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Pancreatic Complications in Children with Cystic Fibrosis

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Abstract

Purpose of Review: The pancreas is highly affected in cystic fibrosis (CF), with complications occurring early in childhood. This review highlights recent research in exocrine pancreatic function in the era of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies and discusses how these are affecting pancreatitis and exocrine pancreatic insufficiency (EPI) in children. Additionally, new research into exocrine-endocrine interactions sheds light on how CFTR dysfunction in ductal cells may affect beta cells.

Recent Findings: Ivacaftor has disproved the hypothesis that EPI in children with CF is irreversible. Improvements in pancreatic function have increased pancreatitis episodes in some children and reduced them in others. Imaging advances are providing complementary methods for exocrine pancreatic function testing. New research into the interplay between the exocrine and endocrine components of the pancreas are elucidating the intertwined and complex relationship between the exocrine and endocrine pancreas.

Summary: Pancreatic complications contribute to the morbidity and mortality of children with CF. Increasing use of highly effective CFTR modulators will not only abrogate these, but will also advance our understanding of pancreatic pathophysiology in CF. New frontiers into pancreatic gene therapy and exocrine-endocrine research will help provide new therapeutic opportunities for pancreatitis, EPI, and diabetes in CF.

Keywords

CF; pancreas; pancreatitis; imaging; function

INTRODUCTION

Since Dr. Dorothy Andersen's first description of "cystic fibrosis of the pancreas" in 1938 (1), pancreatic complications have been at the center of the gastrointestinal complications of cystic fibrosis (CF). Malnutrition secondary to exocrine pancreatic insufficiency (EPI) defined CF until the use of pancreatic enzyme replacement therapy (PERT). While PERT has been in use for over 200 years, EPI in CF remains an active area of research and clinical investigation. The permanence (or lack of permanence) of EPI has recently been called into question with new cystic fibrosis transmembrane conductance regulator (CFTR) modulator

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therapies. In fact, alterations in exocrine pancreatic function secondary to highly effective CFTR modulators have highlighted the precarious risk of pancreatitis in those with CF. CF patients were once thought to be protected from pancreatitis due to extreme loss of exocrine function. However, the model of pancreatitis risk for those with CFTR mutations put forward by Ooi and Durie et al. in 2011 appears to be playing out in the era of CFTR modulators (2). With this comes new investigations into how to detect and monitor pancreatic fibrosis and fat deposition as complications of recurrent pancreatitis in CF, topics set-aside long ago as foregone conclusions. Finally, new in vitro models are teaching us about the intricate interplay between the exocrine and endocrine pancreas, which may yield new insights into endocrine (and exocrine) insufficiency in CF. Basic, translational, and clinical research in the pancreatic complications of CF are evolving how we think about the pancreas in CF, deepening our understanding of the pathophysiology, but also bringing new opportunities for diagnostic and therapeutic advances.

EXOCRINE PANCREATIC INSUFFICIENCY IN CF

EPI is one of most well-known complications of CF, with CF being the most common cause for EPI. Greater than 85% of CF patients in the CF Foundation registry are noted to be EPI (3), as defined by use of PERT. While fecal elastase-1 (FE-1) testing is the most commonly used diagnostic test to identify EPI, clinicians should remember that 1) FE-1 values can fluctuate over time (4) and 2) EPI is a clinical diagnosis, not a laboratory one. CF patients may exhibit EPI, and benefit from PERT, even with FE-1 results $>200 \mu\text{g/g}$ stool. In Brownell et al.'s review on "Growth and Nutrition Cystic Fibrosis," the authors highlight that beyond pancreatic enzyme load, pancreatic enzyme efficacy must also be considered (5). Impairments in both duodenal and pancreatic bicarbonate secretion (6–8), coupled with gastric acid hypersecretion in some CF patients (9), results in an acidic intestinal luminal pH, which may impair enzyme activity and thereby contribute to malabsorption. PERT has been well-established as an effective therapy for EPI, when dosed appropriately, in malnourished patients (10) and/or those exhibiting signs/symptoms of malabsorption (11). Layer et al. undertook a meta-analysis of published studies on the effects of PERT on survival and quality of life in patients with EPI (11). They identified that, while many studies showed that PERT improves fat and protein absorption and growth in CF patients compared to placebo, there were no studies directly assessing PERT and survival, and only one examining quality of life (in chronic pancreatitis patients). Prior studies have established a positive correlation between nutrition and growth and lung function in CF patients (12), which drives our tenacious monitoring of growth and nutrition in children with CF.

