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Cystic Fibrosis in the Intestine and the Influence on Digestion

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Article Info

Abstract

Anything that affects the absorption of nutrients and intestinal function will invariably affect the physical well-being or the health status of an individual. Cystic fibrosis is a disease condition that is autosomal recessive and affects organs that have epithelia including the gastrointestinal tract of which the intestine is part, and is the one that is primarily affected. The major aberration responsible for it is mutations in the cystic fibrosis transmembrane conductance regulator gene. Phenotypical evidence of cystic fibrosis in the intestine includes obstruction, microbial dysbiosis, inflammation, acidity in the intestinal tract, malnutrition, immune dysfunction, intestinal dysmotility, appendiceal aberrations and intussusception. All these manifestations result in maldigestion and malabsorption of lipid, protein and carbohydrate in the intestine. The effect of cystic fibrosis on the digestion of certain micronutrients was also reported.

In this review, the pathophysiology, manifestations of cystic fibrosis in the gastrointestinal tract with emphasis on the small intestine, and the effects on digestion of macronutrients and micronutrients would be discussed.

List Of Abbreviations

CF- cystic fibrosis, CFTR- cystic fibrosis transmembrane conductance regulator, cAMP- cyclic adenosine monophosphate, cGMP- cyclic guanosine monophosphate, mRNA- messenger ribonucleic acid, GIT- gastrointestinal tract, EPI- exocrine pancreatic insufficiency, DIOS- distal intestinal obstructive syndrome, SIBO- small intestinal bacterial overgrowth, GI- gastrointestinal, CD- celiac disease, IBD- inflammatory bowel disease, PERT- pancreatic replacement therapy, PI- pancreatic insufficiency, NF-κB- nuclear factor kappa B, LXR/RXR- liver-X-receptor/retinoid-X-receptor, TLR- toll- free receptor, BMI- body mass index, NSBP -newborn screening-program .

Introduction

Cystic fibrosis (CF) is a disease condition which is precipitated by mutations in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR, a cyclic adenosine monophosphate (cAMP)-regulated chloride ion channel, is well expressed in various epithelia and at much lower levels in many other cell types. CFTR in the intestine facilitates the secretion of chloride, bicarbonate, and fluid. Anderson *et al*[1] reported that the basic roles of the gastrointestinal epithelium are: (1) to act as a physical barrier that selectively permits the absorption of nutrients; as it (2) excludes pathogenic or toxic substances; and (3) to secrete substances that facilitate the digestion process. All of these roles require large amount of water, nutrients, and ions to be transported across the epithelial layer. The impetus for this is made possible through ion gradients and therefore the activity of ion channels such as Na^+, K^+, Ca^{2+}, and other Cl^-

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channels which are regulated by CFTR[2,3]. The deficiency or dysfunction of CFTR would therefore lead to a malfunction in these roles. Moreover, the review by Eisenhut[4] has shown that inflammatory mediators such as tumor necrosis factor, interferon gamma and probably nitric oxide are involved in modulating the activity of the ion channels in the light of CFTR dysfunction, and the messengers involved in the intracellular translation of the signal of the inflammatory mediators are cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) which are linked to protein kinase. Biallelic inactivating mutations in the CFTR gene may result in partial or total dysfunction. This compromise in the milieu is believed to be the major cause of pathogenesis for cystic fibrosis in affected organs, including the intestine[2,3,5].

For clarity, the domains of CFTR, which span the entire membrane, form an aqueous channel that permits the passage of Cl^- and HCO_3^- ions down their electrochemical gradients. In the intestine, this is from the cytoplasm of epithelial cells to the intestinal lumen, especially the intestinal crypt lumen. This movement of ions out of the cell increases osmotic pressure for the passage of water in the same direction. Thus, CFTR can also be said to indirectly determine water homeostasis. In essence, in the gastrointestinal tract (GIT), CFTR function is critical for ion and water homeostasis[3,6-8].

The dehydration of various secretions (e.g. mucus) at affected sites thus sets in and results in the precipitation of secretions and intra-ductal blockage, inflammation, fibrosis and eventual damage to the organs, especially in the presence of digestive enzymes[9,10]. This is the common pathophysiology although the exact manifestation is site-specific[11].

The CFTR gene is strongly expressed all along the intestinal tract[12]. However, there is a cephalo-caudal gradient with CFTR messenger RNA (mRNA) levels highest in the duodenum and mucus secreting Brunner's glands, and levels decrease distally along the small intestine to the ileum with moderate expression in the large intestine. There is also a gradient of expression along the crypt – villus axis with greatest expression in the small intestinal crypts and near the base of the crypts in the large intestine[2,6].

