Role of Enteral Nutrition in the Pathophysiology and Treatment of Pancreatitis and Cystic Fibrosis

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Chronic Pancreatitis

Pathophysiology

Multiple factors have been implicated in the pathogenesis of chronic pancreatitis [1]. Alcohol is the cause in 60–70% of patients. Dietary factors such as high protein or either very high or very low fat content may potentiate the injurious effects of alcohol [2, 3]. In contrast, low protein and very low fat diets have been implicated in patients with tropical pancreatitis [4]. This disease, commonly seen in south India and other parts of the tropics, is no longer thought to be associated with cassava consumption.

Obstruction of the pancreatic duct by conditions such as post-traumatic ductal strictures and periampullary or pancreatic tumors can also lead to chronic pancreatitis. Intraductal protein plugs are generally not observed in these conditions. Sphincter of Oddi dysfunction and pancreas divisum remain highly controversial as causes of chronic pancreatitis.

Systemic diseases have also been associated with chronic pancreatitis. These include cystic fibrosis, systemic lupus erythematosus, and perhaps hyperparathyroidism. However, in 30–40% of patients the disease is considered idiopathic. A form of pancreatitis presenting after the age of 50 years is referred to as senile chronic pancreatitis. It is characterized by a painless clinical course, a higher prevalence in males, and association with atherosclerotic disease. Pancreatic calcification may be present.

Genetic factors have now been described in association with chronic pancreatitis. Hereditary pancreatitis presents initially with recurrent attacks of acute
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Pancreatitis but can eventually lead to chronic disease of the pancreas [5]. The gene has been identified and encodes a form of cationic trypsinogen which, when mutated, cannot be readily degraded following conversion to active trypsin. Preliminary data suggest that the cystic fibrosis gene may also be a predisposing factor in the genesis of disease in patients who have been otherwise labeled as having idiopathic chronic pancreatitis [6].

Hormonal Regulation of the Exocrine Pancreas by Nutritional Substrates

Cholecystokinin (CCK) is the principal hormone activating secretion from the pancreatic acinar cell. CCK release is regulated by substrates that are present in the duodenum. In humans, carbohydrates have relatively little effect on CCK release, proteins and fats being the main stimulants [7]. Triglycerides and long-chain fatty acids produce maximal pancreatic enzyme output, while very little stimulation occurs in response to medium-chain triglycerides [8]. Amino acids (essential) lead to maximal CCK release, similar to that seen with intact proteins [8, 9]. The effects of peptides on CCK release are not known.

The physical state of the meal is important in determining the length of time the exocrine pancreas is stimulated. Complex solids lead to a more prolonged duration of pancreatic secretion than homogenized solids, while liquids produce the shortest duration of stimulation [10].

The release of CCK has been postulated to occur through the following mechanism [11]. CCK-releasing factor (CCK-RF) is a protein produced and released from the duodenum which stimulates CCK release into the blood. In the absence of protein substrates in the duodenum, this trypsin-sensitive protein is degraded and hence little CCK release occurs. Following ingestion of a meal, the presence of proteins in the duodenum competes for trypsin, allowing undegraded CCK-RF to stimulate CCK release. This is the theory that explains how high-dose exogenous pancreatic enzymes are thought to ‘rest’ the pancreas by minimizing CCK release.

Role of Antioxidants in Chronic Pancreatitis

Patients with chronic pancreatitis are relatively deficient in antioxidants – including vitamin C, vitamin E, selenium, and methionine – compared with age- and sex-matched controls [12, 13]. However, these patients are in a catabolic state and hence have increased antioxidant demands. This imbalance favors the generation of free radicals, leading to lipid peroxidation and cellular compromise. This theory is supported by the case report of a 10-year-old boy with calcific chronic pancreatitis who became pain-free with antioxidant treatment [14]. Controlled trials are needed to confirm these results and determine their overall applicability. Our group has found that the use of an enteral formula containing antioxidants minimally increases plasma CCK levels [15] and may be helpful in improving the nutritional status as well as relieving the pain in a subset of patients with chronic pancreatitis whose pain is principally postprandial.
Clearly, addressing the nutritional status of patients with chronic pancreatitis is an important component in the overall treatment of this disease.

**Potential Role of Enteral Treatments in Chronic Pancreatitis**

Two therapeutic approaches could be of benefit to patients with chronic pancreatitis. First, a nutrition supplement which stimulates the exocrine pancreas minimally and yet provides adequate nutrition would allow treatment of patients in the ambulatory setting. Home hyperalimentation is not an optimal alternative. The second therapeutic approach is based on the concept that antioxidants may be effective in the treatment of chronic pancreatitis. Peptamen® (Nestlé Clinical Nutrition, Inc.) may satisfy both these therapeutic approaches on the basis that (i) it contains principally medium-chain triglycerides and hydrolyzed peptides which have a minimal effect on CCK levels, and (ii) it contains a precursor of glutathione production, providing it with antioxidant properties.

