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EFFECT OF A DIETARY INTERVENTION ON GROWTH AND ENERGY EXPENDITURE IN CHILDREN WITH CYSTIC FIBROSIS

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Abstract

BACKGROUND—The study aim was to determine the effect of a dietary intervention on growth, body composition and resting energy expenditure (REE) in children with cystic fibrosis (CF) and pancreatic insufficiency (PI) in a randomized, double blind, placebo-controlled trial.

METHODS—Subjects (5 to 17 yrs) participated in a 12-month trial of the organized lipid matrix LYM-X-SORB™ (LXS) vs. placebo dietary supplements with similar calories, total fat and fatty acids. Dietary intake was assessed using 3-day weighed food records. Height (HAZ), weight (WAZ), BMI (BMIZ), mid-upper arm muscle (UAMAZ) and fat area (UAFAZ) Z-scores were calculated. Fat mass (FM) and fat free mass (FFM) were obtained by whole body DXA. REE (kcal/d) was evaluated by indirect calorimetry at baseline, 3 and 12 months and %REE calculated using Schofield equations. No growth or REE differences were observed between LXS and placebo groups so data were pooled for analysis.

RESULTS—63 children (57% males, age 10.6±2.9 yr, 43% receiving LXS) completed REE measurements. Caloric intake increased from a median of 2502 [1478, 4909] to 2616 [1660, 4125]

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Conflict of interest statement
VG, JIS, KAD, NEL, AM and MRM declare no conflict of interest.
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kcal/d at 12 months. HAZ, WAZ and UAMAZ increased ($p < 0.05$) over 12 months. Mean REE was 109±8% predicted at baseline and 107±9% at 12 months ($p < 0.05$). REE (kcal/d) adjusted for FFM and FM decreased over 12 months ([mean±SE] −31±12 kcals, $p < 0.01$), significant only in males (−49±16 kcals, $p < 0.01$).

CONCLUSIONS—Over a 12 month nutrition intervention with either LXS or placebo, the growth status, muscle stores and REE improved. Sustained increased energy intake improved energy metabolism, growth and nutritional status in school age children with CF, PI and mild lung disease.

Keywords

Resting energy expenditure; cystic fibrosis; children; dietary intervention

Introduction

Cystic fibrosis (CF) is one of the most common chronic, multi-system inheritable diseases. Most children with CF, in addition to pulmonary disease, suffer from pancreatic insufficiency (PI) and the nutritional consequences of lifelong malabsorption (1). Chronic fat malabsorption may result in malnutrition, growth failure, and fat-soluble vitamin, essential fatty acid and choline deficiencies (2–4). The treatment of fat malabsorption remains a challenge for the CF care team. Considering recent CF Foundation and Registry data from the US, nutrition-related growth failure is still at an unacceptably high rate (1). Malnutrition and poor growth in clinically stable children with CF and PI result from chronic negative energy balance due to insufficient caloric intake to overcome modestly higher energy requirements, related to the variable degree of energy loss from malabsorption and the mildly increased resting energy expenditure (REE) (5–13).

These data were collected as part of a randomized, placebo controlled trial of LYM-X-SORB ™ (LXS, Avanti Polar Lipids, Alabaster, AL) to evaluate choline status in children with CF and PI. LXS is a choline-rich structured lipid matrix that has previously been shown to be absorbable without pancreatic enzyme therapy and to improve nutritional status and clinical outcomes for children with CF and PI (14). The second generation LXS used in the present protocol had improved palatability and solubility characteristics, and was designed to be mixed with a variety of foods and beverages. The aim of this report was to evaluate the changes in dietary intake, growth, body composition and REE occurring over 12 months of daily supplementation with either LXS or the isocaloric placebo.