As a result of the aforementioned, gastric acid is not properly neutralized in the intestine by bicarbonate secretion which is highest in the proximal intestine that receives a high acid load from the stomach. This neutralization of acid by bicarbonate supports maximal function of the digestive enzymes from the exocrine pancreas and solubility of bile salts from the biliary tract, and therefore its absence or reduction serves to contribute to poor digestive function in the intestine which is observed in CFTR dysfunction[2]. Furthermore, the intestine receives a large volume of bicarbonate-rich fluid from the pancreas, which is also compromised in CF patients[13].

This review addresses the pathophysiology, signs and symptoms of gastrointestinal manifestations of CF as well as the influence on digestion of macronutrients and micronutrients.

Evidences Of Cf In The Intestine

CF affects the GIT primarily, especially in neonates, resulting in damage[2]. Exocrine pancreatic insufficiency (EPI) is manifest in 60-90% of patients having severe CFTR mutations which progresses to about 85-90% of patients with age[13-16]. The absence of the bicarbonate-rich pancreatic fluids which consists of enzymes essential for the digestion of ingested food further contributes to the symptoms and signs of gastrointestinal manifestations. The manifestations include the following: obstruction, microbial dysbiosis, inflammation, acidity in the intestinal tract, malnutrition, immune dysfunction, dysmotility, appendiceal aberrations and intussusceptions [2,6,17].

Obstruction

The deficiency in bicarbonate secretion, which results in a relatively dehydrated luminal environment and postprandial acidity in the proximal small intestine, culminates in the accumulation of mucus in the CF intestine which appears to be the most important pathological manifestation that precedes other manifestations in CF disease[2,18]. The most severe acute manifestation is obstruction of the terminal ileum (proximal large intestine) which can result in rupture and sepsis if untreated. In CF neonates the condition is called meconium ileum (MI) (i.e. diminished or absent peristalsis due to failure to pass meconium)[2]. In older CF patients, obstruction is called distal intestinal obstructive syndrome (DIOS). The substance responsible for the obstruction in DIOS is made up of mucus and fecal-type matter which is comprised of undigested materials and a high content of bacteria, and is therefore referred to as being "mucofeculant"[2]. DIOS is identified by partial or complete obstruction of feces in the ileocecum and the prevalence has been found to be 7 times more in adults than children with CF in certain studies conducted in Europe[19]. Chronic low-grade obstruction, which presents in CF patients as obstipation or constipation, has also been shown to be prevalent in 26- 46% of patients[20,21].

Microbial Dysbiosis

Dysbiosis is the imbalance in the gut microbiome that results in the manifestation of diseases. This can be as a result of four effects; altered microbiome, antibiotics, altered luminal environment and physiology of the CF small intestine, and mucus accumulation and mucins of which some will be discussed. Moreover, link between carcinogenesis and alteration in GI microbial dysbiosis has recently been proposed [22]. There are two barriers in the colonic epithelium which when compromised can result in damage as a result of immune cell infiltration and

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inflammation: the apical surface of the colonic epithelium and tight junctions between the basolateral surfaces of intestinal epithelial cells[3]. It can also culminate in altered migration and invasion by cancer cells. Microflora also produce signaling molecules that regulate immune cell homeostasis such as lipopolysaccharides that can bind to similar corresponding recognition receptors on epithelial cells to evoke the intestinal cell immune response[3]. Vernocchi *et al.*[23] using targeted-metagenomics and metabolomics demonstrated that the CFTR impairment results in gut ecosystem imbalance.

a)   Effect of altered microbiome

The microbiome in the CF intestine is dense and altered in location, cell density and diversity. Failure in the statutory mechanisms in the small intestine which includes peristalsis, antibacterial proteins, gastric acid, intestinal fluid and the ileocecal valve can result in small intestinal bacterial overgrowth (SIBO). This can advance into abdominal distension, steatorrhea, weight loss, diarrhea, macrocytic anemia and flatulence[24-26]. Moreover, accumulation of mucus, mucosal immune malfunction, ion and fluid abnormalities and malabsorption affect the GI luminal nutrient pool[27,28]. An intestinal parasite, *Giardia lamblia*, has been shown to be involved in diseases linked to pancreatic insufficiency, including cystic fibrosis[17]. Also, Coffey *et al.*[29] have demonstrated that microbial taxonomic dysbiosis (and probably the corresponding functional dysbiosis) have contributed to gastrointestinal disease in paediatric CF.

