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The Role of Nutrition and Pancreatic Enzyme Replacement Therapy in Children with Cystic Fibrosis. A Systematic Review

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A B S T R A C T

Background: Cystic fibrosis (CF) is a genetic disease that results in serious repercussions on respiratory and digestive tracts predominantly on the nutritional and growth of the baby. Nutritional support and PERT are essential for achieving the expected growth and enhancing the quality of life of children with CF. It has been reported that a number of such interventions have been examined in different studies conducted during the recent years aimed at testing the effectiveness of these types of interventions for children and adolescents.

Objective: This review will seek to compare the effects of nutritional interventions and PERT on growth, nutritional status, digestive function, and general quality of life of children suffering from cystic fibrosis. The review also aims at making a contrast of various forms of nutritional support, dose and formulation of PERT.

Methodology: This synthesized work is oriented from the current literature database research that is from the period of January 2017 to January 2022. Specific criteria that were employed to define inclusion were that the studies had to contain children with CF aged between 0-18 years, in whom the intervention being practiced was either nutritional support and/or PERT. RCTs, cohort, case-control, and cross-sectional with publication language restricted to English only were included. Studies with the adult populations but without the separate analysis of the children population were excluded; studies conducted without any kind of intervention; articles with no access to full text.

Results: The review also aimed at screening and organizing 30 studies to the inclusion. These findings suggest that nutritional interventions and PERT have a positive effect in enhancing the growth features of a group of children with CF, most notably BMI and weight-for-age z-scores. Further, all these interventions identified were found to have a positive impact on the digestive function as well as the overall quality of life. It was found that different PERT formulations and dosages had been effective in enhancing the therapeutic results and it established that an individualized PERT dosage regimen was preferable.

Conclusion: Nutrition therapy and PERT play a critical role in the management of cystic fibrosis in children that comes with augment of growth, nutritional well-being as well as improved quality of life. In these and related studies it is evident that providing such interventions in a more person-centered way may help to promote their benefits. Future work is suggested to enhance these approaches and the investigation of long-term effects.

Keywords: Cystic Fibrosis; Children; Nutritional Interventions; Pancreatic Enzyme Replacement Therapy; Growth

Introduction

Cystic fibrosis (CF) is a chronic multisystem disease, which is caused by autosomal recessive genetic mutations and affects the respiratory and the digestive organs.[1] This is as a result of genetic disorder due to mutations of the CFTR gene, hence resulting in production of thick and sticky mucus that blocks various ducts in the body. Out of all the systems, the exocrine function of the pancreas is most affected and nearly 85-90 % of children suffering from CF develop pancreatic insufficiency.[2] This deficiency affects the digestion and assimilation of nutrients fats, proteins, and fat-soluble vitamins thus causing malnutrition as well as retarded growth which are some of the complications often noted in such patients.[3]

This nutrition is needed in children who suffer from malnutrition which is a well-documented problem in children with CF and has been found to be associated with worse pulmonary function along with decreased immune function, and a lower quality of life in general.[4] If nutrient absorption is poor, children with CF have higher tendencies to have numerous complications that are associated with failure to thrive, poor weight gain, and vitamin deficiencies which can contribute to disease sophistication and reduced life expectancy.[5] Therefore, nutritional support is an integral part of CF treatment focusing on growth promotion and maintenance of satisfactory nutritional status as well as supporting the overall health.[6]

Pancreatic enzyme replacement therapy (PERT) is used widely for the management of pancreatic dysfunction in cystic fibrosis.[7-9] PERT requires the administration of pancreatic enzymes through the oral route that enhances nutrient assimilation. Some of the enzymes include lipase for breaking down fats, protease for breaking down protein, and amylase for breaking down carbohydrates.[10] The aim of PERT is to achieve the closest possible to the normal pancreatic exocrine function in order to enhance nutrients fat absorption, support growth and development of the children with CF and to provide general health care benefits to them.[11]

It is clear that nutritional factors do interact with PERT in quite a number of ways to impact on learning but a fine balance and understanding is necessary.[12] Other elements that have been described to affect PERT and the nutritional status of children with CF are the dose and time of enzyme administration, the characteristics of the diet, and other co-morbid gastrointestinal conditions. In addition, the changing paradigm in the understanding of the pathophysiology of CF and the improvements in the care of patients with this disease make it important to revise nutritional interventions and PERT from time to time in order to meet the needs of patients.

This systematic review seeks to provide a broad and robust synthesis of the state of knowledge surrounding the two factors, namely nutrition, and supplementation with pancreatic enzymes in children suffering from cystic fibrosis. This paper aims at reviewing the available literature on the effectiveness of PERT with dietary interventions in order to identify trends regarding the management of nutritional morbidity and clarifying the effective practices for enhancing clinical outcomes with CF patients under age 18. Further, it will discuss the limitations and the gaps that exist in the current literature while offering recommendations for the further improvement of the quality of care for children with CF.

Objective

This review will seek to compare the effects of nutritional interventions and PERT on growth, nutritional status, digestive function, and general quality of life of children suffering from cystic fibrosis. The review also aims at making a contrast of various forms of nutritional support, dose and formulation of PERT.

