Working towards an optimal nutritional status in people with Cystic Fibrosis

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Background

Cystic Fibrosis (CF) is an autosomal recessive disease caused by cystic fibrosis transmembrane conductance regulator (CFTR)-gene mutations affecting chloride secretion, sodium reabsorption, and water transport in epithelial cells. This leads to dehydrated mucus secretions impacting multiple organs (1, 2). Exocrine pancreatic insufficiency (EPI) is the earliest CF manifestation and respiratory failure is the primary cause of death. In Europe, the incidence of CF is approximately 1/3500 Caucasian births, with an incidence of 1/2850 births reported in Belgium (3). CF is associated with co-morbidities such as Cystic Fibrosis related Liver Disease, Cystic Fibrosis Related Bone Disease and Cystic Fibrosis Related Diabetes (CFRD) (2).

EPI impacts nutritional status by causing maldigestion and malabsorption of nutrients in the absence of supplemented pancreatic enzymes. There is a well-established association between nutritional status (expressed as BMI) and pulmonary function (expressed as forced expiratory volume in 1 second, FEV1, percent predicted (pp)), which ultimately affects survival. Therefore improving nutritional status is a cornerstone of CF therapy (2).

The ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children and adults with CF highlighted the need to increase knowledge on nutritional demand and nutritional status in CF (2). This thesis aimed to answer the following research questions (RQ): (a) "Does enteral nutrition have a long-term effect on the nutritional status of children and adults with CF?", (b) "How can the sodium status in children and adults with CF be evaluated?", and (c) "What's the impact of impaired glucose metabolism on nutritional status and pulmonary function?"

Method

As an introduction to the thesis, a narrative review was conducted, focusing on the reconsideration of nutritional therapy in people with CF (pwCF) (1). The narrative review was limited to evaluating the use of growth charts, body composition, pancreatic enzyme therapy, and protein intake and digestion. A literature search was performed across three databases: PubMed, Scopus, and Web of Science, form June 2014 to June 2017.

To study the impact of enteral tube feeding (ETF) on nutritional status and pulmonary function, data from the Belgian CF Registry (BCFR) was used in a retrospective case – control study design (4). All patients (n=1482) in the BCFR were considered. Children and adults who received ETF between 2000 and 2013 and met the inclusion criteria were included. Statistical analysis was performed on 113 cases receiving ETF and 226 age, sex, pancreatic status and genotype class-matched controls. As the BCFR lacked data on growth velocity, a subsequent retrospective case – control multicentre study (UZ Brussel (UB) and Ghent University Hospital (GUH)) was performed (5). This second study aimed to explore the long-term effect of ETF on nutritional status, growth velocity, and pulmonary function in children with CF, comparing the timing of ETF initiation to current European guidelines (2). Children with CF who started ETF between 2006 and 2016 were included. Data from the patients' medical records 3 years before and five years after the start of ETF were collected. A total of 24/197 patients (UB+GUH) and 18 controls (GUH) were included for analysis, matched for age, sex, and pancreatic function.

A narrative review on sodium status and replacement in pwCF served as an introduction to the third part of the thesis (6). In June 2019, an electronic literature search was conducted in the databases PubMed, Web of Science, and Scopus. The literature search was limited to publications in English, focusing on primary research studies published since 1951. Twelve originals studies were identified and analysed. The narrative review addressed the evidence on the pathophysiology, prevalence, and clinical influence of sodium deficiency in people with CF, the indistinct recommendations for infants, children and adults, and the methods to assess sodium status. Based on the results of this review, a prospective study was performed (7). The aim was to evaluate urinary salt parameters as a surrogate for fractional excretion of sodium (FENa) in a large group of children and adults with CF in order to facilitate future follow-up of the sodium status using a spot urine sample. Between January 2019 and December 2020, urine and blood samples were collected from 222 patients followed at the GUH during an annual follow-up visit. FENa and urinary surrogate parameters for sodium status were calculated. The hypothesis was that the urinary sodium/creatinine ratio corresponding to the FENa ≥ 0.5% would differ across age categories in patients with CF.

