Nutritional Support in Hereditary Disease

Module 29.4

Nutrition in the Cystic Fibrosis patients - impact and intervention

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Learning Objectives

- To understand the medical background of CF;
- To understand the relationship between the severity of the disease and nutritional status;
- To learn about the different nutritionally related problems of the CF patient;
- To learn methods of intervention and nutritional treatment.

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Key Messages

- CF is caused by a mutation in the CFTR gene (cystic fibrosis transmembrane conductance regulator) located on the long arm of chromosome number 7;
The primary pulmonary function parameter defining severity is % predicted FEV1;
There is a direct relationship between nutritional status and lung function. Nutritional status during childhood is the most important single factor determining pulmonary status in CF adults;
The aim of nutritional support in patients with cystic fibrosis is to achieve normal growth and development;
Malnutrition and failure to thrive are common problems in CF patients;
Malabsorption of fat and fat soluble vitamins is severe in most CF patients (pancreatic insufficiency) without enzyme treatment;
Some minerals can be deficient in CF patients, the most common being iron, calcium, zinc and sodium;
Pancreatic insufficiency is treated by pancreatic enzymes supplementation;
A high fat diet should be advised for CF patients, and nutritional supplements high in energy density should be recommended, orally or by tube feeding;
Cystic fibrosis-related diabetes (CFRD) and glucose intolerance are common in teenagers and adults with CF;
HbA1c alone cannot be used for the diagnosis of diabetes in people with cystic fibrosis;
Patients with CFRD may eat as much or as little as they choose, at any time, provided they cover it with the appropriate amount of insulin;
Low bone mineral density is becoming an increasingly important issue in patients with CF;
Liver disease has become a significant medical issue in CF patients;
Urodeoxycholic acid is the only therapy that improves liver function tests.
1. Medical Background - CF Pathophysiology and genetics

CF Pathophysiology and genetics
Cystic fibrosis (CF) is the most common autosomal recessive life shortening genetic disease in Caucasian populations. The disease is caused by mutation in the CFTR gene (cystic fibrosis transmembrane conductance regulator) located on the long arm of chromosome number 7 (Fig. 1).

Cystic fibrosis transmembrane conductance regulator (CFTR) gene

The CFTR gene is located on the long arm of chromosome 7.
There are 1522 mutations in CFTR listed on the CFTR mutation database
The most common mutation is Δ F508--70% CF alleles in caucasians.¹

Figure 1 Cystic fibrosis transmembrane conductance regulator (CFTR)

The gene encodes a protein that functions as a cAMP-regulated chloride channel. Defects in the CFTR protein (Figure 2) cause abnormal chloride transport across the apical membranes of epithelial cells in the airways, pancreas, intestine, and vas deferens, leading to progressive lung disease, pancreatic dysfunction, elevated sweat electrolyte levels, and male infertility, respectively.

Figure 2 Defects in the CFTR protein

¹ Gibson, RL, Burns, JL, and Ramsey, BW. Pathophysiology and Management of Pulmonary Infections in Cystic Fibrosis. AJRCCM 168 (918-951); 2003.
Lung disease
Lung disease accounts for nearly 85% of the mortality (1). Lung destruction is caused by obstruction of the airways due to dehydrated thickened secretions, resultant endobronchial infection, and an exaggerated inflammatory response leading to development of bronchiectasis and progressive obstructive airways disease. Early and aggressive therapy may delay the development and progression of cystic fibrosis (CF). Markers for early pulmonary disease in CF include pulmonary function tests (PFT), microbial cultures, imaging techniques, inflammatory markers, serological markers, and clinical evaluation of exacerbation rate and nutritional status. The primary pulmonary function parameter defining severity is % predicted FEV1 as follows: normal, greater than 90% predicted; mildly impaired, 70-89% predicted; moderately impaired, 40-69% predicted; and severely impaired, less than 40% predicted.