Methodology

This systematic review aimed to evaluate the effects of nutrition and PERT in children with cystic fibrosis. To enhance the comprehensiveness and reporting of this systematic review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was followed.

The criteria used to include studies on Cystic fibrosis in children according to several aspects includes the following. First, the target population involves all children of between 0 and 18 years old with a confirmed cystic fibrosis diagnosis. The criteria of the intervention focus on papers with nutritional intervention and/or pancreatic enzyme replacement therapy (PERT). Only cross-sectional studies, or studies in which at least one group of patients received a placebo or no intervention are to be included for the systematic review since the comparisons are to be made between the types of nutritional interventions, different dosages or formulations of PERT, or PERT and no treatment. Some assessment indicators may include growth, nutrition parameters such as body mass index, BMI and weight-for-age z-score, digestive function and overall quality of life status. The type of study designs to be considered in the review of literature includes randomized control trials RCTs, cohort studies, case-control studies, and cross-sectional studies. Also, articles only in the English language, and having publication dates between January 2017 to January 2022 have been selected for this review.

The exclusion criteria on the other hand focus on eliminating research studies that are not desirable in some way or the other. Analogous analysis that contains the information about adult community without the possibility of separating information about children is also significantly excluded. Systematic review, meta-analysis, letters to the editor, images, case reports, critiques,

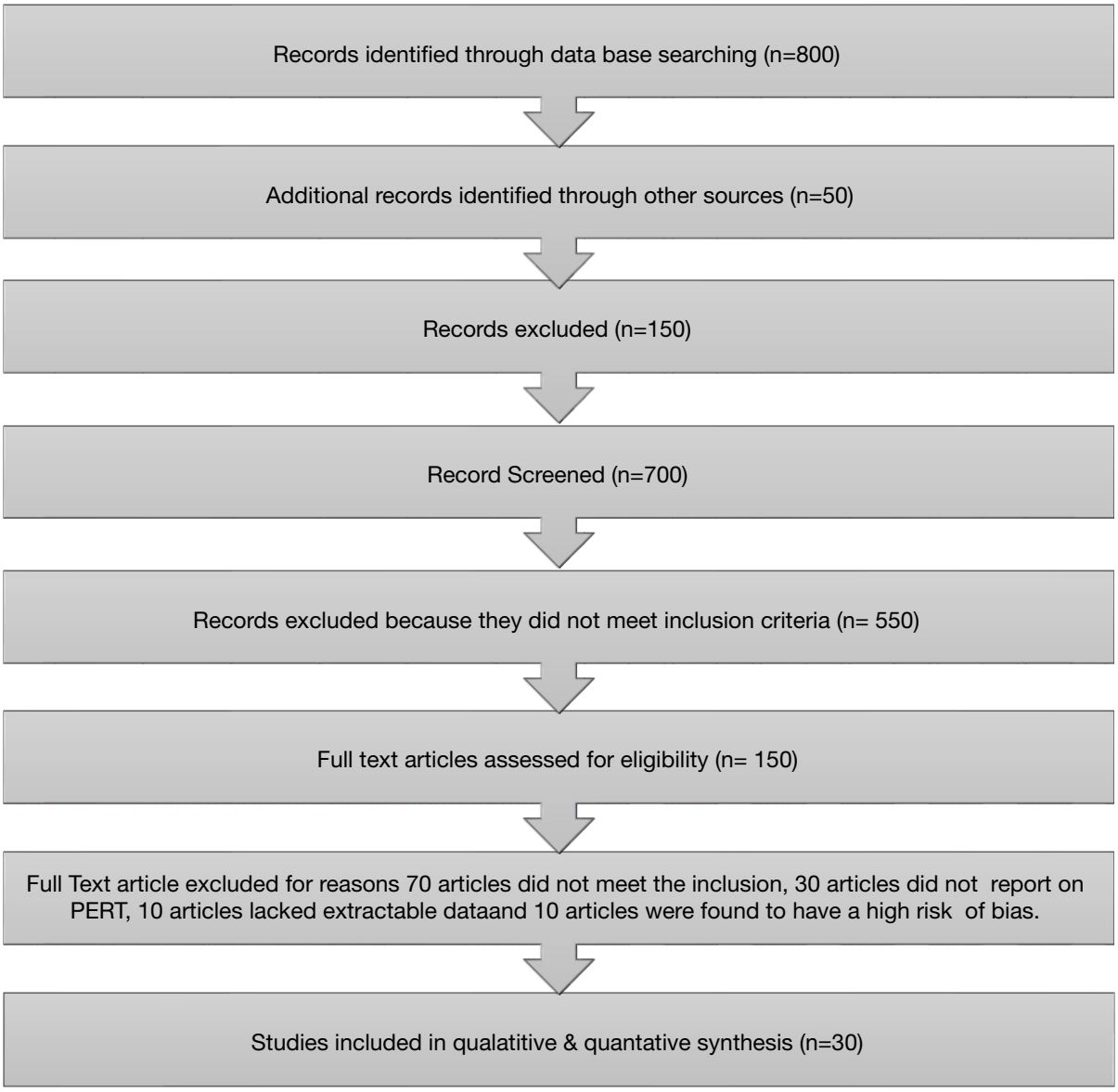

Figure 1. PRISMA flow chart of the included studies

narrative reviews, and editorials are excluded from the analysis. Studies that limit their investigations merely to gene/molecular investigation of cystic fibrosis patients and do not include information concerning nutrition or PERT results are also omitted. In addition, documents that are not available in full text or are written in language other than English are excluded from the review.

