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Effect of Oral Lipid Matrix Supplement on Fat Absorption in Cystic Fibrosis: A Randomized Placebo-Controlled Trial

Virginia A. Stallings, MD^{1,2}, Joan I. Schall, PhD^{1,*}, Asim Maqbool, MB^{1,2}, Maria R. Mascarenhas, MBBS^{1,2}, Belal N. Alshaikh, MD^{1,3}, Kelly A. Dougherty, PhD^{1,4}, Kevin Hommel, PhD⁵, Jamie Ryan, PhD⁵, Okan U. Elci, PhD⁶, and Walter A. Shaw, PhD⁷

¹Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, PA, USA

²Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Address correspondence to: Joan I. Schall, The Children's Hospital of Philadelphia, 3535 Market St., Rm. 1554, Philadelphia, PA 19104, Phone (215)-590-5688, Fax: (215)-590-0604, schall@email.chop.edu.

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Author Contributions to Submitted Work

Virginia A. Stallings, MD contributed to the conception/design of the study, was involved in the acquisition, analysis and interpretation of the work, and drafting and revision of the manuscript. She gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

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Asim Maqbool, MD contributed to the conception/design of the study, was involved in the acquisition and interpretation of the work, and drafting and revision of the manuscript. He gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Maria R. Mascarenhas, MBBS contributed to the conception/design of the study, was involved in the acquisition and interpretation of the work, and drafting and revision of the manuscript. She gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Belal N. Alshaikh, MD contributed to the analysis and interpretation of the work, and drafting and revision of the manuscript. He gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Kelly A. Dougherty, PhD contributed to the acquisition, analysis and interpretation of the work, and drafting and revision of the manuscript. She gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Okan Elci, PhD contributed to the analysis and interpretation of the work, and drafting and revision of the manuscript. He gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Kevin A. Hommel, PhD contributed to the conception/design of the study, was involved in the acquisition, analysis and interpretation of the work, and drafting and revision of the manuscript. He gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Jamie Ryan, PhD was involved in the acquisition, analysis and interpretation of the work, and drafting and revision of the manuscript. She gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

Walter Shaw, PhD contributed to the conception/design of the study, was involved in the acquisition, analysis and interpretation of the work, and drafting and revision of the manuscript. He gave final approval of the version to be published, is accountable for all aspects of the work, and attests to its accuracy/integrity.

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³Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

⁴Stockton University, Pomona, NJ, USA

⁵Center for Adherence and Self-Management, Cincinnati Children's Hospital Medical Center, Division of Behavioral Medicine and Clinical Psychology, University of Cincinnati College of Medicine, Department of Pediatrics, Cincinnati, OH, USA

⁶Westat Biostatistics and Data Management Core, Children's Hospital of Philadelphia, Philadelphia, PA, USA

⁷Avanti Polar Lipids, Inc, Alabaster, AL, USA

Abstract

Pancreatic enzyme therapy does not normalize dietary fat absorption in patients with cystic fibrosis (CF) and pancreatic insufficiency (PI). Efficacy of LYM-X-SORBTM (LXS), an easily absorbable lipid matrix that enhances fat absorption was evaluated in a 12-month randomized, double-blinded, placebo-controlled trial with plasma fatty acids (FA), and coefficient of fat absorption (CFA) outcomes. 110 subjects (age 10.4±3.0 y) were randomized. Total FA increased with LXS at 3 and 12 months (+1.58; +1.14 mmol/L) and not with placebo ($P=0.046$). With LXS, linoleic acid (LA) increased at 3 and 12 months (+298; +175 nmol/mL, $P=0.046$), with a 6% increase in CFA ($P<0.01$). LA increase was significant in LXS vs. placebo (445 vs. 42 nmol/mL, $P=0.038$). Increased FA and LA predicted increased BMI Z scores. In summary, LXS treatment improved dietary fat absorption compared to placebo as indicated by plasma FA and LA and was associated with better growth status.

Keywords

fatty acids; pancreatic insufficiency; linoleic acid; LYM-X-SORBTM

INTRODUCTION

Nutritional status remains suboptimal in patients with cystic fibrosis (CF) and pancreatic insufficiency (PI) despite effort to optimize pancreatic enzymes and diets¹⁻³. Chronic steatorrhea results in loss of fat calories and fat soluble vitamins⁴⁻⁷, and stool coefficient of fat absorption (CFA) often ranges from 81 to 85%⁸⁻¹⁰. In a recent study of over 200 patients, those with CFA < 85% had growth faltering⁶. Essential fatty acid insufficiency has been associated with poorer growth and pulmonary function, and is in part a consequence of chronic fat malabsorption^{9, 11-18}. Second generation LYM-X-SORBTM (LXS) (BioMolecular Products, Byfield, MA; Avanti Polar Lipids, Alabaster, AL)¹⁹, with enhanced taste and mixability is a phospholipid- and triglyceride-rich matrix. The aim of this randomized placebo-controlled double-blinded trial was to evaluate the efficacy of 12-month supplementation with LXS to improve fat absorption indicated by plasma fatty acid (FA) concentrations and stool CFA.