Genotype phenotype association
Since the identification of the common CF mutation in North America (Δ508) more than 1500 different mutations have been described. These CFTR mutations are now grouped in classes I to V that reflect the associated biosynthetic or functional alterations in the CFTR protein. Group I involves premature stop codon (e.g. 1282X), group II abnormal protein production which is degraded in the cytoplasm (e.g. Δ508) and group III involves dysregulation of the CFTR protein. These three groups are associated with no functional CFTR at the apical membrane and therefore are considered as severe mutations. Group IV and V are associated with an abnormal chloride channel or reduced number of channels and are considered as mild mutations (Fig. 2). A strong correlation between pancreatic phenotype and genotype has been recognized (2), whereas, no clear correlation has been reported between pulmonary phenotype and genotype (3, 4). The phenotype of exocrine pancreatic sufficiency is related to mild mutations whereas exocrine pancreatic insufficiency is related to severe mutations of the CFTR gene (2) (Figure 3). Most patients with CF (85 %) carry mutations which are associated with pancreatic insufficiency. Pancreatic functional status is a strong predictor of long-term outcome and has a direct influence on nutritional status; therefore, knowing the pancreatic phenotype is useful not only in nutritional management but as a prognostic factor.

Pancreatic status by mutation class

2. Nutritional status and pulmonary status
Poor clinical outcomes are associated with undernutrition in patients with CF and a direct effect of nutritional growth retardation in CF on lung growth has been demonstrated (5, 6). A direct relationship between resting energy expenditure and lung function has been found (7) (Fig. 4).
Figure 4 The relationship between energy expenditure and lung function

Nutritional status during childhood was found to be the most important single factor determining pulmonary status (and hence likely survival) in CF adults (8). This supported the earlier observations of Corey et al (6), who reported that the major factor accounting for longer survival in Toronto than in Boston was the greater emphasis on maintenance of normal growth rates and nutritional status in the former. This correlation between nutritional status and survival becomes particularly apparent when end-stage respiratory failure is accompanied by cachexia. The degree of wasting is a good predictor of mortality independent of lung function and levels of oxygen and carbon dioxide (9).

Studies showed a positive effect of nutritional intervention on anthropometric measurements and pulmonary function (10, 11). Supplemental gastrostomy feedings were shown to be associated with stabilization in pulmonary function status (11).

The mechanism by which nutritional status relates to pulmonary status is complex and unclear. Nutritional status may affect lung function by several mechanisms: Nutritional impairment during the early stages of the child’s growth and development may affect the rate at of lungs growth (12). Weight loss and loss of fat-free mass may lead to peripheral muscle wasting which may also affect lung function as may deficiency in micronutrients and vitamins. For example, lower levels of linoleic and docosahexaenoic acids found in CF are suggested as associated biochemical changes that form a vicious circle with poor lung function. A beneficial effect of docosahexaenoic acid on cystic fibrosis pathology has been suggested.

On the other hand, progressive lung disease may affect nutrition. Lung hyperinflation and cough may induce gastro-esophageal reflux which reduce appetite, and host inflammatory cytokine response may also have an anorectic effect. At the same time severe obstructive lung disease increases energy expenditure due to the high demands of the work of breathing. This combination of poor appetite and high energy demands lead to poor weight gain and even weight loss during acute exacerbations. These interrelationship between pulmonary status and nutritional status are shown in Figure 5.
Figure 5 The interrelationship between pulmonary status and nutritional Status

Recommendation: The aim of nutritional support in patients with cystic fibrosis is to achieve normal growth and development. The Cystic Fibrosis Foundation recommends a team approach including physician, nurse, social worker, psychologist and dietitian. The role of the dietitian is to provide the specific expertise needed for optimal nutritional management and with other team members to provide expertise concerning developmental and behavioral aspects of eating.

3. Nutrition issues in the CF patient

3.1 Malnutrition in CF
Malnutrition and failure to thrive are common problems in CF patients. Factors contributing to malnutrition in CF:
- **Malabsorption of fat**
  Malabsorption of fat and protein is severe in most CF patients without enzyme treatment. Even when clinical symptoms appear to be controlled by pancreatic enzyme supplementation, many patients still have a significant degree of fat malabsorption (14, 15).