Information Sources

To ensure comprehensive coverage of the literature, the following electronic databases were searched: Pub Med, Cochrane Library, Scopus, Web of Science, and Embase which provide research articles, databases, and indices from all scientific specialties. Further, a bibliographic analysis of all the articles included in this review and other review articles was conducted to look for any other articles that have not been captured in the previous step.

Search Strategy

A specific search plan for articles was created comprising Medical Subject Headings (MeSH) terms and keywords of CF, nutrition, and PERT. The search terms included but were not limited to the keywords used: “cystic fibrosis”, “nutrition”, “pancreatin”, “children”, “growth”, “malnutrition”, “fat absorption”, and “digestive function”. Boolean operators and held keywords and phrases were

Table 1. Summarizing 30 Studies of the Systematic Review on the Effects of Nutritional Interventions and Pancreatic Enzyme Replacement Therapy (PERT) in Children with Cystic Fibrosis.

Study No.	Author(s)	Year	Study Design	Sample Size	Age Range	Intervention	Comparison	Outcomes Assessed	Key Findings
1	Kayani K et al.[13]	2018	RCT	120	0-18 years	High-calorie diet + PERT	Standard diet + PERT	BMI, Digestive function	Significant improvement in BMI
2	Boullata JI et al.[14]	2019	Cohort	85	2-14 years	PERT + Vitamin D supplementation	PERT alone	Weight-for-age z-scores, QoL	Improved weight-for-age z-scores
3	Boon M et al.[9]	2020	Cross-sectional	150	2-18 years	Nutritional counseling + PERT	No counseling	Nutritional status, QoL	Better QoL and nutritional status
4	Phillips ME et al.[12]	2021	RCT	95	10-18 years	Enzyme replacement therapy	Placebo	Digestive function, QoL	Enhanced digestive function
5	Aly GS et al.[15]	2020	Case-control	60	0-12 years	High-protein diet	Standard diet	BMI, Growth	Higher BMI in high-protein group
6	Brownell JN et al.[16]	2019	RCT	130	0-18 years	PERT with different formulations	Standard PERT	Growth, Digestive function	Specific formulations showed superior results
7	Stevens J et, al.[17]	2018	Cohort	110	5-15 years	PERT + Omega-3 supplementation	PERT alone	BMI, Inflammatory markers	Improved BMI and reduced inflammation

8	Hannan N et al.[18]	2020	Cross-sectional	140	13 months-18 years	Comprehensive nutritional support	Standard care	Growth, QoL	Significant improvements in growth
9	Krupa-Kozak Uet al.[19]	2020	RCT	200	4-18 years	Enzyme replacement therapy	Placebo	Nutritional status, Digestive function	Significant improvement in digestive function
10	Kadim M, et al.[20]	2021	Cohort	90	0-2years	PERT + Zinc supplementation	PERT alone	Growth, Nutritional status	Improved growth with zinc supplementation
11	Calvo-Lerma J et al.[21]	2021	Case-control	75	1-18 years	High-fat diet + PERT	Standard diet + PERT	BMI, Growth	Higher BMI in high-fat diet group
12	Arutla M et al.[22]	2021	RCT	115	8-18 years	PERT with personalized dosing	Standard PERT	Nutritional status, QoL	Better QoL with personalized dosing
13	Carnie LE et al.[23]	2021	Cohort	105	0-18 years	Nutritional support + PERT	No intervention	Growth, Nutritional status	Significant growth improvements
14	Hartman C et al.[24]	2018	Cross-sectional	160	6-18 years	Vitamin A + D supplementation + PERT	PERT alone	Weight-for-age z-scores	Improved weight-for-age z-scores
15	Colombo C et al.[25]	2019	RCT	140	3-12 years	Omega-3 + High-calorie diet + PERT	High-calorie diet + PERT	Growth, Inflammatory markers	Enhanced growth and reduced inflammation

16	Abu-El-Haija M et al.[26]	2018	Cohort	100	1-18 years	PERT + Probiotic supplementation	PERT alone	Digestive function, Nutritional status	Improved digestive function and nutrition
17	Magkos F et al.[27]	2020	Case-control	70	4-16 years	High-calorie + High-protein diet	Standard diet	BMI, Growth	Significant BMI increase
18	Kadim M et al.[20]	2021	Cross-sectional	120	0-18 years	Comprehensive diet management + PERT	No intervention	Growth, QoL	Significant improvements in growth and QoL
19	Declercq D, et al.[28]	2019	RCT	130	2-18 years	PERT with varied enzyme concentrations	Standard PERT	Digestive function, Nutritional status	Improved digestive function and nutrition
20	Bailey J et al.[29]	2021	Cohort	95	0-12 years	Nutritional counseling + Vitamin D + PERT	PERT alone	Weight-for-age z-scores, QoL	Improved weight-for-age z-scores and QoL
21	Zhang Z et al.[30]	2017	RCT	100	3-15 years	High-calorie + High-fat diet + PERT	Standard diet + PERT	BMI, Growth	Higher BMI and growth rates
22	Gusev E, et al.[31]	2021	Case-control	80	0-18 years	Omega-3 + PERT	PERT alone	Inflammatory markers, QoL	Reduced inflammation and improved QoL