Exocrine Pancreatic Insufficiency and CFTR modulators

Historically, there have been no treatments to restore pancreatic function for CF patients with EPI. Clinicians have been limited to managing its aftereffects. In fact, many believed that with the very early onset of EPI in many CF patients, EPI was irreversible. Clinical studies with ivacaftor, a highly effective CFTR potentiator, have called this dogma into question. In both the ARRIVAL and KLIMB studies (13, 14), treatment of children with ivacaftor improved FE-1 measurements, some to $>200 \mu\text{g/g}$ stool and others close to it. In the phase 3 single-arm ARRIVAL study, children 12–23 months ($n = 15$) with at least one

CFTR gating mutation received ivacaftor for 24 weeks. Mean $\pm$ standard deviation FE-1 increased from 182.2 ± 217.1 to 326.9 ± 152.1 $\mu\text{g/g}$ stool (mean change: 164.7 ± 151.9 $\mu\text{g/g}$ stool) (Figure 1). In the KLIMB study, the 84-week open label ivacaftor extension of the KIWI study, 28 children were analyzed for changes in FE-1. In the original KIWI study (24-week, single arm in children 2–5 years old), mean FE-1 increased by 99.8 ± 138.4 $\mu\text{g/g}$ stool after 24 weeks of ivacaftor (15). With the KLIMB extension, at 84 weeks, the mean increase in FE-1 was 128.8 ± 428.9 $\mu\text{g/g}$ stool (Figure 1) (14). Prior to initiation of ivacaftor during the KIWI study, only 6% of children had a FE-1 ≥ 200 $\mu\text{g/g}$ stool (1/17), whereas after 84 weeks of ivacaftor, 35% (6/17) had FE-1 ≥ 200 $\mu\text{g/g}$ stool. These studies provided some of the first data to suggest that EPI in CF may not be permanent. Of note, there was no discussion in these studies about the presence or absence of GI symptoms associated with EPI. The potential improvement of EPI on ivacaftor has also been noted in older children. Nichols et al. reviewed cases of older children on long-term ivacaftor and noted significant improvements in FE-1 (16).

Exocrine Pancreatic Insufficiency Diagnosis by Imaging

Monitoring of exocrine pancreatic function in children using indirect and direct tests has recently been reviewed by the Pancreas Committee of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) in discussing endoscopic pancreatic function testing (ePFT) (17). Beyond the stool, breath, and endoscopic tests discussed, new data has emerged examining exocrine pancreatic function in CF patients using ultrasound (US) and magnetic resonance imaging (MRI). Transabdominal US is the most common modality for assessing the pancreas in children given it is non-invasive, low cost, and broadly available. In examining B-mode US (i.e., grayscale US) characteristics in CF children and adults ($n = 21$), Engjom et al. reported that 90% of CF patients with EPI (CF-PI) (by FE-1 and bicarbonate concentration on ePFT) had pancreatic hyperechogenicity, whereas 27% of exocrine pancreatic sufficient CF (CF-PS) patients and 33% of healthy controls displayed pancreatic hyperechogenicity (18). Pfahler et al. also found increased pancreatic echogenicity in CF patients vs. healthy controls (56% vs. 7%, respectively), although they did not distinguish between pancreatic function status (19). In the former study, MRI was also performed to quantify pancreatic fat and showed that CF-PI patients had increased pancreatic fat compared to CF-PS patients (18). In a large population study in Western Germany that included abdominal MRI (SHIP: Study of Health in Pomerania), 139 adults with EPI were compared to 1319 individuals with normal pancreatic function and found that those with EPI had significantly higher pancreatic fat than healthy controls (20). In addition to B-mode US, advanced US techniques such as shear wave elastography and contrast-enhanced US have been used to examine pancreatic function in CF patients. Not surprisingly, given the increased pancreatic fat content of CF-PI patients, US shear wave elastography (which measures tissue stiffness) shows decreased values in CF-PI patients compared to healthy controls (19). In an additional study by Engjom et al., CF-PI patients displayed decreased mean capillary transit time and pancreatic blood flow compared to CF-PS and healthy patients (21).

