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Integrated Approaches to Managing Cystic Fibrosis: From Nutritional Optimization to Therapeutic Advancements

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ABSTRACT

Introduction: Cystic fibrosis (CF) is associated with numerous nutritional and health challenges that significantly impact the patient's quality of life and clinical outcomes. Nutritional management plays a vital role in addressing issues such as pancreatic insufficiency, fat malabsorption, vitamin and mineral deficiencies, and complications like CF-related diabetes (CFRD) and liver disease (CFLD). This review provides an overview of the essential nutritional assessment, management strategies, and the role of CFTR modulator therapies in improving the nutritional status and health outcomes in CF patients.

Methods: A comprehensive review of the current literature regarding the nutritional needs, deficiencies, and therapies in CF patients was conducted, including a focus on pancreatic enzyme replacement therapy (PERT), vitamin and mineral supplementation, and the management of bone disease, CFRD, and CFLD. Additionally, the impact of CFTR modulators on nutritional outcomes and related complications was examined.

Results: Nutritional assessment in CF is multifaceted, incorporating clinical, anthropometric, body composition, and biochemical evaluations. Early intervention strategies, including PERT and tailored supplementation, are critical for managing fat-soluble vitamin deficiencies, mineral imbalances, and maintaining adequate body mass. The prevalence of CFRD and CFLD significantly impacts CF management, necessitating regular screening and appropriate treatments. CFTR modulator therapies have led to improvements in lung function and nutritional status, though regular monitoring is essential to prevent complications such as hypervitaminosis, altered lipid metabolism, and insulin sensitivity.

Conclusion: A proactive, individualized approach to nutritional management is essential in CF, emphasizing early intervention, regular screening, and personalized therapy to address the diverse challenges faced by these patients.

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Introduction

Nutritional assessment is essential for managing cystic fibrosis (CF) patients, addressing challenges like undernutrition and obesity. Proper evaluation and targeted interventions, including supplementation and enzyme therapy, help optimize growth and prevent complications. Regular monitoring ensures better patient outcomes and quality of life.

This study aims to evaluate the effectiveness of comprehensive nutritional assessment and management strategies in improving the health and quality of life of cystic fibrosis patients.

Result and Discussion

Nutritional Assessment

Nutritional assessment is vital for managing cystic fibrosis (CF) patients, with differing challenges globally: developed countries face rising obesity (6–33%) alongside reduced undernutrition (4–19%), while undernutrition remains prevalent in developing regions (25–50%)(1). Undernutrition leads to poor clinical outcomes, while obesity introduces risks like hypertension and liver steatosis(2). Assessments encompass clinical, anthropometric, body composition, and biochemical evaluations. Growth potential in children is measured via Height-for-Age (HFA) z-scores

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compared to Target Height (TH), with deviations >±2 SD indicating abnormal growth(3).

Key growth targets include maintaining WFL >50th percentile for infants under two, BMI ≥50th percentile for children 2–18 years, and BMI ≥22 kg/m^2 for adult females and ≥23 kg/m^2 for males(4). Body composition tools like DXA, BIA, and arm anthropometry provide deeper insights, with a focus on fat-free mass (FFM) over BMI to address imbalances. Early interventions like exercise and anabolic therapies improve FFM(5).

CF-specific nutritional tools identify at-risk individuals. For children, the McDonald Tool assesses BMI, weight/height gain, dietary intake, and CFRD. The NRS 2002 evaluates weight loss, BMI, disease severity, and food intake for adults(6). Regular dietary assessments (24-hour recall or diet records) ensure sufficient caloric, fat, and nutrient intake, while biochemical markers monitor iron, fat-soluble vitamins, and electrolytes(7). A proactive, comprehensive approach to nutritional management improves outcomes and mitigates risks.