To determine the effects of Peptamen on plasma CCK levels, normal healthy volunteers were studied. A 16- to 20-fold increase in plasma CCK over fasting levels was observed in response to a high protein/high fat diet or with Ensure®, an enteral supplement containing intact proteins and full-length triglycerides. In contrast, Peptamen produced a fourfold increase in plasma CCK levels [15].

As the data indicated that Peptamen indeed caused only a minimal increase in CCK levels, the effect of this enteral treatment was studied over a 10-week course in patients with chronic pancreatitis. In a pilot trial of six patients, there was an approximately 70% decrease in pain scores after 10 weeks in those with postprandial pain. This suggests that Peptamen may be of benefit in this group of patients. A larger study is ongoing.

**Cystic Fibrosis**

**Pathophysiology**

Cystic fibrosis is the most common inherited autosomal recessive disorder, with a carrier rate of 1 in 30 among whites [16]. The fall expression of disease occurs in 1 in 2500 live births. Although the gene responsible for cystic fibrosis was identified in 1989 as a chloride channel determinant [17], it remains unclear how the mutation leads to the phenotypic expression of disease.

While recurrent lung infections are the principal cause of death in cystic fibrosis, patients often develop malabsorption owing to a combination of pancreatic insufficiency and intestinal dysfunction [18]. Although the disease generally presents in childhood, recent evidence indicates that at least 68% of patients labeled as having idiopathic recurrent acute or chronic pancreatitis, have mutations in the cystic fibrosis gene [19]. These patients had ‘milder’ mutations, which may explain the single organ involvement presenting in adulthood.
Role of Enteral Nutrition in the Pathophysiology of Malnutrition in Cystic Fibrosis Patients

Malnutrition is a common finding in cystic fibrosis. Although poor nutrition correlates with decreased pulmonary function, it is unclear whether low weight is a cause or an effect of worsening pulmonary function [20]. Essential fatty acid deficiency is particularly common, though its cause is unknown. Studies examining fatty acids in plasma from patients with cystic fibrosis have shown a decrease in the ratio of linoleic to arachidonic acid, while the ratio of eicosatrienoic acid to arachidonic acid was increased [21]. In contrast to healthy controls, plasma phospholipid palmitoleic and eicosatrienoic acids were higher and linoleic and docosahexaenoic acids lower in cystic fibrosis, despite similar lean body mass, fat-free mass, and fat mass between the two groups. This suggests that fatty acid metabolism is specifically altered in cystic fibrosis. Despite this, treatment remains problematic. It generally consists of enteral supplements combined with pancreatic enzyme replacement.

Are Pro-Inflammatory Lipid Mediators Important in the Pathogenesis of Cystic Fibrosis?

Arachidonic acid concentrations are increased in lung lavage fluid from patients with cystic fibrosis [22, 23]. However, this is thought to be secondary to infection rather than being a primary event [24]. Our group has investigated whether there are abnormalities of fatty acid metabolism in the membranes of cells affected by cystic fibrosis. Using cftr–/– mice, we have found that phospholipid-bound arachidonic acid levels are increased twofold, while phospholipid-bound docosahexaenoic acid levels are decreased twofold, compared with wild-type mice [25]. No other lipids were significantly altered. These abnormalities were confined to organs affected by cystic fibrosis, including pancreas, ileum, and lung. No abnormalities were found when plasma or erythrocytes were examined. As phospholipid-bound arachidonic acid levels are normally tightly regulated, cystic fibrosis represents the first disease in which the arachidonic acid level in the membranes of target cells is significantly raised. This abnormality would explain the deficiencies in essential fatty acids previously observed in patients with cystic fibrosis. These results could lead to novel treatments.

References

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Discussion

*Dr. Silk*: I was intrigued by the Peptamen story and the ability you found to blunt the CCK response. How is your strategy developing with these difficult patients? Are you going to go on with this type of feeding in the long term, or is there clinical suggestion that the benefit on the gland is rather more long lasting? In other words, do you envisage
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putting them back on a normal diet for a while, assessing the pain, and if it’s bad, having them in again for another period of treatment.

_Dr. Freedman:_ It’s a good point. There seems to be a pain-free holiday period lasting up to 2 months. So after their 10 weeks of Peptamen they go back to their low fat diet, and they’re relatively pain-free for a while. After four months or so the recurrence of pain is sufficient for them to need to go back on the Peptamen for 2–4 weeks and things settle down. I don’t understand the mechanism of this. Only certain patients seem to respond to Peptamen and that’s why I’ve targeted this very select group.