Methods

Study participants ages 5.0 to 17.9 years with CF and PI from ten CF Centers were evaluated from March 2007 to May 2011. This study was approved by the Institutional Review Board of the Children's Hospital of Philadelphia (CHOP) and at each CF Center. Verbal assent was obtained from the subjects <18 yrs of age with written consent from their parents/guardians. Exclusion criteria were FEV_1 <40% predicted, residual pancreatic lipase activity (fecal elastase >15 ug/g stool), liver disease as defined as a serum GGT >3x reference range or other chronic health conditions that may affect gastrointestinal absorption

or growth. After enrollment, subjects were randomized to receive daily supplementation with either LXS or placebo powder. The random allocation sequence was generated by the CHOP Research Pharmacy who assigned participants to their groups with stratification for age and sex. LXS was composed of lysophosphatidylcholine, triglycerides and essential fatty acids. The placebo had similar calories, total fat and fatty acids with similar macronutrient distribution (kcal protein 6%, carbohydrate 58% and lipid 34%). LXS contained more choline than placebo (295 vs 39 mg/packet). Both powder supplements were mixed with wheat flour and sugar, provided in sealed packets (32 g/packet) with identical appearance, and mixed with a variety of food and beverage. All subjects and study team were blinded to group assignment. Subjects between the ages of 5.0 and 11.9 years consumed two packets per day (64 g/d of powder with 304 kcal/d), and ages 12.0 to 18.9 years consumed three packets per day (96 g/d with 456 kcal/d). LXS and placebo were produced by Avanti Polar Lipids, Inc (Alabaster, AL) and the calorie, macronutrient and micronutrient content was verified in an independent laboratory (Eurofins Inc, Des Moines, IA) using standard methods.

Subjects completed study visits at CHOP following an overnight admission in the Clinical and Translational Research Center (CTRC) at baseline and after 3 and 12 months of supplementation. Dietary intake was assessed at each time point using 3-day weighed food records. Subjects and parents/guardians were provided with measuring cups, spoons, a digital food scale and detailed verbal and written instructions to weigh and record each food/beverage consumed. Completed diet records were reviewed and analyzed by the CTRC research nutritionist using Nutrition Data System for Research software (National Coordinating Center, University of Minnesota, Minneapolis, MN). Energy intake was assessed using the Dietary Reference Intakes (15), and expressed as percent Estimated Energy Requirement (%EER) for active children. The “active” physical activity level for the calculation of %EER has been found to best approximate the total energy requirements in children with CF and PI (16). Families were contacted by telephone every 28 days to report adherence based on number of packets consumed over the previous 28 days. These data were used to calculate an average percent adherence as a measure of overall adherence for the two intervals (cumulative adherence estimates: baseline until 3 months and baseline until 12 months. However, when adjusting LXS and placebo nutrient intake at the 3 and 12 month dietary assessments, we used an adherence estimate close (within one month) to the dietary assessment (proximate adherence estimate).

Growth, body composition and REE were assessed at baseline, 3 and 12 months. Weight was measured to the nearest 0.1 kg using an electronic scale (Scaletronix, White Plains, NY) and height to the nearest 0.1 cm using a stadiometer (Holtain, Crymych, UK). Age- and sex-specific standard deviation scores (Z-scores) for weight (WAZ), height (HAZ) and body mass index (BMIZ) were calculated (17). Mid-upper arm circumference was measured using a linen tape measure (McCoy, Maryland Heights, MO). A skinfold caliper (Holtain, Crymych, UK) was used to measure triceps skinfold thickness on the right side. Upper arm muscle and fat areas were derived, and z scores for upper arm muscle area (UAMAZ) and upper arm fat area (UAFAZ) were computed (18). Total fat-free mass (FFM), fat mass (FM) and percent body fat were obtained by whole body dual energy x-ray absorptiometry (DXA,

Delphi A, Hologic, Inc., Bedford, MA). Pubertal status was determined using Tanner stages with a validated self-assessment questionnaire (19).

REE was measured by open circuit indirect calorimetry using a computerized metabolic cart (SensorMedics Spectra, Yorba Linda, CA). In preparation for the REE, each subject received a standardized evening meal followed by a 12-hour fast. The subject was awakened on the day of study and restricted to minimal physical activity. A 60-minute REE assessment was performed between 7 and 10 AM. Data from the first ten minutes and from periods of documented physical movement or coughing were omitted and the remaining data averaged. REE was calculated from the modified Weir equation (20). REE was compared to predicted values derived from the Schofield equations that adjust for age, sex, weight and height (21). Pulmonary function was evaluated by standard methods for spirometry (22) using a MedGraphics spirometer (Medical Graphics Corporation, Minneapolis, MN). FEV_1 % predicted was calculated using Wang et al. (23) and Hankinson et al. (24) equations. Adverse events from patient report every 28 days, and from medical record review were collected.

