

Review Article

Digestive system dysfunction in cystic fibrosis: Challenges for nutrition therapy

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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.

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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].

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The ducts consist of ductal cells that produce bicarbonate (HCO_3^-) induced by cAMP to alkalise 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 $\Delta 5$ 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 $\text{Cl}^-/\text{HCO}_3^-$ exchange and hence HCO_3^- secretion in the duodenum [36,37], pancreas [5,6] and liver [38]. This is also supported by

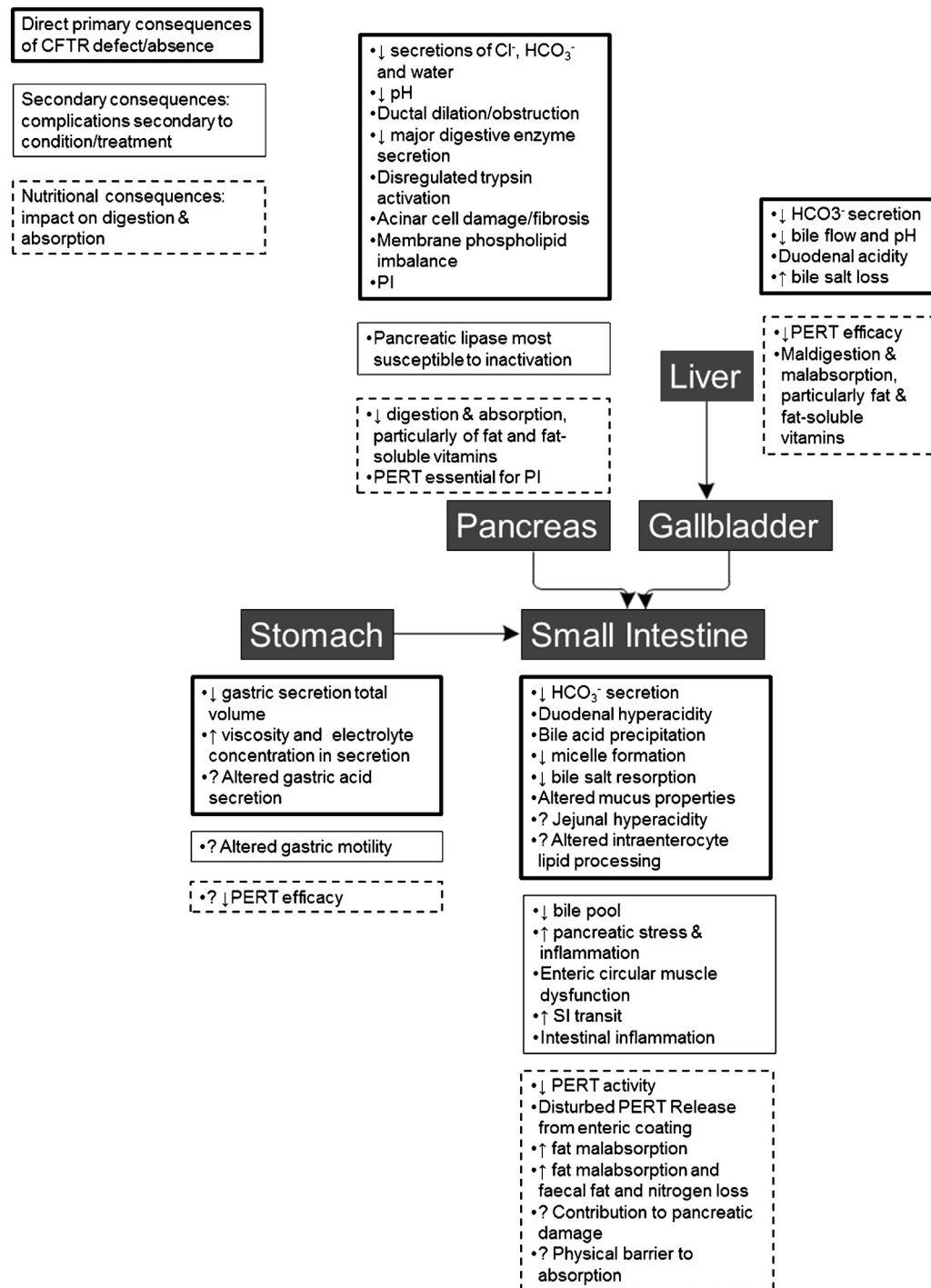


Fig. 1. Schematic representation of pancreatic insufficiency and factors affecting pancreatic enzyme replacement therapy and lipid digestion and absorption. CFTR: cystic fibrosis trans-membrane regulator; PERT: pancreatic enzyme replacement therapy; PI: exocrine pancreatic insufficiency; SI: small intestine.