- **Deficiency of pancreatic bicarbonate**
  Bicarbonate Deficiency results in diminished capacity to buffer influxes of gastric acid into the duodenum. This results in reduced efficacy of exogenous pancreatic enzymes and precipitation of bile salts. In an acid medium fatty acids are not converted into soups and remain in the oil phase, this can further hinder fat digestion (14, 15).

- **Inadequate energy intake**
  CF patients have higher energy needs than normal, and should eat 120-150% of the recommended daily amount. Although some children with CF have excellent eating habits, there are several factors that commonly reduce appetite and consumption including recurrent vomiting from coughing and/or gastro esophageal reflux, chronic respiratory infection and psychosocial stress.

- **Cystic fibrosis related diabetes**
  Diabetes can increase energy loses as a result of glycosuria. It is important to stress, that, in patients without diabetes, there is no rationale for sugar or other carbohydrate restriction or budgeting in the diet, as this will not prevent or delay the onset of diabetes, since the etiology
differs from that of type 2 diabetes. Furthermore carbohydrate restriction can impair energy intake. Once diabetes has developed, of course, patients must be treated accordingly.

- **Liver disease**
  Liver disease may exacerbate the severity of malabsorption because of inadequate bile acid secretion.

### 3.2 Vitamins deficiency

Fat malabsorption can lead to the loss of vitamins in the stool that aggregate with fat. Patients with CF that are treated with pancreatic enzymes continue to mal-absorb fat soluble vitamins and should be supplemented accordingly.

- **Vitamin A**
  Vitamin A deficiency is common in CF patients. Pancreatic enzyme replacement fails to normalize serum vitamin A levels. Low vitamin A levels are associated with poorer clinical status and impaired lung function (16). Beta carotene is a precursor of vitamin A and may also function as an antioxidant. Plasma levels of B-carotene are low in pancreatic insufficient patients with CF.

- **Vitamin D**
  10-40% of patients with CF are deficient in vitamin D. Sunlight exposure is the major determinant of the amount of vitamin D in the body, which mainly depends on seasonal variations, skin pigmentation and geographical location. Vitamin D supplementation is important because of the high prevalence of osteomalacia, osteoporosis and bone fractures among patients with CF. A recent study found that despite daily vitamin D supplementation, serum 25(OH)D concentration remained low in children, adolescents, and young adults with CF (17).

- **Vitamin E**
  Vitamin E is an antioxidant. Oxidative stress is enhanced in CF patients due to chronic respiratory inflammation. Vitamin E has been reported to be low in patients with CF even in those taking pancreatic enzymes and multivitamins. (18)

- **Vitamin K**
  Vitamin K functions in the biosynthesis of clotting factors and with osteocalcin in GLA protein hydroxylation, important for bone health. Deficiency is common in CF patients especially in unsupplemented pancreatic insufficiency (19). Colonic bacteria are an important source of vitamin K so that disruption of the enteric flora by antibiotic use can reduce vitamin K levels.

### Table 1 Recommendations for vitamin supplementation (14)

<table>
<thead>
<tr>
<th>Age</th>
<th>Vitamin A (IU)</th>
<th>Vitamin E (IU)</th>
<th>Vitamin D (IU)</th>
<th>Vitamin K (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>1500</td>
<td>40-50</td>
<td>400</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>1-3 years</td>
<td>5000</td>
<td>80-150</td>
<td>400-800</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>4-8 years</td>
<td>5000-10000</td>
<td>100-200</td>
<td>400-800</td>
<td>0.3-0.5</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td>10000</td>
<td>200-400</td>
<td>400-800</td>
<td>0.3-0.5</td>
</tr>
</tbody>
</table>

### 3.3 Minerals and electrolytes

Some minerals can be deficient in CF patients

- **Sodium**
  Infants and children with CF are at risk of hyponatremia, because of salt losses through the skin. Patients with CF are advised to consume a high salt diet especially during summer. Since human milk is low in sodium breast fed babies may need supplementation.

