CHAPTER 3 THE ROLE OF NUTRITION IN CF CARE

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Cystic fibrosis is the most common lethal autosomal recessive genetic condition affecting Caucasians [186,187]. Over 3500 Australians and New Zealanders live with this condition, with approximately between 80 to 100 new diagnoses in Australia and 10 in New Zealand of CF annually [188,189]. CF is a multi-system condition characterised by abnormally high sweat chloride (and sodium) levels, progressive lung disease, pancreatic insufficiency, as well as hepatobiliary and fertility tract complications. Over 90% of individuals with the condition experience one or more gastrointestinal complications. Optimising growth and nutrition in individuals with CF has been shown to positively influence lung function and survival [190]. This chapter broadly focuses on the role that nutrition plays in CF care.

3.1 Considerations for New Diagnosis

All babies born in Australia and NZ undergo newborn screening for the most common CF-causing genes [2,3]. Most babies with CF (~90%) will be identified using this method [191]. CF may also be suspected in infants who are born with meconium ileus (bowel blockage) and in children and adults who suffer from poor weight gain and suboptimal growth, steatorrhoea or constipation, ongoing sinus issues and/or regular chest infections [192,193]. Individuals who are diagnosed as adults generally have milder forms of CF. Confirmation of a CF diagnosis is made using a sweat test, even in cases where two abnormal CFTR genes are known. Sweat chloride levels > 60mmol/L are diagnostic of CF [192].

People who are newly diagnosed (and their carers/families) require access to a specialist CF team including a specialist dietitian. Promotion of good nutrition is to be commenced as soon as possible and nutrition education is to be provided. Table 3a highlights nutrition considerations for infants, children and adults at time of diagnosis.

Table 3a. Nutritional considerations for people newly diagnosed with CF

Practice considerations to promote good nutrition	
Infants and children	• Conduct a growth assessment. • Pancreatic status is to be promptly assessed and pancreatic enzyme replacement therapy commenced if indicated. • Review fat-soluble vitamin status and liver function. Low fat-soluble vitamin levels can be an early indicator of pancreatic insufficiency. • Encourage and support breastfeeding. Most infants with CF are able to maintain adequate growth while breastfeeding. • The benefits of exclusively breastfeeding a CF baby for the first 6 months include a decreased use of intravenous antibiotics for the first two years of life. • Energy supplements/concentrated infant formula top-ups can be used. • A standard infant formula is usually recommended where breastfeeding is not possible. • Consider routine salt, electrolyte and fat soluble vitamin supplementations.
Adults	• Assess nutritional status and weight history. • Consider if genetic potential for growth has been met. • Pancreatic status is to be promptly assessed and PERT commenced if indicated. • Review fat-soluble vitamin status (A, D, E and K) and liver function. • Consider commencing routine salt and fat soluble vitamin supplementation.

3.2 Effect of Nutrition Status on CF Lung Disease and Survival

The relationship between lung function, survival and nutrition in CF is well established. More specifically, normal body weight is associated with better preservation of lung function [190]. Corey and colleagues (1988) first highlighted the importance of nutrition in their landmark study titled "A comparison of survival, growth, and pulmonary function in patients with CF in Boston and Toronto" [194]. Whilst there was no significant difference in the respiratory care provided at the Boston and Toronto clinics between 1972 and 1981, nutritional management between these two centres varied greatly. In Toronto an aggressive approach to nutrition was recommended (i.e. high fat and high energy diet) whereas the Boston clinic followed standard nutritional practices of the time (i.e. low fat diet to manage symptoms of malabsorption. Toronto's aggressive approach to nutrition resulted in better nutritional status for individuals with CF, and ultimately significantly longer lifespans (median age of survival Toronto 30 years vs Boston 21 years) [194]. A subsequent study showed that after United States of America (US) CF clinics took up the Canadian (Toronto) approach that clinical outcomes were also significantly improved [195]

Of particular clinical interest, however, is that evidence has shown better nutritional status in childhood is associated with improved clinical outcomes (lung function, adult height, fewer CF associated complications) and survival in individuals with CF [196-200]. Poor nutrition has been shown to have adversely impact lung development in pre-adolescent children [196,201]. The pattern of good nutrition and good lung function appears to be lineal, to a certain extent, as individuals with CF grow older [132,190,198,202].