the distribution of CFTR throughout the digestive system revealed in rat and human intestinal biopsies [7,39]. Relevant locations include duodenal Brunner's glands, crypt cells, ductal cells in the pancreas and liver, and epithelial cells along gallbladder lumen that secrete HCO_3^- . Consequently, in CF where functional CFTR is absent, HCO_3^- content in the duodenum is diminished and may fail to neutralise the acidic gastric content [40,41]. This is thought to account for lower pH in the CF duodenum compared with that of healthy controls [42,43]. In the liver and gallbladder, HCO_3^- and fluid are either secreted through or mediated by CFTR to alkalise and hydrate bile [7,38,44]. This modification of bile is impeded in

CF, possibly mediated by ATP, which is normally regulated by functional CFTR [38,44,45]. Subsequently, the volume and pH of bile flow is reduced, adding to duodenal hyperacidity. Indeed, basal duodenal pH in CF is approximately 5.0 (cf. 6.0 in healthy controls) [25]. The difference is even greater postprandially (mean pH 3.6, cf. 5–7).

Hyperacidity in the duodenum hinders PERT efficacy by impeding the release and/or activity of pancreatic enzymes [42]. The enteric coating allows the enzyme release at $\text{pH} > 5.0$ [9,25,46]. The low duodenal pH is likely to hamper the dissolution of the acid-resistant coating and consequently postpone or even inhibit

the enzyme release until chyme has passed the major absorption sites in the duodenum and jejunum [42,46]. The acidic milieu also markedly reduces PERT activity (optimal pH range of 7–9) [9,47–49]. Consequently, the low pH in the CF duodenum reduces the therapeutic value of PERT in correcting maldigestion and malabsorption.

The pH status and hence the action of PERT in the CF jejunum is less clear. Although normal jejunal pH values (5.5–6.5) have been observed, pH values <5 have also been reported [25,50], indicating that PERT efficacy may be compromised in some cases despite relatively normal jejunal CFTR expression in CF [7].

In the ileum, pH status may be unaltered in CF [25,50], but its influence on PERT efficacy remains unclear. Ileal CFTR expression patterns resemble the duodenum and jejunum, apart from lacking the isolated distribution of cells with high CFTR expression [7]. However, its relevance to ileal pH status in CF awaits investigation. A mean pH of 7.23 in the CF terminal ileum has been reported [25,50], within the optimal pH range for PERT enzyme release and activation. Such CF ileal pH status may be explained *in vitro* where HCO_3^- secretion appears to be mediated by $\text{Cl}^-/\text{HCO}_3^-$ exchangers, in addition to CFTR [51]. However, the influence of the ileal pH status on PERT efficacy as well as digestion and absorption in CF requires evaluation.

Gastrointestinal motility may also be altered in CF, affecting PERT efficacy [42]. Investigations into the fasting motility of the upper GI tract in CF have shown variable results [27,52]. The postprandial gastric emptying rate may be either increased [53,54] or impaired in CF [52,55]. One study observed delayed gastric emptying in one third of the adults with CF [55]. These various disparities may be due to methodological variations. For example, increased gastric emptying rates were detected in studies employing scintigraphy [53,54], whereas decreased rates were observed in studies using other measuring approaches [52,55]. The macronutrient content of a meal, in particular fat content, can also modulate gastrointestinal motor function including gastric emptying [56]. However, the caloric and macronutrient contents of test meals were often not specified in these studies. Delayed gastric emptying may correlate with high oesophageal total bile exposure [55], which can occur in CF [57]. Gastric motility may also be influenced by total gastric secretion, which can be reduced in CF [27,58], thus increasing viscosity and electrolyte concentrations [58]. The increased viscosity of CF gastric mucin arises from augmented levels of covalently bound and associated fatty acids [59]. The viscosity of the total gastric content can change gastric motility and the emptying rate, which influences the delivery of PERT and hence nutrient digestion and absorption in CF with PI [42]. Thus, altered gastric motility, combined with hyperacidity determines the PERT efficacy. This in turn has important consequences for digestion and absorption in CF, particularly fat and fat-soluble vitamins.