b)   Effect of antibiotics

Antibiotics, when ingested, douse or remove the normal commensal bacterial strains and may also enhance selective antibiotic-resistant bacterial overgrowth[30]. In CF patients, *Oxalobacter formigenes* (an important commensal bacteria that metabolizes oxalate), is usually lost after antibiotic use. This results in CF patients being at increased risk of formation of calcium-oxalate kidney stones and hyperoxaluria. Also, *Clostridium difficile* infection occurs often after antibiotic use in CF patients. However, most of these patients are asymptomatic. This may be as a result of the deficiency of functional CFTR because *C. difficile* induces secretory diarrhea as a result of a toxin that activates CFTR-dependent Cl⁻ secretion[2,31].

c)   Effect of mucus accumulation and mucins

Accumulation of mucus in the intestinal lumen in CF provides an environment for abnormal microbial colonization which can result in microbial dysbiosis such as SIBO[2]. Intestinal motility and gel-forming soluble mucins (majorly MUC2) secreted from goblet cells serve to maintain low bacterial load in the proximal small intestine[22,33]. Mucus can be adherent and at the same time act as a lubricant. Bacteria bind to the complex oligosaccharides on the mucin molecules

while intestinal motility removes the mucus-bacteria complex distally toward the large intestine. In the face of CF, the mucus is excessively sticky and slimy, and intestinal motility is abnormally slow. In the light of these, bacteria bind to the static mucus and this culminates in abnormal colonization and overgrowth of the small intestine[2].

Inflammation

a)   CF and GI disease

Increased levels of inflammatory markers in the lumen of CF small intestine were revealed by endoscopic lavage[34]. Another endoscopic study presented normal morphology of the CF duodenum but the biopsied tissue showed increased levels of several inflammatory markers[35]. Werlin *et al.*[36], using video-equipped capsule endoscopy, showed morphological aberrations which included erythema, ulcerations, edema and mucosal breaks in the ileum and jejunum in >60% of CF patients with significant increases of fecal calprotectin (a neutrophil secretory product) as is expected in intestinal inflammation[27]. Ikpa *et al.*[28] demonstrated in the ileum of CFTR null mice that gut inflammation was associated with a marked overall reduction in the activity of type II ligand-dependent nuclear receptors, which was proposed to strongly affect fatty acid, sterol, bile acid and xenobiotic metabolism and transport. Moreover, in addition to these marked effects on lipid handling, Ikpa *et al.*[28] noted that CF was associated with reduced expression of genes involved in the absorption of other nutrients. Also, most of the observed changes in gene expression in the ileal sections were corrected by antibiotic treatment. Thus suggesting that dysbiosis markedly affects enterocyte maturation in CF[27]. *Escherichia coli* is a bacterium whose chief source of nutrients has been found to be mucus-associated sugars in healthy GI tract and the proliferation of mucus-metabolizing *E.coli* populations could, therefore, be favoured by accumulated mucus[27,37]. Martinez-Medina *et al.*[38] and Hoffman *et al.*[27] amidst other studies by other researchers have shown that inflammation, as a result of changes in the CF intestinal lumen, increases the colonization of the gut mucosa by *E. coli* and further promote inflammation. Based on scientific evidences, Hoffman *et al.*[27] have deduced that early determination of *E. coli* dysbiosis could indicate severe GI disease, resultant poor growth and associated CF clinical observations. When the disease has advanced, regardless of the mechanism, the presence of high fecal *E. coli* could be contributory to inflammation in the GI, affect lipid metabolism and absorption, malnutrition and exacerbate the disease condition (i.e. CF GI disease)[39,40].

b)   CF and celiac disease

CF can result in the development of celiac disease (CD) as a result of pancreatic insufficiency leading to impaired protein digestion which normally degrades the gliadin

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antigen[2]. Wheat gliadin and prolamine protein present in grains elicit the immune response that occurs in CD, which is a destructive autoimmune disease of the small intestinal mucosa that precipitates malnutrition and is prevalent in CF[41,42]. Therefore, removal of wheat-derived products from the diet can help the disease condition. Small intestinal biopsy and histological diagnosis, which is based on observing villus atrophy and elevated intraepithelial lymphocytes, are the most reliable methods of detection[2]. Also, inflammatory bowel disease (IBD) can also ensue as a result of CF and the diagnosis is similar to that of celiac disease[19].

c) CF and Crohn's disease

A 12.5-fold increased prevalence of Crohn's disease has been reported in CF patients compared to the general population. This is because genetic and environmental factors which include exposure to bacterial antigens or pathogenic bacteria and immunological interactions with gut microflora are present in CF patients[43]. However, since serum biomarkers for inflammatory bowel disease may be falsely negative or positive in CF patients (i.e they lack sensitivity and specificity), cases need to be confirmed with combination of these biomarkers and especially biopsy[44,45]. Rectal biopsy has been shown to be very effective in clarifying CF cases and there are two methods; intestinal current measurement and intestinal organoids. Therefore it is preferred because rectal tissue can be collected safely and painlessly[17].

