0031-3998/88/2403-0353$02.00/0
PEDIATRIC RESEARCH

Vol. 24, No. 3, 1988
Printed in U.S.A.

Supplemental Calories Improve Essential Fatty Acid Deficiency in Cystic Fibrosis Patients

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ABSTRACT. Fatty acid composition of plasma lipids was analyzed in malnourished cystic fibrosis patients undergoing 6 months of nutritional rehabilitation. There were three males and five females (mean age 15.1 yr); five patients had pancreatic insufficiency. Nutritional rehabilitation in seven of eight patients was accomplished by nocturnal nasogastric infusion of a high-carbohydrate semisynthetic diet, in addition to daily meals. One patient received high-energy food supplements as snacks in addition to regular meals. All patients were moderately to severely malnourished on entry to the study and showed significant improvement over the 6 months in ($\bar{x}$ ± SE) energy intake (96 ± 8.0 to 126 ± 11% recommended daily allowance) and body composition (80 ± 4 to 90 ± 4% ideal body weight). Daily intakes of linoleic acid were not significantly different before or during nutritional rehabilitation either as an absolute amount (383 ± 45 to 557 ± 124 mg/kg/day) or as a percentage of total calories (4.50 ± 0.40 to 4.73 ± 0.14%). In comparison to the controls, the relative percentage of plasma cholesterol ester fatty acids of the CF patients on entry into the study showed a marked decrease of linoleic acid (52.7 ± 1.0 *versus* 42.3 ± 2.7%) with elevated palmitoleic (2.34 ± 0.2 *versus* 5.64 ± 0.7%) and oleic (18.7 ± 1.0 *versus* 25.2 ± 1.4%) acids; a pattern consistent with essential fatty acid deficiency. However, this pattern is not truly characteristic of a pure linoleic acid deficiency as the metabolites of linoleic acid were not decreased. After nutritional rehabilitation the linoleic acid concentration reached control values in the phospholipid and cholesterol ester plasma lipids in six of eight and five of eight patients, respectively. These findings indicate a low caloric intake is an important factor in determining the essential fatty acid status of cystic fibrosis patients and recovery of both the body composition and essential fatty acid deficiency can be accomplished by increasing the caloric intake to 150% of recommended daily allowances. (*Pediatr Res* 24: 353–356, 1988)

Abbreviations

EFA, essential fatty acid
CF, cystic fibrosis
RDA, recommended daily allowance

Many investigators have described a high incidence of biochemical EFA deficiency in CF patients (1–5). These patients usually have decreased linoleic acid (18:2ω6) and increased oleic (18:1ω9) and palmitoleic (16:1ω9) acids. Several mechanisms have been suggested for the abnormal fatty acid pattern, including *1*) part of the primary genetic defect of CF (6, 7); *2*) dietary deficiency and/or malabsorption of EFA secondary to pancreatic insufficiency (3); *3*) abnormal metabolism of linoleic acid to its metabolites (6, 8); and *4*) energy malnutrition with oxidation of linoleic acid for ATP production (9). This study examines the role of caloric supplementation for the correction of EFA deficiency in malnourished CF patients.

Malnutrition, characterized by decreased growth or decreased weight for height, is a common finding in CF patients (10). The malnutrition results from energy intake below requirement (11), increased stool energy losses, and/or increased metabolic energy needs (12, 13). Abnormalities in plasma EFA status have been previously associated with malnutrition syndromes such as anorexia nervosa (14), marasmus (15), and kawshiorkor (16, 17). Recent technological advances allow the nutritional status of malnourished CF patients to be normalized and hence permit clarification of the effects of malnutrition on plasma EFA of CF patients.

METHODS

The study population consisted of eight CF patients who met the following selection criteria: *1*) weight and/or height less than the 3rd percentile for age; *2*) persistent fall in weight percentile over the previous 12 months, and *3*) age more than 6 yr (to facilitate compliance). All patients had clinical findings indicative of CF and elevated sweat electrolytes. This study was approved by the Ethics Committee of the University of Calgary and patients and/or parents gave written informed consent.