2.3. Other factors influencing lipid digestion and absorption

Hyperacidity in the CF duodenum may exacerbate pancreatic inflammation [35] and hence PI. Duodenal hyperacidity causes excessive pancreatic HCO_3^- secretion in CFTR knockout mice, leading to up-regulation of pancreatic stress and inflammation genes [35]. CFTR expression in the proximal intestine is higher in murine than in rat or human models [60], while the opposite is seen in the pancreas [7,35]. Thus, whether duodenal hyperacidity aggravates pancreatic inflammation and contributes to PI in human CF needs clarification.

Hyperacidity in the CF duodenum may also precipitate bile [61]. This can impede micelle formation, and therefore lipid absorption by intestinal mucosa [62], when duodenal bile acid concentration drops below the critical micelle concentration [61]. Bile salt precipitation may also reduce the total bile pool [61] when the liver

is unable to fully compensate for excessive loss *via* enterohepatic circulation [62]. This loss is worsened when unabsorbed protein and neutral lipids bind to bile salts. Consequently, maldigestion and malabsorption of lipids is exacerbated by the hyperacidity in CF duodenum and by the lack of lipases due to PI (Fig. 1).

Lipid digestion and absorption in CF can be hindered by reduced bile acid resorption (Fig. 1). As the primary site for bile salt resorption, the terminal ileum has a highly efficient active Na-bile salt co-transport system [62]. The daily synthesis rate of bile salt is 0.2–0.4 g. Therefore, any chronic loss exceeding this amount can deplete the bile salt pool, impeding micelle formation and substantially contributing to fat maldigestion and malabsorption [63] irrespective of exocrine pancreatic function. Up to 50% of dietary fat can be lost in faeces in the absence of bile. In CF, reduced bile acid absorption is common. The cause appears to be multifactorial, including a primary defect in the CF ileal mucosa [64] and enhanced micelle formation owing to the presence of certain undigested and unabsorbed lipids in the ileum [65]. One study in adults with CF, however, excluded the role of intraluminal fat, together with small bowel bacterial overgrowth [66]. Correlations between bile acid excretion (and hence bile salt resorption) and faecal fat content (representing luminal fat content) as well as hydrogen breath excretion (indicating small bowel bacterial growth) have not been observed. Instead, mucosal defects due to thickened mucus and a negative regulatory role of CFTR in ileal bile acid resorption have been proposed [67]. Mucosal damage secondary to ageing may suppress bile acid uptake [63]. Although infants with CF have similar bile acid absorption rates to non-CF infants, the older age of the controls may have influenced the results, since animal models imply that uptake of bile acid increases with age during infancy [63]. Despite the unconfirmed mechanism, bile acid absorption in CF seems to be impaired in the ileum, where most bile acid should be reabsorbed and recycled to the bile salt pool. Increased faecal bile salt loss has also been ascribed to the lowered pH of bile flow due to decreased HCO_3^- secretion [45]. However, faecal bile loss may not be associated with fat malabsorption in CF murine models [68]. To what degree impaired absorption and increased loss of bile in CF have an impact on lipid digestion in humans with CF thus requires further investigation.

Another factor that can contribute to lipid malabsorption in CF is the impaired intra-enterocyte processing of lipids (Fig. 1) [69]. CF duodenal biopsies have shown grossly decreased esterification and secretion of lipids and significant reductions of lipid and apolipoprotein synthesis, despite normal transfer protein activity levels. This implies that altered intra-enterocyte processing of lipids may partly account for persistent fat malabsorption in individuals with CF on PERT in the duodenum. It remains unclear whether this is also the case in the lower intestine.

