Review of the Dietetic and MDT Management of Cystic Fibrosis

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Abstract

INTRODUCTION: Cystic Fibrosis (CF) is an autosomal recessive disorder due to mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene leading to abnormality of chloride channels in mucus and sweat producing cells. The respiratory system (lungs) and digestive system (GIT) are primarily impacted, leading to life threatening complications (Rafeeq and Murad, 2017). Ireland has the highest incidence of CF in the world. Approximately 1 in 19 Irish people are said to 'carry' one copy of the altered gene that causes CF (Cystic Fibrosis Ireland, 2023). More than 1900 mutations of CF have been identified (Rafeeq and Murad, 2017).

METHODS: Articles for review were sourced from the academic database PubMed. Results were screened using PICOS criteria, focusing on dietetic management of CF. Papers dating back as far as the 1980's were included in the review due to their continuing relevance in CF treatment today.

RESULTS: Initial database searches identified 61 results, which were then screened for relevance to the objectives of this review. Treatment of CF requires a multi-disciplinary team approach, for which Nutrition and Dietetic management is integral. Lifelong management of CF includes pharmaceutical treatment to manage symptoms, case specific diet and lifestyle therapy, management of complications and co-morbidities, and novel therapies such as CFTR modulators.

CONCLUSION: The identification of the faulty CFTR gene that causes CF was an important step in managing the disorder, yet has not led to a cure for the condition. Life expectancy for patients with CF has steadily improved during the last three decades, with medical management of symptoms and advances in CF therapies. Complications associated with the condition are treated on a case-by-case basis due to complexity of symptoms and individuality of the condition. Dietetic management includes a high calorie, high salt, and high protein diet and routine monitoring for changes in symptoms and

nutritional deficiencies.

KEYWORDS: Cystic Fibrosis, dietetic management, CFTR gene, physical activity in cystic fibrosis, prevalence of cystic fibrosis in Ireland

Introduction

Cystic Fibrosis is an autosomal recessive disorder due to mutations in the CFTR gene leading to abnormality of chloride channels in the lungs and sweat producing cells. Respiratory system and GIT are primarily involved, but eventually multiple organs are affected leading to life threatening complications. CF management requires drug therapy, physiotherapy, and nutritional support.

Life expectancy for patients with CF has steadily improved during the last three decades, and death in childhood is now uncommon. Nutrition is a critical component of the management of CF.

Nutritional status is directly associated with both pulmonary status and survival (Dodge et al.,

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2007). Poor clinical outcomes are often associated with undernutrition (Kalnins and Wilschanski, 2012).

Complications of CF, including liver disease and CF-related diabetes, pose further challenges to medical management of the condition. Glucose intolerance and diabetes affect at least 25% of CF adults. The diabetes differs from both types 1 and 2 diabetes mellitus, but it inversely correlates with prognosis (Dodge et al., 2007). The CFTR gene is located at 7q31.2. More than 1900 mutations have been identified of which 'F508del' (deletion of three bases coding for phenylalanine at the 508th position) is the most common (Rafeeq, 2017).

Prevalence and testing

CF is more common in adults than children in countries with well-developed healthcare systems. The number of adults continues to increase and will further increase if the new CFTR modulators are disease modifying. Most of the complex morbidity and almost all the mortality of CF occurs in adults. It will increasingly follow this pattern even with new effective modulator therapies. Maintaining good quality of life including social functioning and maximizing survival for adults are the key priorities.

This requires a highly knowledgeable and adaptable multidisciplinary team, which, though focused on maintaining lung health, requires an increasing range of other disciplines and specialties to maximize well-being (Elborn, 2019).

All newborn babies in Ireland are now screened for CF as part of the newborn heel prick test carried out shortly after birth. If the screening test suggests a child may have CF, additional tests are carried out to confirm the diagnosis. For example, a sweat test measures the amount of salt in sweat, which will be abnormally high in someone with CF. Alternatively, a genetic test sample of blood or saliva is checked for the faulty gene that causes CF. These tests can also be used to diagnose CF in older children and adults who didn't have the newborn test (Fitzgerald et al., 2020).

Complications of Cystic Fibrosis

CFTR protein enables chloride to pass through the mucus producing cells where water follows and mucus becomes thin. Defective CFTR results in thick and sticky mucus obstructing the pathways (Cystic Fibrosis Foundation, 2016), leading to serious bacterial lung infections. Neutrophil elastase (NE) is a major inflammatory protease released by neutrophils and is present in the airways of patients with CF. Although NE facilitates leukocyte transmigration to the site of infection and is required for clearance of Gram-negative bacteria, it also activates inflammation when released into the airway milieu in chronic inflammatory airway diseases (Voynow and Shinbashi, 2021). In the GIT, the mucous plugs obstruct the canaliculi of pancreas and gall bladder duct preventing enzyme and bile flow into duodenum triggering malabsorption and digestion abnormalities (Houwen, 2010).