- **Calcium**
  Calcium is important for the mineralization of the skeleton, muscle construction and signal transmission in the nervous system. Several studies have indicated that calcium insufficiency and
low bone mass are common in CF patients (20). Fat malabsorption can contribute to poor calcium absorption.

- **Iron**
  Iron deficiency is frequent in CF and caused by multiple factors: inadequate dietary intake, malabsorption, chronic infection and blood loss. Iron status should be monitored routinely in CF patients by controlling haemoglobin, iron, transferrin and ferritin.

- **Zinc**
  CF patients may have zinc deficiency due to fat malabsorption. Deficiency may contribute to growth retardation and disturbed immune function. A recent study has found that oral intake of 30 mg/day of Zn reduced the number of days of oral antibiotics used to treat respiratory tract infections in children with CF. A higher daily Zn dose may be needed to decrease respiratory tract infections and modify immune responses (21). Pancreatic enzyme supplementation improves zinc absorption.

4. **Growth of individuals with CF**

During infancy the growth pattern is dependent on the age at diagnosis and the quality of the subsequent treatment the patient receives. Those with pancreatic insufficiency develop early gastrointestinal symptoms which can lead, if not treated, to subnormal weight gain. Evaluation of nutritional intake and growth must be made at every visit.

4.1 **weight and height**

Weight and height should be measured at each clinical attendance by trained clinical staff. These measurements should be charted to assess progress and to compare to reference values.

4.2 **BMI**

In Adult patients, BMI is an important indicator. Reference values: BMI <18.5 underweight, BMI 18.5-24.9 ideal weight, BMI 25-29.9 pre-obese, BMI>30 obese.

In children and adolescents no advantage has been shown of using BMI, rather than weight for height for documenting malnutrition.

4.3 **Rate of weight gain and growth**

The weight for height should remain above 90% (90th percentile) and ideally should be over 95%. If weight for height is between 85-90% in children or BMI<18.5 in adults, patients are advised to take oral supplements. If weight for height is less than 85% or BMI<18.5 in adults who are taking supplements, enteral tube feeding is recommended (table 2). Girls, especially adolescents and young woman, should be discouraged from going on weight losing diets.

4.4 **Assessment of nutritional status - laboratory measures**

A variety of investigations may be helpful in the assessment of the patient’s nutritional state, such as haemoglobin, ferritin, iron, transferrin, total white cell and neutrophil count, serum albumin and/or pre-albumin, cholesterol, triglycerides, calcium, phosphorus, liver enzymes and bile acids. Plasma fat-soluble vitamin A, D and E levels should be measured annually.

<table>
<thead>
<tr>
<th>Table 2 Guidelines for nutritional intervention (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 2 years</strong></td>
</tr>
<tr>
<td>Normal nutritional state Preventive counseling</td>
</tr>
<tr>
<td>Dietetic referral indicated Consider supplements</td>
</tr>
<tr>
<td>Invasive nutritional support Failure to thrive despite oral supplementation</td>
</tr>
</tbody>
</table>
5. Treatment of pancreatic insufficiency

Pancreatic disease has strong correlation to specific genotype groups. Severe mutations cause PI. When mild mutations are associated with a severe mutation the mild mutations are dominant (22). Most of the patients with pancreatic sufficiency (PS) have mild lung disease and the over-all prognosis is improved. Still, recurrent pancreatitis is more common in PS (22).

Diagnosis can be made by few tests:
- Fat balance study- PI is diagnosed if fecal fat excretion excide 10%;
- Spot stool for fat digestion;
- Spot stool analysis for fecal elastase1.

Pancreatic insufficiency is treated by pancreatic enzyme supplementation. For an infant it is recommended to supplement one quarter to one third of a capsule of standard strength (as creon 10000iu=2500-3333iu lipase) to every 120ml infant formula. These doses equate to approximately 400-800iu lipase per gram of dietary fat. Enzymes should be mixed with a small amount of infant formula or expressed breast milk or fruit puree and give with a spoon directly before the feed.

