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Review Article

Digestive system dysfunction in cystic fibrosis: Challenges for nutrition therapy

Li Li[a], Shawn Somerset[b,*]

[a] School of Medicine, Griffith Health Institute, Griffith University, Brisbane, Queensland, Australia
[b] School of Allied Health, Faculty of Health Sciences, Australian Catholic University, Brisbane, Australia

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ABSTRACT

Cystic fibrosis can affect food digestion and nutrient absorption. The underlying mutation of the cystic fibrosis trans-membrane regulator gene depletes functional cystic fibrosis trans-membrane regulator on the surface of epithelial cells lining the digestive tract and associated organs, where Cl^- secretion and subsequently secretion of water and other ions are impaired. This alters pH and dehydrates secretions that precipitate and obstruct the lumen, causing inflammation and the eventual degradation of the pancreas, liver, gallbladder and intestine. Associated conditions include exocrine pancreatic insufficiency, impaired bicarbonate and bile acid secretion and aberrant mucus formation, commonly leading to maldigestion and malabsorption, particularly of fat and fat-soluble vitamins. Pancreatic enzyme replacement therapy is used to address this insufficiency. The susceptibility of pancreatic lipase to acidic and enzymatic inactivation and decreased bile availability often impedes its efficacy. Brush border digestive enzyme activity and intestinal uptake of certain disaccharides and amino acids await clarification. Other complications that may contribute to maldigestion/malabsorption include small intestine bacterial overgrowth, enteric circular muscle dysfunction, abnormal intestinal mucus, and intestinal inflammation. However, there is some evidence that gastric digestive enzymes, colonic microflora, correction of fatty acid abnormalities using dietary $n-3$ polyunsaturated fatty acid supplementation and emerging intestinal biomarkers can complement nutrition management in cystic fibrosis.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive condition caused by mutations of the cystic fibrosis trans-membrane regulator (*CFTR*) gene. The consequence is a deficiency or absence of functional CFTR proteins on the apical membrane of secretory and absorptive epithelial cells in multiple organs throughout the digestive system [1]. The absence of functional CFTR proteins disables the trans-epithelial movement of Cl^- ions through CFTR-associated Cl^- channels, which normally drives the secretion of fluid and other ions [2]. Dehydration of various secretions (*e.g.* mucus) at affected sites thus occurs, resulting in the precipitation of secretions and intra-ductal blockage, inflammation, fibrosis and eventual damage to the organs, particularly in the presence of digestive enzymes [3]. Although the exact manifestation is site-specific, the common pathophysiology is described above.

Numerous studies on single or multiple challenges in the digestive system in CF have been published. This review aims to integrate the manifestations and complications of CF throughout the entire digestive system and the changes in the digestion of food and absorption of nutrients to highlight the potential impact on nutrient acquisition and nutritional status in CF.

2. Factors influencing digestion and absorption

2.1. Pancreatic manifestations of CF and lipid maldigestion and malabsorption

Despite its exo-gastrointestinal anatomical location, the pancreas is the major organ responsible for the digestion of carbohydrate, protein and lipid through the secretion of various digestive enzymes into the duodenum [4]. These enzymes mainly include pancreatic amylase, protease, lipase and colipase. Pancreatic acinar cells secrete inactive pancreatic digestive enzymes into the acinar lumen, which extends to the pancreatic ducts [3,5].

* Corresponding author at: School of Allied Health, Faculty of Health Sciences, Australian Catholic University, Brisbane, 1100 Nudgee Road, Banyo, Queensland 4014, Australia. Tel.: +61 7 3623 7183.
E-mail addresses: li.li14@griffithuni.edu.au (L. Li), shawn.somerset@acu.edu.au (S. Somerset).

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The ducts consist of ductal cells that produce bicarbonate (HCO_3^-) induced by cAMP to alkalinise and dilute the acinar secretions and neutralise gastric acid in the duodenal lumen [6,7].

Cystic fibrosis trans-membrane regulator is normally highly expressed in the pancreas, particularly in the small intercalated ducts that connect the acini [7]. Deficiency of functional CFTR in CF thus leads to decreased ductal cell secretions of Cl^-, water and HCO_3^-, which also lowers pH [3,5]. The concentrated secretions cause dilation and obstruction of the ducts, particularly in the presence of macromolecules [3] such as inactive digestive enzymes. Digestion and neutralisation of the acidic duodenal content is hindered by suppressed secretion of pancreatic digestive enzymes and HCO_3^-. The lower ductal pH can also damage the pancreatic epithelium [4,8]. The inactive form of trypsin (trypsinogen) remains inactive only in the normal alkaline milieu of the pancreatic duct. Ductal secretion of HCO_3^- is diminished in the presence of trypsin [8]. Irreversible damage to the acinar cells and fibrosis arising from luminal obstruction and premature activation of pancreatic protease due to lowered pH further reduces the synthesis and exocytosis of pancreatic digestive enzymes and HCO_3^- [9]. The resultant exocrine pancreatic insufficiency (PI) is the leading cause of maldigestion and malabsorption in CF (Fig. 1) [10]. Clinical manifestation of PI occurs when less than 5–10% of the normal prandial enzymes are produced [4,9,10]. A compensatory release of pancreatic enzyme in response to nutrients (particularly undigested triglycerides) can occur in moderate PI [10]. However, the prevalence of PI in CF still approximates 85–90% worldwide, an incidence that increases with age [3,5,11–13].