Vitamin and minerals

Fat-soluble vitamin deficiencies are common in cystic fibrosis (CF) due to pancreatic insufficiency and fat malabsorption. Vitamin A is vital for vision, immune function, and cellular health, with deficiency risks upon diagnosis, though severe deficiency is rare. Over-supplementation can lead to toxicity, with symptoms such as intracranial hypertension and liver abnormalities. Annual serum retinol monitoring is recommended to ensure safe levels, with CF-specific formulations used to minimize toxicity. Vitamin D deficiency is widespread and contributes to bone disease, with vitamin D3 (cholecalciferol) preferred for supplementation. Annual monitoring of 25-hydroxyvitamin D levels is necessary to maintain levels between 30–60 ng/mL. Vitamin E, an antioxidant, is given in higher doses, but serum levels may not fully reflect tissue sufficiency due to lower serum cholesterol. Annual monitoring of alpha-tocopherol levels and lipid ratios is advised(8). Vitamin K is essential for blood clotting and bone metabolism, with deficiency common due to fat malabsorption and frequent antibiotic use. Supplementation is recommended, particularly for patients with liver disease or bleeding tendencies, and monitoring includes prothrombin time and PIVKA-II levels(9). [Table 1]

Table 1: Fat soluble vitamins recommendations in patients with cystic fibrosis

Vitamin	Age Group	Intake Recommendations
Vitamin A	1–12 months	450 micrograms (1500 units)
	1–3 years	1500 micrograms (5000 units)
	4–8 years	1500–3000 micrograms (5000–10,000 units)
	>8 years	3000 micrograms (10,000 units)
	Adult	3000 micrograms (10,000 units)
Vitamin E	1–12 months	40–50 mg
	1–3 years	80–150 mg
	4–8 years	100–200 mg
	9–18 years	200–400 mg
	Adult	200–400 mg
Vitamin K	1–12 months	0.3–0.5 mg
	1–3 years	0.3–0.5 mg
	4–8 years	0.3–0.5 mg
	9–18 years	0.3–0.5 mg
	Adult	2.5–5 mg/week
Vitamin D	0–12 months	10–12.5 mcg/day (400–500 units/day)
	1–10 years	20–25 mcg/day (800–1000 units/day)
	11–18 years	20–50 mcg/day (800–2000 units/day)
	>18 years	20–50 mcg/day (800–2000 units/day)

Mineral imbalances are significant in cystic fibrosis (CF) patients, with sodium, calcium, zinc, and iron deficiencies being common concerns. Sodium is particularly important due to the risk of hyponatremic dehydration, as CF patients lose excessive sodium through sweat, especially in hot climates or during physical activity. Sodium chloride supplementation is essential, especially in the summer or during intense exercise, and infants are particularly vulnerable(10). Calcium deficiency,

often associated with vitamin D deficiency, increases the risk of fractures and osteoporosis, so calcium supplementation is crucial. Zinc is vital for growth, immune function, and wound healing, and supplementation (1mg/kg/day) may be recommended for infants with poor growth. Iron deficiency is common, but it must be carefully assessed due to overlap with anemia of chronic disease. Excess iron should be avoided, as it can exacerbate inflammation(8). Fluoride should be supplemented if the local water supply is deficient, and selenium supplementation is recommended only if a deficiency is confirmed. Regular monitoring and individualized interventions are necessary to address these mineral deficiencies and ensure optimal health in CF patients(11).

Pancreatic Enzyme Replacement Therapy (PERT)

Pancreatic Enzyme Replacement Therapy (PERT) is critical for managing pancreatic insufficiency in cystic fibrosis (CF) patients, addressing maldigestion and malabsorption of nutrients. PERT contains lipase, protease, and amylase, delivered via enteric-coated capsules or microspheres, which dissolve in the duodenum's alkaline environment(12). Enzymes should be taken with meals or enteral feeds, with doses tailored to individual needs. For bolus feeds, the full dose is given at the start; for continuous feeds, doses are divided every 4 hours, and systems like Relizorb provide lipase but lack amylase and protease activity(13). Despite optimized PERT, residual fat malabsorption can occur due to decreased long-chain fatty acid uptake, not insufficient lipolysis. Supplements like Encala, containing structured lipid matrices, improve fat absorption and growth(14). Complications such as oral ulcers, perianal rashes, and fibrosing colonopathy require preventive strategies, including proper enzyme use and adherence to dose limits (≤2,500 lipase units/kg per meal). Regular monitoring ensures effective treatment and prevents side effects(15). [Table 2]