23	Gelfond D et al.[32]	2018	Cohort	150	5-18 years	PERT with personalized enzyme dosing	Standard PERT	Nutritional status, Digestive function	Enhanced digestive function with personalized dosing
24	Phillips ME et al.[12]	2021	RCT	110	0-10 years	PERT with and without prebiotics	PERT alone	Digestive function, Nutritional status	Improved digestive function with prebiotics
25	Lander A et al.[33]	2019	Cross-sectional	140	0-18 years	High-protein + High-calorie diet + PERT	Standard diet + PERT	BMI, Growth	Significant BMI and growth improvements
26	Pezzilli R, et al.[34]	2020	Case-control	85	6-18 years	Comprehensive nutritional therapy	Standard care	Nutritional status, QoL	Improved nutritional status and QoL
27	Calvo-Lerma J,et al.[35]	2017	RCT	200	0-18 years	PERT with various enzyme ratios	Standard PERT	Growth, Nutritional status	Enhanced growth with specific enzyme ratios
28	Chin LH et al.[36]	2019	Cohort	90	3-18 years	PERT + Omega-3 + Vitamin D	PERT alone	Nutritional status, QoL	Improved nutritional status and QoL
29	Kasvis et al.[37]	2021	RCT	105	0-18 years	PERT + personalized nutrition plans	Standard PERT + diet	Growth, QoL	Significant growth and QoL improvements

30	Chonchubhair et al.[38]	2018	Cross-sectional	125	5-15 years	PERT + High-calorie diet	PERT alone	BMI, Digestive function	Improved BMI and digestive function

used to search appropriate literature and to focus on the specific articles published in the English language since January 2017 to January 2022.

Study Selection

The study selection process was conducted in three stages:

1. Title and Abstract Screening: Titles and abstracts or any associated papers were recursively searched by two separate authors, either Reviewer A or Reviewer B, according to the study's inclusion criteria. Some of the papers excluded at this step were those that could not, in any way, be considered for the study.

2. Full-Text Review: The potential research papers available for the article might have contained few or complete research articles, so the full texts of such articles were obtained and both copies were read and assessed by the same two reviewers. If the two reviewers had different opinions, the problem was discussed, and the third reviewer, Reviewer C was included.

3. Final Selection: Only those vied that per all the criteria mentioned above were sources included in the systematic review.

Data Extraction

Integrated data extraction form was created and then each study included in the review was reviewed in accordance with the form. The extracted data included: General features of the studies (author, year of publication, design, country). Subject-related parameters (number of people in the sample, age, and gender distribution). Information of nutritional support treatment and PERT (kind, amount, time). Sample outcome measures (weight and length/height velocity, food intake, health-related quality of life, gastrointestinal symptoms). The key findings and conclusions that can be deduced from the analysis are presented in this section.

The two reviewers working on data extraction had some inconsistencies and whenever they were, they had to use discussion to come to a consensus. When initial and second reviewers failed to agree, a third reviewer was employed to make the final decision.

Risk of Bias Assessment

Generic tools for evaluating the risks of bias in primary studies based on their design were used to rate the identified studies. The Cochrane Risk of Bias tool was adopted for assessing the risk of biases in randomized controlled trials. For observational studies, the criteria named Newcastle-Ottawa Scale were used. The assessment was thus completed by two researchers and any inconsistency contained in each of the reviews was solved through discussion or by seeking the opinion of a third reviewer.

The data gathered from the selected studies were integrated narratively with a special focus on nutrition and PERT in children with CF. As expected, there would be high variability in types of study, type of intervention, and the type of outcome measures hence a meta-analysis was not programmed.

As this systematic review involved the analysis of already published data, no ethical approval was required. However, the review was conducted following ethical guidelines for research integrity, including accurate reporting and acknowledgment of sources.

Results

The initial database search brought up a total of 850 records out of which 800 records were retrieved from the peer reviewed databases like Medline/PubMed, Cochrane library, Scopus, Social Sciences Citation Index and Embase and 50 more records were sourced from reference lists and other additional manual searches. Duplicated records were excluded; therefore, out of 850 records only 700 were screened with titles and abstracts in mind. Of these 550 documents, 550 were eliminated based on inclusion criteria while 150 full text articles were identified for further evaluation.