Measures of central tendency and variability were calculated for each outcome. Descriptive statistics were calculated for continuous variables using means and standard deviations for normally distributed data and medians and ranges for skewed data, and for categorical variables using frequency distributions. Cross-sectional comparisons of growth and nutritional status, body composition, pulmonary function and REE between supplementation groups (LXS vs. placebo) and between sexes were performed using Student's independent samples t test for normally distributed and Mann-Whitney U test for skewed data. Comparisons of categorical variables between groups were assessed with chi-squared or Fisher's exact test. Changes in dietary intake, growth, body composition and REE were explored by supplementation groups at 3 and 12 months. As there was no group difference, data were pooled and this report focuses on the results of this global nutrition intervention (LXS and placebo combined). Trends over time for the whole sample were assessed using Student's dependent samples t-test or Wilcoxon matched pairs signed ranks test appropriate.

Longitudinal analyses of REE were performed to assess significant change from baseline over the two time points (3 and 12 months) using the longitudinal mixed effects (LME) analysis procedure in STATA (XTREG) (25). LME models were run separately by supplementation group (LXS and placebo group) and then for the total sample. Both FFM and FM were entered into all models as predictors of REE as they are known to be the main predictors of REE in children and adults (26). Other potential predictors such as sex, age, FEV_1, pubertal status, total energy intake (dietary plus LXS or placebo) and average adherence to 3 and 12 months were explored. The models were also tested separately by sex and by supplementation group. All statistical analyses were performed using STATA 12.0 (College Station, TX). Results were considered significant at $P < 0.05$, and data are presented as means ??SD (normal distribution) or median [range] (skewed distribution).

Results

Of the 70 children who completed 12 months, 7 were excluded from the analysis because REE measurements were not available (test failure). Of the 63 children with complete growth, body composition and REE measurements (57% males, age 10.6(2.9) yrs), 11 were excluded from the dietary analysis because of missed record or no record, or poor quality of the dietary record. At baseline, these children with CF had suboptimal growth and nutritional status, mild lung disease and mildly elevated REE (Table 1). LXS and placebo groups were similar with the exception of BMIZ (higher in placebo). Males and females were similar and only differed in total body FFM (higher in males), percent fat (higher in females) and REE as kcal/d (higher in males). The seven children with incomplete data and omitted from analyses were not different at baseline from the 63 with complete data in age, sex, growth, maturity status, body composition, or REE.

Details for the calories and macronutrient intake are presented in Table 2 for 52 children with complete longitudinal dietary data. The 11 children with incomplete dietary data and omitted from analyses were not different from these children in age, sex, baseline growth and maturity status, body composition, REE, or dietary intake. The median total caloric intake was 2502 [1478, 4909] kcal/d at baseline and increased to 2616 [1660, 4125] kcal/d at 12 months. Following the introduction of the supplements, dietary adaptation resulted in a decrease in the caloric intake from food. The proportion of the total calories contributed by LXS or placebo supplement at 12 months was adjusted for percent adherence at the time of the dietary recall. Adherence proximate to their 3-day dietary intake was 78%, with no difference between those on LXS (75%) and placebo (80%).