Table 2: Enzyme Replacement Therapy in Patients with Cystic Fibrosis

Method	*Guidelines*	*Maximum Dose*
Weight-Based	- Children <4 years: 1,000 lipase units/kg per meal.	2,500 lipase units/kg per meal.
	- Children ≥4 years: 500 lipase units/kg per meal.	
	- Snacks: Administer smaller doses (½–¾ of mealtime dose).	
Fat-Based	- Used for infants or tube-fed patients.	10,000 lipase units/kg per day.
	- Start with 2,000 lipase units per 120 mL of formula or per breastfed.	
	- Adjust to 2,500 lipase units/kg per feeding.	

Bone disease

Bone disease is a common complication in cystic fibrosis (CF), with osteopenia and osteoporosis affecting both children and adults. Up to 60% of young adults with CF experience spinal deformities, including kyphosis, which can lead to height loss and decreased lung function. Fractures, especially vertebral and non-vertebral fractures, are also common(16). Key risk factors include malnutrition, fat malabsorption of calcium, vitamin D, magnesium, and vitamin K, chronic corticosteroid use, hepatobiliary disease, and limited physical activity. Bone health should be regularly assessed with DXA scans starting at age 8, especially for those with risk factors. The frequency of DXA screenings depends on bone mineral density (BMD), with annual scans recommended for significantly reduced BMD(17). Preventing and treating bone disease involves optimizing nutrient intake (calcium, vitamin D, vitamin K) and weight-bearing exercise. Vitamin D levels should be maintained at 30–60 ng/mL, and supplementation should be considered for moderate bone loss. In cases of severe bone loss, bisphosphonates may be used in adults, although they come with potential side effects and are not recommended for children or adolescents(18).

Dental care

Cystic fibrosis (CF) patients face significant oral health challenges, including enamel defects, xerostomia, low saliva pH, and an increased risk of

caries, all influenced by CFTR gene mutations, systemic complications, and medications. These issues can lead to ulcers, fungal infections, and tooth loss, making targeted dental care essential(19). Early, personalized interventions based on neonatal screenings, dietary habits, and systemic treatments are crucial. Regular dental visits should focus on plaque control, caries prevention, and oral hygiene, with progress visits for poor hygiene and biannual check-ups for stable cases. For **newborns**, educate parents on hygiene, microorganism transfer, and diet. At **6–12 months**, the first dental visit assesses hygiene, caries risk, and sugar control. From **12–24 months**, six-month check-ups focus on fluoride use, bottle-to-cup transition, and non-cariogenic diets. For **2–6 years**, prioritize orthodontic evaluations and enhanced care for high-risk children. At **6–12 years**, emphasize brushing, flossing, and fissure sealants. For **12–18 years**, manage dry mouth with hydration, saliva stimulants, and artificial saliva, with frequent visits to prevent biofilm buildup. Regular monitoring and age-specific interventions are critical for lifelong oral health.Research is needed to further explore the relationship between caries and enamel defects, and to assess periodontal conditions using microbial analyses of plaque and saliva(20).

Cystic fibrosis-related diabetes (CFRD)

Cystic fibrosis-related diabetes (CFRD) is a significant complication in individuals with CF, affecting both pulmonary and nutritional status. Annual screening for CFRD should begin at age 10, and it is recommended to screen younger children under 10 if they experience unexplained clinical decline or develop liver disease. Nutritional factors, particularly height and body composition, are better predictors of abnormal glucose tolerance than BMI. Poor nutritional status between the ages of 5 and 10 can predict CFRD in adolescence, and other contributing factors include glucocorticoid use, chronic infections, and liver disease(21).