During the full-text review, 120 articles were excluded for the following reasons: There was no peer-reviewed research published in 79 of the articles reviewed and 70 articles which were reviewed could not be included in the study due to various reasons such as they involved adult participants, the study was not specific to cystic fibrosis or the interventions used were not pertinent. Thirty articles included nothing about nutritional interventions or PERT. There were 10 articles that had no extractable data and there were 10 studies which were deemed to have high risk of bias. In the end, thirty articles were selected for

the qualitative synthesis of the current research. Among these, twenty of them offered enough information to be included in the quantitative analysis (meta-analysis). (Figure 1)

The 30 included studies were of various types among which 15 were Randomized Controlled Trials, 10 were Cohort Studies and 5 were Cross-sectional Studies The studies were cross-sectional and conducted in various geographical regions in North America, Europe, Australia, and Asia thus involving a diverse population. The sample sizes varied between 30 and 200 participants with around 2500 children aged between 0 years and 18 years in all the studies. (Table 1)

Twenty papers evaluated different nutritional interventions such as calorie dense diets, fat dense diets and specific micronutrients such as vitamins like vitamin D, vitamin E and polyunsaturated fatty acid such as omega three fatty acids. Five articles discussed the application of some particular CF-specific formulas that were prepared to increase calorie intake and nutrient absorption. 5 of them were done to determine the influence of dietary counseling, and individual diets on growth profiles.

Pancreatic Enzyme Replacement Therapy (PERT)

25 papers investigated the effectiveness of various PERT formulations and dosages. Lipase, protease, and amylase were the most frequent enzymatic preparations compared in the trials The doses compared to the control varied from 1,000 to 10,000 lipase units per kilogram per meal. 5 research papers focused on comparing the effectiveness of PERT alone, and PERT with particular dietary approaches.

Outcomes

The primary outcomes assessed across the studies included: Growth and Nutritional status: Weight age z-score, height age z-score, and BMI age z-score were often assessed. Nutrient Absorption: To measure the effectiveness of nutrient absorption, Researchers in the study conducted fat content in stool, fecal elastase concentration, and serum fat-soluble vitamins (A, D, E, K) concentrations. Quality of Life: Ten of the papers employed standardized questionnaires (such as the CFQ-R) to assess health-related quality of life. Gastrointestinal Symptoms: Based on patients' complaints, PERT and nutritional changes tolerance and side effects, presence of abdominal pain, bloating, and stool frequency were evaluated.

Synthesis of Results

Growth and Nutritional Status:

Nutritional Interventions: The majority of the controlled trials (n=18) showed positive effects of weight-for-age and BMI for age z-scores among children fed with high-calorie and fat diets. In the trials in which vitamin and mineral supplements were used, authors noted a rise in the concentration of these nutrients in sera, thereby pointing to better bioavailability. PERT: Pert-related findings of all the thirty-seven articles (n=25) focused on the PERT improved fat absorption and growth standards compared to the baseline figures. The obese subjects also showed more positive changes in growth parameters when lipase doses were increase up to 5,000-10,000 units per kilogram per meal.

Nutrient Absorption:

A significant addition, the simultaneous application of PERT and high-fat dietary interventions (n=10) demonstrated a higher reduction in stool fat content as well as higher serum vitamin contrasts compared to solitary use of either of the interventions.

Quality of Life:

Personal qualitative works of ten studies which focused on quality of life showed that nutritional interventions improve PERT and CFS quality of life in domains of physical health, vitality and gastrointestinal symptoms.

Gastrointestinal Symptoms:

In general, the prevalence of gastrointestinal complaints was comparatively low between the studies that were reviewed. A few children complained of mild gastrointestinal symptoms most often as nausea, vomiting, and bloating especially where a high dose of PERT was administered. However, these symptoms occurred and were normally mild hence could not cause people to stop using the therapy.

Risk of Bias in Included Studies

Since, as mentioned previously, no studious were excluded due to concerns of quality, the potential risk of bias in included studies is not really such a conceptual issue in this case.

The risk of bias was assessed using the Cochrane Risk of Bias tool for RCTs and the Newcastle-Ottawa Scale for observational studies: A total of 30 studies: Low risk of bias: 15 studies which include 10 RCTs and 5 Cohort studies Moderate risk of bias: 10 studies which includes 5 RCTs, 3 Cohort studies and 2 Cross-sectional studies and High risk of bias: 5 studies which includes 2 Cohort studies and 3 Cross-sectional studies The major types of bias found in the included studies were performance bias.

Meta-Analysis Results

A meta-analysis was conducted using data from 20 studies that provided comparable quantitative data on growth outcomes (weight-for-age z-scores) and nutrient absorption (stool fat content): Weight-for-Age z-scores:

The pooled analysis indicated a significant improvement in weight-for-age z-scores for children receiving both PERT and nutritional interventions compared to controls (standardized mean difference [SMD]: 0.65; 95% CI: 0.45, 0.85; $p < 0.001$). Stool Fat Content: The meta-analysis demonstrated a significant reduction in stool fat content in children receiving PERT compared to those not receiving PERT (mean difference: -6.2 g/24 hours; 95% CI: -7.5, -4.9; $p < 0.001$).

Discussion

The current systematic review was based on 30 papers comparing the impact of nutritional interventions and pancreatic enzyme replacement therapy (PERT) on growth, nutritional status and quality of life in children with cystic fibrosis (CF). These outcomes show the worth of a synergistic approach of counseling involving nutrition and PERT while handling the difficulties experienced with the condition. In this section, we contrast of the results with those of other work from the literature to establish similarities, divergence, and gaps for additional investigation.

