Diet

General nutrition recommendations in cystic fibrosis

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Background

Nutritional status is indicated as a relevant factor determining the long-term survival and well-being of CF patients.

Recently , the Academy of Nutrition and Dietetics Evidence Analysis Center conducted a systematic review of the literature with the aim to develop evidence-based practice guidelines for primary nutrition issues in CF, including recommendations on nutrition screening, nutrition assessment, and dietary intake derived from all over the world (McDonald CM et al, 2021).

Malnutrition is an important problem in CF, although now not as common as in the past, with a lower percentage of children and adolescents whose weight and height are less than the 5th percentile. As pointed out in an editorial (Wolfe SP, 2017) and confirmed by updated european standards of care (Castellani C et al, 2018) the face of nutrition in CF is changing, with one major advance due to national newborn screening programmes, with the subsequent ability to start treatment early. In clinical trials, poor weight and height have been shown to be independent predictors of mortality in CF. New therapies with approved modulators further increase weight gain.

Generally, inadequate weight gain is mainly caused by an energy imbalance resulting from chronic respiratory disease, malabsorption of nutrients, anorexia and increased metabolic rate.

In particular:

- when present, fat malabsorption leads to increased energy losses in the stools. However, even with adequate control of fat malabsorption using pancreatic enzyme supplements in subjects affected by pancreatic insufficiency, several people with CF may still be unable to meet their increased energy need;
- oral caloric intake may be reduced by a general malaise associated with respiratory infection, nausea from swallowed sputum or nausea as a side effect of medications or anosmia in patients with advanced disease;
- the exact mechanism of anorexia in CF remains uncertain. The aetiology of anorexia is likely to be multifactorial; it may be caused in part by chronic infection due to factors such as increased mucus production and in part by the anorectic effects of elevated serum inflammatory cytokines, such as TNF-alfa. In addition, anorexia is likely to be related to chronic sinusitis, gastroesophageal reflux, and protein or energy malnutrition or both when present;
- in the past intrinsic mechanisms of the underlying disease have been proposed to determine the height outcomes for patients with CF. A reduced mean neonatal length (with and without adjustment for gestational age) and reduced blood levels of insulin-like growth factor 1 (IGF-1)have been found in patients with CF in previous studies as a peripheral resistance to GH was hypothesized in the light of low basal and post-stimulus plasma levels of IGF-1 and IGFBP-3 in patients with CF compared to controls (Ferrari V et al, 2022);
- alteration of the GH-IGF-1 axis can induce growth failure by chronic inflammation. In particular IL-6 interferes with the action of GH by disrupting its major signaling pathway (JAK-STAT)and IL-1 disrupts the expression of STAT5 and STAT3 (Cirillo F et al, 2017);
- several therapies used to control CF, including systemic and inhaler-administered glucocorticoids, can lead to growth failure via pathways that interfere with GH secretion and its effect on the formation of collagen and bone and in nitrogen retention;
- chronic insulin deficiency may contribute to poor linear growth due to its anabolic effects (Cheung MS et al, 2009).

To offset the energy needs of CF patients, treatment recommendations just pointed out many years ago (Stallings VA, 2008), including the need of an energy consumption of 120 up to 150% of the recommended daily allowance (RDA) for calories and adequate pancreatic enzyme replacement therapy.

Recently (Wilchanski M et al, 2024) the first ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults have been updated by an international multidisciplinary working group in accordance with officially accepted standards ,discussing PICO questions and utilizing the GRADE system. Reccomendations confirm that supplementation of vitamins and pancreatic enzymes have a relevant role in controlling the nutritional status in CF. More chapters heve been expanded including pregnancy, CF-related liver disease, and CF-related diabetes, bone disease, nutritional and mineral supplements, and probiotics, as new chapters on nutrition with highly effective modulator therapies and nutrition after organ transplantation.

Issues

- How to achieve normal growth in childhood and to maintain this in adult life in CF.
- To identify what are the evidences in favor of enteral tube feeds (nasogastric or gastrostomy) usually overnight when routine treatments and oral supplements fail to reach normal nutritional status.

What is known

A not-recent CDSR last updated in 2014 (Chinuck Ruth, 2014) systematically evaluated evidence on the beneficial effects of appetite

stimulants in the management of CF-related chronic anorexia and data regarding any side-effects through randomised and quasi-randomised controlled trials, as cyproheptadine hydrochloride and megesterol acetate, compared to placebo or no treatment for at least one month up to nine months in adults and children with CF. Despite a larger increase in weight z-score at three months compared to placebo the small number of recruited subjects (N=47) and the quality of data cannot be conclusive to recommend appetite stimulants.

This CDSR was updated. In CDSR (McTavish D, 2022) 4 trials were selected including 70 participants where treatment with appetite stimulants (cyproheptadine hydrochloride and megestrol acetate) was compared to placebo; the numbers of adults or children within each trial was not always reported. The certainty of evidence was low due to the small number of participants, incomplete or selective outcome were reported, and risk of selection bias was unclear. At six months in adults and children, appetite stimulants improved only two of the defined outcomes: weight (or weight z score) and subjectively reported increased appetite. Insufficient reporting of side effects prevented a full determination of their impact.

1 CDSR (Conway S, 2019) attempted to evaluate growth, nutritional status, respiratory function and mortality in CF patients of any age with enteral tube feeding, but no clinical trial satisfied inclusion criteria.

