Life expectancy in Cystic fibrosis patients has significantly increased in recent years. Nutrition is considered one of the key targets of management. To achieve and maintain an adequate nutritional status results in a milder decline of pulmonary function, better prognosis and improvement in quality of life. In spite of great advances in knowledge, a significant number of individuals living with cystic fibrosis remain, according to different international registries, under proposed nutritional goals. Several nutritional aspects of the disease must be addressed: intake evaluation, behavioral issues and enrichment of diet. Likewise, a number of patients persist with vitamin and mineral deficit, despite correct supplementation as stated in available international consensus reports. Nutritional interventions are indicated when patients fail to achieve an adequate nutritional status and previous strategies were implemented. Enteral tube feeds are indicated in around 10% of cystic fibrosis patients being evaluated and treated in different CF centers, showing favorable impact on nutritional status and lung function decline. Nevertheless, nutritional recovery as reflected by body mass index (BMI), is not an adequate measure of body composition. Cystic fibrosis related diabetes develops in nearly half of adult patients. It is necessary to highlight the importance of screening, early diagnosis and implementation of insulin treatment in order to prevent lung function and nutritional deterioration and higher mortality rates. Adherence to treatment and therapies results in better outcome, as occurs in other chronic diseases.

**Key words:** Cystic fibrosis, Nutrition, Body composition, Vitamins, Minerals, Enteral tube feeding

### INTRODUCTION

Cystic fibrosis (CF) is a multi-system disease characterized by elevated sweat electrolytes; progressive pulmonary damage caused by inflammation and chronic infection, leading to respiratory failure; pancreatic dysfunction; liver disease that may progress to cirrhosis and gut motility problems. It is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene resulting in alteration of chloride and sodium transport through apical membrane of cells. Over 1,900 mutations are known to cause CF. Due to the complexity of the disease, CF patients should be assessed and followed in specialized centers by a team of caregivers. Incidence of CF may vary in different regions, being 1: 3500-8500 newborns in Latin America; 1: 3500 in North America and 1: 2000-3000 newborns in European derived populations. In India, incidence of cystic fibrosis is estimated to be 1: 40000-100000 live births. Near 90% of patients suffer from pancreatic insufficiency (PI). Although this condition might not be present at birth, pancreatic function can decline throughout the first years of life. Pancreatic sufficient (PS) patients should be reevaluated annually for the progression to PI, especially if genetic testing reveals two CFTR mutations associated with PI phenotype. Most pancreatic function must be lost before symptoms are apparent. Pancreatic functional status has a direct influence on nutritional status and is a strong predictor of long term outcome. When PI is present, patients should receive enzyme replacement therapy and vitamin supplementation. The complexity and life long duration of CF treatment, as in many other chronic diseases, interferes with adherence to medication and therapies. Adherence is estimated to be near 50%. Patients tend to overestimate their adherence to treatments. Adherence to physiotherapy and nutritional supplements is usually low (40-55%), but increases when considering enzyme replacement therapy and antibiotics (75-90%). On the whole, adherence might be affected by a number of different factors such as: age, socioeconomic environment, educational level, social and family support, behavioral issues and many others to be considered when evaluating individual...
patients. Recently, drugs that correct the CFTR defect were developed and evaluated in a series of trials. The CFTR potentiator Ivacaftor showed positive results when treating CF patients with G551D, a class III mutation, in lung function, quality of life scores and body mass index and significantly reduced pulmonary exacerbations. An association between Ivacaftor and CFTR corrector Lumacaftor was evaluated in DF508 homozygous patients resulting in a net effect of 3% FEV1% benefit compared to placebo and increased BMI by +0,26 Kg/m² and a modest effect in a validated symptoms score. While the effects of this combination appear beneficial among DF508 homozygous patients, they remain modest when compared with Ivacaftor monotherapy in class III mutations. Patients treated with CFTR correctors and potentiators are encouraged to continue enzyme replacement therapy, vitamin supplementation and physiotherapy. Median life expectancy in CF patients has increased from only a few months when the disease was first described in 1940 to as high as 41 years in many countries at present. The predicted median survival of people with CF born today continues on the rise.