Marked improvements in the nutritional status of CF populations have been demonstrated over recent decades, including in Australian and New Zealand populations. Collins et al reported improvement in the mean height Z-score of 10-15 year olds with CF in Newcastle between 1993 and 1997 from -0.88 to -0.05 [203]. Richardson et al compared adult cohorts from Melbourne in 1983 and 1997, finding height advantages in the 1997 cohort of 8cm and 5cm in males and females respectively, and weight advantages of 13 kg and 12 kg respectively [204]. More recent registry data demonstrates ongoing improvements in the nutritional status of local CF populations and reduction in the prevalence of nutritional deficits. Between 2004 and 2014, the proportion of children with CF in Australia with a height less than the 10th percentile decreased from 19% to 12% [188,205]. Correspondingly, the prevalence of BMI less than the 10th percentile fell from 10.4% to 6.6% and the proportion of adults with a BMI less than 20 kg/m^2 fell from 27% to 20% [188,205].

NUTRITION DEFICITS IN CF

Despite the improvement in the overall nutritional status of CF populations, nutritional deficits are still prevalent. They may be present in people with CF from a young age[1] and may persist throughout life, normalize with intervention, or emerge episodically. While nutritional status in populations diagnosed early, including through newborn screening, is better than in those where CF has been diagnosed later in life, deficits may still be seen in those diagnosed through newborn screening (NBS) programs [1].

Nutrition deficits observed at an individual and/or population level in CF include:

- retardation in weight gain and linear growth in children [197,206,207]
- delayed onset of pubertal growth spurts and lower peak pubertal height velocity compared to healthy population reference values in some [197], but not all [208] studies
- lower height, weight and BMI, whether measured as percentiles, Z-scores or mean adult levels, when compared to healthy population data [204,207,209]
- reduced body fat stores in some individuals [206,210,211]
- reduced fat-free mass (FFM) (also known as lean body mass), whether measured as FFM or using other indices such as total body nitrogen, total body potassium or body cell mass [19,212-219]
- reduced rates of accretion of fat free mass in children over time [206,211]
    - FFM deficits tend to be greater than decreases in fat stores [210,214,220-222]
    - Low FFM stores are not confined to those who are underweight, but may also be seen in those with normal BMI [213,223-226]. This shows that those with normal body weight or BMI cannot be assumed to have normal FFM stores.
    - Despite fat free mass being the major contributor to total body weight, loss of, or gain in, fat-free mass stores cannot be assumed from change in total body weight, as less than 40% of the variability in weight change over time is accounted for by change in FFM [214,227].

It is not possible to synthesise the results of all studies to define the prevalence of reduced fat-free mass due to heterogeneity in terms of the age and disease severity of the study populations, body composition methods, criteria used to define FFM depletion, and the country and the decades in which studies were undertaken.

While risk factors for poor accretion of fat-free mass in childhood and/or fat-free mass depletion in adults are not yet universally accepted, identified correlates of lower fat-free mass include lower forced expiratory volume in 1 second (FEV_1) and higher levels of circulating inflammatory cytokines [19,219,222-224,227,228]. Further research will be required to identify if modification of these associated clinical variables prevents or reverses FFM depletion.

SO, WHAT DOES THIS MEAN FOR PRACTITIONERS?

- Achieving near normal nutritional status for CF populations is now an achievable goal.
- Nutritional deficits are still prevalent in a significant proportion of the CF population and thus surveillance to identify those at risk of undernutrition is a vital component of CF care.
- Nutrition support should be implemented early for people with CF, and regular monitoring and evaluation is vital [78].

3.3 Complications of CF with Nutrition Implications

Concurrent complications and co-morbidities which can place individuals at further risk of poor nutritional status include malnutrition, pancreatic insufficiency and pancreatitis, GOR, constipation and DIOS, CF-related liver disease, intestinal dysbiosis, CF-related diabetes, bacterial overgrowth and dyslipidaemia. Each complication is briefly outlined here – for more detailed information please refer to the corresponding guideline chapter.

UNDERNUTRITION (Chapter 5 and 6)

- Recent figures show that undernutrition affects approximately 6% of adults (BMI<18.5 kg/m^2) and 6.6% of children (BMI<10th percentile) with CF [188].
- Median height and BMI percentiles in children with CF are lowest in adolescence [188]
- Causes of undernutrition are generally multifactorial – physiological and socio-economic.
- Persistent undernutrition is associated with significant morbidity and mortality.
- If not corrected, undernutrition may result in:
    - altered pulmonary defence mechanisms [78]
    - altered pulmonary muscle function [78]
    - decreased exercise tolerance [78]
    - immunology impairment [78]
    - growth defects [229]
    - inadequate accretion of bone minerals [230]

PANCREATIC INSUFFICIENCY AND PANCREATITIS (Chapter 10)

- Pancreatic insufficiency affects up to 90% of people with CF [188,189,205].
    - Being pancreatic sufficient however, still indicates some impairment and is not equivalent to normal pancreatic function [231].
- Some individuals with pancreatic sufficiency are at risk of progressing to pancreatic insufficiency, particularly after the development of recurrent episodes of pancreatitis [232].
- Pancreatic insufficiency is generally associated with more severe CFTR mutations (i.e. class I, II, III) [233].
- Pancreatic insufficiency is a main factor contributing to undernutrition in CF.
- If poorly managed, pancreatic insufficiency can result in nutritional decline in:
    - fat soluble vitamin levels (A, D, E, K),
    - growth and body composition,
    - attainment/maintenance of peak bone mass
    - gastric motility [233]
- Individuals with pancreatic sufficiency have an approximately 20 to 40% lifetime chance of developing pancreatitis [232].