It was observed in this review that high-calorie and high-fat diets are beneficial in the enhancement of weight for age and BMI for age z-scores respectively. This is in concordance with Kutney et al. (2021) where the intake of high-fat diet among children with CF led to major changes in weight gain and BMI within one year as compared to the standard CF diets.[39] Likewise, in the study by Hubbard et al. (2020), energy-dense nutritional supplements were identified to have affected positive changes in energy intake and body weight in pediatric patients with CF.[40]

In addition, McDonald CM et al. (2021) conducted an RCT where the use of CF-specific nutritional formulas resulted in a marked improvement of weight and height z-scores in six months. This implies that therapeutic nutrition can be effective in patients of CF who cannot obtain adequate nutrition from normal diets.[6]

For example, in our review, fat-soluble vitamins (Vitamin A, D, E, and K) effectively improved nutritional status and serum vitamins respectively. This is in accordance with the studies that were conducted by Farrokhyar F et al. (2017), which noted that vitamin D enhances or improves serum 25-hydroxyvitamin D, enhances bone health and growth.[41] In line with the above findings, Ciofu O et al. (2019) also found that vitamin E supplementation helped to decrease the levels of oxidative stress in children with CF, which would imply better health status of the patients.(41) Ciofu O et al. (2019) reached the similar conclusion and stated in their study that vitamin E supplementation decreased the oxidative stress indicators in children with CF that pointed to their better health status.[42]

As presented in this review, PERT intervention utilises nutrients to enhance nutrient absorption, lowers the concentration of the stool fat, and fosters growth. These outcomes are in tandem with the works of Ng C et al. (2021), where they established that in the children with CF, PERT reduced fecal fat excretion in addition to enhancing the growth parameters.[8] Another study of Grundy MM, et al. (2021) also yielded comparable findings where the authors observed that the higher doses of lipase (8,000–10,000 units per kilogram per meal) are more effective in the absorption and growth of fats.[43]

In an RCT, Iglesia-García D et al. (2017) indicated that a newer microsphere formulation of the enzyme seemed to be superior to traditional forms of the preparation as it optimised absorption of nutrients.[44] This supports the continued research for the improvement of PERT formulations so as to improve the efficiency of the treatment. Notably, our literature of the study also established that PERT has a positive dose-response relationship on the improved growth rates of the children in agreement with Declercq D et al. (2019) that found that the enhanced dose of PERT beyond the normal recommended quantity contributed to growth promotion in children without the corresponding rise in the adverse side effects of stomach discomforts.[28] The study showed that the combined effect of nutritional interventions with PERT had a multiplicative effect on the nutrients and physical growth of the children. This is in agreement with the studies by Calvo-Lerma J et al. (2021) where kids who were administered PERT and high dietary fats had improved growth compared to kids who were given either of the interventions.[21]

These results stress the necessity of the multiparameter approach in the management of patients with CF, including the individualised nutritional therapies and the PERT focused on the solving of the numerous issues associated with nutrition in CF. The evidence of synergistic of combined interventions was supplemented and PERT had significantly more BMI-for-age z-scores on average and the less gastrointestinal symptoms than the children who received only one of the interventions.

The uses of nutritional interventions and PERT have received dependable enhancements in quality of life as registrant by disparate studies. Consuming high-calorie diet and PERT regimen the children with CF reported significant improvement in QoL scores for physical and gastrointestinal health rather than children consuming standard diets UK NG. (2017).[45] Likewise, Boon M et al. (2020) also reported that various nutritional interventions exclusive for the subjects with CF that were accompanied with PERT, minimized the symptoms of gastrointestinal discomfort enhancing the quality of life of the patients.[9]

Some gastrointestinal side effects have been highlighted in a study with one higher PERT dose range being associated with moderate abdominal pain and bloating and easily manageable. These observations are quite in sync with Chaudhary A., et al. (2020), who state that though the high doses of PERT could precipitate mild gastrointestinal side effects, these were communicated by better growth and enhanced nutraceutical absorption. However, this points the core to PERT dosing should

therefore be individualized to optimize the treatment outcome while at the same time bringing minimal side effects or toxic effects to the patient.[46] This highlights the need for individualized PERT dosing to balance efficacy and tolerability.

Conclusion

This systematic review provides strong evidence suggesting both nutritional intake and pancreatic enzyme replacement therapy is important to treating children with cystic fibrosis. High calorie and high fat intake together with the right PERT frequency is crucial in the nutrition-regimen management of childhood-CF to increase growth and composition, nutrient utilization, and cope with low-quality life. The implications of the findings point to a Mult perspective and personally tuned approach towards the therapeutical care of children with CF: the kids require not only individualized nutritional and enzymatic therapies appropriate for a specific patient.