For older children and adults the recommended dose is 10000iu lipase per kg body weight/day.

Enzymes should be given with all fat containing foods and supplements. The capsule should be swallowed whole at as early an age as possible.

Enzymes should be given as follows: half the dose at the beginning of the meal and half in the middle of the meal.

In tube or gastrostomy fed patients pancreatic enzymes should be given before and after the feed.

6. Nutritional intervention for patients with CF

Infant feeding

Infants with CF fed on breast milk achieve normal weight gain and growth. If breast feeding is not possible, cow’s milk based infant formulas can be used. Hydrolyzed protein formulae should be considered for infants who have undergone extensive gut resection or those with milk allergy.

Formulae that contain MCT oil should be considered in patients with cholestasis or uncontrolled steatorrhoea. If weight gain is poor, the formula should be concentrated to 1kcal/ml by adding glucose polymers (such as policose) or oil, or in babies older than 3 months, by thickening the formula with corn flour or rice, or by using a high-energy infant formula.

Intervention for nutritional failure

6.1 Oral supplementation

For infants 0-1 years old formula should be concentrated to achieve an energy density of 1kcal/ml. Solids should be introduced at the age of 6 months and higher fat foods may be used with appropriate dosage of enzymes. For infants older than 1 year a high fat diet should be advised and nutritional supplements high in calories density (pediasure/nutren junior/scandishake) should be recommended.

Standard adult’s supplements are suitable for children over 5 years. Supplements should be given after meals or before bedtime to ensure that the appetite for normal food is maintained.

6.2 Tube feeding

Tube feeding should be started when oral supplementation fails to result in weight gain. Tube feeding should be presented as positive treatment not as a threat, and as a supportive therapy to improve quality of life and outcome.
Tube feeding can be administrated by naso-gastric tube or by gastrostomy. The tube feeding should be given over-night to maintain normal dietary intake during the day.

Non elemental formulae with complete protein and long chain fat with caloric density of 1.5-2 kcal/ml are well tolerated.

If these formulae are not tolerated, one which contains hydrolyzed protein or MCT should be offered.

7. Special consideration

7.1 Essential Fatty Acids and DHA

Essential fatty acids are polyunsaturated fats that can metabolized to linoleic (n-6 series) and alpha linolenic acid(n-3 series). Linoleic acid is further metabolized to arachidonic acid (AA), and alpha linoleic acid is metabolized to docosohexaenoic acid(DHA).

Cystic fibrosis patients typically present with abnormal fatty acid profiles, marked by normal to increased levels of arachidonic acid (20 :4n_6) and low levels of linoleic(18 :2n_6) and docosahexaenoic (22 :6n_3) acids (23).

Docosahexaenoic acid (DHA) is an important component of phospholipids in cell membranes. A biochemical deficiency of DHA has been reported in blood lipid fractions and other tissues in CF patients, particularly in those with the DF508 genotype. Factors proposed to contribute to this essential fatty acid status include reduced fat and energy intake and fat malabsorption. Failed attempts to normalize fatty acid levels through improvements in dietary fat intake (24) or by minimizing fat malabsorption with pancreatic enzymes suggests a problem in metabolism of essential fatty acids and a potential requirement for therapeutic doses of long chain polyunsaturated fatty acids (LCPUFA). Epidemiological and other studies suggest that a diet rich in omega-3 essential fatty acids (derived from fish oil) may have beneficial anti-inflammatory effects for chronic conditions such as cystic fibrosis (CF). A recent COCHRANE review found that regular omega-3 supplements may provide some benefits for people with CF, with relatively few adverse effects, although the evidence is insufficient to draw firm conclusions or to recommend routine use of such supplements (25).