.Generally, the intestinal inflammation markers found enhanced in CF patients are cytokines (IL-8, IL-1β), cellular constituents (neutrophil elastase, eosinophil cationic protein), plasma proteins (IgG, albumin, alpha-1-antitrypsin IgG) in whole–gut lavage samples, and elevated calprotectin in fecal samples[17].

The effect of acidity in the Intestinal tract

In CF, the acidic pH of the proximal small intestine can precipitate bile salts and thus contribute to their inability to digest and assimilate lipid[11]. With the aid of endoscopy in several studies, the pH in the intestinal tract of CF patients has been measured. The findings have shown increased acidity in the proximal small intestine for a longer time than in control patients[46-48]. This was further corroborated by the findings of Gelfond *et al*.[18] using capsule endoscopy (SmartPill). This showed that for the first 30 mins, the CF small intestine was abnormally acidic after gastric emptying, which is a critical time for mixed micelle formation of bile salts with lipid digestion products. Furthermore, it is a critical time for pancreatic replacement therapy (PERT) tablet dissolution, thus affecting its efficacy. PERT is produced as microbeads containing enzymes, which are enteric coated so that the enzymes can pass unaffected through the acidic lumen of the stomach and then dissolve in the less acidic pH of the duodenum[2].

Malnutrition

The major cause of maldigestion in CF is exocrine pancreatic insufficiency which can be treated by PERT[49]. However, low body mass index which is an indication of nutritional deficit, is also observed in a significant proportion of pancreatic-sufficient patients[50], thus, pointing to abnormality in the small intestine. Steatorrhea (malabsorption of lipids) and malabsorption of fat-soluble vitamins are also observed[51]. Proper fat digestion and assimilation processes are biochemical and occur in the gut lumen with the absorptive enterocytes being involved. Several studies have been carried out to investigate these processes in CF patients[52,53]. Using stable isotope-labelled fatty acids, biopsies and other conventional methods, it has been revealed that re-esterification of absorbed fatty acids and release from enterocytes was slower and it has also been shown that postlipolytic solubilization and/or uptake of long chain fatty acids was impaired. Thus indicating altered luminal environment and intestinal mucosal aberrations respectively. Furthermore, the altered microbiome in the intestine of CF patients discussed above can contribute to malnutrition by deconjugating bile salts which then makes them ineffective to emulsify fats for digestion and absorption, as well as competing with the host for ingested nutrients. Inflammation can also ensue as a result of these effects and impair mucosal digestive functions[2,54].

Immune Dysfunction

There are observations that the dysregulation of CFTR expression in various immune cell populations in CF patients contribute to aberrant immune cell activity in several organs, especially the lung and also likely in the GI tract. CFTR expression and dysfunction have been detected in monocytes/macrophages and dendritic cells of the peripheral innate immune response. These cells, via antigen presentation, can also influence adaptive T cell responses. The immune response may also be influenced by CFTR through its expression in lymphocytes and natural killer (NK) cells[55,56]. Moreover, neutrophil intrinsic impairment linked to degranulation has been shown to be as a result of CFTR dysregulation of neutrophils in CF patients[57].

Intestinal Dysmotility

Although the etiology of dysmotility in CF may be multifactorial, Dorsey and Gonska[6] have proposed that the smooth muscle function (i.e. the migrating motor complex) may be affected and SIBO may contribute to it. Gastroparesis (delayed gastric emptying) is a clinical phenotype of CF dysmotility that occurs frequently among CF patients[6].

Appendiceal aberrations

Appendiceal aberrations are reported lower in the cystic fibrosis population (1%) compared to the general

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population (7%). However, delayed diagnosis results in more complications including appendiceal abscess as this is masked by difficulties in interpreting ultrasonography findings, incorrect diagnosis of DIOS and acute symptoms by chronic antibiotic use[10,17,58,59]. A small paediatric study, with asymptomatic patients having cystic fibrosis and without appendicitis, revealed that 83.3 % of patients had an increased appendiceal diameter (> 6 mm) as a result of a mucus-filled lumen as shown by ultrasonography. This is usually a marker for acute appendicitis but this study shows that it is not a good criterion for diagnosing appendicitis in patients with cystic fibrosis[17,59].

Intussusception

One to two percent of patients with cystic fibrosis have one part of the intestine sliding into an adjacent part. An aberration known as intussusception and at a rate 10-20 times higher that observed in the general population[10]. It

is initiated by thickened muco-feculent material adhering to the intestinal mucosa or appendiceal mucocele[10,17]. Most intussuceptions are ileocolonic in nature of which about 25% of them are linked with small bowel obstruction[17,60].