2.4. Factors influencing digestion and absorption of other nutrients

In the duodenum, the products of the pancreatic breakdown of proteins and carbohydrates are further hydrolysed into monomers by intestinal brush border glycosidases [34] and peptidases, and by intracellular mucosal cell peptidases [62,70]. This process of terminal digestion occurs all along the SI, but the duodenum and jejunum are the major sites for digestion and absorption. The ileum plays a major role in the terminal digestion of oligosaccharides and peptides, reflected by the high distribution of maltase and some peptidases [71–73]. The brush border digestive enzymes appear to be distributed unevenly along the SI segments [72,73].

Although carbohydrate and protein digestion and absorption seem to be less affected in CF, some evidence indicates alterations to brush border digestive enzyme activity and the uptake of final digestion products (Fig. 2). In CF, the activity of these brush border

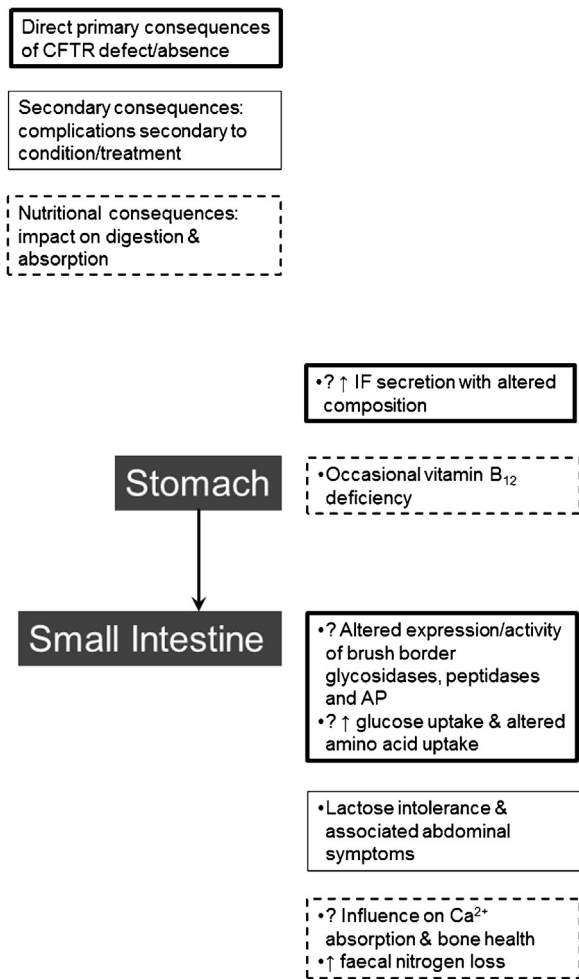


Fig. 2. Schematic representation of factors influencing digestion and absorption of nutrients other than fat and fat-soluble vitamins. AP: alkaline phosphatase; CFTR: cystic fibrosis trans-membrane regulator; IF: intrinsic factor.

digestive enzymes varies according to specific enzymes [74–77]. Maltase and sucrase activity in CF seem unaffected [77], but lactase activity can be lower in CF mucosa [74,76,77]. The quantity of lactase in CF may also be suppressed, depending on the genotype [78]. On the other hand, the higher frequency of genetic predisposition of lactase suppression among homozygous $\Delta F508$ may warrant the monitoring of lactose intolerance in this group. The possibility of lactase deficiency secondary to mucosal damage in CF, as occurs in coeliac disease, and the influence of *CFTR* on lactase gene expression still awaits confirmation. Lactose intolerance is an independent risk factor for low bone mineral density (BMD) in children with CF [79]. Clinical symptoms such as flatulence, abdominal pain and diarrhoea correlate with reduced calcium intake and BMD [80], contributing to impaired bone health in CF [81]. A better understanding of the dynamics of lactase activity in CF will assist in addressing bone health issues in this condition.

Reduced peptide hydrolysis activity and intestinal uptake of some amino acids have been reported in jejunal biopsies from children with CF [76]. Although *CFTR* expression is high in isolated mucosal cells throughout the crypts and villi [7,39], it is unclear whether functional *CFTR* absence affects brush border enzyme secretions. A better understanding of SI brush border digestive enzyme activity in CF will potentially inform clinical recommendations on the specific types of carbohydrates and proteins that are affected in CF.