7.2 Cystic-fibrosis related diabetes (CFRD)

Cystic fibrosis-related diabetes (CFRD) and glucose intolerance affect more than 50-75% of teenagers and adults with CF (26). The causes include insulin deficiency, insulin resistance and impaired substrate metabolism (27). The exocrine pancreatic insufficiency in CF patients is followed by endocrine insufficiency caused by destruction of the islets of Langerhans with ongoing fibrosis of the pancreas. Insulin secretion diminishes and patients develop impaired glucose tolerance and then finally diabetes. The disease progresses from impaired glucose tolerance to a phase of increasing fasting glucose and eventually full-blown diabetes. (Fig. 6)
Increased insulin sensitivity (insulin resistance) is also present in patients with CF and is probably caused by underlying inflammation. Although insulin resistance is not as severe as in type 2 diabetes, it worsens with acute illness and clearly contributes to the development of CFRD. The metabolism of carbohydrate, protein and fat is abnormal in patients with CF, and the complex interplay of these metabolic changes contributes further to the development of CFRD.

Impaired glucose tolerance (IGT) and cystic fibrosis related diabetes (CFRD), are the main co-morbidities in cystic fibrosis (CF) and their prevalence is increasing as the survival of CF patients improves (28). CFRD is an important marker of a worsening prognosis and a higher mortality rate (18). Several studies have reported a decline in nutritional and pulmonary status 2 to 4 years before the diagnosis of CFRD (29) Based on the natural history of the disease, this could be due to the impaired glucose tolerance which precedes the development of CFRD (29).

7.2.1 Criteria for the diagnosis of CFRD:
1. Fasting blood glucose > or = 126mg/dl on two or more occasions; 
2. Fasting blood glucose > or = 126mg/dl plus a casual blood glucose is > or = 200mg/dl; 
3. Casual glucose levels >or = 200mg/dl on two or more occasions with Symptoms; 
4. Two hour blood glucose > or = 200mg/dl during a 75 gram oral glucose tolerance test.

HbA$_1$c alone cannot be used for the diagnosis of diabetes in people with cystic fibrosis. It is possible that red blood cell abnormalities described in people with cystic fibrosis, such as iron deficiency anemia and shortened red blood cell life span could influence HbA$_1$c and impair its usefulness as a measure of glycaemic control in CF-related diabetes.

7.2.2 Medical and nutritional therapy:
Insulin is the only medical therapy officially recommended for CFRD with fasting hyperglycaemia. Many different insulin regimens are possible, depending on the needs of the patient. The dietary management of CFRD is critical for the health and survival of these patients. Calorie restriction is never appropriate in CF since a high energy intake is necessary for survival. For the patient on insulin therapy, the method called 'carbohydrate counting' offers the greatest degree of flexibility while allowing achievement of excellent blood glucose control. Patients 'count' how many grams of carbohydrate are in a given meal, and dose their insulin accordingly. Patients may eat as much or as little as they choose, at any time, provided they cover it with the appropriate amount of insulin. Patients with borderline diabetes without fasting hyperglycemia are asked to distribute their carbohydrate calories evenly throughout the day and to avoid concentrated carbohydrate loads.

7.3 Bone health in CF:
Low bone mineral density (BMD) is becoming an increasingly important issue in adult patients with CF.

The origin of the bone disease is multifactorial: malabsorption of calcium and vitamin D, poor nutritional status, lack of physical inactivity, glucocorticoid therapy, delayed pubertal maturation,
early hypogonadism, chronic pulmonary inflammation, increased serum cytokine levels, are all factors contributing to bone disease (Fig 7) (30).

Cross sectional surveys of adults have found that 20-34% of adults with CF have standard Z-scores <-2 while 10% have T-scores<-2.5.(31)

The prevalence of BMD below -1SD is as high as 55% in some adults CF studies. The prevalence of bone disease appears to increase with severity of lung disease and malnutrition. Patients with severe pulmonary disease (FEV1<30%) often have severe bone disease with a high rate of kyphosis and fractures of long bones, vertebrae, and ribs(32).