The patients commenced a 6-month period of nutrient supplementation designed to achieve 150% of their RDA for calories. All patients received a standard North American diet. Seven patients received supplementation by nocturnal nasogastric feeds of a semisynthetic formula (Vital, Ross Laboratories, Montreal, Quebec, Canada). This formula provided 16.7% of calories as protein, 9.3% as fat, and 74.0% as carbohydrate. Therapy was initiated in hospital and continued at home. A silastic nasogastric tube was inserted each night and the formula infused at 100–150 ml/h over 8 to 10 h. Nonenteric-coated pancreatic enzymes (Cotazym, Organon, Ontario, Canada) were added to the formula, 1 capsule/300 ml, for those patients with pancreatic insufficiency. The 8th patient achieved 150% of the RDA for calories by ingestion of high-energy food supplements in addition to regular meals. Routine vitamins and physiotherapy were continued. Patients were assessed by the clinic physician, study coordinator, and dietitian at 2-month intervals. Antibiotic therapy was begun if sputum production increased and pulmonary function deteriorated.

Seven-day dietary records were analyzed (NUTS Nutrition Assessment System, Version 2, Quilchena Consulting Ltd., Vic-

Received May 11, 1987; accepted January 11, 1988.
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Supported by a grant from the Canadian Cystic Fibrosis Foundation.

toria, B.C., Canada) for dietary composition, including linoleic acid, at 2-month intervals. Body composition was determined by deuterium dilution (18). Deuterium oxide (99.98 atoms %, MSD Isotopes, Montreal, Canada) was administered as deuterium at 0.014 g/kg/body weight. Lean body mass was calculated from the relationship lean body mass = total body water/0.73. Body fat was calculated as body weight minus lean body mass (19). Ideal body weight was defined as the weight percentile corresponding to the height percentile using growth curves for North American children (20) and height/weight tables for adults (21).

Fecal fat excretion was quantitated on entry to the study, from a 3-day stool collection (22), which coincided with the last 3 days of a 7-day dietary record, and expressed as a percentage of fat intake. Blood samples were collected in EDTA at 0 and 6 months of therapy and the plasma stored at −70° C until analyzed for fatty acid profiles. Plasma lipids were extracted in chloroform-methanol (2:1) (23) and separated into cholesterol esters and phospholipids by thin-layer chromatography (24). The fatty acids of the isolated cholesterol esters and phospholipids were determined by gas-liquid chromatography for methyl esters prepared with boron trifluoride (25) as previously described. The retention time of eicosatrienoic acid (20:ω39) was established by using plasma from weanling male rats which had received a fat-free diet for 4 wk. A mixture of fatty acids (Applied Sciences Laboratories, State College, PA) of known composition was used as a reference standard for identification of other fatty acids. Essential fatty acid deficiency was defined as decreased linoleic and increased palmitoleic and oleic acids.

Eight North American subjects who were in good health and who ingested a standard North American diet served as controls. Results were analyzed for significance using Student's t test, paired t test and one-way analysis of variance. Where appropriate differences between samples were assessed by the Neumann-Kreul test and the data expressed as $\bar{x} \pm$ SEM.

RESULTS

Three male and five female CF patients with a mean age of 15.1 yr (range 8–27 yr) entered and completed the 6-month study period. There were five patients with, and three without, pancreatic insufficiency. With no exocrine pancreatic supplementation, patients had coefficients of fecal fat excretion 42.7 ± 5.1% and 5.0 ± 1%, respectively. Fat excretion in the former patients decreased to 20 ± 5.0% with enzyme administration. The nasogastric tube feedings were well tolerated, with no gastrointestinal symptoms or other complications.