Absorption of some amino acids may be altered in CF. Although glucose uptake may be enhanced, due to either a decreased perfusion barrier secondary to abnormal mucus [82] or enhanced Na-coupled nutrient transport from increased mucosal membrane potential due to defective Cl^- transport [83], this seems not to be the case for amino acids. Some studies found enhanced uptake of amino acids, while others observed reduced or normal uptake [83], particularly of neutral amino acids and dipeptides respectively [84]. The exact nutritional consequence of such malabsorption is unclear. However, significantly increased faecal nitrogen loss in CF children and young adults, partially attributed to excessive faecal amino acid loss, has been documented [85,86]. A CF murine model has highlighted that genetic factors other than *CFTR* mutations may have an impact upon nutrient absorption in the CF jejunum [87]. Further investigation into the absorption of amino acids and dipeptides in humans with CF is required.

Adding to macronutrient and fat-soluble vitamins, vitamin B₁₂ and calcium acquisition may also be impeded in CF. Parietal cells secrete intrinsic factor (IF), which mediates the digestive transport and absorption of vitamin B₁₂ [88]. Elevated secretion of IF upon stimulation by pentagastrin was reported in a small study of children with CF [89]. Unaltered biological activity of IF was observed in another paediatric CF group, but the carbohydrate composition of IF appeared altered [90]. However, food-derived B₁₂ assimilation is probably not greatly affected in CF [89], with only occasional reports of vitamin B₁₂ deficiency [91]. In contrast to observations in humans, decreased absorption of vitamin B₁₂ has been demonstrated in CF murine models, in which the gene coded for the endocytic receptor for absorption of the IF–vitamin B₁₂ complex was down-regulated [92]. The extent of the impact of CF on vitamin B₁₂ assimilation in humans requires clarification. Meanwhile, reduced activity of brush border alkaline phosphatase [93], which suppresses intestinal calcium uptake induced by high luminal calcium concentrations [94], may be related to calcium absorption and bone health in CF, in addition to potential lactose intolerance. Further research is required to assess its influence on calcium absorption, since bone disease has emerged as a common comorbidity with increasing life expectancy in the CF population [95].

2.5. Other contributors of maldigestion and malabsorption

Other complications in the CF small intestine that may contribute to maldigestion and malabsorption include small intestine bacterial overgrowth (SIBO), enteric circular muscle dysfunction, abnormal intestinal mucus, SI inflammation and decreased gastrointestinal transit time (Fig. 3). Prevalence of SIBO based on breath test results is 30–50% among CF patients [96]. Bacterial overgrowth can compete for ingested nutrients, interfering with digestion and absorption. Certain bacteria such as *Clostridium perfringens* produce hydrolases that can deactivate bile acids [97], leading to impaired micelle formation and consequently impaired lipid digestion and absorption. Approximately 6% of the bacterial overgrowth in the SI of a CF knockout murine model consists of *C. perfringens* [98]. Significant weight gain has been observed in CF mice whose SIBO was eliminated using antibiotics, implying that SIBO might impair nutrient acquisition in CF. Delayed SI transit may impede digestion and absorption in CF indirectly by disrupting the interdigestive migrating motor complex, which helps to minimise the bacterial load in the SI between meals [99]. Dysfunctional circular smooth muscle has been observed in CF murine SI [100]. This dysfunction relates to prostaglandin levels modulated by intestinal bacteria such as *Escherichia coli* and *Enterobacteriaceae*, which predominate in the microbiota of SIBO. Prolonged SI transit may also be caused by undigested lipid due to insufficient active forms of bile acids, leading to activation of the ileal brake, which slows SI transit [96]. Distribution