METHODS

Subjects aged 5.0 to 17.9 years with CF, PI and mild to moderate lung disease were recruited from ten CF Centers. LXS is composed of lysophosphatidylcholine, triglycerides and FA which form an organized lipid matrix complexed to wheat flour and sugar. Subjects aged 5.0–11.9 years received two packets/day, and subjects aged 12.0–17.9 years received three packets/day. The placebo had similar calories (~150 kcal/packet), total fat, FA and macronutrient distribution. The inclusion/exclusion criteria, study design and method details, LXS composition, and the results for LXS impact on choline status have been previously reported^{10, 20, 21}.

Dietary intake was assessed using 3-day weighed records^{22, 23}. A 72-hour stool sample was collected and total fat content determined (Mayo Medical Laboratories, Rochester, MN), and CFA calculated⁸. Daily pancreatic enzyme medication use was determined. Subjects completed the Pediatric Quality of Life Inventory (PedsQL 4.0)²⁴, and Cystic Fibrosis Questionnaire-Revised (CFQ-R)^{25, 26}.

Quantitation of morning fasting plasma FA was performed in two steps: 1) acid-base hydrolysis; 2) hexane extraction/derivatization with pentafluorobenzyl bromide (Mayo Medical Laboratories). Separation/detection was accomplished by capillary gas chromatography electron-capture negative ion-mass spectrometry, with quantitation based on analysis in selected ion-monitoring mode using 13 stable isotope-labeled internal standards²⁷.

Descriptive statistics were presented as frequency counts and percentages for categorical variables and mean $\pm$ standard deviation (SD) for continuous variables. Two-sample t-test (unpaired) or Mann-Whitney U test for continuous variables and chi-square tests of independence for categorical variables compared characteristics at baseline. Paired t-tests were used to determine the significance of change in quality of life scores from baseline to 12 months.

Changes in outcome measures over time, the main effect of randomization groups, and randomization group (R) by time (T) interactions were investigated on an intent-to-treat basis using mixed effects linear regression models implemented via maximum likelihood accounting for correlations arising from the repeated-measures²⁸. Whether changes in outcomes over time differed by randomization groups were evaluated by examining the interaction effects of randomization group by time ($R \times T$). Similar secondary analysis limited to subjects with LA in the lower quartile range at baseline were performed. Group comparison of percent change in FA over 3 and 12 months was analyzed using Wilcoxon rank-sum tests. Exploratory analyses using regression models assessed associations among baseline plasma total FA or LA and change () in total FA or LA status and change in clinical outcomes over time, adjusted for age, sex, and adherence to supplement use. Stata 12.1 was used with significance at 0.05.

RESULTS

There were 110 subjects recruited, 56 randomized to placebo and 54 to LXS supplementation. Subjects (10.4 ± 3.0 years), were 57% male, 57% F508 homozygous, and had mild pulmonary disease (FEV_1 : 95 ± 23 % predicted), suboptimal growth status (height-for-age Z score: -0.4 ± 0.9 ; weight-for-age Z score (WAZ): -0.4 ± 0.8 ; BMI-for-age Z score (BMIZ): -0.2 ± 0.8), and moderate fat malabsorption (CFA: 83 ± 12 %). The overall quality of life score (PedsQL) was 82 ± 12 for parent-assessed and 81 ± 13 for the child-assessed measures. The randomization groups did not differ at baseline for any measure.

Twenty-four subjects after baseline (10 placebo, 14 LXS) and 16 subjects after 3 months (7 placebo, 9 LXS) withdrew from the study. Neither the attrition rate nor the reasons for dropping out differed by randomization group²⁹ (see Supplemental Digital Content Figure 1). Dropouts and study completers did not differ at baseline in age, sex, genotype, growth status, plasma FA, intake of dietary fat, LA or pancreatic enzyme use.