All patients were moderately to severely below ideal body weight on entry to the study. There were significant improvements over the 6-month period in the daily energy intake, body weight, adipose tissue mass, and nonsignificant improvement of lean body mass (Fig. 1). Mean daily intakes of energy, protein, linoleic acid, and zinc at the onset and completion of the study are shown in Table 1. Subjects demonstrated a significant increase in protein, energy, and zinc intake, whereas linoleic acid intake, expressed either as a percentage of total calories or as an absolute amount, showed no significant change. During the study period, linoleic acid ingestion (mg/kg/day) ranged from −8.5 to 99.4% of initial pretreatment intake.

On entry to the study, the fatty acid composition of plasma lipids differed between CF and control subjects (Table 2). In plasma cholesterol ester fatty acids the relative amount of linoleic acid (18:2ω6) was decreased whereas palmitic (16:0), palmitoleic (16:1ω9), and oleic (18:1ω9) acids were increased ($p < 0.05$); arachidonic (20:4ω6) acid was at control levels. In addition, the absolute amount of cholesterol ester fatty acids was decreased; palmitic, oleic, and linoleic acids were significantly less than control levels. The mean triene/tetraene [eicosapentanoic (20:3ω9)/arachadonic (20:4ω6) acid] ratio was not significantly different from control levels. In one patient the triene/tetraene ratio was more than 0.4. Plasma phospholipid fatty acids (not shown) mirrored the cholesterol esters.

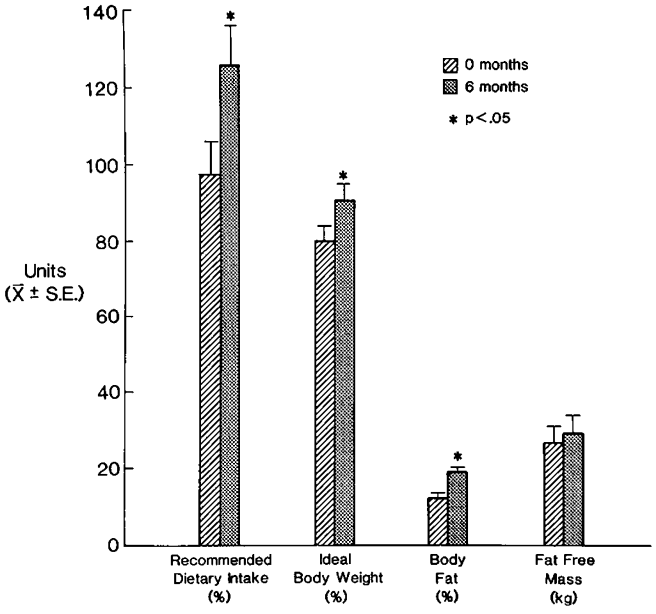

Fig. 1. CF characteristics on entry and end of study.

After 6 months of nutritional rehabilitation, the absolute amount of linoleic acid in the plasma phospholipid of CF patients increased significantly ($p < 0.05$), with six of eight returning to control levels (Fig. 2). The two patients in whom the phospholipid linoleic acid did not reach control levels had steatorrhea and their weight had increased to 85 and 89% of ideal body weight. Similarly, the cholesterol ester linoleic acid concentration improved significantly with five of eight patients reaching control levels. The sum of the concentrations of the cholesterol ester fatty acids significantly increased during the nutritional rehabilitation period but did not reach control levels; palmitic and oleic acids reached control values whereas palmitoleic acid was increased. When the fatty acids are expressed as the relative amount of the total cholesterol esters fatty acids nutritional support significantly increased linoleic acid whereas oleic acid fell. Nonetheless, linoleic acid remained below control levels and palmitic and palmitoleic remained elevated. The 20:4ω6/18:2ω6 ratio decreased, as a result of the nutritional support, but remained elevated compared to control levels. The triene/tetraene ratio fell below 0.4 in the one patient in whom it had been elevated on entry to the study.