CF is a significant burden to both the sufferer and their family, requiring regular review of symptoms, medical testing and treatments to manage symptoms and maximise quality of life. Common complications of the condition include impaired mucus clearance in the lungs, leading to chronic bacterial infections in the lungs, bronchiectasis, dehydration, damage to both the endocrine and exocrine pancreas which results in fat malabsorption, macro and micronutrient deficiencies and often diabetes. CF can also damage the hepatobiliary system, resulting in cholestasis, cholelithiasis, liver cirrhosis and hypertension. Colon cancer is also common in people with CF, as is Osteoporosis.

Fertility problems are common, particularly in men with CF. It is possible for women with CF to have children, but men won't be able to father a child without fertility specialists (Konrad et al., 2022).

Abdominal pain is a very common symptom in CF and may affect nutritional status as the patient fails to reach required intakes (Kalnins and Wilschanski, 2012). Abnormal bile salt metabolism, liver disease, mucosal absorptive abnormalities and short bowel syndrome after intestinal resection in the neonatal period may all contribute.

Stool energy losses account for 10% of gross energy intake in CF patients, three times higher than normal. Sodium losses are important, and subclinical salt depletion can result in growth impairment, particularly in infancy. Factors associated with reduced appetite include chronic respiratory infection, and other

complications of CF such as distal ileal obstruction syndrome and gastro-oesophageal reflux result in oesophagitis, pain, and vomiting (Murphy et al., 1991).

Dietetic Managment of CF

A range of treatments can help control the symptoms, prevent, or reduce complications, and make CF easier to live with. MDT involvement is needed to detect and treat changes and complications with the condition. Malnutrition is both a frequent feature and a comorbidity of CF, with nutritional status strongly associated with pulmonary function and survival. Nutritional management is therefore standard care in CF patients (Turck et al., 2016).

A diet composed of 35%–40% calories from fat is recommended in order to meet the energy demands of those with CF (Kalnins and Wilschanski, 2012). This is a higher fat diet than the European Food Safety Authority (EFSA) 2010 recommendation for non-CF general population, which is 20% to 35% daily energy from fat. The nutritional problems in CF are multifactorial, and include increases in intestinal losses, energy requirements, and urinary glucose losses. One or more factors almost invariably coexist in combination with an inadequate energy intake. Malabsorption in CF mainly results from maldigestion secondary to pancreatic insufficiency.

Malabsorption is characterised by foul smelling, loose, pale stools. The degree of fat malabsorption is usually taken as the marker of intestinal malabsorption. The gold standard for measuring fat absorption is an assessment of the fat excretion over 3 days and its relation to dietary fat intake over the same time period (Sinaasappel et al., 2022).

People with CF struggle to gain weight due to high nutrient losses and malabsorption. Dietetic management centres on a high energy, high fat/high protein diet including foods such as full cream milk, full fat cheese, meat, eggs, full fat butter, bread, and cream, as well as sources of polyunsaturated fats like oily fish, tailored to the individual with consideration for lifestyle, clinical conditions/co-morbidities, nutritional state, social/financial circumstances, dietary beliefs and attitudes, appetite, and activity levels. Nutritional counselling should always be age appropriate. Dieticians develop education programmes and information booklets and teaching materials to support each patient (McDonald et al., 2021).

Pancreatic Enzyme Replacement Therapy (PERT), the most common form being Creon®, is administered at an appropriate and individualised dose with every meal and snack to improve fat absorption and prevent steatorrhea (oily, fatty stool). Requirements can vary widely from 500-2,500 IU lipase per gram of fat (Conway, 2008). Dose should be monitored and adjusted to the fat content of meals and individual symptoms. There are now three preparations which are currently approved: Creon®, Zenpep®, and Pancreaze® (Kalnins and Wilschanski, 2012). In the 1940's, prior to the development of effective PERT, a low-fat diet was prescribed to patients with CF to control side effects such as malabsorption and steatorrhea. After enteric coated pancreatic enzymes were developed in the 1980's, a high fat diet was recommended for CF management, which improved growth and weight stabilisation. These enzymes resist stomach acid and are only released when the more alkaline environment of the upper small intestine is reached. While enzyme therapy for those with pancreatic insufficiency does allow for normal growth and weight gain in most individuals with CF, they do not completely correct nutrient malabsorption.

A broad recommendation for energy requirements in CF has been stated to be approximately 110- 150% and even up to 200% of those required by healthy individuals of the same age, sex, and size (Turck et al., 2016).

People with CF are prescribed NSAIDs, antibiotics, and laxatives to treat symptoms of inflammation, bacterial infections, and constipation respectively. Routine biochemical monitoring, usually annually, is needed to assess status of fat-soluble vitamins (A, D, E and K) and minerals such as zinc and iron due to risk of deficiencies. Albumin and prothrombin are also routinely measured (MacDonald, 1996). These nutrients are often supplemented. Calcium and vitamin D supplements are administered to prevent osteoporosis due to malabsorption and fecal losses. Vitamin D deficiency has been reported in 22% of infants at diagnosis and suboptimal levels reported in more than 90% of older patients (Turck et al., 2016)

Normally there is no need to recommend additional sodium, but salt depletion can occur in hot weather, through physical exercise causing increasing sweating, and in infancy if an infant is on a normal low electrolyte formula. Routine salt supplementation may be needed during hot weather and in all infants on normal infant formulas (MacDonald, 1996).