NUTRITIONAL GOALS

In spite of recent advances in cystic fibrosis treatment, malnutrition continues to be an issue, affecting a great number of patients throughout the World. The main cause of malnutrition varies (e.g.: malabsorption; increased energy expenditure; altered intake; lack of adherence to medication, nutritional intervention or a combination of the previous), but regardless of its cause, malnutrition produces a direct impact on pulmonary function. Achieving a correct growth during the first years of life is a key goal, because those first steps will determine future success. Several authors have demonstrated that malnutrition in early childhood is associated with impaired growth later on, together with a greater impact in pulmonary function.

An adequate growth assessment must be part of routinely evaluation in patients with CF. The Cystic fibrosis Foundation (CFF) in USA recommends that every child must accomplish a BMI percentile greater than 50, male grown-ups a BMI of at least 23 and at least 22 for female adults, but this parameter alone could underestimate the lack of progression in height and the adequate percentage of lean body mass. A recent study, body composition was evaluated via total corporal dual X-ray absorptiometry (DEXA). Male patients who were evaluated presented a reduced lean mass and this was associated with further impaired poorer lung function, a condition which was unrelated to their BMI percentile. In everyday clinical practice, the evaluation of body composition could be a complex task. For instance, Bioimpedance has failed in being a suitable an adequate tool to evaluate lean mass in this population. In CF patients, lean mass loss affects respiratory muscles like the diaphragm and accessory muscles, resulting in impaired poorer lung function. This loss is associated with different conditions, such as inflammation, chronic respiratory infection, lack of exercise, impaired glucose metabolism and prolonged use of steroids among others and is observed mostly in adolescents and adult patients. These factors affect the nutritional status as well as the response to nutritional interventions.

VITAMINS AND MINERALS

Vitamins A, D, E and K

Cystic fibrosis patients suffering from pancreatic insufficiency typically present lipid malabsorption and liposoluble vitamins (A, D, E and K) should be administered routinely. A great percentage of infants present this deficiency at the moment of diagnosis through neonatal screening, and many children still present deficiencies in spite of supplementation.

Table 1. Vitamins A, D, E and K Recommended Dose for Cystic Fibrosis†

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>0-12 months</th>
<th>1-3 years</th>
<th>4-9 years</th>
<th>+10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (UI)</td>
<td>1500</td>
<td>5000</td>
<td>5000-10000</td>
<td>10000</td>
</tr>
<tr>
<td>D (UI)</td>
<td>400-500</td>
<td>800-1000</td>
<td>800-1000</td>
<td>800-2000</td>
</tr>
<tr>
<td>E (UI)</td>
<td>40-50</td>
<td>80-150</td>
<td>100-200</td>
<td>200-400</td>
</tr>
<tr>
<td>K (mcg)</td>
<td>300-500</td>
<td>300-500</td>
<td>300-500</td>
<td>300-500</td>
</tr>
</tbody>
</table>


Several authors have reported deficiencies of vitamin A in 20-40% of the patients, vitamin D in 25-90%, vitamin E in 23-38% and vitamin K in 60-70% and these deficiencies persist even with higher dose supplementation.

Several causes have been pointed as responsible for decreased serum retinol levels. On the one hand serum retinol is often reduced during pulmonary exacerbations and its measurement should be avoided until the patient is stable. Causes associated to persistent low values of serum retinol, other than poor adherence to supplements, are: zinc or copper deficiency, alcohol intake, liver disease or intestinal resections. A Cochrane review published in 2014 highlights the lack of randomized trials to establish an adequate supplementation in each clinical scenario.

Maqbool A et al. have reported elevated serum retinol levels in 58% of a pancreatic insufficient population of cystic fibrosis patients between 8 and 25 years of age. These results were not correlated with vitamin A intake. Given the liver toxicity of high levels of vitamin A, it is important to monitor individual levels annually, as it has been agreed.

