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NEGOTIATING THE COMPLEXITIES OF EXOCRINE AND ENDOCRINE DYSFUNCTION IN CHRONIC PANCREATITIS

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Abstract:

Chronic pancreatitis is a chronic inflammatory disease of the pancreas characterized by irreversible morphological change and typically causing pain and/or permanent loss of function. This progressive, irreversible disease results in destruction of healthy pancreatic tissue and the development of fibrous scar tissue. Gradual loss of exocrine and endocrine function follows, along with clinical manifestations such as steatorrhoea, abdominal pain and diabetes. It is often asserted that >90 % of the pancreas must be damaged before exocrine insufficiency occurs; however, an exploration of the original studies from the 1970s found that the data do not support this assertion. The management of steatorrhoea with pancreatic enzyme replacement therapy is the mainstay of nutritional management, and early identification and treatment is a key. The presence of steatorrhoea, coupled with poor dietary intake (due to intractable abdominal pain, gastrointestinal side effects and often alcoholism) renders the chronic pancreatitis patients at considerable risk for undernutrition, muscle depletion and fat-soluble vitamin deficiency.

Keywords: *Chronic pancreatitis, Nutrition, vitamin deficiency, Exocrine insufficiency, Endocrine insufficiency, Diabetes*

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INTRODUCTION:

Chronic pancreatitis is a debilitating condition, where the pathology and management are often overlooked in favour of the more recognisable acute form of the disease. Chronic pancreatitis is a slow, irreversible process characterised by pancreatic parenchymal loss, fibrosis and possible calculus formation.Its principal etiological factor in Western countries is the consumption of alcohol. Despite a distinctly different pathogenesis, many cases of acute pancreatitis harbour underlying chronic pancreatitis. Thus, effective management is often compromised as the only interface such patients have with the health system is in an acute context, typically consisting of admission to a surgical unit.

Chronic pancreatitis, first and foremost, presents a diagnostic dilemma. If defined in strictly histological terms, the gold standard test would be a pancreatic biopsy; but this is not feasible or safe for diagnostic work-up in clinical practice. The radiological gold standard diagnostic test has been endoscopic retrograde cholangiopancreatography (ERCP), but this can no longer be justified for purely diagnostic purposes because of potential risks. Other morphologically based investigations, such as magnetic resonance cholangiopancreatography (MRCP)and endoscopic ultrasound (EUS), are better alternatives. Various functional tests, largely based on the premise that exocrine insufficiency is a proxy for parenchymal damage, are also possible. The most readily available and practicable of these is the faecal elastase-1 concentration, which requires collection of a random stool sample.

Review:

Malabsorption:

Destruction of the pancreatic acinar cells results in a decrease in the production and secretion of pancreatic enzymes. This leads to malabsorption of macronutrients and micronutrients, severe and distressing gastrointestinal symptoms, and if untreated, nutrient deficiency and undernutrition. Lipase is particularly vulnerable to destruction, and therefore malabsorption of fat is especially problematic and clinically evident. Malabsorption is exacerbated by precipitation of bile acids and impaired gastric emptying. Excretion of abnormal amounts of fat in the faeces (steatorrhoea) occurs, and fat loss of >15 g/d is considered severe. Exocrine impairment (termed pancreatic exocrine insufficiency (PEI)) may be measured directly by intubating the duodenum and measuring lipase output following hormonal stimulation. However, this invasive technique is rarely performed outside of specialist research centres. Therefore, indirect methods of measuring PEI are required, including measurement of faecal fat, measurement of the enzyme faecal elastase-1 or in some cases, evidence of pathological pancreatic function along with clinical signs of malabsorption. Symptoms of PEI include fatty diarrhoea (pale, bulky stools that are difficult to flush), bloating, abdominal cramping, flatulence and abdominal pain with dyspepsia. However, PEI may still exist even in the absence of obvious clinical symptoms. The gold standard treatment of PEI is the administration of exogenous enzymes (pancreatic enzyme replacement therapy, which reduce fat malabsorption thereby helping to achieve normal nutritional status. It is believed that 90 % of the pancreas must be destroyed before malabsorption occur. . Microbes in the human gut play a vital role in the balance between health and disease. Dysbiosis has been linked to the activation of inflammatory cytokines in several inflammatory-mediated diseases. Associations between dysbiosis and coeliac disease, irritable bowel disease and inflammatory bowel disease have been described; however, there are few studies for chronic pancreatitis, or for pancreatic disease in general. Only a few studies have examined a link between alterations in intestinal microbiota and chronic pancreatitis. However, in these limited studies, some tentative patterns are apparent. A higher level of Bacteroidetes and a lower level of Faecalibacteria were found in diabetic chronic pancreatitis patients v. non-diabetic patients. Lower levels of Bifidobacteria were found in diabetic patients with PEI, compared with those with intact exocrine function. One study found lower levels of Bifidobacteria and Lactobacillus in patients with chronic pancreatitis, along with higher levels of Escherichia coli, Enterococcus faecalis and Enterococcus faecium. Another study also reported decreased levels of Lactobacillus and Bifidobacterium. Bifidobacteria and Lactobacilli belong to the lactic acid bacteria group and are considered to be health enhancing, with the former believed to relieve diarrhoea and malabsorption, produce SCFA (including acetate, propionate and butyrate), reduce luminal pH (inhibiting pathogenic micro-organisms) and increase the absorption of some nutrients. Therefore, based on a limited number of studies, decreased levels of Bifidobacteria in chronic pancreatitis may be clinically relevant.

Nutrient deficiency:

The prevalence of biochemical vitamin deficiency in chronic pancreatitis differs widely between studies and between countries, and individual studies vary greatly regarding quality. Vitamin A deficiency in chronic pancreatitis was reportedly as low as 3 % (the Netherlands) and as high as 40 % (Japan). For

vitamin E deficiency, which should be measured as a ratio of blood lipid, prevalence varied from 25 % (Ireland) to about 75 % (South Africa) of patients with chronic pancreatitis . There is some evidence that vitamin E deficiency is more prevalent in chronic pancreatitis patients with steatorrhoea. Regarding vitamin K, no study has measured this vitamin using the recommended methods; either undercarboxylated osteocalcin or proteins of vitamin K absence. Measurement of serum vitamin K or prothrombin time is inaccurate; therefore, the occurrence of vitamin K deficiency in chronic pancreatitis is unknown. Of the fatsoluble vitamins, serum 25-hydroxyvitamin D (25OHD) deficiency has been the most studied; however, prevalence varies greatly, largely depending on the definitions of deficiency used.

Chronic systemic infection:

Irrespective of the aetiology of chronic pancreatitis, the end result is the same. Inflammation destroys pancreatic tissue leading to pancreatic fibrosis, and ultimately, impairment of pancreatic function. Chronic pancreatitis is also associated with accelerated biological ageing, with premature death (patients typically die 8 years earlier than age- and sex-matched controls). Death is due to a higher occurrence of diseases such as diabetes, cerebrovascular disease, pulmonary disease, ulcer disease and renal disease. Inflamaging is characterised by elevated proinflammatory cytokines (IL6, IL4, TNF, T-cell factor-β, IL8) and lower anti-inflammatory cytokines (including IL10). Systemic inflammation in chronic pancreatitis (exacerbated by a chronically poor diet, smoking and malabsorption) results in an aged phenotype, specifically osteoporosis and sarcopenia . To date, there has been little research on sarcopenia in chronic pancreatitis.

Bone health and Osteoporosis:

Osteoporosis is a major concern in chronic pancreatitis. Bone demineralization is caused by poor dietary intake, malabsorption, 25OHD deficiency, low physical activity, heavy smoking and is likely to be driven by chronic systemic inflammation. The first study that reported osteoporosis in this disease was an uncontrolled study published in 1997, reporting on just fourteen patients. Since then, there have been many studies (most in the past few years) showing that osteoporosis and osteopenia occur frequently and prematurely in chronic pancreatitis. We performed a systematic review and meta-analysis of many studies and reported that in a pooled sample of 513 patients, a quarter had osteoporosis and 65 % had either osteoporosis or osteopenia. However, only two studies from the meta-analysis provided usable control data, with an osteoporosis prevalence among healthy controls of 8·6– 10·2 % . This review showed that there was some association with PEI with some (but not all) studies reporting an association between low bone mineral density and fat malabsorption. There was no apparent relationship between osteoporosis and serum 25OHD in chronic pancreatitis, likely to be due to the variable definitions for vitamin D deficiency, as well as seasonal differences in measurement. Since then, several studies have shown that low bone mineral density translates into a real risk of atraumatic fracture. In a population-based study from Denmark, there was a higher fracture rate among chronic pancreatitis than controls, with an adjusted hazard ratio of 1·7 (95 % CI 1·6, 1·8). A US study similarly found that the risk of fracture in chronic pancreatitis (4·8 %) was similar, or higher, than in comparable gastrointestinal disorders such as celiac disease (5 %), Crohn's disease (3 %), post-gastrectomy (5·4 %) and cirrhosis (4·8 %) . The rate for healthy controls was 1·1 %. Notably patients with chronic pancreatitis do not have the additional risk factors of long-term steroid use or hypogonadism that drive bone demineralisation in other gastrointestinal conditions; therefore, the comparably high rates of osteoporosis and fracture in this disease are unexpected.

Endocrine Insufficiency:

The subgroup of diabetes mellitus that occurs in conjunction with diseases of the exocrine pancreas is termed type 3c diabetes (or pancreatogenic diabetes) . Type 3c diabetes tends to be misclassified, usually as type 2 diabetes; however, there are important clinical and metabolic factors, which distinguish type 3c diabetes from other diabetes types. Due to its association with pancreatic disease, patients with type 3c diabetes tend to be undernourished and have nutrient deficiencies. Management is complicated by malabsorption, excess alcohol intake (for some) and poor dietary intake (due to chronic abdominal pain, anorexia, heavy smoking and/or symptom avoidance). As well as low insulin levels, patients with type 3c diabetes will have reduced glucagon secretion from the pancreatic α-cells and lower levels of pancreatic polypeptide. A reduction in pancreatic polypeptide can contribute to decreased hepatic insulin sensitivity and unsuppressed hepatic glucose production. Together, these factors lead to the characteristically 'brittle' diabetes that is difficult to control, with erratic swings in blood glucose levels from hypoglycemia to hyperglycemia. Research into type 3c diabetes is lacking in general, and in fact patients with this diabetes subgroup tended to be specifically excluded from major diabetes studies. Several recent publications have drawn attention to

type 3c diabetes; however, clinical management guidelines remain scarce, those that exist have tended to draw from studies on type 1 and type 2 diabetes (in the absence of type 3c-specific data) . Nevertheless, type 3c diabetes is not uncommon. It is thought that about 8 % of all diabetes cases may be type 3c diabetes . In chronic pancreatitis, the prevalence is higher in heavy smokers, those who have had a distal pancreatectomy (due to the high concentration of islets cells in the tail), those with longer duration of disease and those with pancreatic calcifications.

Modifiable risk factors	Non-modifiable risk factors
Undernutrition (low BMI, low muscle mass/sarcopenia)*	Increasing age
Malabsorption/pancreatic exocrine insufficiency (especially if undertreated or poorly managed)*	Female sex
Poor diet (vitamin D and/or calcium intake; overall quality and quantity of diet)*	History of previous low trauma fracture
Low serum 25OHD*	Family history of osteoporosis
Smoking	
Poor mobility/low physical activity levels	
Chronic inflammatory state (potentially modifiable)	

CONCLUSION:

Efforts should be made to understand the potential relationship between the microbiome and inflammation in chronic pancreatitis and to explore the potential for therapeutic agents that may modulate the disease process and improve outcomes. Ultimately, the potential to ameliorate the inflammatory process by dietary or pharmacological means may open up new therapeutic avenues. By addressing these substantial research gaps through the establishment of well-funded, high-quality, multidisciplinary, multicentre studies, we may begin to achieve real clinical benefits for patients with this neglected disease.