Most infants with pancreatic insufficiency thrive on a normal energy intake of 100-130 kcal/kg in adjunct with pancreatic enzymes. Breastmilk is suitable for infants with CF. It contains lipase, long chain polyunsaturated fatty acids, provides some immunological protection against infection, and may be psychologically better for the mother (MacDonald, 1996). Infants on breast milk and pancreatic enzymes grow and gain weight appropriately with near zero z scores (Holliday et al., 1991). One possible concern is the possibility of electrolyte depletion on this low sodium milk, so routine sodium supplements are administered to all breastfed babies and some formula fed babies and urinary electrolytes are monitored if weight gain is poor (Laughlin et al., 1981).

Breastfeeding has been shown to be protective for the infant with CF. Breastfed compared with formula-fed infants with CF had improved lung function and a reduced incidence of infections in the first 3 years of life in a study from Italy (Colombo, 2007). Breast milk can provide complete nutritional support for infants with CF for the first 4–6 months of age, though supplemental energy may sometimes be required by fortifying a portion of the breast milk feeds with formula (Kalnins and Wilschanski, 2012).

Lung transplant (LT) is a treatment option for some people with end stage CF which can offer a survival benefit and improved quality of life (Yeung et al., 2020). Optimising nutritional status pre- transplantation is recommended as it can improve perioperative and post LT survival outcomes (Lederer et al., 2009).

Diabetes and CF

HBA1C is monitored routinely at appointments. Cystic Fibrosis Related Diabetes (CFRD) can occur. The primary aetiology is relative insulin insufficiency secondary to destruction of pancreatic islets. The diabetes is non-ketotic, has a slow onset, but is usually insulin dependent. No clear guidelines have been issued on ideal dietary management for patients with both CF and diabetes, although advice should be tailored according to the severity of the CF. The prevalence of CFRD increases with age and affects approximately 2% of children, 19% of adolescents and 40-50% of adults (Grandos et al., 2019).

Providing optimal nutrition for the CF patient is still of paramount importance and any dietary restriction should be avoided. Where possible, sugar free soft drinks, exchange glucose polymer supplements for fortified milk supplements, and some unrefined carbohydrate is given at regular meals, snacks, and bedtime. With the exception of drinks, simple sugars are not prohibited, but intake is encouraged alongside unrefined carbohydrates. Diabetic control is improved by alterations in insulin treatment rather than imposing dietary restrictions which may adversely affect nutritional status (MacDonald, 1996). Patients with CFRD should follow the same dietary advice as CF patients without CFRD (Turck et al., 2016).

Exercise and CF

Physical activity (PA) is associated with a number of potential benefits in the management of CF including positive effects on lung function (Schneiderman et al., 2014), mucociliary clearance (Dwyer et al., 2019), bone health (Garcia et al., 2011) and hospitalisation frequency (Cox et al., 2016).

Declining levels of exercise leads to low cardiorespiratory fitness, which is a strong, independent predictor of mortality in patients with CF. As a result, exercise training has become a commonly accepted form of treatment for patients with CF (Burnett et al., 2020).

Novel CF treatment

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators are small molecules that directly impact the CFTR protein, improving the function of the CFTR chloride and bicarbonate channel. Beginning in 2012 with the Food and Drug Administration approval of the first CFTR modulator, Ivacaftor, this class of medications has had largely positive effects on many outcomes in people with CF,

including lung function, growth, and other clinical parameters (Goetz and Savant, 2020). A limitation of this novel treatment is that it only works when a specific mutation is present and is very expensive, so it is not suitable for all people with CF.

Discussion

Treatment of cystic fibrosis has advanced greatly in recent decades, with better understanding of the condition and advances in medicine and medical technology. Life expectancy has increased, and quality of life has improved. The significant number of CF mutations suggests that a range of specific CFTR modulator treatments may be required. There is a critical need for further research of the genetic condition, of the medicines and biotechnology interventions, and to establish clear guidelines for the MDT medical and dietetic treatment of the differing mutations of CF. With increases in numbers of adults with CF, the health system must adapt services to this demographic shift. Patient empowerment principles potentially lend themselves to cystic fibrosis care, particularly in adults. A randomized controlled trial of a 10-week home-based behavioural nutrition intervention, "Eat Well with CF," was carried out by Registered Dietitians and nutrition researchers to assess patient understanding of cystic fibrosis management. Outcome measures over 6 and 12 months were compared between the intervention group (n=34) and a standard care control group (n=34). This study revealed gaps in basic nutrition knowledge and skills, inadequate knowledge of diet-disease links and pancreatic enzyme replacement therapy (Watson et al., 2008), indicating the efficacy of such programmes, in adjunct with individualised medical and dietetic care to manage the diverse needs of the growing population of adults with CF.

Conclusion

Current CF treatments focus on symptom management, regularly monitoring and adapting treatment to disease progression to maximise quality of life. Medical advice and treatment are case specific and require an MDT approach, in which the dietician plays a crucial role. Nutritional support and advice must be tailored to meet the changing clinical and psychosocial needs of people with CF.

Declaration of Competing Interest

No competing interests to declare.

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