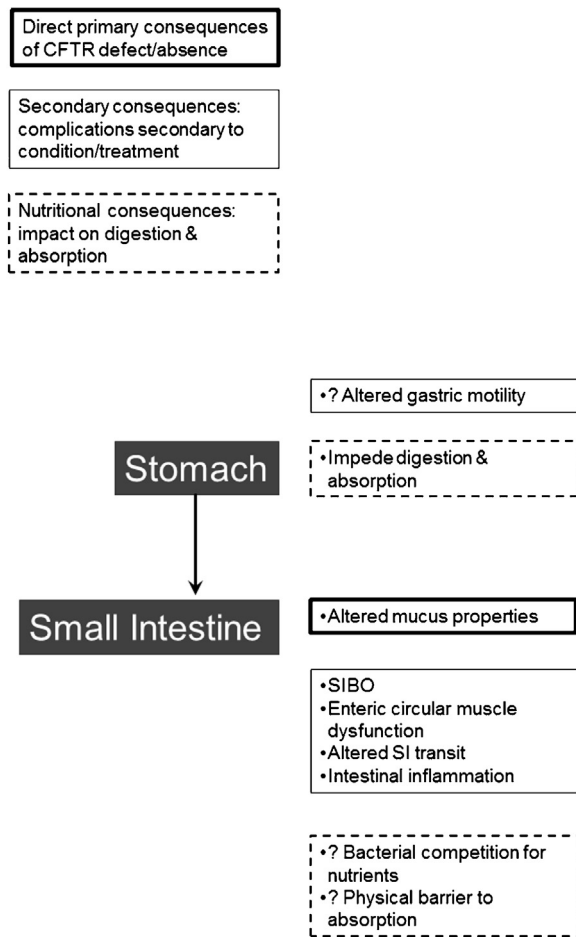


Fig. 3. Schematic representation of other factors influencing digestion and absorption in cystic fibrosis. CFTR: cystic fibrosis trans-membrane regulator; SI: small intestine; SIBO: small intestinal bacteria overgrowth.

and components of enterocytes with notably high CFTR expression in the rodent SI implies an important role for these cells in clearing adherent mucus from the epithelium for effective nutrient absorption by the secretion of a high volume of fluid [101]. Thus, fat and fat-soluble vitamin absorption may be distorted by abnormal SI mucosa [42], since the diffusion of micelles across the thickened, dehydrated unstirred water layer may be less efficient [11]. Murine CF models have also demonstrated weakly acidic and sulphated intestinal mucus that may alter SI function and nutrient diffusion [42]. Low grade SI inflammation, found in both murine and human CF models [42,92,102], may also impede mucosal function, further impairing fat and, possibly, vitamin B₁₂, absorption [11]. In addition, accelerated gastrointestinal transit due to aberrant enzyme output in CF with PI, independent of PI aetiology, may also impede digestion and absorption [9].

Throughout the process of digestion and absorption, carbohydrates and proteins are digested by enzymes secreted by the salivary, gastric, pancreatic and intestinal glands. Therefore, protein and carbohydrate digestion is substantially maintained in the absence of pancreatic proteases and amylase and thereby in CF with PI [10]. Conversely, the major enzymes responsible for lipid digestion are secreted by the pancreas. Decreased pH secondary to impaired HCO₃⁻ secretion by the pancreas, duodenum, liver and gallbladder due to defective or absent CFTR can affect PERT efficacy, despite adjunct therapy. This is likely exacerbated by the susceptibility of pancreatic lipase to proteolysis. Consequently, maldigestion and malabsorption, particularly of dietary fat and