Table 1 presents dietary intake of fat, pancreatic enzyme use, fat absorption, and FA for placebo and LXS groups. There were no differences between randomization groups at baseline. The dietary intake included both food intake and supplement (LXS or placebo) adjusted for adherence. Energy intake averaged 119% of the EER, 36% of fat calories. Refer to Supplemental Digital Content Table 1 for the expanded list of dietary intake and plasma FA variables. LXS and placebo supplements provided 300 to 450 calories/day depending on age. Enzyme medication use was less in LXS than placebo group at 12 months ($p=0.007$). Intake of LA was similar in both groups throughout the study (see Supplemental Digital Content Table 1). CFA improved significantly (6%) in LXS only at both 3 and 12 months ($P<0.01$). For the LXS group, 39% had moderate fat malabsorption (CFA <80 %) at baseline and declined to 11% at 3 months ($P=0.013$) and 15% at 12 months ($P=0.025$), with no change in the placebo group. Cumulative adherence to supplements was 80 vs. 76% at 3 months, and 75 vs. 71% at 12 months for placebo vs. LXS, respectively.

LXS supplementation was associated with increased absorption of total FA over 3 and 12 months ($R \times T$, $P_{0.3-12}=0.046$), and monounsaturated FA (MUFA, $R \times T$, $P_{0.3-12}=0.043$), and of saturated FA (SFA) and MUFA over 3 months ($R \times T$, $P_{0.3}=0.022$) compared to placebo with the intent-to-treat approach (see Supplemental Digital Content Table 1). Increase from baseline in fasting plasma total FA, SFA, MUFA, polyunsaturated FA (PUFA) and LA was robust (11 to 18%) with LXS compared to small increases (2 to 6%) for placebo (see Supplemental Digital Content Figure 2). Palmitic acid (most abundant SFA), and oleic acid (most abundant MUFA) were significantly increased in LXS compared to placebo. LA (the most abundant PUFA) significantly increased within LXS group only at 3 and 12 months ($P<0.05$); the difference from placebo approached significance at 3 months ($R \times T$, $P_{0.3}=0.069$). The baseline mean triene: tetraene ratio (T:T ratio) was 0.05 ± 0.02 in both groups. Elevated T:T ratio above 0.05, a cutoff used to indicate EFA deficiency using non-CF-specific laboratory reference ranges²⁷, was documented in 41% at baseline (39 and 43% in placebo and LXS), and was 26% after 12 months supplementation (23 and 29% placebo and LXS, respectively). This decline was significant for the groups combined (one-sided Fisher's exact test, $P=0.025$).

The impact of change in total FA (total FA, increase or decrease) and LA status (LA) on clinical outcomes was explored in the LXS and placebo groups combined. Adjusted for baseline status, age, sex and adherence, total FA positively predicted BMIZ (β coefficient = 0.04, $P=0.011$) and fat free mass (FFM) ($\beta = 0.19$, $P=0.005$), while LA positively predicted WAZ ($\beta = 0.10$, $P=0.042$) and BMIZ ($\beta = 0.07$, $P=0.003$) (see Supplemental Digital Content Table 2). Improved weight and BMI status was largely attributable to increases in FFM.

Change in LA in subjects whose baseline LA was in the lowest quartile range for this sample (< 1920 $\mu\text{mol/L}$) was analyzed (10 in placebo and 17 in LXS group). These subjects had lower BMI at baseline compared to the other quartiles combined (-0.48 ± 0.82 vs. -0.11 ± 0.73 ; $P=0.03$). LA increased significantly in LXS group from baseline to 3 and 12 months (1640 ± 198 to 1936 ± 392 and 2120 ± 580 nmol/mL , respectively, $P=0.002$). No significant change in LA occurred in placebo group (1693 ± 184 to 1806 ± 429 and 1752 ± 332 nmol/mL , respectively). LA change over time between LXS and placebo was significant at 12 months ($R \times T$, $P_{0-12} = 0.038$).

We have previously reported that both LXS and placebo were safe^{10, 29}, and growth status improved in both groups^{10, 21}. Quality of life score indicated by the PedsQL or CFQ-R did not change and there were no differences by randomization group. When the groups combined, there were significant increases from baseline to 12 months in child-assessed emotional functioning subscales from both the PedsQL (75.7 ± 18.5 to 80.8 ± 16.2 , $P=0.01$ by paired t-test) and the CFQ-R (76.8 ± 15.3 to 81.2 ± 14.4 , $P=0.01$), and social functioning and perceived body image (67.0 ± 18.4 to 72.1 ± 16.6 and 77.4 ± 26.0 to 85.3 ± 22.2 , respectively, $P<0.01$) on the CFQ-R.

