nice.org.uk/guidance/ng69 (accessed 8 November 2021)

Norris ML, Harrison ME, Isserlin L et al. Gastrointestinal complications associated with anorexia nervosa: a systematic review. Int J Eat Disord. 2016;49(3):216–237. https://doi.org/10.1002/eat.22462

Pitchumoni CS. Pancreas in primary malnutrition disorders. Am J Clin Nutr. 1973;26(3):374–379. https://doi.org/10.1093/ajcn/26.3.374

Portelli M, Jones CD. Severe acute pancreatitis: pathogenesis, diagnosis and surgical management. Hepatobiliary Pancreat Dis Int. 2017;16(2):155–159. https://doi.org/10.1016/S1499-3872(16)60163-7

Sandhyamani S, Vijayakumari A, Balaraman Nair M. Bonnet monkey model for pancreatic changes in induced malnutrition. Pancreas. 1999;18(1):84–95. https://doi.org/10.1097/00006676-199901000-00011

Santonicola A, Gagliardi M, Guarino MPL et al. Eating disorders and gastrointestinal diseases. Nutrients. 2019;11(12):3038. https://doi.org/10.3390/nu11123038

Shah AP, Mourad MM, Bramhall SR. Acute pancreatitis: current perspectives on diagnosis and management. J Inflammation Res. 2018;11:77–85. https://doi.org/10.2147/JIR.S135751

Spanier BWM, Dijkgraaf MGW, Bruno MJ. Epidemiology, aetiology and outcome of acute and chronic pancreatitis: an update. Best Pract Res Clin Gastroenterol. 2008;22(1):45–63. https://doi.org/10.1016/j.bpg.2007.10.007

Spigset O, Hägg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors. Int Clin Psychopharmacol. 2003;18(3):157–161. https://doi.org/10.1097/01.yic.0000066455.73432.d2

Trepte CJC, Bachmann KA, Stork JH et al. The impact of early goal-directed fluid management on survival in an experimental model of severe acute pancreatitis. Intensive Care Med. 2013;39(4):717–726. https://doi.org/10.1007/s00134-012-2775-x

Van Dijk SM, Hallensleben NDL, Van Santvoort HC et al. Acute pancreatitis: recent advances through randomised trials. Gut. 2017;66(11):2024–2032. https://doi.org/10.1136/gutjnl-2016-313595

Verhoef PA, Rampal A. Unique challenges for appropriate management of a 16-year-old girl with superior mesenteric artery syndrome as a result of anorexia nervosa: a case report. J Med Case Rep. 2009;3(1):1–5. https://doi.org/10.1186/1752-1947-3-127

Wall I, Badalov N, Baradarian R et al. Decreased mortality in acute pancreatitis related to early aggressive hydration. Pancreas. 2011;40(4):547–550. https://doi.org/10.1097/MPA.0b013e318215368d

Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. World J Gastroenterol. 2009;15(12):1427–1430. https://doi.org/10.3748/wjg.15.1427

Wesson RN, Sparaco A, Smith MD. Chronic pancreatitis in a patient with malnutrition due to anorexia nervosa. JOP. 2008;9(3):327–331

Winter TA, Marks T, Callanan M, O'Keefe SJD, Bridger S. Impaired pancreatic secretion in severely malnourished patients is a consequence of primary pancreatic dysfunction. Nutrition. 2001;17(3):230–235. https://doi.org/10.1016/S0899-9007(00)00575-X

Zhao XL, Zhu SF, Xue GJ et al. Early oral refeeding based on hunger in moderate and severe acute pancreatitis: a prospective controlled, randomized clinical trial. Nutrition. 2015;31(1):171–175. https://doi.org/10.1016/j.nut.2014.07.002