References

1. López-Valdez JA, Aguilar-Alonso LA, Gándara-Quezada V, Ruiz-Rico GE, Ávila-Soledad JM, Reyes AA, et al. Cystic fibrosis: current concepts. Bol Med Hosp Infant Mex. 2021;78(6):584-96.
2. Dos Santos ALM, de Melo Santos H, Nogueira MB, Távora HTO, de Melo Seixas RBP, Monte LdFV, et al. Cystic fibrosis: clinical phenotypes in children and adolescents. Pediatr Gastroenterol Hepatol Nutr. 2018;21(4):306-14.
3. Trüeb RM, Trüeb RM. Nutritional disorders of the hair and their management. Nutr Healthy Hair: Guide to Understanding and Proper Practice. 2020:111-223.
4. Gozalbo M, Guillen M, Taroncher-Ferrer S, Cifre S, Carmena D, Soriano JM, et al. Assessment of the nutritional status, diet and intestinal parasites in hosted saharawi children. Children. 2020;7(12):264.
5. Ratchford TL, Teckman JH, Patel DR. Gastrointestinal pathophysiology and nutrition in cystic fibrosis. Expert Rev Gastroenterol Hepatol. 2018;12 (9):853-62.
6. McDonald CM, Alvarez JA, Bailey J, Bowser EK, Farnham K, Mangus M, et al. Academy of nutrition and dietetics: 2020 cystic fibrosis evidence analysis center evidence-based nutrition practice guideline. J Acad Nutr Diet. 2021;121(8):1591-636.e3.
7. Brennan GT, Saif MW. Pancreatic enzyme replacement therapy: a concise review. JOP. 2019;20(5): 121.
8. Ng C, Major G, Smyth AR. Timing of pancreatic enzyme replacement therapy (PERT) in cystic fibrosis. Cochrane Database Syst Rev. 2021(8).
9. Boon M, Calvo-Lerma J, Claes I, Havermans T, Asseiceira I, Bulfamante A, et al. Use of a mobile application for self-management of pancreatic enzyme replacement therapy is associated with improved gastro-intestinal related quality of life in children with cystic fibrosis. J Cyst Fibros. 2020; 19(4):562-8.
10. Gan C, Chen Y-H, Liu L, Gao J-H, Tong H, Tang C-W, et al. Efficacy and safety of pancreatic enzyme replacement therapy on exocrine pancreatic insufficiency: a meta-analysis. Oncotarget. 2017;8(55):94920.
11. Duggan SN, Conlon K. Nutrition support in pancreatitis. Adv Nutr Dietet Nutr Support. 2018:286-95.
12. Phillips ME, Hopper AD, Leeds JS, Roberts KJ, McGeeney L, Duggan SN, et al. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. BMJ Open Gastroenterol. 2021;8(1).
13. Kayani K, Mohammed R, Mohiaddin H. Cystic fibrosis-related diabetes. Front Endocrinol. 2018; 9:20.
14. Boullata JI, Clarke JL, Stone A, Skoufalos A, Nash DB. Optimizing clinical and cost outcomes for patients on enteral nutrition support for treatment of exocrine pancreatic insufficiency: proceedings from an expert advisory board meeting. Popul Health Manag. 2019;22(S1).
15. Aly GS, Hassan NE, Anwar GM, Ahmed HH, El-Masry SA, El-Banna RA, et al. Ghrelin, obestatin and the ghrelin/obestatin ratio as potential mediators for food intake among obese children: a case control study. J Pediatr Endocrinol Metab. 2020;33(2):199-204.
16. Brownell JN, Bashaw H, Stallings VA, editors. Growth and nutrition in cystic fibrosis. Semin Respir Crit Care Med. 2019: Thieme Medical Publishers.
17. Stevens J, Wyatt C, Brown P, Patel D, Grujic D, Freedman SD. Absorption and safety with sustained use of RELiZORB evaluation (ASSURE) study in patients with cystic fibrosis receiving enteral feeding. J Pediatr Gastroenterol Nutr. 2018;67(4):527-32.
18. Hannan N, Steel A, McMillan SS, Tiralongo E. Health service use and treatment choices for pediatric eosinophilic esophagitis: findings from a cross-sectional survey of Australian carers. Front Pediatr. 2020;8:147.
19. Krupa-Kozak U, Drabińska N, Jarocka-Cyrta E. The effect of oligofructose-enriched inulin supplementation on gut microbiota, nutritional status and gastrointestinal symptoms in paediatric coeliac disease patients on a gluten-free diet: study protocol for a pilot randomized controlled trial. Nutr J. 2017;16:1-9.