DISCUSSION

LXS was developed to improve dietary fat absorption when combined with foods and beverages. In children with CF and PI, daily oral supplementation with this easily absorbable phospholipid- and triglyceride-rich lipid matrix was safe and effective, as indicated by increased fasting plasma FA and 6% increase in stool CFA. With fewer pancreatic enzymes, absorption improved with LXS in SFA, MUFA and PUFA compared to placebo, and in LA in the LXS group only, despite similar energy and fat intake in both groups. Improvement in total FA and LA concentrations was associated with better weight and BMI status. Participants had dietary patterns that closely adhered to CF recommendations, with high calorie intake (119 to 124% EER), high fat intake of 97 to 106 g per day (34 to 36% kcal from fat) and appropriate doses of pancreatic enzyme medication for meals and snacks¹⁻⁴. CFA at baseline was 82% in this cohort of diet- and enzyme-adherent subjects, compared with the reference value of 93% dietary fat absorption in healthy people^{5, 30}.

Chase et al³¹ was among the first to provide oral LA and follow the fasting plasma FA absorption response. McKenna et al³² then used both naturally occurring and structured triglycerides to identify fat sources that would enhance absorption in CF and PI. They concluded that both long-term adequate calories as well as supplemental LA were necessary

to prevent essential FA deficiency, with optimized pancreatic enzyme replacement. A number of studies to improve LA status with different designs and different LA sources have been conducted more recently^{32–37}, none of which offered LA in a more readily absorbable form. In our CF study, baseline dietary intake of LA was 159% of recommendation for healthy people (~18g/day). Both LXS and placebo supplements contained a small amount of LA, and daily intake increased about 15% (to 21 g) in both groups. Only the LXS group showed a significant increase in the fasting plasma LA, and particularly among those with the lowest baseline LA concentrations. These findings indicate that the unique LXS lipid structure and composition resulted in improved LA absorption efficiency.

The more frequently described FA abnormalities in CF include low LA, docosahexaenoic acid (DHA), PUFA, and high T:T ratios^{13–15}. Few subjects in the current study had baseline LA concentrations below laboratory reference range. However, over 1/3 had essential FA insufficiency based upon the laboratory reference range for the T:T ratio. It is notable, however, that for subjects more at-risk for LA insufficiency at baseline (LA 1920 $\mu\text{mol/L}$), LA concentrations increased by 29% over 12 months in LXS with no change in placebo group. The proportion of subjects with EFA insufficiency based upon the T:T ratio declined significantly from 41% at baseline to 26% after 12 months, with no group difference. This was expected for the LXS group with improved absorption of multiple FAs, but the reason for this improvement in the placebo group was less clear. Perhaps the additional dietary energy, FA and LA in either LXS or placebo supported change in this ratio. It should be noted that this ratio method was developed before reliable actual measurement of plasma LA was clinically available to detect this specific essential FA deficiency.

LA deficiency has clinical consequences including impaired growth, wound healing, and seborrheic dermatitis³⁸. In addition to PI and fat malabsorption^{5, 39}, plasma FA abnormalities may relate to increased energy expenditure, increased oxidative stress^{40, 41}, increased cell membrane turnover⁴², abnormal release of FA from the cell membrane⁴³, and defects related to specific CF genotypes^{12, 44}. Suboptimal FA status has been associated with poorer pulmonary and growth outcomes in CF^{13, 45, 46}. The type and amount of dietary fat intake predicts FA status including plasma LA, T:T ratio and DHA status in CF^{9, 47}. Here LXS improved overall fat absorption and total FA and LA status improvement was associated with increased WAZ and BMIZ, likely attributable to increased FFM relative to FM. Children with lowest LA concentrations at baseline had significantly lower BMIZ. This may indicate that LXS has the potential to impact growth and nutritional status in children with CF at risk for essential FA insufficiency. HRQOL improved in the domains of emotional functioning, social functioning, and body image, suggesting that the improved weight status observed in both randomization groups was psychosocially beneficial, though this requires further examination.

Study strengths included a study design that supports generalizability with enrollment from 10 CF Centers, successful randomization, and good adherence. Limitations include subject attrition that may have introduced bias, however, there was no evidence that dropouts and completers differed at baseline in demographic, clinical outcome measures, or plasma FA status. Reasons for dropping out did not differ by randomization groups. The study design did not include either a CF or a non-CF, non-intervention group for comparison. The dose of

LXS was based on a prior study with LXS in which increased FA concentrations were observed. A higher dose may have a different effect on the outcomes of interest.

