Systematic Review of Diet in the Pathogenesis of Acute Pancreatitis: A Tale of Too Much or Too Little?

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ABSTRACT

Background/Aim: The role of diet as the cause of acute pancreatitis (AP) has been suggested. The aim of the current review was to determine if there exists sufficient evidence linking nutrition, or the lack of it, to the pathogenesis of AP. **Patients and Methods:** A systematic search of the scientific literature was carried out using Embase, PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials for the years 1965 - 2011 to obtain access to studies involving dietary factors and the pathogenesis of AP. **Results:** A total of 17 studies were identified describing diet and AP. These included 12 human and 5 animal studies. 8 reports were found to link malnutrition and/or refeeding to the pathogenesis of AP. Two studies found an increased consumption of fats and proteins in patients with alcohol-related AP while 1 study noted a lesser intake of carbohydrate in patients. However, none of these differences attained statistical significance. A recent prospective case-control study found a significantly higher risk for AP amongst patients eating par-boiled rice and fresh water fish. **Conclusions:** Evidence from literature does not appear to support the role of diet as a single bolus meal as a cause for AP. Prolonged consumption of diets rich in proteins and fats may work synergistically with gallstones / alcohol to trigger an attack of AP indicating a possible role of diet as a cofactor in the development of AP possibly by lowering the threshold needed by these other agents to lead to the attack of AP.

Key Words: Carbohydrates, fats, proteins

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Patients presenting with acute pancreatitis (AP) often report their pain coming on after a large meal or following a period of starvation which may often be associated with an alcohol binge. This suggests a role for diet in the development of AP, a role that has been investigated in animal models[1-3] as well as in humans.[4-6] On the other hand, lack of nutrition as well as malnutrition have also been linked to the development of AP.[7,8] Additionally, the consumption of large quantities of rice[9] and even drinking water[10] have been postulated to cause AP.

The aim of the current study was to determine if there exists sufficient evidence in published literature linking diet, or the lack of it, to the pathogenesis of AP.

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PATIENTS AND METHODS

A systematic search of the scientific literature was carried out using Embase, PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials for the years 1965 - 2011 to obtain access to all publications, especially randomized controlled trials (RCTs), systematic reviews, and meta-analyses involving dietary factors and the pathogenesis of AP. The search strategy was that described by Dickersin *et al.*[11] with the appropriate specific search terms, namely, "acute pancreatitis", "proteins", "fats", "carbohydrates", "systematic" and "randomized controlled trials". All available publications from the past 50 years were considered. Inclusion criteria: Studies specifically addressing a pathogenetic role of diet and dietary constituents in the causation of AP.

Exclusion criteria

Studies on the pathogenesis of diet in chronic pancreatitis
Studies pertaining to the dietary aspects in the management of an attack of AP.

RESULTS

Using the above search strategy, a total of 550 publications were retrieved of which 17 studies [Algorithm 1] were identified describing diet in the development of AP. These included 12 human studies (case control and cohort studies, case series and case reports) and 5 animal studies.

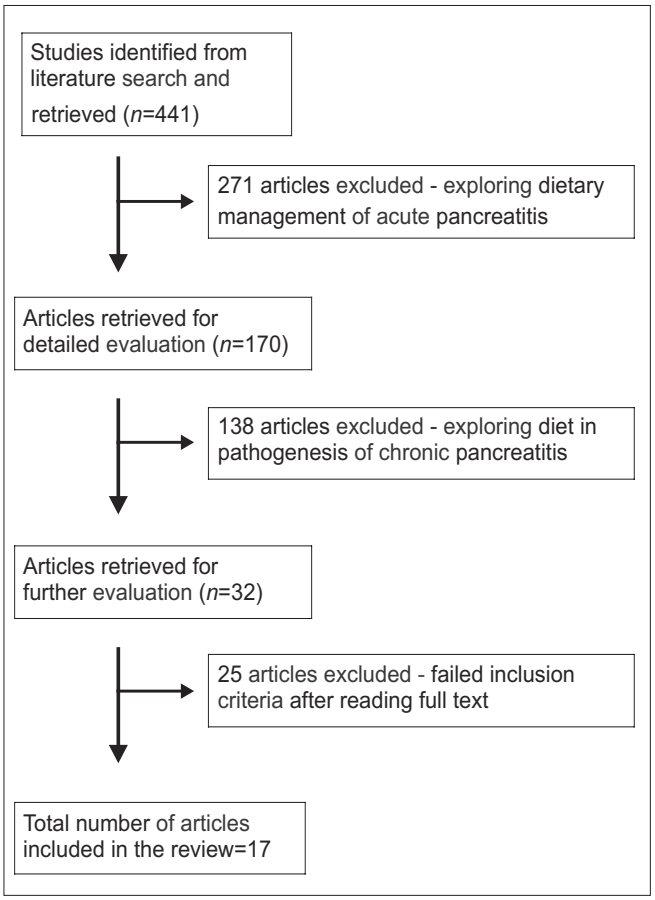
Effects of dietary constituents (fats, proteins and carbohydrates)