All of these manifestations enumerated above has been corroborated by various studies using different transgenic mouse models of CF as well as crossing them with other transgenic lines[61-70]. These studies have supported the following sequence of events for the pathophysiology of CF in the intestine: (1) loss of functional CFTR results in deficient anion and fluid transport; (2) the altered luminal environment impairs turnover and clearance of mucus; (3) static mucus allow abnormal bacterial colonization (microbial dysbiosis); (4) microbial dysbiosis alters immune system behavior; and (5) immune responses further stimulate mucus production and other events[2].

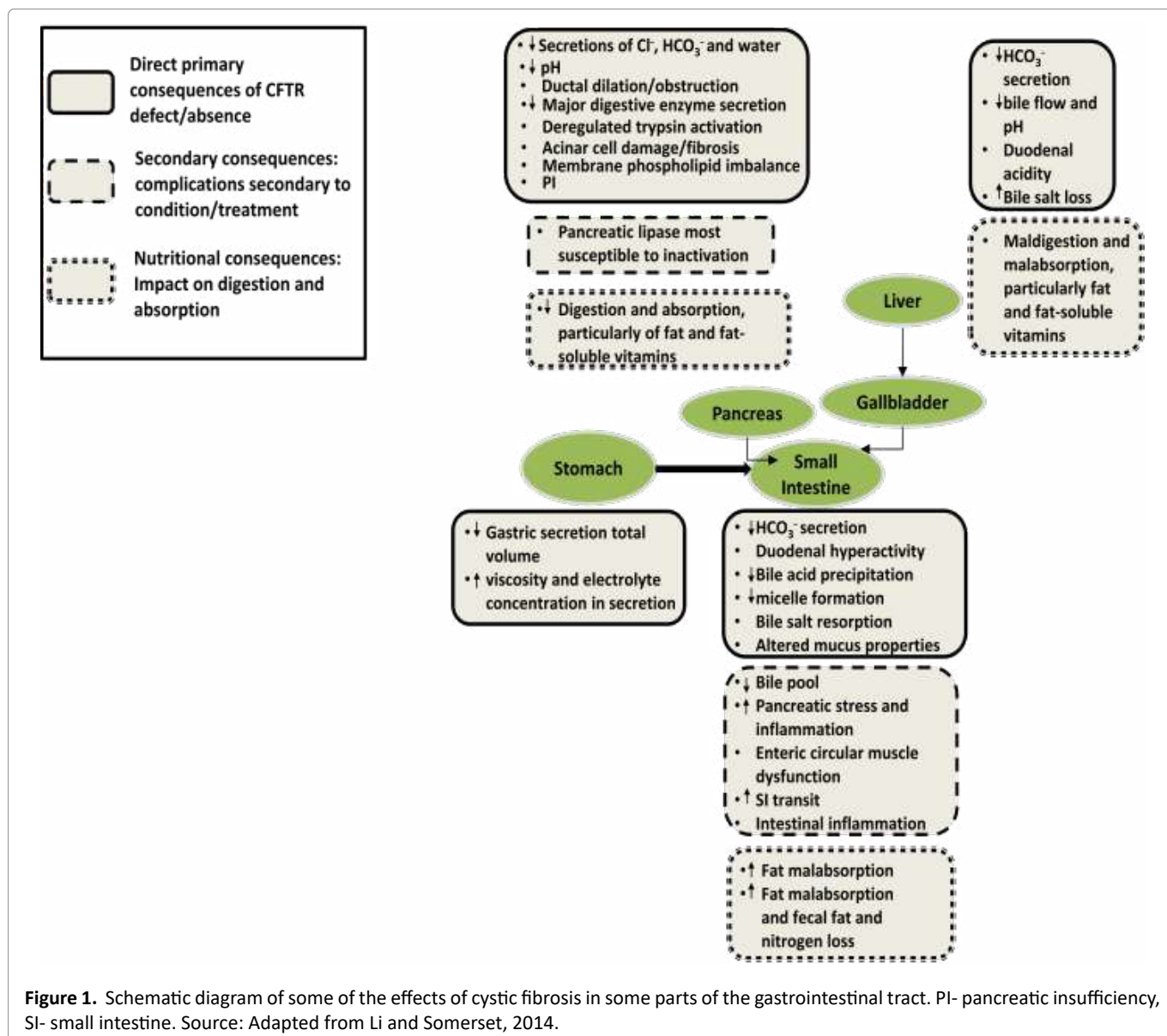Below in Figure 1 is a model to illustrate some of the

Figure 1. Schematic diagram of some of the effects of cystic fibrosis in some parts of the gastrointestinal tract. PI- pancreatic insufficiency, SI- small intestine. Source: Adapted from Li and Somerset, 2014.