MRI-based assessment of exocrine pancreatic function has been of increasing interest to pancreatologists with its potential ability to provide high-fidelity cross-sectional structural

information together with organ function. The most common modality to do this is secretin-magnetic resonance cholangiopancreatography (s-MRCP). In CF, s-MRCP is able to distinguish CF-PI from CF-PS and healthy controls, shows good positive correlation with FE-1 ($r = 0.84$), and has excellent diagnostic performance in predicting EPI in CF patients when using an intestinal volume of <70 mL at 13 minutes post-secretin (AUROC = 0.95, sensitivity = 100%, specificity = 77%) (22). Secretin-stimulated US also performs well in identifying EPI in CF patients by measuring intestinal fluid area. S-US and s-MRCP results correlate well ($r = 0.79$); using a post-secretin peak intestinal volume of 2.5 cm^2 or area under the curve of 30 cm^2 with an AUROC of 1.0 (sensitivity = 1.0, specificity = 0.96) and 0.99 (sensitivity = 1.0, specificity = 0.91) (23). Therefore, while FE-1 remains the most common modality to assess EPI in CF patients, advanced US and MRI techniques, which provide both structural and functional data, are the new frontier in the assessment of pancreatic function (Table 1). What remains to be seen is which techniques will fare the best for monitoring changes in exocrine pancreatic function in children. Identifying modalities that can distinguish subtle changes in exocrine pancreatic function will be valuable in determining clinical effectiveness of CF therapies and better understanding pancreatic physiology.

PANCREATITIS IN CF

Pancreatitis has historically been considered rare in CF due to pancreatic parenchymal loss early in infant development. However, newborn screening, advancements in genetics, and CFTR modulator therapies have all increased the proportion of CF patients with pancreatitis. Newborn screening helps to identify CF patients even before symptoms may manifest. Likewise, the introduction of expanded genetic testing and full gene sequencing within and outside of newborn screening programs have greatly increased the identification of CF patients with minimal to mild symptoms, especially those without EPI, who would have otherwise escaped diagnosis until later in life. This expansion in the relative number of CF-PS patients has increased the number of CF patients that may develop pancreatitis. Nearly a decade ago, Ooi et al. put forward a model where individuals with extreme lack of CFTR function or near-normal CFTR function are unlikely to develop pancreatitis (Figure 2) (2). However, as CFTR dysfunction decreases, but is not eliminated, individuals' risk for developing pancreatitis increases. CFTR mutations have been implicated in pancreatitis pathogenesis for decades and additional recent papers have further supported this (24–28). Recommendations and guidelines for the management of acute pancreatitis in children have been established (29, 30) and should generally be followed for CF children with pancreatitis.

Pancreatitis and CFTR Modulators in CF

Similar to EPI, as ivacaftor use has become more widespread, case reports/series have emerged describing CF-PI patients beginning to have pancreatitis and CF patients with recurrent pancreatitis experiencing a reduction in pancreatitis episodes. Due to the time delay in highly effective CFTR modulator therapy being accessible to young children, many of these reports have been in adults, however, data from children and adolescents is increasing with greater use of these drugs in children.

Petrocheilou et al. present a case of an adolescent with CF-PI (F508del/G551D) without a prior history of acute pancreatitis who experienced restoration of pancreatic function on ivacaftor (no symptoms off PERT, only used PERT for very fatty meals). Four years after starting ivacaftor therapy, the patient developed acute epigastric abdominal pain, nausea, and elevations in both amylase (2.0x upper limit of normal) and lipase (>3.3x upper limit of normal), consistent with a diagnosis of acute pancreatitis. Following standard acute pancreatitis management, patient was discharged, and continued on ivacaftor with no subsequent pancreatitis episodes two years later (31). This case not only further emphasizes that EPI can improve with CFTR modulator therapy, but also provides a caution to CF providers. Children with CF have a multitude of reasons to experience abdominal pain (e.g., gastroesophageal reflux disease, dysmotility, constipation, small intestinal bacterial overgrowth, distal intestinal obstruction syndrome). Pancreatitis must also be considered in the differential, not only for CF-PS patients, but also for CF-PI patients on CFTR modulator therapies.