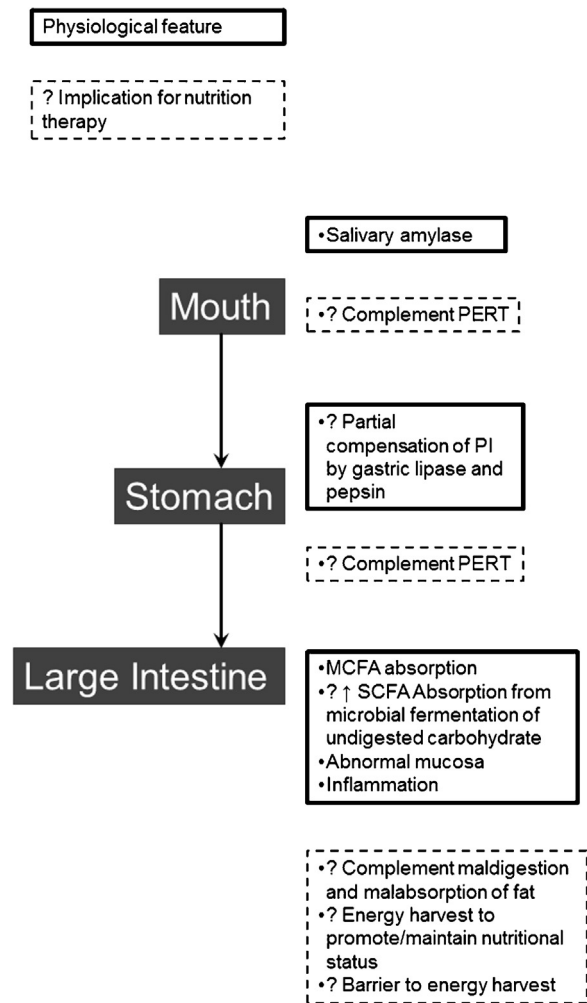


Fig. 4. Potential enhancers of and associated barriers to nutrition therapy. MCFA: medium chain fatty acid; SCFA: short chain fatty acid; PERT: pancreatic enzyme replacement therapy.

fat-soluble vitamins, is common and remains a priority for nutrition therapy in CF [68].

3. Potential enhancers of nutrient and energy acquisition

While CF manifestations and complications in the digestive system can impede nutrient acquisition, other aspects of the digestive system in CF may potentially enhance energy and nutrient acquisition (Fig. 4).

Salivary amylase and gastric lipase and pepsin may compensate for the maldigestion and malabsorption in CF due to PI. Similar salivary amylase activity levels have been found in CF children and controls [103]. Several small studies have highlighted the potential value of lingual lipase for lipid digestion in CF [104–106]. Subsequently, gastric lipase was found to account for almost all pre-duodenal lipase activity in humans, with limited lingual lipase contribution [107]. Indeed, studies on gastric lipase and protease have reported more promising findings. Gastric lipase and protease (pepsin) are secreted by chief cells in the stomach [34,108], which also express CFTR [7]. Intriguingly, one paediatric CF study showed that the basal and postprandial output and activity of these two enzymes are similar to, if not higher than, normal adult references [109]. These results are likely to be relevant to adults with CF, since CFTR functions in foetal and adult digestive tracts are comparable, unlike those in the respiratory system [7]. In addition, gastric

lipase, with an optimal pH of 5.4 [110], seems to have a higher activity in the acidic CF duodenum [111], in contrast to PERT lipase. Thus, the acidic duodenal environment may extend the activity of gastric lipase and partially compensate for fat maldigestion in PI. These two enzymes may partially alleviate maldigestion and malabsorption due to PI in CF [108,111]. Notably, gastric lipase accounts for up to 90% of total postprandial lipase activity in the upper small intestine in patients with CF and PI [109]. Despite this, exogenous enzyme supplementation still seems necessary, particularly for the high fat diet commonly recommended for individuals with CF and PI [112]. This is because the output and activity levels of gastric lipase and pepsin in participants with CF do not seem to increase with dietary fat content [109]. Moreover, most studies investigating the efficacy of gastric lipase in CF engaged only small samples and are somewhat dated. Even fewer studies have examined the efficacy of pepsin in CF. Further studies with larger samples are needed to evaluate the potential therapeutic value of these enzymes to complement PERT, which has shown variable efficacy in CF [68,112].

Apart from PERT usage, the large intestine and its microbiota may offer the potential to increase energy harvest in CF [113]. Only small amounts of the nutrients not absorbed in the upper GI tract can be salvaged by the colonocytes alone [34]. These are mainly water and electrolytes, the majority of which have already been absorbed in the jejunum and proximal ileum [11]. However, CF murine models have demonstrated that medium chain fatty acids, C18 in particular, can also be absorbed in the colon [114,115]. Microbial metabolites of nutrients that have escaped absorption in the upper GI tract (e.g. short chain fatty acids [SCFA]) are also absorbed here [34]. In humans with intestines of normal length and function, approximately 5–10% of energy requirements are derived from the colonic microbial fermentation of undigested and/or unabsorbed food components [116]. In patients with substantial intestinal resection, colonic fermentation can provide up to 1000 kcal/day [117]. Absorption of SCFAs may be enhanced in CF [118], although major SCFA species can stimulate glucagon-like peptide 1 production [119] and intestinal gluconeogenesis [120] associated with reduced weight and adiposity. Further research is warranted to evaluate the therapeutic potential of the colonic microbiota in rescuing energy lost in the upper GI tract due to PI and other GI manifestations of CF.