_Dr. Larsson:_ Could you comment a little more about the mechanism. There are some ideas about the mechanisms of pain in chronic pancreatitis.

_Dr. Freedman:_ Well, lots of mechanisms are proposed. One problem with the pain of pancreatitis is that if the entire pancreas is removed, a few months later you may get the same pain again. So just decreasing the inflammation or removing the gland may not do anything. The problem seems to lie in changes in the nerves or changes in the brain, or both. A lot of neurotransmitters have now been implicated, but obviously this is a very complicated problem, and that’s what complicates our treatment. This is why I keep emphasizing that one treatment is not going to make everybody better.

_Dr. Beaufrère:_ How did you measure the CCK plasma levels? The reason I ask is that radioimmunoassay or ELISA may give poor results because of cross-reaction with various antibodies. Did you use a biological assay?

_Dr. Freedman:_ Yes, we did a bioassay.

_Dr. Beaufrère:_ There are data suggesting that some bioactive peptides of casein could influence CCK secretion. I’m thinking particularly of a peptide called glycosylated micropeptide or GMP. Could you speculate on the possible role of this peptide on CCK regulation?

_Dr. Freedman:_ Actually, I don’t know any more than you do about this peptide or its regulation of CCK. I don’t know how Peptamen makes patients better either. I’m just thankful it does. It could be through affecting antioxidants, through improving nutrition, through minimizing CCK drive of the exocrine pancreas, and so on.

_Dr. Larsson:_ Do you think it improves pancreatic function?

_Dr. Freedman:_ The answer is no, in that many of these patients are on pancreatic enzyme supplements and if you look at the number of pills they need that doesn’t change.

_Dr. Hunter:_ I was intrigued by your fatty acid results. Eicosapentaenoic acid, which is also an ω–3 fatty acid, is thought to have the same sort of immunomodulatory effects as DHA. Did you make any measurements of that in your mice? Secondly, to manipulate the ω–6 pathways, some people are recommending γ-linoleic acid, and I wondered if you’d tried that as well.

_Dr. Freedman:_ We do complete gas chromatography/mass spectroscopy analysis. The only lipids that are altered are arachidonic acid, docosahexaenoic acid, and 22:5, the precursor of docosahexaenoic acid. No other lipids are altered in this model. We’ve looked at feeding the mice many different fatty acids. Our goal was to try to manipulate DHA and arachidonic acid levels. I told you that if you bring up DHA levels in the CF knockout mouse and bring down arachidonic acid levels, things normalize. The question is, could you bring DHA levels down even further and worsen the CF phenotype, and in fact that’s the case. We can do that by feeding the animals 18:3. If you feed them 18:3, their arachidonic acid levels get suppressed to the level found in a wild-type animal, and the DHA levels go down even further. These animals actually are dead within 5 or 6 days with severe manifestations of CF. If you look at the inflammatory response to pseudomonas, it is much increased.

_Dr. Hunter:_ Have you looked at the series-2 prostaglandins at all?
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Dr. Freedman: We’ve looked at several prostaglandins but we haven’t found any obvious differences.

Dr. Dobbie: Does it make any difference whether you feed Peptamen orally for the pancreatitis, or whether you feed it by tube distal to the ligament of Treitz? Does this distal feeding add additional benefit to the oral feeding?

Dr. Freedman: I haven’t looked at that in our chronic pancreatitis patients. My feeling is that with chronic pancreatitis it probably would not make much difference. In acute pancreatitis there is some evidence that you should probably get the tube past the CCK-releasing area.

Dr. Young: Is long-chain PUFA metabolism normal or in any way altered in chronic pancreatitis?

Dr. Freedman: I don’t think that has been well looked at. We’ve spent a lot of effort developing a very large clinic of patients with idiopathic chronic pancreatitis, and we know that 91% of them are CFG mutations, so we’re hunting carefully in those right now to answer that question.

Dr. Reeds: Have you looked at fatty acid concentrations in the small intestinal mucosal membrane, and are they altered? Second, in the resolution of the inflammation within the pancreas, are there alterations in either mucin structure or secretion, and if so, what do you think the link is between membrane fatty acid composition and production of mucins for a particular physical property?