A preliminary matched control study (Galiniak S et al, 2022) was performed to determine several hormones in the serum of patients with CF as ghrelin, putative peptide YY (PYY), Agouti-signaling protein (ASP), and alphamelanocyte-stimulating hormone (a-MSH). using enzyme-linked immunosorbent assays in 38 patients from a single CF care center, compared to healthy controls. Correlations between the tested hormones and parameters of the patients' clinical status were also estimated. A significant reduced serum levels of ghrelin and ASP was found in patients with CF($p<0.01$). There was no difference in PYY and a-MSH levels between participants with CF and healthy subjects, no difference between females and males as well as between type of gene mutation. Ghrelin was negatively correlated with age, body mass index, and C-reactive protein, while PYY was negatively associated with the age of the patients.

Regarding the first issue how to achieve normal growth in childhood and to maintain this in adult life in CF nutritional education of the CF patient and family, involving nutritional information, the correct use of pancreatic enzyme replacement in subjects with pancreatic insufficiency, the positive reinforcement of appropriate eating and the use of high-calorie supplements, when indicated, may ensure a more optimal nutritional status. In order to help CF clinicians guidelines have been published for the care of preschool children between the ages of 2 and 5 years performed by a multidisciplinary committee convened by the CF Foundation to develop comprehensive evidence-based and consensus recommendations on routine surveillance for nutritional care (Lahiri T, 2016). Further guidelines were developed by an international multidisciplinary working group to define nutritional care recommendations in infants, adolescents and adults with CF, in accordance with officially accepted standards (Turk D et al, 2016). Some of the key points in the nutritional management of people with CF were updated in 2018 (Collins S, 2018).

The relevance of the long-term follow-up of diet on the impact of nutrition has been previously reported (Woestenenk JW et al, 2014). A dietary food record was performed in over 1500 children and adolescents with CF compared with that of healthy controls by using independent sample t-tests. Caloric intake varied highly with age (88-127% estimated average requirement EAR), which is below or in the lower range of the recommended 110-200% EAR. However, the absolute caloric intake in CF children was significantly higher compared to controls at all ages, although the fat intake resulted in a considerable consumption of saturated fat. A Cochrane Database Systematic Review (Francis DK, et al, 2015) was unable to show whether oral protein calorie supplements may improve the nutritional status of children with chronic diseases including CF.

Regarding the second issue enteral tube feeding is widely accepted as a treatment or intervention in CF Care Centers for selected cases, but the evidence based for this does not include RCTs. As reported in the European Cystic Fibrosis Society Standard of Care (Castellani C et al, 2018) interventions should be tried stepwise for a limited period of time or until nutritional status is optimised, depending on the severity of malnutrition and the age of the patient.

Few clinical randomized controlled trials are available that may respond to specific issues. A RCT (Stallings V et al , 2016) including 110 children showed that an absorbable lipid matrix (LYM-X-SORBTM) improved dietary fat absorption compared to placebo as indicated by plasma FA and LA and was associated with better growth. Behavioral intervention appeared to be as effective in improving weight gain in patients with CF as more invasive medical procedures. A published RCT (NCT NCT00241969) showed that behavioral and nutritional intervention may improve energy intake and height Z-score for preschoolers aged 2 to 6 years with CF and pancreatic insufficiency (Powers SW et al, 2015), but not weight z-score. Further data from this trial suggested that dietary monitoring may optimize intake of macronutrients that promote growth, especially fat and protein (Filigno SS et al, 2017).

Published data derived from a clinical trial (NCT01897233) evaluated the effect of Lumacaftor/Ivacaftor in patients aged 6-11 years with CF and homozygous for F508del-CFTR, showing improvement in nutritional status beyond lung clearance index, sweat chloride, and health-related quality of life after 24 weeks of treatment (Milla CE et al, 2017). These new therapies are expected to further improve caloric intake (Kerem E 2017).

Recently published data derived from a clinical european multicenter study conducted in 84 children with CF and PI indicated that the use of a self-management mobile app could represent a useful tool to self-monitor dietary intake, increasing adherence to guideline recommendations. Three-day food records were compiled in the app at baseline and after 3 and 6 months of use. Compared to baseline, better macronutrient distribution was registered increasing protein and lipid by 1.0 and 2.1% of the total energy intake, respectively, by the end of the study and decreasing carbohydrate intake (Calvo-Lerma J et al, 2021).

A retrospective study (Kennedy K et al, 2023) evaluated 62 pediatric patients with CF who received cyproheptadine or mirtazapine for appetite stimulation for at least 6 consecutive months. Weight z scores were collected for each patient at baseline, 3, 6, and 12 months of therapy, if available. Main results showed that weight z score after 3 months of therapy was statistically significant based on both univariable and multivariable models when evaluating the entire cohort. The adjusted mean difference for change in weight z score was 0.33 ($P < 0.001$) from baseline to month 3. There was a statistically significant improvement in pulmonary function after 3 and 6 months of therapy .

Unresolved questions

Several anecdotal reports concerning appetite stimulants in CF are not conclusive for their use, in particular for:

- glutamine alone or combined with rhGH;
- cyproheptadine, mirtazapine, pizotifen, dronabinol or other anti-psychotic drugs;
- megestrol acetate;
- IGF-1 as promoting linear growth in prepubertal children with CF and increasing insulin sensitivity;
- oxandrolone and prednisone as anabolic androgenic steroids;
- insulin therapy for improving body mass index (BMI).

There is no consensus regarding appetite stimulant therapy in patients with CF.

Keywords

Failure to Thrive; Nutrition Disorders; Amino Acids; Carbohydrates; Essential fatty acids; Food; Proteins;