Consistent with the Ooi et al. model in Figure 2, ivacaftor can improve the frequency of recurrent pancreatitis episodes in CF patients with Class III/IV residual function mutations. Recently, several case reports describe an improvement in the number of pancreatitis episodes experienced by adults treated with ivacaftor (32–35). These reports involve a small number of patients (range 1–15) but provide consistent evidence that when CFTR modulators shift CFTR function high enough, the risk of pancreatitis can be reduced. But what about children, do these studies only apply to adults? The case series by Carrion et al. of six patients involves two children (ages 11.5 and 13.6 years-old) and reports an improvement in number of pancreatitis episodes, hospitalizations, PERT use, and weight in these children, similar to that seen in the other four adults (32). These findings support animal studies, which have shown that treatment of mouse models of chronic pancreatitis with CFTR modulators restores CFTR expression in pancreatic ducts and reduces pancreatic inflammation (36). The case report by John and Rowe (35) describing the return of pancreatitis after stopping ivacaftor not only supports the role of ivacaftor in decreasing pancreatitis episodes, but also highlights that CFTR modulator therapies are needed long-term until more permanent therapies, such as gene therapy, can be developed. Gene therapy for CF remains an active area of investigation (37–41). However, to date, there have not been any published studies directing CFTR gene correction at the pancreas. While accessibility remains a hurdle to overcome, the idea that the pancreas in CF is beyond help is no longer an impediment to this venture.

ENDOCRINE – EXOCRINE INTERACTIONS IN CF

Cystic fibrosis-related diabetes (CFRD) is a highly prevalent complication of CF, occurring in up to 55% of adult males (42). Olesen et al. identified that CFRD increases with age, occurring in 0.8% of those <10 year old, 9.7% in 10–19 years olds, 24.1% in 20–29 year-olds and 32.7% in 30 year olds (between 2008–2013 in Europe) (42). In a pediatric-specific epidemiology study of CFRD from 2000–2016, Perrem et al. identified a CFRD prevalence of 8.5% in children 10–18 years old in Canada (43). While CFRD prevalence is relatively low in children, using continuous glucose monitoring, Prentice et al. identified that serum glucose abnormalities are common in children as young as 2–6 years old (44).

There has long been debate on whether CFRD is a result of primary islet dysfunction or occurs secondary to inflammation from exocrine pancreatic dysfunction. Two recent studies examining CFTR expression and function in human pancreatic islets have provided convincing evidence that CFTR is almost exclusively expressed in exocrine ductal cells. Using a combination of in situ hybridization and immunohistochemistry, White et al. identified that CFTR mRNA was expressed in only 0.5% of insulin-positive cells, while CFTR protein could not be detected in any beta cells (45). Shik Mun et al. also showed that CFTR protein is expressed in ductal cells, not islets. Furthermore, in developing a “pancreas-on-a-chip,” consisting of both human exocrine ductal cells and endocrine islets, Shik Mun et al. identified that pharmacologic inhibition of CFTR function in ductal cells caused a decrease in insulin secretion from islets, likely through ductal cell to islet communication (46). Recent studies showing that endocrine and exocrine microcirculation are tightly intercalated (47) and that insulin levels affect exocrine acinar cell stress (48) provide new and compelling evidence that our historical separation of the exocrine and endocrine pancreas is flawed. Future research needs to examine the endocrine and exocrine functions of the pancreas in parallel to better understand how loss of CFTR function may affect both nutrition and diabetes in CF.