REFERENCES:

1.Conwell, DL, Lee, LS, Yadav, D et al. (2014) American pancreatic association practice guidelines in chronic pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas* 43, 1143–1162.

2. Working Party of the Australasian Pancreatic Club, Smith, RC, Smith, SF et al. (2016) Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. *Pancreatology* 16, 164–180

3. de-Madaria, E, Abad-González, A, Aparicio, JR et al. (2013) The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). *Pancreatology* 13, 18–28

4. Hoffmeister, A, Mayerle, J, Beglinger, C et al. (2015) English language version of the S3-consensus guidelines on chronic pancreatitis: definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. *Z Gastroenterol* 53, 1447–1495

5.Spanier, BWM, Dijkgraaf, MGW & Bruno, MJ (20 08) Epidemiology, aetiology and outcome of acute and chronic pancreatitis: an update. *Best Pract Res Clin Gastroenterol* 22, 45–63

6.Midha, S, Singh, N, Sachdev, V et al. (2008) Cause and effect relationship of malnutrition with idiopathic chronic pancreatitis: prospective case-control study. *J Gastroenterol Hepatol* 23, 1378–1383.

7.Imoto, M & DiMagno, EP (2000) Cigarette smoking increases the risk of pancreatic calcification in late-onset but not early-onset idiopathic chronic pancreatitis. *Pancreas* 21, 115–119.

8.Lin, Y, Tamakoshi, A, Hayakawa, T et al. (2000) Cigarette smoking as a risk factor for chronic pancreatitis: a case-control study in Japan. Research committee on intractable pancreatic diseases. *Pancreas* 21, 109–114

9. Pitchumoni, CS (2000) Does cigarette smoking cause chronic pancreatitis? *J Clin Gastroenterol* 31, 274–275

10.NíChonchubhair, HM, Bashir, Y, McNaughton, D et al. (2017) Hospital discharges and patient activity associated with chronic pancreatitis in Ireland 2009–2013. *Pancreatology* 17, 56–62.

11.Díte, P, Starý, K, Novotný, I et al. (2001) Incidence of chronic pancreatitis in the Czech Republic. *Eur J Gastroenterol Hepatol* 13, 749–750

12. de la Iglesia-García, D, Huang, W, Szatmary, P et al. (2016) Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis.

13.Thorat, V, Reddy, N, Bhatia, S et al. (2012) Randomised clinical trial: the efficacy and safety of pancreatin enteric-coated minimicrospheres (Creon 40000 MMS) in patients with pancreatic exocrine insufficiency due to chronic pancreatitis–a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 36, 426–436

14.Whitcomb, DC, Lehman, GA, Vasileva, G et al. (2010) Pancrelipase delayed-release capsules

(CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. *Am J Gastroenterol* 105, 2276–2286

15.DiMagno, EP, Go, VL & Summerskill, WH (1973) Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 288, 813–815

16. Duggan, SN, Ní Chonchubhair, HM, Lawal, O et al. (2016) Chronic pancreatitis: a diagnostic dilemma. *World J Gastroenterol* 22, 2304–2313

17.Lankisch, PG, Lembcke, B, Wemken, G et al. (1986) Functional reserve capacity of the exocrine pancreas. *Digestion* 35, 175–181.

18.Sikkens, ECM, Cahen, DL, van Eijck, C et al. (2012) Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. *Pancreatology* 12, 71–73

19.Imrie, CW, Connett, G, Hall, RI et al. (2010) Review article: enzyme supplementation in cystic fibrosis, chronic pancreatitis, pancreatic and periampullary cancer. *Aliment Pharmacol Ther* 32, 1–25

20.Capurso, G, Signoretti, M, Archibugi, L et al. (2016) Systematic review and meta-analysis: small intestinal bacterial overgrowth in chronic pancreatitis. *United Eur Gastroenterol J* 4, 697–705

21.Ni Chonchubhair, HM, Dobson, M, Ryan, B et al. (2017) Small intestinal bacterial overgrowth in chronic pancreatitis patients with pancreatic exocrine insufficiency; a prospective cohort study. *Ir J Med Sci* 186, s41–s118