Animal studies

Experimental studies in murine models have confirmed that diets rich in proteins, carbohydrates and fats stimulate the trypsin, amylase and lipase content of pancreatic tissue, respectively.[12-15] Wilson *et al.*[16] found that administering a protein-deficient diet resulted in a reduction in the acinar lipase content in rats, while chronic ethanol consumption increased the lipase content as well as the secretory capacity of the acini. They thus postulated that if it is the enzyme secretory capacity that determines the risk of AP, then in chronic alcoholics, a high protein diet could potentiate an attack of AP. Additionally, lobular and acinar atrophy were noted in monkeys fed protein-deficient diets.[17]

The role of individual dietary constituents, such as fats, proteins and carbohydrates, has been studied in animal models of AP [Table 1].[1-3,18,19]

Ramo *et al.*[3] demonstrated that, histologically, the pancreata of animals fed ethanol and carbohydrate showed the most severe form of AP. This, however, did not correlate with the observed mortality noted amongst animals fed fat- and protein-rich diets. Thus, there is little evidence to suggest carbohydrates have a role in initiating or exacerbating experimental AP.



Algorithm 1: Quorum chart depicting the search strategy employed

Table 1: Animal studies exploring the effect of dietary constituents on AP

Author / Reference	Year	Species / Model	Protocol	Conclusions
Maki *et al.*[1]	1967	Rat / Duct-ligation	AP induced in 6 groups of rats fed for 4-6 months, various diets containing high proteins, carbohydrates and fat – alone and in combinations	Highest mortality - high protein diet. Severe parenchymal necrosis - high fat and high protein diet, but not high carbohydrate diet.
Brian Haig *et al.*[18]	1970	Canine / retrograde duct injection of bile/trypsin	AP induced in groups of dogs fed for 6 weeks, various diets containing high fat, protein, carbohydrate or balanced diets	Severe AP – animals fed on high fat diet
Ramo[2]	1987	Rat / retrograde duct injection of bile	Rats fed 15% ethanol (v/v) or water and specialised (rich in fats, proteins or carbohydrates) or standard diets for 12 weeks	Protein and fat rich diets increased mortality rate on background of long term ethanol consumption. Carbohydrates did not alter severity.
Ramo *et al.*[3]	1987	Rat / retrograde duct injection of bile	Rats fed 15% ethanol (v/v) or water and specialised (rich in fats, proteins or carbohydrates) or standard diets for 12 weeks	Histology – most severe AP with carbohydrate rich diet. Highest mortality - with protein and fat rich diets. Poor correlation between mortality and histology
Czako *et al.*[19]	2007	Rat / CCK and L-arginine	Rats fed 3% cholesterol-enriched or normal diet – oedematous or necrotising AP induced	Hyperlipidemia causes no difference in oedematous AP, but can aggravate necrotising AP

CCK: Cholecystokinin, AP: Acute pancreatitis

Human studies

Experimental studies in humans on the role of diet on pancreatic enzyme release have indicated that, in the short term (<14 days), altering the constituent (fats, proteins and carbohydrates) composition in the meal does not induce major changes in enzyme release[20] as was previously noted in animal studies, or more specifically, murine models. However, Boivin *et al*.[21] have demonstrated that diets rich in proteins and fats, but low in carbohydrates, stimulated the inter-digestive and post-prandial outputs of trypsin and amylase.

The 3 large human studies on the role of nutrition in AP were published prior to 1985.

In the first retrospective study by Sarles *et al*.,[5] comparing nutritional intake amongst 22 patients with AP and two control cohorts, they found no significant difference in nutrient intake (proteins / carbohydrates / and fats) between the AP and the control groups. Although, patients with AP tended to consume fewer carbohydrates than the controls, the difference was not found to be statistically significant ($P < 0.067$).