Vitamin D has received increased attention in recent years, not only because of its importance in bone metabolism, but because of its key roles in the immunological system, inflammation and growth later on, together with a greater impact in pulmonary function.
pulmonary function. Several reports have described the difficulty in achieving adequate levels of vitamin D, using 25-hydroxyvitamin D (25(OH) D) as a serum marker. Elevated deficiency percentages have been reported, mainly in adolescents at the end of the winter, even for those living in areas near the Equator. In 2012 a consensus report was published in which the use of cholecalciferol (D3) supplements and increased doses in patients with deficits were recommended.

Regarding vitamin E, and similarly to what occurs with serum retinol, high, normal and low serum values have been reported in CF patients receiving supplementation. For its accurate interpretation, vitamin E serum levels should be considered by calculating their relation to serum lipids.

On the other hand, Vitamin K sub-optimal levels have been reported despite adequate supplementation.

Although pancreatic sufficient patients do not require routine supplementation, administration of vitamins A, E and D could have beneficial clinical effects on pulmonary health.

It is clear that we still don’t have enough knowledge regarding the relationship between dosing of supplemented vitamins and their serum levels in CF patients, which is why more studies are required to answer this question properly.

Minerals: Sodium chloride, Zinc and Magnesium

The main minerals affected by CF are sodium chloride, zinc and magnesium. The principal loss of sodium chloride is represented due to sweat, and specific supplement recommendations starting from the initial diagnosis of the disease are agreed upon. Sodium deficit interferes with adequate growth and leads to a greater risk of hyponatremic and hypochloremic metabolic alkalosis. Infants and toddlers with cystic fibrosis are especially susceptible to this deficit because neither mother’s milk nor formulas or baby foods have enough sodium in their formulations. In these patients a daily dose of 1/8 teaspoon (12.5 mEq sodium chloride) is recommended as supplementation. In older children, adding salt to main foods and choosing salted snacks (up to 25 mEq/day, not exceeding 4 mEq/kg/day) would be accurate. For those patients who practice sports, the intake of food and beverages with added salt is recommended, in order to stimulate thirst. In a recent study, Knepper et al. have stated that sodium depletion can be undetected by measurement of natremia, and linked this subclinical depletion with impaired growth and malnutrition.

Zinc deficiency is present in most patients with CF and pancreatic insufficiency from the moment of diagnosis. Very few trials have evaluated zinc requirements in this group of patients. The Cystic Fibrosis Foundation Report on Nutrition for pediatric patients recommends supplementation with 1 mg/kg/day of elemental zinc (up to 25 mg/total) for 6 months in those patients with failure to thrive in spite of an adequate caloric intake and enzyme replacement therapy, diminished intake, chronic or prolonged diarrhea, severe malabsorption and those who present vitamin A deficiency despite correct supplementation.

Low magnesium levels has been reported in CF patients, mostly in older patients and related to the use of aminoglycosides. Magnesium is an intra-cellular ion and only 1% can be encountered in blood, the rest being present in bone and muscle. Due to this fact, detection of magnesium deficit is challenging. The main role of this mineral is related to muscular strength in general and of the respiratory muscles in particular. In a recent systematic review it was stated that hypomagnesemia affects more than half of the CF patients with advanced disease. Magnesemia, which is normally age-independent, relevantly decreases with age in CF. Aminoglycoside antimicrobials frequently induce both acute and chronic renal magnesium wasting. Sweat magnesium concentration was normal in cystic fibrosis patients and limited data suggest the existence of an impaired intestinal magnesium balance. It is suggested that patients should undergo annual evaluation of magnesium serum levels.

**NUTRITIONAL INTERVENTIONS**

**Intake, behavioral issues, nutritional supplements and enteral tube feeding**

Nutritional intervention must be set in action from the moment of diagnosis and throughout the life in patients with CF. Different approaches have demonstrated beneficial effects in the nutritional status of patients, such as the evaluation of intake, behavioral issues, dietary counseling, nutritional supplements and enteral tube feeding.

Appetite-stimulants have been proposed as an alternative for patients with low caloric intake due to frequent cough augmented respiratory secretions and periodic respiratory exacerbations. The most commonly used appetite-stimulants used are megestrol, ciproheptadine, dronabinol and mirtazapine. However, they all present some collateral effects, such as sedation and somnolence, impaired glucose metabolism and adrenal suppression especially in the case of megestrol that need be considered.