22.Verdu, EF, Galipeau, HJ & Jabri, B (2015) Novel players in coeliac disease pathogenesis: role of the gut microbiota. *Nat Rev Gastroenterol Hepatol* 12, 497–506

23. Distrutti, E, Monaldi, L, Ricci, P et al. (2016) Gut microbiota role in irritable bowel syndrome: new therapeutic strategies. *World J Gastroenterol* 22, 2219–2241

24. Sheehan, D, Moran, C & Shanahan, F (2015) The microbiota in inflammatory bowel disease. *J Gastroenterol* 50, 495–507.

25.Farrell, JJ, Zhang, L, Zhou, H et al. (2012) Variations of oral microbiota are associated with pancreatic diseases including pancreatic cancer. *Gut* 61, 582–588

26.Jesnowski, R, Isaksson, B, Möhrckea, C et al. (2010) Helicobacter pylori in autoimmune pancreatitis and pancreatic carcinoma. *Pancreatology* 10, 462–466

27.Savitskaya, K, Melnikova, Y, Vorobyev, A et al. (2002) Evaluation of the colonic content microenvironment in patients with chronic pancreatitis. *Vestnik-rossiiskala Acad meditskikn Nauk* 4, 20–23

28.Gorovits, E, Tokareva, E, Khlynova, O et al. (2012) Complex evaluation of intestine microbiocenosis condition in patients with chronic pancreatitis. *Zhurnal Mikrobiol Epidemiol i Immunobiol* 4, 73–76

29.Manasa, JS, Harish, V, Madhulika, A et al. (2015) Study of gut microbiome in chronic pancreatitis. *Clin Gastroenterol Hepatol* 13, e101

30.Sikkens, ECM, Cahen, DL, Koch, AD et al. (2013) The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatology* 13, 238–242

31.Nakamura, T, Takebe, K, Imamura, K et al. Fat-soluble vitamins in patients with chronic pancreatitis (pancreatic insufficiency). *Acta Gastroenterol Belg* 59, 10–14

32.Marotta, F, Labadarios, D, Frazer, L et al. (1994) Fat-soluble vitamin concentration in chronic alcohol-induced pancreatitis. Relationship with steatorrhea. *Dig Dis Sci* 39, 993–998

33.Jaganath, VA, Fedorowicz, Z, Thoher, V et al. (2011) Vitamin K supplementation for cystic fibrosis. *Cochrane database Syst*

34.Dujsikova, H, Dite, P, Tomandl, J et al. (2008) Occurrence of metabolic osteopathy in patients with chronic pancreatitis. *Pancreatology* 8, 583–586

35.Girish, BN, Rajesh, G, Vaidyanathan, K et al. (2009) Zinc status in chronic pancreatitis and its relationship with exocrine and endocrine insufficiency. *JOP* 10, 651–656

36.Glasbrenner, B, Malfertheiner, P, Büchler, M et al. (1991) Vitamin B12 and folic acid deficiency in chronic pancreatitis: a relevant disorder? *Klin Wochenschr* 69, 168–172.

37.Papazachariou, IM, Martinez-Isla, A, Efthimiou, E et al. (2000) Magnesium deficiency in patients with chronic pancreatitis identified by an intravenous loading test. *Clin Chim Acta* 302, 145–154

38.Yokota, T, Tsuchiya, K, Furukawa, T et al. (1990) Vitamin E deficiency in acquired fat malabsorption. *J Neurol* 237, 103–106

39.Reynaert, H, Debeuckelaere, S, De Waele, B et al. (1993) The brown bowel syndrome and gastrointestinal adenocarcinoma. Two complications of vitamin E deficiency in celiac sprue and chronic pancreatitis? *J Clin Gastroenterol* 16, 48–51

40.Benítez Cruz, S, Gómez Candela, C, Ruiz Martín, M et al. Bilateral corneal ulceration as a

result of caloric-protein malnutrition and vitamin A deficit in a patient with chronic alcoholism, chronic pancreatitis and cholecystostomy. *Nutr Hosp* 20, 308–310