In the fourth study, we examined the impact of impaired glucose metabolism on nutritional status and FEV1pp in pwCF who were not previously diagnosed with diabetes (8). Since the insidious nature of CFRD and the lack of clinically relevant continuous glucose monitoring (CGM) indices, we studied diurnal and nocturnal CGM-derived glycaemic patterns. Additionally, CGM-derived indices of glycaemic control were studied in relation to FEV1pp and nutritional status. Patients with an impaired OGTT and/or increased HbA1c were recommended to wear a CGM (Dexcom® G4) for seven days. CGM data of 47 pwCF, followed at the Ghent University Hospital (children, n = 26) was analysed.

All studies were approved by the Ethical Committee of the Ghent University Hospital.

Results

"*Does enteral tube feeding have a long-term effect on the nutritional status of children and adults with CF?*"

To address this RQ the findings from our longitudinal registry study and multicentre study will be discussed (4, 5). Some pwCF are unable to consume an adequate amount of nutrients, affecting weight gain and growth. CF centres use ETF to increase nutrient intake (2). In our longitudinal study, age of ETF initiation varied widely. Approximately 50% of the patients were < 10 years of age, and ± 25% were ≥ 18 years of age. All ETF-patients had lower BMI and height z-scores at the first registration in the BCFR compared to controls. After 3 years, their BMI z-scores recovered to the levels observed approximately 4 years before starting ETF but never reached the recommended threshold. We did not observe significant improvements in height z-scores in children.

In our multicentre study, we found a delay in ETF initiation compared with the guidelines, with 60% of the patients already having a BMI z-score < 1.3 three years before starting ETF (5). This percentage increased to 80% at ETF initiation, with six out of 24 patients already stunted. After starting ETF, growth velocity increased in the first year, but patients remained below their genetic potential for height. We could not recommend an ideal ETF start time, but younger patients showed greater height z-score improvement. Overall, ETF prevented further decline in BMI and FEV1pp over a period of five years but should be commenced in time (4, 5).

"How can the sodium status in children and adults with CF be evaluated?"

PwCF have hypertonic sweat which increases the risk for electrolyte disturbances. Monitoring sodium status in individuals with CF, especially in infants, is imperative. Relying solely on serum sodium as a clinical parameter may delay the diagnosis of deficiency. FENa is cumbersome as it requires simultaneous urine and blood samples. Since sodium requirements and thus supplementation change based on patients' circumstances, repeated measurements are necessary. In our study we observed a strong age-dependent correlation between FENa cut-offs and the urinary sodium/urinary creatinine ratio (Una+/Ucreat) (7). In the future, monitoring UNa+/Ucreat will be important as variant-specific therapies in CF reduce salt losses via sweat. Salt supplements and diet will need to be adjusted accordingly.

" What's the impact of an impaired glucose metabolism on nutritional status and pulmonary function?"

CGM has revealed abnormal glucose profiles in pwCF even when fasting and post-OGTT glucose levels are normal. Glucose tolerance tends to decline over time, progressing from normal to impaired glucose tolerance and eventually diabetes. CFRD is associated with a worse nutritional status and pulmonary function (9). We observed in our study cohort disrupted circadian CGM-profiles in all but two adult patients. We found no significant associations between CGM-indices and FEV1pp or BMI in the paediatric cohort, but in our adult cohort, we observed a strong association between moderate hyperglycaemia during night and a worse concurrent pulmonary function. Specifically, every increase of 1% time > 140 mg/dL during the night associated with a 0.76% lower FEV1pp. Our study was the first to explore nocturnal and diurnal glycaemic profiles in children and adults with CF, revealing deviations from healthy individuals' profiles. While this is relevant in establishing CGM cut-offs, associations between CGM-indices and CF outcomes were absent in our small paediatrics cohort, suggesting the need for age-specific indices. Thirdly, the increase in nocturnal glycemia may challenge current CF nutritional interventions, warranting a reconsideration.

Conclusion

Therapy in CF has dramatically evolved in the last decade which is expected to increase life expectancy, but as a consequence, an increase in co-morbidities is expected. Optimizing nutritional status remains a pillar in CF therapy. Our findings can set the path for a further improvement of nutritional care in CF.

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