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effects of cystic fibrosis in some parts of the gastrointestinal tract.

Cf And The Pancreas

Although the pancreas is not part of the GIT, it secretes digestive enzymes such as pancreatic amylase, colipase, lipase and protease which are responsible for the digestion of protein, carbohydrate and lipid by the secretion of the enzymes into the duodenum[71-73]. Inactive pancreatic digestive enzymes are secreted by the pancreatic acinar cells into the acinar lumen and extends to the pancreatic ducts[10,72,74]. In the ducts are ductal cells, which upon induction by cAMP, release bicarbonate (HCO_3^-) to make the acinar secretions alkaline and dilute as well as neutralize gastric acid present in the duodenal lumen[12,75].

Moreover, CFTR is highly expressed in the pancreas under normal conditions, especially in the small intercalated ducts that link the acini[12,13]. Therefore the dysfunction of CFTR in CF thus leads to decreased ductal cell secretions of HCO_3^-, Cl^-, water and lowers pH . The resultant concentrated secretions, especially in the presence of macromolecules cause dilation and obstruction of the ducts[10,75,76]. Other aberrations include (i) damage of the pancreatic epithelium as a result of lower ductal pH because trypsinogen (inactive trypsin) remains inactivated in the normal alkaline medium in the pancreatic duct, therefore when ductal secretion of HCO_3^- is diminished, trypsinogen is activated into trypsin and irreversible damage is done to the acinar cells with fibrosis which further reduces the synthesis and exocytosis of pancreatic digestive enzymes and HCO_3^- (ii) depreciation in the digestion and neutralization of the acidic duodenal content[73,77,78].

The outcome of all these dysfunctional events is exocrine pancreatic insufficiency (PI) which is the leading cause of maldigestion and malabsorption in CF and manifests clinically when less than 5–10% of the normal prandial enzymes are secreted. Although in moderate PI, a compensatory release of pancreatic enzyme in response to nutrients (particularly undigested (triglycerides) can occur[71,73,77,79,80]. As earlier stated, the prevalence of PI in CF condition increases with age and it has been shown to affect approximately 85–90% of CF patients worldwide[10,74,81,82].

Scientific evidence of other factors that contribute to PI have also been documented or proposed and this include (i) inappropriate incorporation, especially in excess, of membrane phospholipids (such as arachidonic acid and docosahexaenoic acid)[74,83,84] (ii) abnormal profile of essential fatty acids[83,85] (iii) strong correlation with the ΔF508 mutation (the most common mutation) of CFTR gene[83,86].

Influence Of Cf On Digestion

a) CF and lipid maldigestion and malabsorption

The nature of the macronutrient determines the effect of PI on digestion and absorption[73]. Lipid digestion is markedly affected in CF with PI, resulting in steatorrhoea in untreated patients. This is as a result of the effect of low pH, low bile acid content and proteolysis by pancreatic chymotrypsin on pancreatic lipase[11,74,79]. Gastric lipase liberates only about 10–30% of fatty acids from fat emulsions[73]. Therefore, it is the maldigestion and malabsorption of dietary lipids and hence fat-soluble vitamins in the majority of individuals with CF if untreated, that contribute to the malnutrition. As a result of this, patients with CF and PI are supplemented with exogenous pancreatic enzymes, which is called pancreatic enzyme replacement therapy (PERT)[11].

Other factors may also contribute to these observations. Although yet to be confirmed in humans, it has been shown using CFTR knockout mice that duodenal hyperacidity results in excessive pancreatic HCO_3^- secretion thus exacerbating pancreatic inflammation up-regulation of pancreatic stress and inflammation genes[87]. Pencharz and Durie[88] have also reported that hyperacidity in the CF duodenum may also precipitate bile, resulting in micelle formation and lipid absorption by intestinal mucosa being hindered because duodenal bile acid concentration has reduced below the critical micelle concentration. Furthermore, the precipitation of bile salt may also reduce the total bile pool as a result of the liver being unable to fully compensate for the excessive loss via enterohepatic circulation. This loss is exacerbated when unabsorbed neutral lipids and protein bind to bile salts. Thus, maldigestion and malabsorption of lipids is exacerbated by the hyperacidity in CF duodenum and by the lack of lipases due to PI[11,88].