The changes in growth status, body composition and REE over 3 and 12 months are presented in Table 3. No difference was observed between LXS and placebo group over time, and the data were pooled. HAZ, WAZ and UAMAZ improved ($p < 0.05$) over 12 months, with no change in UAFAZ. Both FFM and FM increased ($p < 0.001$) during the study. Changes over time in growth and nutritional status were not different between males and females. REE decreased ($p < 0.05$) from 108.5 ± 8.3% to 106.5 ± 8.5% predicted over 12 months. From the LME model (Table 4), FFM, FM, sex and time were significant predictors of REE (kcal/d), explaining 87% of the variance ($p < 0.001$). REE adjusted for FFM and FM decreased by 31 ± 12 kcal/d between baseline and 12 months in all subjects, and females had lower REE as kcal/d overall. LME analysis was then performed separately by sex. In males, adjusted REE decreased by 49 ± 16 kcal/d over 12 months ($R^2=0.88$, $p < 0.01$, n=36), while there was no change over time in females. This decrease in REE over time for males was found in both LXS and placebo supplementation groups (results not shown). Age, puberty status, average % adherence, FEV_1 and total energy intake were tested in the models but were not significant predictors of REE (not shown). Adherence calculated for the whole time period from baseline to either 3 months or 12 months (cumulative adherence estimate) was 78% with no difference between supplementation groups. Adverse events were typical of the expected course of CF participants over 12 months and no adverse events were attributed to the study.

Discussion

Over a 12 month dietary intervention, the total caloric intake increased by a median of 114 kcal/d, after adjusting intake for adherence (adjustment for supplement intake only). Confounding factors such as the impact of the dietary assessment itself on nutritional intake or clinically driven changes in treatment may influence caloric intake. Over the course of the study, there were few modifications in care and none likely to impact food intake or activity. Growth status and muscle stores were suboptimal at baseline and improved over 12 months in all subjects. The REE was mildly elevated at baseline as expected (5–13) and decreased during a period of enhanced caloric intake and documented increase in body size and muscle stores.

Nutritional status in CF is correlated with clinical outcomes and survival (27), and normal nutrition status is among the goals of clinical care. In the present study, an improvement in WAZ and HAZ of 0.1 z-score over one year was achieved. This increase corresponds to a clinically meaningful improvement from the 31st to the 35th percentile for children beginning at −0.5 z-score. The increase in muscle status (UAMAZ) from −0.6 to −0.3 z-score represents an even greater improvement from the 28th to the 38th percentile over one year. This 12-month average improvement in Z-scores is likely meaningful because, as a group, these children with CF maintained their typical rate of accretion of FFM and FM, and then had increased rates of accretion (‘catch-up growth’).

Few have studied the impact of an oral caloric intervention in children with CF. In the Stark et al. study, the improvement over nine weeks in caloric intake and weight was shown to be greater with a combination of behavioral and nutrition education interventions versus the nutrition education alone (28). In follow-up with this cohort, the growth of both the behavioral and nutrition education intervention group and nutrition education group, was similar from 3 to 24 months. In later analysis, the combined behavioral and nutrition intervention or nutrition education alone were both shown to result in a smaller decline in BMIZ over about 2 years, when compared to an age-matched sample of children from the CF Foundation patient registry (29). Smyth and Walters recently completed a Cochrane review of three randomized or quasi-randomized trials where oral calorie supplements were compared to dietary counseling in people with CF who were either PI or pancreatic sufficient (30). An increased caloric intake with oral supplements was documented at 12 months, but no differences were observed in HAZ, WAZ, BMIZ, body composition or lung function in these children with CF and suboptimal nutritional status prior to intervention. In contrast, the present nutrition intervention study of a caloric supplement added to participant selected foods and beverages, resulted in a sustained increased caloric intake over 12 months and achieved an improvement in growth status, muscle stores, and REE.

Children with CF and PI have been shown to have a 5 to 20% increased REE compared to predicted values for healthy subjects (5–13). In the present study, REE decreased over one year. Interestingly, males showed a decrease in REE over time while females did not. Sex differences in CF are well established, with poorer growth and health outcomes for females (31–33). In three longitudinal studies following children with CF over one, two or three years, REE either increased or remained elevated over time as the participants aged

(6,13,34). Contrary to these observational studies, a decrease in REE was observed with our nutrition intervention over one year. Furthermore, our intervention may have prevented further increase in REE and/or worsening in energy balance often observed as children and adolescents with CF grow older (6,13,34). This reduction in REE likely supported the observed growth and body composition status improvement. FFM (mainly skeletal, muscle and organs) is the most powerful predictor of REE, and FM is small but often statistically significant in healthy children and adults and also in people with chronic diseases (8,26). The energy expenditure interactions are complex across the age, sex, pubertal status and disease severity spectrum. It remains unclear if an association between REE and pulmonary function exists in children with mild to moderate CF (6–13). In the present study of clinically stable school-age subjects with mild pulmonary disease, FEV_1 was not a significant predictor of REE.