In summary, LXS treatment improved dietary fat absorption compared to placebo as indicated by plasma FA, LA and CFA in children with CF and PI who had similar intake of energy, fats and LA, and less pancreatic enzyme medication use. Increased total FA and LA absorption may support better growth status in school aged children. Based on these results and clinical experience, LXS has potential to reduce fat malabsorption in CF clinical care. Further investigation is needed to evaluate the effectiveness of LXS to reduce fat malabsorption and treat or prevent malnutrition in patients with other diagnoses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is Known

- Chronic fat malabsorption and loss of dietary calories persists in children and adults with CF and PI in spite of optimization of pancreatic enzyme replacement therapy and diet

What is New

- A randomized double blind clinical trial showed that supplementation with an easily absorbed structured lipid improved dietary fat absorption and fatty acid status, as indicated by increase total fatty acid and linoleic acid concentrations and improved stool coefficient of fat absorption
- Improved total fatty acid and linoleic acid concentrations were associated with improved growth status in children

Table 1

Dietary Intake, Stool Fat Absorption, Plasma Fatty Acids by Placebo and LYM-X-SORB (LXS) at Baseline, 3 and 12 Months

	Time Point		Effect of treatment	
	Baseline	3 month	12 month	P ₀₋₃ ³ P _{0-3,12} ⁴
Dietary Fat, g^{1,5}				
Placebo	98 ± 40 ²	102 ± 30	106 ± 32	0.86 0.57
LXS	97 ± 29	99 ± 34	105 ± 36	
Pancreatic Enzymes, Lipase Units^{1,6}				
Placebo	315,938 ± 129,583	327,870 ± 126,817	340,410 ± 123,118	0.80 0.48
LXS	288,062 ± 123,885	289,709 ± 128,251	264,533 ± 97,713	
Coefficient of Fat Absorption, %⁷				
Placebo	84 ± 12	85 ± 19	88 ± 11	0.16 0.34
LXS	82 ± 11	88 ± 7**	87 ± 8**	
Lauric (C12:0), nmol/L^{1,8}				
Placebo	23 ± 15	21 ± 12	24 ± 19	0.035 0.039
LXS	19 ± 12	34 ± 55*	22 ± 23	
Palmitoleic (C16:1ω7), nmol/L⁸				
Placebo	243 ± 154	221 ± 101	236 ± 116	0.003 0.009
LXS	214 ± 105	299 ± 186***	292 ± 173**	
Linoleic Acid (C18:2ω6), nmol/L⁸				
Placebo	2333 ± 491	2380 ± 552	2358 ± 500	0.15
LXS	2230 ± 528	2522 ± 754**	2405 ± 571*	
Oleic (C18:1ω9), nmol/L^{1,8}				
Placebo	1872 ± 557	1798 ± 488	1839 ± 490	0.017 0.046
LXS	1762 ± 367	2068 ± 775**	1997 ± 589*	
Arachidonic (C20:4ω6), nmol/L⁸				
Placebo	454 ± 143	432 ± 129	458 ± 138	0.023 0.047
LXS	430 ± 127	463 ± 161	460 ± 143**	
Docosatetraenoic (C22:4ω6), nmol/L^{1,8}				

Time Point			Effect of treatment	
	Baseline	3 month	12 month	P ₀₋₃ ³ P _{0-3,12} ⁴
Placebo	25 ± 9	23 ± 8	23 ± 8	0.037
LXS	22 ± 7	28 ± 13**	26 ± 11**	
Total Fatty Acids, mmol/L ^{1,8}				
Placebo	9.16 ± 2.18	9.12 ± 2.26	9.30 ± 2.00	0.015
LXS	8.56 ± 1.64	10.14 ± 3.63**	9.70 ± 2.83**	0.046

¹ Log transformation was applied for skewed variables in the mixed models.

² Mean ± SD (all such values).

³ P₀₋₃ is testing for partial randomization group × time interaction between baseline and 3 month from a mixed effects linear regression model that included baseline, 3, and 12 months data (i. randomization group × time interaction was used).

⁴ P₀₋₃₋₁₂ is testing for randomization group × time interaction between baseline and 3, and 12 month.

⁵ n=54, 37, and 35 for Placebo group, and n=44, 31, and 23 for LXS group at baseline, 3, and 12 months, respectively.

⁶ n=56, 46, and 39 for Placebo group, and n=54, 40, and 30 for LXS group at baseline, 3, and 12 months, respectively.

⁷ n=41, 36, and 30 for Placebo group, and n=35, 27, and 20 for LXS group at baseline, 3, and 12 months, respectively.

⁸ n=56, 46, and 39 for Placebo group, and n=51, 40, and 31 for LXS group at baseline, 3, and 12 months, respectively.

* (P<0.05) ** (P<0.01) *** (P<0.001) difference from baseline within randomization group.