Li and Somerset[11] and Sarenac and Mikov[89] have reported that lipid digestion and absorption in CF can be hindered by reduced bile acid resorption, which takes place primarily at the distal ileum because of a highly efficient active apical Na-dependent bile acid transporter (ASBT) located in the apical membrane of the enterocyte. This is regardless of exocrine pancreatic function. Moreover, there is scientific evidence that CFTR dysfunction does not play any role in ileal bile acid resorption[11].

The findings of Mailhot et al.[86] indicated that fatty acid homeostasis, in the light of CFTR depletion, is disrupted in enterocytes through alterations in fatty acid uptake and transport in conjunction with the stimulation of lipogenesis which occurs by a liver-X-receptor/retinoid-X-receptor (LXR/RXR)-independent mechanism. These findings exclude a contributing role of CFTR in CF-associated fat malabsorption[86].

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Impaired intra-enterocyte processing of lipids is another factor that can affect lipid malabsorption in CF[11]. This has been buttressed by observations in CF duodenal biopsies where significant decreased esterification and secretion of lipids and marked reductions of lipid and apolipoprotein synthesis have occurred inspite of normal transfer protein activity levels[53]. However, Mailhot *et al.*[90] have demonstrated an inverse relationship between CFTR expression and intestinal lipid metabolism using intestinal Caco-2/15 cell line i.e. CFTR disruption evoked the stimulation of intestinal lipid synthesis and absorption, thus indicating that the primary gene defect is not responsible for the persistent fat malabsorption in CF patients although variation in CFTR protein expression appears to regulate lipid homeostasis[86].

b) CF and carbohydrate maldigestion

The products of the pancreatic breakdown of carbohydrates are further hydrolysed into monomers by intestinal brush border glycosidases in the duodenum[91]. This terminal digestion occurs throughout the small intestine while the major sites for digestion and absorption are the duodenum and jejunum both for carbohydrates and proteins. The role of the ileum in the terminal digestion of oligosaccharides and proteins is shown by the high distribution of maltase and some peptidases, respectively, within it. There is evidence that the brush border digestive enzymes maybe unevenly distributed along the small intestine[11]. Apart from reports indicating modifications in the brush border digestive enzyme activity and absorption of the terminal digestion products, carbohydrate digestion and absorption seem to be less affected in CF, and the activity of the brush border digestive enzymes varies according to specific enzymes. This is also similar with proteins. The activities of maltase and sucrase seem to be unaffected in CF while lactase activity, which may be suppressed as determined by the genotype, maybe lower in the mucosa[11]. Also in CF, children lactose intolerance is not related to low bone mineral density. However, a number of the clinical symptoms of lactose intolerance such as abdominal pain, diarrhea and flatulence have been shown to correlate with decreased intake of calcium and bone mineral density thus contributing to defective bone health in CF patients[92,93]. Further investigation is needed to confirm these observations. Reduced perfusion barrier following abnormal mucus or enhanced Na-coupled nutrient transport, as a result of elevated mucosal membrane potential following defective Cl^{-} transport, seem to improve glucose uptake but this may not be so with amino acids[94,95].

c) CF and protein maldigestion

Further degradation of the products of proteins from the catabolism in the pancreas into monomers by peptidases and intracellular mucosal cell peptidase takes place in the duodenum. Observations of decreased peptide hydrolysis and intestinal uptake of some amino acids in jejunal biopsies from CF children have been documented[96]. Moreover, studies have shown that the uptake of amino acids varies. The uptake may be increased, decreased or normal, especially the neutral amino acids and dipeptides[94,97]. In CF young adults and children, excessive fecal amino acid loss, has been shown to be responsible for significantly elevated fecal nitrogen loss[98,99].

Goblet cells are the major cell type of the gastrointestinal epithelium involved in mucin granules exocytosis. Using intestinal organoids from a CF mouse model, Liu *et al*[100] demonstrated that CF goblet cells have altered exocytosis mechanism which involved intrathecal granule swelling that was closely followed by incomplete release of partially decondensated mucus. Their findings also indicated that the dysfunction is an epithelial-autonomous defect in the CF intestine that likely contributes to the pathology of mucoviscidosis and intestinal manifestations of inflammation and obstruction. Also, paneth cells (another cell type of the gastrointestinal epithelium) have toll-free receptors (TLRs) on the epithelial surface and in humans there are ten TLR family members. TLRs are capable of identifying pathogen associated molecular patterns[101,102]. Impaired TLR signaling can result in decreased antimicrobial function, causing increased bacterial translocation and systemic inflammation via nuclear factor κB (NF-κB) activation, cytokine production and chemokine-mediated recruitment of acute inflammatory cells[103]. All of these effects in the goblet and paneth cells would contribute to malabsorption of macronutrients from the diet.