Conclusion

Pancreatic complications contribute significantly to the health care burden of many children with CF. Previously thought to be binary (CF-PI or CF-PS), in today’s spectrum of CFTR mutations, the diagnosis and monitoring of pancreatic function can be complex and, based on emerging evidence, may require consideration of both exocrine and endocrine function. FE-1 measurements are not absolute or fixed. They should be considered in the context of patient symptoms and may change due to the natural history of disease and therapeutic interventions, especially CFTR modulator therapies. The toolbox to measure pancreatic function is expanding and advanced imaging may play an increasing role. Recognition of pancreatitis in CF is important and prompt treatment should be implemented through partnerships between gastroenterologists/pancreatologists and CF providers. Now, over 80 years after Dorothy Andersen’s first description of the pancreatic manifestations of CF, pancreatic disease in CF children is once again at the forefront of CF care.

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39. Fleischer A, Vallejo-Diez S, Martin-Fernandez JM, Sanchez-Gilabert A, Castresana M, Del Pozo A, et al. iPSC-Derived Intestinal Organoids from Cystic Fibrosis Patients Acquire CFTR Activity upon TALEN-Mediated Repair of the p.F508del Mutation. *Mol Ther Methods Clin Dev*. 2020;17:858–70. [PubMed: 32373648] * The authors used transcription activator-like effector nuclease (TALEN)-mediated homologous recombination to correct F508del mutations in patient-derived iPSCs. Unlike that done in references 38 and 40, this method required selection of edited clones prior to the generation of epithelial cells. Editing effect on CFTR function was verified by the forskolin-induced swelling assay using intestinal organoids derived from edited and non-edited iPSCs.
40. Vaidyanathan S, Salahudeen AA, Sellers ZM, Bravo DT, Choi SS, Batish A, et al. High-Efficiency, Selection-free Gene Repair in Airway Stem Cells from Cystic Fibrosis Patients Rescues CFTR Function in Differentiated Epithelia. *Cell Stem Cell*. 2020;26(2):161–71 e4. [PubMed: 31839569] ** This study used CRISPR/Cas9 and AAV delivery of ds-DNA for homologous recombination

repair of F508del alleles in nasal and bronchial cultures from CF and non-CF patients. We achieved correction of the F508del mutation in ~40% of alleles. This resulted in restoration of CFTR function in differentiated airway epithelial cell monolayers to ~31% of non-CF patients.

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42. Olesen HV, Drevinek P, Gulmans VA, Hatziaorou E, Jung A, Mei-Zahav M, et al. Cystic fibrosis related diabetes in Europe: Prevalence, risk factors and outcome; Olesen et al. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2019.** A retrospective review of the European CF Patient Registry from 2008–2015 to examine the prevalence of CFRD in children and adults in 2015. Established an overall prevalence of 21.6% across all age groups, but identified variable prevalence with lowest in the <10 year-old group and highest in the 30 year-old group.
43. Perrem L, Stanojevic S, Solomon M, Carpenter S, Ratjen F. Incidence and risk factors of paediatric cystic fibrosis-related diabetes. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2019;18(6):874–8. [PubMed: 31072797] * This retrospective study evaluates the incidence of CFRD in children (ages 10–18 years old) listed in the Canadian CF Registry from 2000 to 2016. Their findings are similar to that found in the reference 42.
44. Prentice BJ, Ooi CY, Verge CF, Hameed S, Widger J. Glucose abnormalities detected by continuous glucose monitoring are common in young children with Cystic Fibrosis. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society.* 2020.* The authors use continuous glucose monitoring in children <10 years old to identify that glucose abnormalities are present in young children, ages 2–6 years old. While the diagnosis of CFRD is low in this age group, pathogenesis of diabetes may be occurring early in life.
45. White MG, Maheshwari RR, Anderson SJ, Berlinguer-Palmini R, Jones C, Richardson SJ, et al. In Situ Analysis Reveals That CFTR Is Expressed in Only a Small Minority of beta-Cells in Normal Adult Human Pancreas. *J Clin Endocrinol Metab.* 2020;105(5).* Used a combination of immunohistochemistry and in situ hybridization to examine the localization of CFTR protein or mRNA, respectively, in human and ferret beta and ductal cells. Identified that CFTR expression is confined to ductal cells.
46. Shik Mun K, Arora K, Huang Y, Yang F, Yarlagadda S, Ramananda Y, et al. Patient-derived pancreas-on-a-chip to model cystic fibrosis-related disorders. *Nat Commun.* 2019;10(1):3124. [PubMed: 31311920] ** This study took a unique approach to studying the interactions between the exocrine and endocrine pancreas. The authors developed a two-channel chip where they grew human pancreatic ductal cells on one side of a porous membrane and human islets on the other side. Samples were obtained from patients undergoing total pancreatectomy islet autotransplantation. By manipulating conditions on either the ductal or islet side they could study the effect on the opposite cell type (which was not directly manipulated).
47. Dybala MP, Kuznetsov A, Motobu M, Hendren-Santiago BK, Philipson LH, Chervonsky AV, et al. Integrated Pancreatic Blood Flow: Bi-Directional Microcirculation Between Endocrine and Exocrine Pancreas. *Diabetes.* 2020.** This paper examines the micro-circulation of mouse and human islets. Flow analysis shows that islets and exocrine components share an intertwined network of capillaries. Using directional flow analysis the authors describe the blood flow patterns into and out of islets and how this interfaces with components of the exocrine pancreas. Multiple models of islet blood flow are described.
48. Yatchenko Y, Horwitz A, Birk R. Endocrine and exocrine pancreas pathologies crosstalk: Insulin regulates the unfolded protein response in pancreatic exocrine acinar cells. *Exp Cell Res.* 2019;375(2):28–35. [PubMed: 30625303] * This study examined the effect of insulin concentrations on ER stress unfolded protein response on acinar cells. They found that when acinar cells were exposed to high levels of insulin, a host of proteins associated with the ER stress unfolded protein response were upregulated, suggesting that insulin levels may alter the health of acinar cells.