Dr. Freedman: Good questions. We find the same lipid abnormality in the ileum as in the duodenum as far as arachidonic acid and DHA abnormalities are concerned. We haven’t looked at colon. Mucin hypersecretion is definitely a feature of CF, though it’s still unclear exactly why or how it occurs. There have now been studies showing that both qualitatively and quantitatively mucins are normal in CF patients, so it’s unclear whether it’s the mucin that’s the problem or the hydration. We have been looking at mucin secretion in the ileum in our animals. In the CF knockout mouse the intestinal defect is very severe, which is why our animals have to be on a liquid diet to survive. We have found that mucin secretion is upregulated and that PGE2 seems to mediate that in part. If you pretreat the animals with DHA from one week, mucin secretion goes down to wild-type levels. That’s all the data we have so far.

Dr. Larsson: Can pancreas regenerate and can nutritional support be part of that?

Dr. Freedman: The consensus among most pancreatologists is that the exocrine pancreas does not regenerate to a great degree. There clearly is a fair amount of reserve, so if you can stop the damage to the pancreas you might get some restoration of function. The situation is complicated by the fact that we do appear to see some patients in whom pancreatic exocrine function gets better. The reason may be related to ischemia. We know from work in a cat model that if the pancreatic duct is partially obstructed blood flow to the tissue adjacent to the pancreatic duct is reduced. So it is possible that if you do a decompressive procedure, you will relieve ischemia and improve exocrine function.

Dr. Larsson: One of the big problems is that it’s so difficult to measure pancreatic function.

Dr. Haschke: When you treated the knockout mice with 40 mg DHA/day, what was the dosage of antioxidants you gave?

Dr. Freedman: The amount of antioxidants that we add is negligible compared with what’s in the Peptamine. The animals consume 14 ml peptamen/day for 24 h.

Dr. Rowe: What property of Peptamen do you think is responsible for the effect? Is it the high MCT or is it the peptides? Your mice might be the place to explore this. There are MCT-rich whole protein formulations and pure amino acid preparations that could be tested.
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Dr. Freedman: We could actually do that in healthy volunteers. If we could isolate just the peptide protein component of Peptamen and give them that, we could then see what effect it had on plasma CCK levels.

Dr. Silk: I have a feeling it’s probably nothing to do with the peptides. When I was working with McGregor many years ago in San Francisco, he was examining what aspects of dietary protein stimulated CCK. These are pretty old data but I believe he found that the aromatic amino acids were the most powerful stimulants of CCK, and they act both in the free and peptide-bound form. I think what is happening here is probably that the MCT is blunting the CCK release. Obviously it would be fascinating to do more studies, but I guess it’s the MCT.

Dr. Hunter: I support Dr. Silk’s view. We did a study in which we looked at CCK release in normal human volunteers who were taking either a diet with a regulated amount of fat or one in which the fat was replaced by sucrose polyester. We found that on the sucrose polyester diet there was no CCK release at all, compared with the usual release on a normal fat diet. So I agree that it is probably the MCT that is effective and not the Peptamen.

Dr. Larsson: Did any of the patients in your chronic pancreatitis group have endocrine dysfunction?

Dr. Freedman: None was diabetic.

Dr. Larsson: So would you say they had relatively mild chronic pancreatitis?

Dr. Freedman: In the sense that when you get endocrine dysfunction you’ve got severe destruction and most of the gland is destroyed, yes, these were milder patients. They do not have calcification of the pancreas and their pancreatic ducts show minimal bleeding, but they all had dramatically abnormal secretin pancreatic function testing. That’s why I keep coming back to the fact that this is a very selected group. I’ve found that patients with diabetes or with severe ductal changes tend to have a lot of nausea and vomiting and can’t tolerate Peptamen at all.

Dr. Larsson: Did you assess improvements in their nutrition on Peptamen?

Dr. Freedman: We did it very crudely – they weighed themselves each day and we measured plasma albumin. Mostly the albumin values were barely altered, though the mean value rose a little with Peptamen. Body weight also increased slightly. These patients were not very thin to begin with. They maintain their energy intake on soda, so they get a huge amount of sugar and eat very little else. Thus we’re basically replacing that with something better.

Dr. Bentsen: Do you happen to know whether patients with the Shwachman syndrome have the CF mutation? The reason I ask is that we have just diagnosed two children and they also have inflammatory changes in their livers.

Dr. Freedman: No, they don’t have the CF gene mutation. There’s another gene.

Dr. Larsson: What developments do you foresee in the next couple of years?

Dr. Freedman: We are working with the CF Foundation, the FDA and others to start clinical trials in no more than one year from now with this therapy for CF, especially now that we’ve found that the same defect exists in humans as in the mouse model, so I think our therapy should work. The problem is to know what formulation of DHA to give to humans. Human absorption is very different from a mouse’s. Also children with CF tend to be noncompliant. They won’t even take pancreatic enzymes. So there are a number of considerations. We are close to a final formulation and doing toxicology studies right now, so hopefully within a year from now we’ll be able to see whether we’ve made a dent in this disease.