Sarles[4] then conducted a large international study involving autopsy patients ($n = 681$) as well as patients who were administered a dietary questionnaire ($n = 205$) from all continents. The dietary intake of the cases was compared to national nutritional data. A positive correlation between fats and proteins and AP was found when comparing national nutritional data with autopsy results.

Wilson *et al*.[6] compared the dietary intake of alcoholic patients with AP and cirrhosis and found that although patients with AP consumed more fat and protein than those patients with cirrhosis, the difference did not reach statistical significance.

Recently, a prospective case-control study from Goa, India[22] looking at the role of diet in the development of AP noted that the consumption of fresh water fish (OR = 3.94, CI =1.63-9.4, $P < 0.002$) and parboiled rice (OR = 2.10, CI = 1.07-4.13, $P < 0.04$) was significantly associated with the risk of AP. Other foods such as salt water fish, beef, mutton, chicken, the use of coconut oil and steamed rice had no significant association (*P*- not significant) with the development of AP.

Malnutrition

Malnutrition has been linked to the development of chronic pancreatitis (CP).[23] The underlying mechanisms for such an association include oxidative damage in a system with poor antioxidant reserves, and inflammatory damage involving interleukin-1, interleukin-6 and tumour necrosis factor-α. This could lead to the activation of pancreatic stellate cells and consequent inflammation and fibrosis.[24] Prolonged periods of malnutrition have been shown experimentally to cause damage to the pancreas. It was demonstrated that Bonnet monkeys fed with a protein deficient diet exhibited lobular and acinar atrophy.[17] This was also noted on autopsy studies on malnourished IBO children, in which acinar atrophy and fibrosis were seen.[25]

In AP, however, the impact of malnutrition is sparse. Anorexia nervosa and bulimia, and even, refeeding after periods of anorexia have been reported to cause AP. Table 2 provides a review of the cases reported in literature.[7,26-32] Cox *et al*.,[34] however, pointed out an association between protein calorie malnutrition and abnormalities in pancreatic enzyme levels in the serum being misconceived as AP.

Refeeding

Refeeding after a prolonged period of starvation has also been linked to the development of AP. Based on the studies by Gryboski *et al*.[30] and Keane *et al*.[28] it has been suggested that refeeding worsens gastric dilatation and duodenal ileus which is associated with anorexia nervosa leading to retrograde pressure and reflux of duodenal contents into the pancreatic duct triggering off an attack of AP. Although these are the only two studies specifically addressing refeeding following anorexia, the development of pain following refeeding even in patients with AP due to other

Table 2: Studies on the role of malnutrition and refeeding in the causation of AP (Modified and updated from Morris *et al*.[7])

Author / Reference	Year	Type of study (N)	Anorexia / Refeeding	Level of evidence[26]
Nordgren *et al*.[27]	1977	Case report (2)	Anorexia Nervosa	IV
Keane *et al*.[28]	1978	Case report (1)	Refeeding following anorexia	IV
Schoettle *et al*.[29]	1979	Case report (1)	Anorexia nervosa-like state in a child	IV
Gryboski *et al*.[30]	1980	Case series (3)	Refeeding following anorexia	IV
Rampling[31]	1982	Case report (1)	Anorexia nervosa	IV
Backett[32]	1985	Case report (1)	Anorexia nervosa	IV
Morris *et al*.[7]	2004	Case report (1)	Anorexia nervosa	IV
Gwee *et al*.[33]	2010	Case report (1)	Anorexia nervosa	IV

N: Number of patients, PD: Pancreatic duct, AP: Acute pancreatitis

causes who were fasted owing to their presentation has been well appreciated over the years.[35] Pain in this setting has been reported to be due to re-stimulation of the pancreatic secretion by oral bolus feeding, which may activate dormant enzymes and the inflammatory process.[36]

DISCUSSION

In summary, the above studies indicate that dietary constituents do affect pancreatic enzyme output. In animals, this may be noted as an acute phenomenon. However, in humans, a prolonged exposure to a diet rich in protein and fats appears to alter enzyme levels in the pancreas. In terms of the dietary factors and their association with the risk of developing AP, human studies have indicated that diet may play a role. However, there is no conclusive evidence of direct causative role although the evidence supports the role for diet as a co-factor to other agents (alcohol, gallstones). Animal studies certainly provide possible mechanisms as to how this may happen.