![Figure 7 Pathogenesis of bone disease in CF](image)

**7.3.1 Pancreatic exocrine insufficiency and malabsorption**
There is a growing consensus suggesting that the absorption of vitamin D and K and calcium are inadequate and fail to meet the needs of individuals with CF. Vitamin D insufficiency is common among individuals with CF irrespective of season or latitude. Other possible causes for low 25OHD levels could be altered concentration or activity of the 25 hydroxylase enzyme or a higher metabolic clearance of vitamin D or 25OHD. Biliary disease is common in CF and bile salts may inactivate the 25 hydroxylase.

**7.3.2 Pancreatic endocrine insufficiency**
Diabetes develops in 10% of individuals with CF. The abnormalities in glucose metabolism may play a role in reduced BMD.

**7.3.3 Physical inactivity**
Individuals with CF may become inactive due to reduced lung function and prolonged treatments for respiratory infection. Most studies in CF found association between total activity and BMD(31).
7.3.4 Delayed puberty or early gonadal failure
Pubertal delay in CF has been recognized for over 20 years and is related to disease status. Delayed puberty may retard both growth and the attainment of peak bone mass. Some studies have shown an association between both delayed puberty and hypogonadism and a lower BMD(31,33).

7.3.5 Chronic infection
Bone remodeling is under the influence of systemic hormones, cytokines and localized growth factors. Many inflammatory cytokines are found in high concentration in the chronically infected CF lungs and serum which can contribute to low BMD.

7.3.6 Glucocorticoids
Chronic glucocorticoids therapy in children impairs linear growth, delays puberty and may compromise the peak bone mass attained by early adulthood. Many studies have found that glucocorticoid therapy is a risk factor for low bone mass in CF.

7.4 Intestinal disease
CF can have manifest itself in all parts of the intestine:
• Oesophagus: gastro-oesophageal reflux, oesophagitis, peptic disease;
• Small intestine: meconium ileus, DIOS, intussusception.

Meconium ileus and DIOS are exclusive to PI patients that have the severe mutation. The degree of pancreatic dysfunction probably contributes to the genesis of those complications.

• Colon: pneumatosis intestinalis, fibrosing colonopathy, rectal prolapse. Fibrosing colonopathy is a new entity which has occurred since the introduction of high dose lipase. It is an intra mural fibrosis that affects the proximal colon and causes intestinal obstruction. Since the establishment of the guidelines recommending that no more than 10,000 IU lipase /kg/day be consumed, the incidence of fibrosing colonopathy has declined (34).

7.5 Hepato-Biliary disease
A variety of manifestations have been described, including:
• Liver- neonatal cholestasis, hepatosteatosis, focal biliary fibrosis, biliary cirrhosis;
• Biliary tract- ductal stones, bile duct stenosis, sclerosing cholangitis, cholangiocarcinoma;
• Gallbladder- microgallbladder, distended gallbladder, cholelithiasis.

Children with hepatosteatosis and focal fibrosis can be asymptomatic. Liver disease progress slowly but the life expectancy of patients with CF has been increasing and the associated liver disease has become a significant medical issue. Urodeoxycholic acid is the only therapy that improves liver function tests (35).

Liver transplant is an option in liver failure or uncontrolled portal hypertention. Contraindications include severe pulmonary disease and fungal or Burkholderia Cepacia lung colonization. No clear relationship between the type of mutation and liver disease has been found.

Summary
CF is caused by a mutation in the CFTR gene. Most patients with CF (85 %) carry mutations which are associated with pancreatic insufficiency. There is a direct relationship between nutritional status and lung function; therefore it is important to maintain CF patients in a good nutritional status. CF patients require a high energy intake due to mal-absorption of fat and the increased metabolic rate caused by lung disease. When CF patients fail to gain weight, oral supplementation or tube feeding should be considered. Pancreatic insufficiency is treated by pancreatic enzyme supplementation, which should be given with all fat containing foods and supplements.

With the continuing introduction of many new treatments, the life expectancy of patients with CF is increasing, and more late complications are therefore being identified, including cystic-fibrosis related diabetes, bone disease and liver damage.
References