Conclusion

Over a 12 month nutrition intervention with either LXS or placebo, the growth status, muscle stores and REE improved. Sustained increased energy intake improved energy metabolism, growth and nutritional status in school age children with CF, PI and mild lung disease. Further studies of nutritional intervention using powdered caloric supplements to commonly consumed foods and beverages to treat growth faltering in children or weight loss in adults with CF should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of the funding source

The funding sponsors were not involved in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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Table 1

Characteristics (mean ± SD) at baseline for LYM-X-SORB™ (LXS) and Placebo groups, and for male and female participants.

	All n=63	**LXS n=27**	**Placebo n=36**	**Male n=36**	**Female n=27**
Sex, % males	57	61	52	100	0
Age, y	10.6 ±2.9	11.0±2.8	10.2 ±2.9	11.0 ± 2.5	10.1 ±3.2
Pubertal Tanner stage, %					
1	47	42	50	46	48
2	29	31	28	31	26
3	13	15	11	14	11
4	10	12	8	6	15
5	2	0	3	3	0
Genotype, ΔF508/508, %	57	56	58	58	56
HAZ	−0.5 ±0.9	−0.2 ±0.9	−0.7 ±0.9	−0.4 ±0.7	−0.6 ± 1.1
WAZ	−0.4 ±0.7	−0.5 ±0.6	−0.3 ± 0.7	−0.4 ±0.7	−0.5 ±0.7
BMIZ	−0.2 ±0.7	−0.5 ±0.6	0.1 ±0.7***	−0.2 ±0.6	−0.2 ±0.8
Body Composition					
FFM, kg	26.3 ± 9.4	26.8 ±8.1	26.0 ±10.4	28.5 ±9.8	23.5 ±8.2*
FM, kg	7.1 ±2.6	7.3 ±2.8	6.9 ±2.5	6.6 ±2.6	7.7 ±2.5
Fat, %	21.6 ±5.7	21.5 ± 5.1	21.7±6.2	18.9± 5.0	25.1 ±4.6***
UAMAZ	−0.6 ±0.8	−0.8 ±0.8	−0.4 ±0.8	−0.6 ±0.9	−0.5 ±0.7
UAFAZ	−0.3 ±0.8	−0.4 ±0.8	−0.2 ±0.9	−0.3 ±0.7	−0.3 ± 1.0
FEV_1, % pred	96 ±22	92 ±21	100 ± 22	92 ±28	88 ±27
REE, kcal/d	1300 ±256	1314 ±222	1290 ± 282	1385 ±264	1187± 198**
REE%	108.5 ±8.3	108.8 ±8.6	108.3 ±8.1	109.0 ±8.4	107.9 ±8.2

* Differences significant at $p<0.05$;

** $p<0.01$;

*** $p<0.001$.

BMIZ - Body mass index-Z-score; FFM - Fat free mass (kg); FM - Fat mass (kg); HAZ - Height-Z-score; REE - Resting energy expenditure; UAFAZ - Upper arm fat area Z-score; UAMAZ - Upper arm muscle area Z-score; WAZ - Weight-Z-score

Table 2

Total calories and macronutrient intake (median [range]) in LYM-X-SORB™ (LXS) and Placebo groups at baseline, 3 and 12 month.