d) CF and maldigestion of certain micronutrients

Apart from macronutrient and fat-soluble vitamins absorption, that of vitamin B12 and calcium acquisition may also be impaired in CF. Increased secretion of intrinsic factor (whose function is to facilitate the transport and absorption of vitamin B12) by the parietal cells, after stimulation by pentagastrin, was observed in a small paediatric CF while another displayed unaffected biological activity of intrinsic factor study of children but the carbohydrate composition of the intrinsic factor appeared distorted[104-106]. There are few reports of vitamin B12 deficiency but Naimi *et al.*[105] showed that absorption of food-derived B12 may not be significantly impaired in CF[105,107]. In CF murine models, as a result of the down-regulation of the gene coding for the endocytic receptor for the assimilation of the intrinsic factor-vitamin B12 complex, absorption of vitamin B12 was reduced in contrast to report in humans, although this report needs to the confirmed[11,67]. In addition to potential lactose intolerance, decreased activity of brush border alkaline phosphatase (which suppresses intestinal

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calcium uptake precipitated by elevated luminal calcium concentrations), may be related to calcium absorption and bone health in CF[11]. In CF individuals, bone disease has been found to be an additional reason for morbidity as the CF patient advances in age. Therefore, further studies in order to investigate the effect of CF on calcium assimilation needs to be conducted[11,14]. It's established that severe vitamin D deficiency causes rickets in children and osteomalacia in adults. Therefore, suboptimal vitamin D levels in CF patients can contribute to low bone mineral density and increase the risk of low trauma fracture. This can be as a result of the following factors: reduced exposure to sunlight due to photosensitivity of quinolone antibiotics or poor health, reduced levels of vitamin D binding protein, impaired hepatic hydroxylation of vitamin D, reduced absorption of dietary vitamin D and supplement resulting from pancreatic insufficiency and low body mass index (BMI) leading to reduced capacity for adipose tissue vitamin D storage[108-111].

In the light of the variations stated above in the digestion of macromolecules, patients with CF and PI are supplemented with exogenous pancreatic enzymes, which is called pancreatic enzyme replacement therapy (PERT), and the dosage is determined by the fat content of the diet rather than the carbohydrate or protein content[11]. Moreover, using CF murine models, it has been shown in the jejunum that other genetic factors affect nutrient absorption apart from CFTR mutations[112].

Perspectives On Nutritional Intervention Protocols

Early diagnosis of CF is critical for commencement of treatment to avoid the development of complications, which is usually observed after 6 weeks of birth, especially severe pulmonary disease. This treatment, medical and nutritional, with detailed attention to the nutritional management of CF patients has led to improvement in them being able to thrive. The predicted median age for the survival of CF patients in the UK in 2014 was 40.1 years; 45 years for babies born in the 2010 in the U.S and 49.7 years in Canada based on the data in 2007[111,113]. In addition to newborn screening-program (NSBP), which enables early diagnosis, patients are also referred to multidisciplinary CF centers which are staffed with a ranged of professionals which include specialist CF dietician, pulmonologists, social workers, psychologists, pharmacists and microbiologists. Thus resulting in fewer hospital admissions and the children leading healthier lives[111,113].

It has been established that nutritional management is an essential part of multidisciplinary care for peadiatric and adult CF patients. Therefore, periodic and regular assessment by a specialist CF dietician would serve to provide early detection of any adverse change in nutritional status (which includes weight, height, BMI and occipital-frontal or head circumference)[111]. For over 35 years, a high-fat, high-energy diet has been an integral part of the nutritional management of CF. Moreover, apart from increasing the energy content of the diet, fat-soluble vitamin supplementation, oral nutritional supplementation, behavioural interventions, enteral tube feeding (including employment for PERT) and parenteral nutrition have all been shown to improve weight gain in CF patients, which in turn has improved growth and nutritional status of the patients and therefore enhanced thriving[111,114,115]. Since Cochrane reviews have stated a lack of controlled trials that are randomized to examine the outcomes of nutritional interventions for weight gain in CF patients, nutritional guidelines are largely based on experiential learning, expert opinion and therefore advise a stage approach to nutritional intervention[111,116-119]. Moreover, the position of the CF patient with regards to pancreatic sufficiency or insufficiency determines the nutritional regimen[111].

Conclusion

Maldigestion and malabsorption of lipids is exacerbated by the hyperacidity in CF duodenum and by the lack of lipases due to pancreatic insufficiency, as well as reduced bile acid resorption in the ileum. Carbohydrate and protein digestion and absorption seem to be less affected in CF while that of vitamin B12 and calcium still needs to be well established in the CF condition of humans.

Conflict Of Interest

The author declares that there is no conflict of interest.

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