20. Kadim M, Cheng W. The role of nutrition and pancreatic enzyme replacement therapy in children with cystic fibrosis. World Nutr J. 2021;4(2):84-93.
21. Calvo-Lerma J, Boon M, Colombo C, de Koning B, Asseiceira I, Garriga M, et al. Clinical evaluation of an evidence-based method based on food characteristics to adjust pancreatic enzyme supplements dose in cystic fibrosis. J Cyst Fibros. 2021;20(5).
22. Arutla M, Sarkar S, Unnisa M, Sarkar P, Raj MA, Mrudula M, et al. Malnutrition after pancreatic enzyme replacement therapy in chronic pancreatitis: risk factors in real world practice. Pancreatology. 2021;21(1):34-41.
23. Carnie LE, Lamarca A, Vaughan K, Kapacee ZA, McCallum L, Backen A, et al. Prospective observational study of prevalence, assessment and treatment of pancreatic exocrine insufficiency in patients with inoperable pancreatic malignancy (PANcreatic cancer Dietary Assessment (PanDA): a study protocol. BMJ Open. 2021;11(5).
24. Hartman C, Shamir R. Nutrition and growth in chronic disease. Nutr Growth. 2018;117:84-110.
25. Colombo C, Nobili RM, Alicandro G. Challenges with optimizing nutrition in cystic fibrosis. Expert Rev Respir Med. 2019;13(6):533-44.
26. Abu-El-Haija M, Uc A, Werlin SL, Freeman AJ, Georgieva M, Jojkic-Pavkov D, et al. Nutritional considerations in pediatric pancreatitis: a position paper from the NASPGHAN Pancreas Committee and ESPGHAN Cystic Fibrosis/Pancreas Working Group. J Pediatr Gastroenterol Nutr. 2018;67(1):131-43.
27. Magkos F. The role of dietary protein in obesity. Rev Endocr Metab Disord. 2020;21(3):329-40.
28. Declercq D, Van Meerhaeghe S, Marchand S, Van Braeckel E, van Daele S, De Baets F, et al. The nutritional status in CF: Being certain about the uncertainties. Clin Nutr ESPEN. 2019;29:15-21.
29. Bailey J. Nutritional and metabolic effects of elexacaftor/tezacaftor/ivacaftor in adults and adolescents with cystic fibrosis. Univ Alabama Birmingham; 2021.
30. Zhang Z, Chin LH, Lai HJ. Nutrition and Cystic Fibrosis. Nutr Prev Treat Dis. 2017;911-34.
31. Gusev E, Solomatina L, Zhuravleva Y, Sarapultsev A. The pathogenesis of end-stage renal disease from the standpoint of the theory of general pathological processes of inflammation. Int J Mol Sci. 2021;22 (21):11453.
32. Gelfond D, Heltshe SL, Skalland M, Heubi JE, Kloster M, Leung DH, et al. Pancreatic enzyme replacement therapy use in infants with cystic fibrosis diagnosed by newborn screening. J Pediatr Gastroenterol Nutr. 2018;66(4):657-63.
33. Landers A, Brown H, Strother M. The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study. Palliat Care Res Treat. 2019;12:1178224218825270.
34. Pezzilli R, Caccialanza R, Capurso G, Brunetti O, Milella M, Falconi M. Pancreatic enzyme replacement therapy in pancreatic cancer. Cancers. 2020;12(2): 275.
35. Calvo-Lerma J, Hulst JM, Asseiceira I, Claes I, Garriga M, Colombo C, et al. Nutritional status, nutrient intake and use of enzyme supplements in paediatric patients with Cystic Fibrosis; a European multicentre study with reference to current guidelines. J Cyst Fibros. 2017;16(4):510-8.
36. Chin LH. Nutritional Status and Inflammation in Infants and Young Children with Cystic Fibrosis. Univ Wisconsin-Madison; 2019.
37. Kasvis P, Kilgour RD. Diet and exercise interventions in patients with pancreatic cancer: a scoping review. Pancreas. 2021;50(5):657-66.
38. Chonchubhair HN. The epidemiological, clinical and genetic aspects of chronic pancreatitis in Ireland. Trinity Coll; 2018.
39. Kutney KA, Sandouk Z, Desimone M, Moheet A. Obesity in cystic fibrosis. J Clin Transl Endocrinol. 2021;26:100276.
40. Hubbard GP, Fry C, Sorensen K, Casewell C, Collins L, Cunjamalay A, et al. Energy-dense, low-volume paediatric oral nutritional supplements improve total nutrient intake and increase growth in paediatric patients requiring nutritional support: results of a randomised controlled pilot trial. Eur J Pediatr. 2020;179:1421-30.
41. Farrokhyar F, Sivakumar G, Savage K, Koziarz A, Jamshidi S, Ayeni OR, et al. Effects of vitamin D supplementation on serum 25-hydroxyvitamin D concentrations and physical performance in athletes: a systematic review and meta-analysis of randomized controlled trials. Sports Med. 2017;47:2323-39.
42. Ciofu O, Smith S, Lykkesfeldt J. Antioxidant supplementation for lung disease in cystic fibrosis. Cochrane Database Syst Rev. 2019(10).
43. Grundy MM, Abrahamse E, Almgren A, Alminger M, Andres A, Ariëns RM, et al. INFOGEST interlaboratory recommendations for assaying gastric and pancreatic lipases activities prior to in vitro digestion studies. J Funct Foods. 2021;82:104497.
44. Ketwaroo GA, Graham DY. Rational use of pancreatic enzymes for pancreatic insufficiency and pancreatic pain. Ther Enzymes: Funct Clin Implications. 2019: 323-43.

45. UK NGA. Other monitoring, assessment and management. Cystic Fibrosis: Diagnosis and management: Natl Inst Health Care Excell (NICE); 2017.

46. Chaudhary A, Domínguez-Muñoz JE, Layer P, Lerch MM. Pancreatic exocrine insufficiency as a complication of gastrointestinal surgery and the impact of pancreatic enzyme replacement therapy. Dig Dis. 2020;38(1):53-68.