Abnormal colonic mucosa may also have an impact upon energy harvest in CF. Increased accumulation of insoluble mucus in the CF colon, together with other abnormalities in mucus quantity and thickness [121] may relate to abnormal transport of Na^+ and possibly HCO_3^- . Since normal mucins trap and bind bacteria [121], such mucosal abnormalities may affect the energy harvest from SCFA and potentially energy compensation by gut bacteria in CF. Furthermore, the microbiota may be altered in inflammatory bowel disease, particularly Crohn's disease [122]. A CF knockout murine model has indicated altered expression of genetic factors involved in the development of colitis or Crohn's disease [123]. In CF, altered gut microbiota has also been reported [124–126]. The extent to which bowel inflammation can affect the gut microbial community and its capacity to rescue energy in health and CF await investigation. The extent of the influence of mucus abnormalities on potential colonic energy harvest in CF is undetermined and the therapeutic value of colonic energy harvested from SCFA also needs further analysis. A CFTR-knockout murine model has also implied the potential absorption capacity of fat soluble vitamin E in the CF colon [115]. This requires investigation so that supplementation regimens for fat-soluble vitamins including vitamin E in CF can be optimised.

Alleviation of an abnormal EFA profile using n-3 polyunsaturated fatty acid (PUFA) supplementation may also potentially improve digestion and contribute to nutritional management in

CF owing to its anti-inflammatory [127] and anti-bacterial effect [128]. Although publications on the efficacy of dietary n-3 PUFA supplementation in improving digestive functions (including the pancreas and intestine) in CF are lacking, improved EFA profiles in the CF intestine [129,130] and blood (serum and red blood cells) [129–132] *in vivo* and in the respiratory tract *in vitro* [133,134] post-supplementation have been reported. Despite controversies [129,130,132], improved lung function, inflammatory markers and nutritional status have been reported after one-year oral supplementation of mixed n-3 PUFA [131]. However, the different supplementation regimes and study designs have not allowed the Cochrane Systematic Review to confirm the efficacy of n-3 PUFA supplementation in CF management [127]. In fact, the influence of dysfunctional digestion and absorption in CF on the uptake of n-3 PUFA has not been reported. The efficacy and effectiveness of such dietary supplementation in improving the digestive function in CF require evaluation, as abnormal EFA metabolism in CF may be indirectly linked to dysfunctional CFTR by activation of a protein kinase-regulating lipid metabolism *via* abnormal cellular Ca^{2+} metabolism [135].

Interestingly, abnormalities in the CF intestine may serve as biomarkers to complement CF diagnosis, particularly in cases of 'non-classic CF', and/or indicate clinical outcomes for trials of CF therapeutics [136], thus paving the way for more efficient CF management including digestive health. Examples are the intestinal current measurement [137,138] and faecal fat tests [139]. Protein biomarkers constitute another such group, which can potentially be identified using various proteomic techniques [140] adapted for use in the CF context [136]. Faecal calprotectin is such an example, which can be used to indicate intestinal inflammation [124].

4. Conclusion

In summary, it seems that a variety of manifestations of CF and associated complications contribute to maldigestion and malabsorption, affecting nutritional status in the long-term. Acquisition of fat and fat-soluble vitamins remains the major nutritional challenge in CF owing to the susceptibility of pancreatic enzymes and variable efficacy of PERT in individuals with CF and PI. Nutritional status of vitamin B₁₂ and calcium also requires regular monitoring for individuals with specific GI complications. Gastric digestive enzymes and gut microbial bacteria may have the therapeutic potential to complement current PERT and dietary therapies to improve nutritional status and hence survival in CF. Correction of EFA abnormalities in the CF digestive system using dietary n-3 PUFA supplementation has shown some promise, and the use of intestinal biomarkers has shown potential in the diagnosis of CF and/or evaluation of CF therapeutics. Future investigation is required to evaluate the feasibility and efficacy of these approaches to further improve CF management.

Conflict of interest

None declared.

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