GASTRO-OESOPHAGEAL REFLUX (Section 11.1)

- Reflux is common in both children and adults with CF.
- Reported prevalence rates vary from 20-85%.
- Unique pathophysiology – mechanism includes increased intrathoracic inspiratory pressure from respiratory disease.
- May contribute to respiratory decline through aspiration [233].

DIOS AND CONSTIPATION (Section 11.2)

- DIOS is a specific and unique complication of CF.
- DIOS is characterised by:
  - acute onset of abdominal pain
  - abdominal distention
  - faecal mass in the ileocaecum
  - radiographic signs of distal small bowel distention or obstruction
- Risk factors for DIOS may include suboptimal adherence to PERT and dehydration [234].
- Constipation is very common in CF, and usually presents with a more gradual onset of symptoms and is easier to relieve.
- Altered intestinal fluid composition is considered the main cause of constipation.
- It is very important that clinical teams distinguish between symptoms of chronic constipation and DIOS in individuals with CF [233].

CF-RELATED LIVER DISEASE (Section 11.4)

- CF-related liver disease, predominately liver cirrhosis, is the third leading cause of death amongst individuals with CF. Liver disease may also be expressed as impaired bile flow and/or general hepatic dysfunction.
- CF-related liver disease places individuals with CF at increased risk of malabsorption, undernutrition and fat soluble vitamin deficiencies [233].

INTESTINAL INFLAMMATION (Section 11.5)

- There may be a correlation between poor weight and height measures with gut inflammation [235]
- Intestinal dysbiosis (small intestinal bacterial overgrowth) is common in people with CF however [236] the potential significance of this is not well understood [236,237].

CF-RELATED DIABETES (Chapter 12)

- Prevalence of CF-related diabetes increases with age, with greater than 50% of people being affected at age 40 [238]
- CF-related diabetes has a complex pathophysiology. Loss of pancreatic islet cells lead to both insulin and glucagon deficiency [238].
- CF-related diabetes is associated with worsening pulmonary and nutritional outcomes [239,240].

DYSLIPIDAEMIA (Chapter 7)

- Fatty acid profiles are commonly affected in people with CF [241], specifically:
  - altered serum phospholipid profiles, and
  - low LDL and HDL-cholesterol lipoproteins.
- Fat malabsorption may contribute to abnormal lipoprotein delivery in blood circulation [242].

3.4 Monitoring Nutrition Outcomes

Disease progress in people with CF is monitored in Australia and NZ through the use of data registries - namely, the Australian CF Data Registry (Australia) and Port CF (NZ). The national data registries are overseen by CFA and CFNZ, with each having its own governing committee. Importantly, there is a dietitian representative on both the Australian and NZ data registry governance committees. Dietitian representation helps to ensure appropriate collection and evaluation of nutrition related data.

It is anticipated that continuous improvements will be made to the Australian and NZ CF data registries. In the next five years, dietitians can expect to see more information reported about nutritional parameters. This will allow dietitians to evaluate nutritional status of the CF population (at an individual, clinic, state or country level) to be evaluated against the interventions provided. An advocacy campaign to bring the growth charts used in NZ Port CF system consistent with international practice is also planned.

In Australia dietitians can arrange data registry access via their CF specialist centre director. In NZ access can be arranged through CFNZ.

Table 3b. Comparison of data references for Australian and New Zealand data registries

CF data registries	
Australian CF Data Registry	Uses World Health Organisation (WHO) growth charts for 0-2 year olds and Centre of Disease Control (2000) growth charts for children older than 2 years. **ACFDR Patient summary reports** Provides a visual display of hospitalisations, clinic visits, and trends in pulmonary function and nutrition. Also shows microbiology history over time and current CF-related complications. These reports can be used for pre/post clinic staff meetings and patient/family education.
New Zealand - Port CF	Uses UK-90 growth charts for 0-18 year olds. **PORT CF Patient summary reports** Provides a visual display of pulmonary function and nutrition trends. **Port CF Nutritional summary reports** Provides a narrative summary for practitioners or patient/family use. Reports can be used as a shortcut for calculations of average weight gain per day, average linear growth per year, and enzyme doses.