Other factors contributing to PI have also been reported (Fig. 1). Correlation with the ΔF508 mutation of *CFTR* is very strong [5]. Imbalance of membrane phospholipids in pancreatic cells may also contribute to pathogenesis [5]. Murine models of CF have demonstrated elevated membrane-bound arachidonic acid (AA) levels in pancreas compared with controls [14,15]. The level of membrane-bound docosahexaenoic acid (DHA) may be either elevated or unaltered. Excessive incorporation of AA instead of DHA into membrane phospholipids can influence membrane fluidity and thereby permeability to ions such as Cl^- and HCO_3^- and water [5]. Reduced production of DHA and enhanced synthesis of docosapentaenoate, the precursor of DHA, has been observed in total pancreatic phospholipids in a *CFTR*-knockout murine model [16]. Abnormal profiles of essential fatty acids (EFA) have been indicated in CF human tissues and plasma [15,17]. However, the relevance of investigations to date remains uncertain since fatty acid profiles can vary between different phospholipid species related to specific membrane domains [16,18]. Also, the activity of Δ5 desaturase, critical in AA synthesis, is higher in murine than in human models [18]. Genetic background, diet, age and gender of CF murine models may also influence EFA status in tissues, including the pancreas [17,19]. Thus, the relationship between membrane phospholipid and PI [5] needs further investigation.

The impact of PI on digestion and absorption varies according to macronutrient [4]. Individuals with chronic pancreatitis (and consequent diminished pancreatic enzyme output) can absorb around 90% of a carbohydrate load compared with 80% in healthy participants with deactivated amylase [4], implying that carbohydrate digestion and absorption reach reasonable levels in CF with PI [4]. However, since products of microbial fermentation of carbohydrate exert higher osmotic pressure, symptoms such as abdominal distension, flatulence and diarrhoea may present because of an overload of undigested carbohydrate, along with changes in nutritional status [4]. Protein digestion also appears to be moderately compensated for, in both a porcine model and in humans with PI [4]. In contrast, lipid digestion is significantly impaired in CF with PI, causing steatorrhoea in untreated patients. This latter issue is attributable to the susceptibility of pancreatic lipase to low pH, low bile acid content and proteolysis by pancreatic chymotrypsin [5,10,20]. Moreover, gastric lipase seems to only be capable of liberating 10–30% of fatty acids from fat emulsions [4]. Thus, maldigestion and malabsorption occur mainly with dietary lipids and hence fat-soluble vitamins in the majority of individuals with CF if untreated. It is therefore common practice to supplement individuals with CF and PI with exogenous pancreatic enzymes, which is called pancreatic enzyme replacement therapy (PERT), and the dosage is matched with the fat content of meals or enteral feeds rather than protein or carbohydrate [9,12,21–23].

2.2. Factors affecting PERT efficacy

The goal of PERT is to compensate for maldigestion and malabsorption of nutrients in the duodenum by sufficient delivery of active pancreatic enzymes into the duodenum with ingested food [21]. Despite the large range of treatment options available [24], clinical outcomes of PERT may be compromised [12] owing to factors such as release of enzymes from their acid-resistant enteric coating not coinciding with the arrival of chyme in the small intestine (SI) [9]. Compositional variations in enzyme preparation and coating, the size of enzyme particles, GI transit, and the ratio of enzyme to dietary fat content can all contribute [9,10,12]. Other factors include hyperacidity in the stomach/SI and abnormal GI motility (Fig. 1).

At a pH below 6.0, PERT enzymes remain inactive owing to the acid-resistant coating that prevents the enzymes from denaturation [25]. Gastric and SI pH is thus critical in the timing and location of enzyme release [25]. The impact of CF on gastric pH remains unclear. A range of characteristics have been observed, including elevated basal and/or secretagogue-induced gastric acid secretion [26] and pre- and postprandial [25], as well as interdigestive gastric, pH [27], similar to the healthy controls. Severity of pulmonary disease or steatorrhoea and level of acid secretion seem not to be correlated [26]. The weight status of CF patients may account for some of this uncertainty, since the acid secretion level is calculated relative to the body weight [25]. Similarly, the role of CFTR in gastric acid secretion is not entirely clear. Secretagogue-induced gastric acid secretion in CF murine models can be considerably depressed by CFTR-specific inhibitors [28,29], implying that CFTR channels play a role in gastric acid secretion by interfering with other ion channels or transporters [28]. This parallels the early observation that the CFTR expression along the GI tract in adult humans was low throughout the gastric mucosa, including parietal cells [7]. Therefore, CFTR may not be the dominant Cl^- channel involved in gastric acid secretion, although its regulatory role in gastric secretion cannot be ignored. In addition, gastric secretion of HCO_3^-, which might affect gastric pH, has rarely been investigated. A single study reported gastric HCO_3^- secretion in CF comparable to healthy controls [27]. Thus, gastric pH may be normal and may not affect PERT enzyme release in the SI. However, further investigations to confirm gastric pH status and clarify the role of CFTR in gastric acid secretion in CF may further help to improve the efficacy of PERT. Indeed, increasing the pH in the proximal SI by either suppressing gastric acid secretion or administering HCO_3^- with PERT has been indicated in some studies to improve PERT efficacy [21,30–33].

Hyperacidity in the SI may relate to diminished HCO_3^- secretion from intestinal mucosa, pancreas, liver and gallbladder where functional CFTRs are absent. The emptying of gastric contents into the duodenum [34] stimulates HCO_3^- secretion from duodenal submucosal (Brunner's) glands, the intestinal crypt epithelium and the ductal systems of the liver and pancreas [35]. The alkaline HCO_3^- rich secretions neutralise the acidic chyme in the duodenum [34]. Accumulating evidence suggests that CFTR is involved in Cl^-/HCO_3^- exchange and hence HCO_3^- secretion in the duodenum [36,37], pancreas [5,6] and liver [38]. This is also supported by