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1. Introduction

Chronic pancreatitis (CP) has been defined as a continuing inflammatory disease of the pancreas characterized by irreversible morphological changes, often associated with pain and with the loss of exocrine and endocrine function which may be clinically relevant (Clain JE Surg Clin North Am 1999). Pain is the principal cause of intractability and together with pancreatic insufficiency may have a significantly deleterious effect on a patient’s quality of life as well as their ability to work and contribute to society, often leading to loss of their social support network (Lankisch PG Digestion 1993). Progressive disease may culminate in severe and disabling symptoms requiring narcotic analgesia and frequent hospital admission with a consequent impact on health resources (Bornman PC W J Surg 2003; Braganza JM The Lancet 2011). The incidence and prevalence of disease has not been well documented however it is considered uncommon in Europe and the USA. This is in contrast to data available from South India where a prevalence of 114-200/100 000 people has been documented. Alcohol is the leading cause in western developed countries and some developing countries such as Brazil, Mexico and South Africa while idiopathic disease predominates in Asia and the subcontinent (Braganza JM The Lancet 2011; Garg PK J Gastroenterol Hepatol 2004).

Despite extensive study, the pathogenesis of chronic pancreatitis and the mechanisms which result in the development of pain remain poorly understood. As a result, treatment strategies have been largely empirical and based on symptoms, management of clinically evident exocrine and endocrine dysfunction and gross morphological abnormalities. Modalities employed have included medical support (with analgesics, anti-diabetic medication, pancreatic enzyme replacement, nutrient support and steroids in autoimmune disease), interventional endoscopy and surgery. The role of surgery has been primarily to relieve pain refractory to medical therapy, to address complications and to resect suspected or confirmed neoplastic disease (Bornman PC S Afr Med J 2010). The causes of pain in CP are likely multifactorial and proposed factors include excessive oxygen-derived free radicals, tissue hypoxia and acidosis, inflammatory infiltration accompanied by an influx of pain transmitted substances into damaged nerve ends and the development of pancreatic ductal and tissue fluid hypertension (Bornman PC W J Surg 2003). Surgical intervention for the relief of pain focuses primarily on the latter two proposed mechanisms. Two distinct principles have been applied in the development of
arterial supply (Braganza JM Lancet 2011). When the acinar cell’s defence mechanisms are insufficient to meet the increased oxidant load from ROS and xenobiotic metabolites, electrophilic stress results (Braganza JM Digestion 1998; Braganza JM JOP 2010; Foster JR. Toxicology of the exocrine pancreas. In: General and applied toxicology 2009). Dietary insufficiency of micronutrients and ascorbic acid may predispose to this (Braganza JM Digestion 1998). Electrophilic stress in turn results in pancreastasis, the failure of apical exocytosis in the acinar cell (Sanfey H Ann Surg 1984; Leung P Antioxid Redox Signal 2009). Enzymes (both newly synthesised & those stored in zymogen granules) not able to be released apically, are released via the basolateral membrane into the interstitium, lymphatics and bloodstream (Cook LJ Scand J Gastroenterol 1996). Entrance of enzymes and free radical oxidation products into the interstitium causes mast cell degranulation, resulting in local inflammation, activation of nociceptive axon reflexes and fibrosis. (Cook LJ Scand J Gastroenterol 1996; Braganza JM Digestion 1998). This inflammatory response is potentiated by cytokines produced by the damaged acinar cell as a result of activated signaling cascades caused by the release of ROS. (Leung P Antioxid Redox Signal 2009).

2.4 Fibrosis as a result of pancreatic stellate cell activation in the necrosis-inflammation-fibrosis sequence and sentinel acute pancreatitis events

Pancreatic stellate cells play a central role in the fibrotic process associated with chronic pancreatitis (Stevens T Am J Gastroenterol 2004). This is particularly relevant in the necrosis-inflammation-fibrosis sequence, the most widely accepted hypothesis in the pathogenesis of chronic pancreatitis (Bornman PC in Chronic pancreatitis. Hepatobiliary and pancreatic surgery – a companion to specialist surgical practice. 2009). Initially this hypothesis held that fibrosis developed as a stepwise progressive process from recurrent bouts of acute pancreatitis (Comfort MW Gastroenterology 1946; Kloppel G Hepatogastroenterol 1991). An alternative theory suggested that alcohol might be directly toxic to the acinar cell through a change in cellular metabolism (toxic-metabolic theory). Alcohol was purported to produce cytoplasmic lipid accumulation within the acinar cell, leading to fatty degeneration, cellular necrosis and eventual fibrosis (Bordalo O Am J Gastroenterol 1977). More recently the theory of a sentinel acute pancreatitis event (SAPE) has been proposed. This theory hypothesizes that stimulation of the pancreatic acinar cell by alcohol or oxidative stress activates trypsin which results in a sentinel acute pancreatitis event. This is followed by a dual phase chronic inflammatory response, with the early phase characterised by a pro-inflammatory cell infiltrate including macrophages and lymphocytes. Cytokines released during the early phase also attract a later anti-inflammatory cellular infiltrate comprising pro-fibrotic cells, including stellate cells. These cells, once attracted, are activated by lipid peroxidation products (caused by excess ROS) and mast cell degranulation products, and are considered “primed”; continued stimulation by cytokines (in particular TGF-β1) produced by acinar cells, inflammatory cells or the stellate cells themselves as a result of oxidative stress, alcohol or recurrent acute pancreatitis, cause these activated stellate cells to deposit collagen, resulting in fibrosis and the features of chronic pancreatitis (Whitcomb DC Best Pract Res Clin Gastroenterol 2002). The transient formation of fatty acid ethanol esters and the role of macrophages and lymphocytes in pancreatic tissue destruction are also thought to be integral to this process (Pandol SJ Pancreatology 2007). It is suggested that the contractive potential and perivascular location of the stellate cells results in fibrosis that leads to microvascular ischaemia and pain (Wells RG Gastroenterol 1998).