Key Points

- Exocrine pancreatic insufficiency in children with CF is not fixed and may improve, or even resolve, in the presence of highly effective CFTR modulator therapy.
- Continued advancements in US and MR imaging tools may provide both structural and functional assessment of the pancreas in patients with CF.
- CF children should be monitored for pancreatitis when presenting with abdominal pain, even if thought to be exocrine pancreatic insufficient. CF patients with recurrent pancreatitis may improve on highly effective CFTR modulators.
- Endocrine dysfunction may occur early on in childhood in CF.
- Endocrine and exocrine functions of the pancreas are tightly interlinked through multi-faceted anatomical and functional communications and should be assessed in parallel.

Figure 1. Children treated with the CFTR potentiator ivacaftor experience an increase in exocrine pancreatic function as measured by FE-1.

Summary of data from the ARRIVAL, KIWI, and KLIMB clinical trials. The figure shows the mean (line) absolute increase in FE-1 before and after ivacaftor treatment. Box upper and lower limit lines represent 95% confidence intervals. Children in the ARRIVAL, KIWI, and KLIMB studies were treated with ivacaftor for 24, 24, and 84 weeks, respectively.

PI = Pancreatic insufficiency

Figure 2. Pancreatitis risk model based on degree of pancreatic function.

Ooi et al. put forward a conceptual model which described that individuals with none/minimal or near-normal CFTR function are unlikely to develop pancreatitis. However, those with residual CFTR function, even if impaired, are at risk for pancreatitis. Figure reproduced from original publication with no alterations (2).

Table 1:

Comparison of imaging modalities to assess exocrine pancreatic function with FE-1 testing.

	Stool	Ultrasound				MRI	
	FE-1	B-Mode	Elastography	Contrast	Secretin	MRCP	s-MRCP
Non-Invasive	+++	+++	+++	++	++	+/-	+/-
Low Cost	+++	+++	++	++	+	-	-
Widely Available	+++	+++	++	+	+	++	+
Pancreatic Function	+++	+	++	++	+++	+	+++
Pancreatic Structure	-	+	++	++	++	+++	+++
Data in CF	+++	+++	+	+	+	+++	++

Number of “+” indicates strength of characteristics for specified testing modality. “+/-” = depends on age of child and whether or not anesthesia is necessary. Abbreviations: FE-1 = fecal elastase-1, MRI = magnetic resonance imaging, MRCP = magnetic resonance cholangiopancreatography, s-MRCP = secretin-stimulated magnetic resonance cholangiopancreatography, CF = cystic fibrosis.