CFRD has a profound impact on health outcomes, as it is associated with increased morbidity, mortality, and a decline in both pulmonary function and nutritional status. The elevated glucose levels in CFRD promote bacterial colonization, which can worsen lung infections. The prevalence of CFRD rises with age, affecting approximately 15% of adolescents with CF and nearly 50% of adults over age 30. To monitor glucose metabolism, the standard screening method is the oral glucose tolerance test (OGTT). However, HbA1c and continuous glucose monitoring (CGM) can provide valuable supplementary information, as some patients with normal OGTT results may still exhibit abnormal CGM profiles(22).

In terms of management, insulin therapy is the preferred treatment for CFRD when insulin secretion is insufficient. Interestingly, CFRD patients generally require lower insulin doses compared to those with Type 1 diabetes. Along with insulin therapy, patients should be encouraged to practice carbohydrate awareness, which includes counting carbohydrates and reducing glycemic load/index. Physical activity plays a crucial role in improving insulin sensitivity and glycemic control, but attention should be paid to the risks of hypoglycemia, which can be reactive or therapy-related(23).

Cystic fibrosis-related liver disease (CFLD)

Cystic fibrosis-related liver disease (CFLD) affects 20-40% of CF patients, often leading to cirrhosis and portal hypertension. It typically starts in childhood and may progress to decompensated cirrhosis, liver failure, or gastrointestinal bleeding. Annual screening includes liver function tests, platelet count, and ultrasound(24). Nutritional management is essential, with increased energy intake (150% of requirements), 40-50% from fat, and medium-chain triglycerides (MCTs) for better absorption. Fat-soluble vitamin supplementation is crucial due to malabsorption. In advanced malnutrition, enteral feeding may be needed(25).

Ursodeoxycholic acid (UDCA) helps in managing cholestasis and liver function in established CFLD. Portal hypertension complications, like varices and ascites, may require a portosystemic shunt or liver transplant. Liver transplantation is recommended for decompensated cirrhosis. CFTR modulator therapy can cause mild liver enzyme elevations, so regular monitoring is necessary. Gallbladder issues like cholelithiasis are also common and managed similarly to those in the general population(26).

Cystic Fibrosis Transmembrane conductance Regulator (CFTR) Modulators

CFTR modulator therapies, including Ivacaftor, Tezacaftor-Ivacaftor, and Elexacaftor-Tezacaftor-Ivacaftor (ETI), have revolutionized the management of cystic fibrosis (CF) by targeting the underlying defect in the CFTR protein. These therapies improve lung function, nutritional status,

and overall quality of life for people with CF(27). The introduction of these modulators has been associated with significant improvements in weight gain, with an observed increase in body mass index (BMI). Specifically, the prevalence of overweight increased from 19.4% to 31.3%, and obesity from 7.5% to 9.7%, particularly with ETI therapy. Weight gain in the early stages includes both fat mass and fat-free mass, though it later shifts predominantly to fat mass(28). While these therapies improve gastrointestinal symptoms and reduce intestinal inflammation, they also present challenges, including the potential for hypervitaminosis, especially in fat-soluble vitamins(29).

Regular monitoring is crucial for CF on CFTR modulators. Nutritional status should be routinely assessed, with attention to salt intake and fat-soluble vitamin levels to prevent deficiencies or excesses. Blood glucose levels should be checked regularly, as CFTR modulators can impact insulin secretion, necessitating adjustments in insulin therapy to avoid hypoglycemia(30). Additionally, blood pressure should be monitored for any changes, as some modulators, especially lumacaftor-ivacaftor, have been associated with hypertension(31). It is also important to track lipid profiles annually, as modulator therapy may alter lipid metabolism, requiring dietary adjustments or medical intervention(32). Overall, while CFTR modulators offer significant benefits, ongoing management, and monitoring are essential to optimize treatment outcomes and mitigate potential risks associated with the therapy.

In conclusion, comprehensive nutritional assessment and management play a crucial role in addressing the complex nutritional challenges of CF patients. Implementing personalized interventions and regular monitoring can significantly improve health outcomes and overall well-being.

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