Nutritional counseling regarding strategies to achieve a high-protein high-caloric diet must be a part of the periodic assessment of CF patients. Chronic diseases are in general associated to behavioral issues related to food and intake, and in the case of CF patients it has been demonstrated that approaches that consider conduct-modulation and nutrition yield the best results.

High-caloric high protein supplements have failed to demonstrate consistent benefit in this group of patients. Nonetheless, they constitute a relatively common choice in treatment, 43% of patients receive these supplements in order to augment caloric intake without replacing principal meals (Cystic Fibrosis Patient Registry, 2013).

Near 10% of CF patients will require enteral tube feeding nasogastric tube or gastrostomy tube. This strategy must be arranged with patients and their families, as well as among the whole team of caregivers, especially when other interventions have failed. Some of the benefits reported for enteral tube
feeding are increased caloric intake, better nutritional status in general, and delayed decline of pulmonary function.\textsuperscript{55,56,57,58} In general, there is still no consensus among physicians, regarding the administration of enzymes during enteral feeds, although several strategies have been proposed.\textsuperscript{59,60} Impaired glucose metabolism must be evaluated when considering enteral tube feeding as a possibility, and insulin administration has been indicated in patients with cystic fibrosis related diabetes (CFRD).\textsuperscript{61} A recent report in adult patients receiving enteral tube feeding has demonstrated improvements in nutritional status due to fat mass, which constitutes a risk factor for diabetes, and low impact response in lean mass.\textsuperscript{62}

**CYSTIC FIBROSIS RELATED DIABETES**

CFRD prevalence increases with age up to 40-50\% of adult population.\textsuperscript{63} CFRD is associated with great impact on nutritional status and body composition, decline of lung function and a rise in mortality rates.\textsuperscript{64} CFRD presents unique characteristics that differentiate it from types I and II diabetes and manifests through an insufficient insulin secretion. A strong genetic link between CFRD and type II diabetes patients has been observed. It has been reported in a multicenter trial that susceptibility of type II diabetes gene \textit{TCF7L2}, plays an important role in modifying risk of CFRD.\textsuperscript{65}

CF patients can present different stages of insulin resistance associated with pulmonary exacerbations or exogenous factors such as the use of systemic steroids.\textsuperscript{66} A sub-group of CFRD patients will not present fasting hyperglycemia which is why CFRD diagnosis is confirmed through oral glucose tolerance test (OGTT) with a glucose doses of 1.75 g/kg up to 75 grams. OGTT should be performed annually starting at age 10.\textsuperscript{67} Glicosilated hemoglobin (HbA1c) should not be used to perform CFRD screening in an isolated way because it underestimates glycemic control and has shown poor correlation with OGTT. CF patients have high red blood cells turnover, which explains the presence of low levels of HbA1c.\textsuperscript{68}

A group of CF patients will show alterations of glucose metabolism that won’t fall in the CFRD or intolerance categories. These patients present with 1-h OGTT >11.0 mmol/L but 2 h-OGTT<7.8 mmol/L and are identified as indeterminate, unfortunately, we don’t have enough information regarding treatment or prognosis of these glucose metabolism alterations.\textsuperscript{69}

Treatment with insulin, an anabolic hormone, results in a better nutritional status, lung function and longer life expectancy in CFRD patients. Hyperglycemia is associated with deleterious effects that promote inflammation and bacterial infection of the respiratory environment. A recent study showed association between hyperglycemia and lung bacterial clearance mechanism deterioration, pointing the negative effect of alterations in glucose metabolism over lung function.\textsuperscript{70}

**SUMMARY**

Prognosis and life expectancy in CF patients are linked with the evolution of pulmonary disease. The relationship between an adequate nutritional status and a slower decline in lung function has been demonstrated. Achieving nutritional goals in CF patients requires of an adequate approach from the moment of diagnosis and the whole life. A different number of nutritional factors need to be considered to fulfill these goals. Although there has been a significant change in the evolution of this group of patients in recent years, it is necessary to continue investigating different nutritional aspects of CF to improve care.

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