The role of diet in the development of AP has often been considered. The problem with the large human studies[4-6] examining such an association is that they were published prior to 1985. The incidence of obesity has dramatically increased the world over since then.[37] Besides, obesity is a low grade pro-inflammatory state.[38] Obesity contributes to the generation of mediators potentially involved in the induction of the systemic inflammatory response.[39]

Hong *et al.*[40] recently analysed the relationship between a high body mass index and the risk of developing AP as well as the risk of morbidity and found that obesity is not only associated with an increased risk of AP development, but it is also a poor prognostic factor for AP.

What is also fascinating is that at the other end of the spectrum, malnutrition has also been linked to the development of AP.[7]

In terms of human studies exploring the dietary constituents, the only study examining such a role in AP found an increased relative risk for AP amongst people who ate par-boiled rice and fresh water fish.[22] The significance of these findings was not elucidated. This study supports the paper by Chen[9] who hypothesized that the repeated consumption of large quantities of rice could predispose to the development of AP over a period of time. Chen[9] postulated the development of changes occurring in the sphincter of Oddi following repeated consumption of large boluses of rice and proteins which empty into the duodenum and overstimulate the sphincter, resulting in oedema. These findings although apparently contradictory to the findings of Sarles *et al.*[5] indicating that the subjects with AP tended to consume smaller quantities of carbohydrates, may provide an important difference in the pattern of consumption of rice in the two continents.

In the case of malnutrition, the human and animal studies indicate that it is the lack of adequate quantities of dietary constituents that induce a change in the pancreatic exocrine architecture as well as possible changes in the oxidant and antioxidant balance over a period of time. Despite there existing a temporal association between malnutrition and AP, the available data appears insufficient to suggest an aetiological role for malnutrition in the development of AP. It can only be hypothesized that a reduction in the release of enzymes over prolonged periods of malnutrition may result in a potential down-regulation in the intra pancreatic protective mechanisms, such as pancreatic secretory trypsin inhibitor (PSTI). This may make an individual susceptible to other potential triggers by lowering the threshold for the achievement of the 'critical mass'.[41] Alternatively, a sudden change in the dietary intake with the introduction of a nutrient-rich meal may result in a surge in the enzymes released which could potentially overwhelm the existing protective mechanisms resulting in an attack of AP. In the event that an association between malnutrition and AP does prove to exist based on future studies, one potential mechanism that could contribute to the development of AP would be oxidative stress.[42,43]

Clues to the mechanism of development of AP by high protein or fat diets come from the animal studies. In animal studies, adding triglycerides to the perfusate of *ex vivo* pancreata harvested from rats in whom AP was induced, resulted in an increase in the amylase and lipase levels in the portal venous effluent.[44] Similarly, changes consistent with AP were induced in *ex vivo*, perfused canine pancreata when triglycerides or free fatty acids were added to the perfusate.[45] Using an *in vivo* model, it was shown that high and very high levels of dietary unsaturated fats potentiated the harmful effects of ethanol consumption on the pancreas.[46] Zhang *et al.*[47] found that chronic high fat diet increased pancreatic free fatty acids and lipid peroxidation associated with pancreatic injuries and collagen synthesis by activated pancreatic stellate cells in rats. It has been consistently shown that high protein and fat diets potentiate the severity of experimentally-induced AP in animals.[1-3,18,19] Contrary to the above studies, Sarles *et al.*[48] found that the administration of different diets to rats fed on ethanol produced changes in the pancreas no different to those fed on water. However, there have been no studies that have shown high protein or fat diets actually cause AP by themselves. Although we have pointed out earlier that obesity has emerged as a serious problem the world over and obese individuals are at an increased risk of developing AP, to date there are no studies correlating the food consumed

by obese individuals found to have a high risk of AP and the actual risk of development of the disease. Such a study would, thus, seem prudent as it would aid in health education in this group of patients besides corroborating the mechanisms of disease pathogenesis that has been elucidated in some of the animal studies.

CONCLUSION

In conclusion, evidence from literature does not appear to support the role of diet as a single bolus meal as a cause for AP. Prolonged consumption of diets rich in proteins and fats may work synergistically with gallstones / alcohol to trigger an attack of AP indicating a possible role of diet as a cofactor in the causation of AP possibly by lowering the threshold needed by these other agents to lead to the attack of AP.

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