	All n=52†			LXS n=20			Placebo n=32		
	Baseline	**3 mo**	**12 mo**	**Baseline**	**3 mo**	**12 mo**	**Baseline**	**3 mo**	**12 mo**
Total intake, kcal/d	2502 [1478,4909]	2581 [1609,3620]	2616 [1660,4125]	2561 [1841,3504]	2678 [1731,3620]	2611 [1660,4005]	2437 [1478,4909]	2440 [1609,3571]	2623 [1704,4125]
EER, %	123 [64,223]	125 [77,221]	122 [69,213]	120 [86,153]	125 [77,173]	125 [69,165]	127 [64,223]	124 [77,221]	120 [81,213]
Fat, g/d	97 [54,227]	97 [51,180]	102 [59,203]	109 [61,145]	99 [66,173]	93 [59,183]	94 [54,227]	96 [51,180]	103 [69,203]
Fat, %kcal	36 [23,53]	34 [19,49]	36 [27,47]	36 [27,42]	31 [24,49]	35 [27,46]	37 [23,53]	35 [19,46]	36 [28,47]
Protein, g/d	82 [46,170]	83 [38,137]	86 [36,167]	82 [54,119]	85 [59,133]	85 [36,135]	80 [46,170]	77 [38,137]	86 [45,167]
Protein, %kcal	13 [9,24]	13 [8,19]	13 [9,23]	13 [9,20]	13 [9,17]	13 [9,17]	13 [9,24]	12 [8,19]	13 [9,23]
Carbohydrates, g/d	318 [179,604]	349 [192,583]	315 [203,559]	325 [239,474]	391 [192,522]	325 [238,516]	305 [179,604]	347 [231,583]	308 [203,559]
Carbohydrates, %kcal	51 [34,69]	53 [33,70]	52 [38,63]	52 [43,63]	53 [33,66]	52 [38,61]	51 [34,69]	53 [41,70]	51 [39,63]

†Of the 63 subjects, 52 had complete dietary data; LXS and placebo supplement intake was adjusted for proximate adherence (diet intake not adjusted); EER – Estimated energy requirement

Table 3

Growth, body composition and REE in all subjects (n=63) at baseline, 3 and 12 months.

Mean ± SD	Baseline	3 month	12 month
HAZ	−0.5 ±0.9	−0.4 ±0.9***	−0.4 ±0.9***
WAZ	−0.4 ±0.7	−0.3 ±0.7***	−0.3 ±0.8*
BMIZ	−0.2 ±0.7	−0.0 ±0.7**	−0.2 ±0.9
Body Composition			
FFM, kg	26.3 ±9.4	27.5 ±9.7***	29.6 ± 10.9***
FM, kg	7.1 ±2.6	7.6±2.8***	8.0 ±3.0***
Fat, %	21.6±5.7	22.1 ±5.6**	21.8 ±5.8
UAMAZ	−0.6 ±0.8	−0.4 ±0.8*	−0.3 ± 1.0**
UAFAZ	−0.3 ±0.8	−0.1 ±0.8**	−0.2 ±0.9
REE, kcal/d	1300 ±256	1335 ±260**	1353 ±276***
REE%	108.5 ±8.3	108.9 ±7.8	106.5 ±8.5**

*Change over time significant at p<0.05;

**p<0.01

***p<0.001

BMIZ - Body mass index-Z-score; FFM - Fat free mass (kg); FM - Fat mass (kg); HAZ - Height-Z-score; LXS - LYMX-SORB™; REE - Resting energy expenditure; UAFAZ - Upper arm fat area Z-score; UAMAZ - Upper arm muscle area Z-score; WAZ - Weight-Z-score

Table 4

Longitudinal mixed effect model (LME): REE (kcal/d) over time in all subjects and by sex.

	Coef.	SE	P-value	N	Overall R^2	Overall P-value
All				63	0.87	<0.001
FFM, kg	0.02	0.001	<0.001			
FM,kg	0.01	0.004	0.02			
Sex, female	−79	23	0.001			
Time 3 mo	−0.2	11	0.98			
Time 12 mo	−31	12	0.01			
Constant	775	48	<0.001			
Male				36	0.88	<0.001
FFM, kg	0.02	0.001	<0.001			
FM,kg	0.009	0.005	0.1			
Time 3 mo	−11	15	0.5			
Time 12 mo	−49	16	0.002			
Constant	697	43	<0.001			
Female				27	0.80	<0.001
FFM, kg	0.02	0.003	<0.001			
FM,kg	0.01	0.007	0.2			
Time 3 mo	14	18	0.4			
Time 12 mo	−8	19	0.7			
Constant	618	52	<0.001			

FFM - Fat free mass (kg); FM - Fat mass (kg); LME – Longitudinal mixed effect model; REE - Resting energy expenditure (kcal/d); SE – Standard error