The clinical and pulmonary status of these patients before and after nutritional rehabilitation has been reported elsewhere (13). In summary, there was no change in pulmonary status, but sense of well being was improved and hospitalizations for pulmonary infections were decreased.

DISCUSSION

On entry to the study, the CF patients showed biochemical evidence of a suboptimal EFA status. Reduced tissue levels of linoleic acid were associated with increased palmitoleic and oleic acid. The cause of the abnormal EFA status does not appear to be purely dietary in origin as the intake of linoleic acid in all CF patients, on entry to the study, was above the RDA of 3% of total calories. The deficit in EFA status also cannot be attributed to decreased fat absorption as three of the eight patients did not have pancreatic insufficiency as they demonstrated normal fecal fat excretion (<7% of intake). Clearly the nutritional therapy was successful in improving body composition and EFA status. Although there was a significant improvement in body weight and EFA status they did not achieve control levels. With im-

Table 1. *Plasma cholesterol fatty acids of control and CF patients at 0 and 6 mo of nutritional rehabilitation**

	Control		0 Mo		6 Mo	
Fatty acid	%	mg/dl	%	mg/dl	%	mg/dl
14:0	1.58 ± 0.09	1.06 ± 0.02	1.90 ± 0.15	0.59 ± 0.23	2.39 ± 0.64	1.11 ± 0.22
16:0	10.40 ± 0.20	7.13 ± 0.39	13.78 ± 0.94†[a]	3.83 ± 1.05[a]	14.07 ± 1.21[b]	5.37 ± 0.66
16:1	2.48 ± 0.19	1.71 ± 0.17	7.80 ± 1.96[a]	1.80 ± 0.33	7.06 ± 1.58[b]	3.51 ± 0.90[b,c]
18:0	1.12 ± 0.07	0.77 ± 0.07	1.84 ± 0.43	0.46 ± 0.15	1.11 ± 0.19	0.57 ± 0.15
18:1	19.56 ± 0.96	13.57 ± 1.25	27.24 ± 1.24[a]	7.43 ± 1.95[a]	20.20 ± 1.31[c]	10.31 ± 1.66
18:2	55.04 ± 0.78	37.60 ± 1.62	34.02 ± 2.31[a]	10.80 ± 3.45[a]	44.30 ± 3.28[b,c]	23.30 ± 3.95[b,c]
20:3ω9	0.90 ± 0.77	0.76 ± 0.13	1.84 ± 0.70	0.46 ± 0.14	1.06 ± 0.12	0.55 ± 0.11
20:4	6.99 ± 0.38	4.74 ± 0.20	8.70 ± 0.75	2.91 ± 1.03	8.11 ± 0.86	4.10 ± 0.65
22:6	1.16 ± 0.23	1.12 ± 0.14	2.88 ± 1.15	1.40 ± 1.04	1.39 ± 0.45	0.75 ± 0.23
Sum =	100	68.5 ± 62	100	29.7 ± 4.2[a]	100	49.56 ± 5.1[b,c]
Ratio						
20:4/18:2	0.11 ± 0.01		0.25 ± 0.2[a]		0.19 ± 0.02[b,c]	
20:3ω9/20:4ω9	0.15 ± 0.02		0.28 ± 0.16		0.14 ± 0.02	

* Minor fatty acids 14:0, 18:3ω6, 18:3ω3, 20:3ω6, 20:5ω3, 22:5ω6, 22:5ω3 not shown.
† $p < 0.5$ (control–0 mo)[a]; (control–6 mo)[b]; (0–6 mo)[c].

Table 2. *Protein, energy, linoleic acid, and zinc intakes at 0 and 6 mo ($\bar{x} \pm SE$)*

Months	Protein (% RDA)	Energy (kcal/kg/day)	Linoleic acid (mg/kg/day)	Linoleic acid (% kcal)	Zinc (mg/day)
0	170 ± 26	80 ± 12	383 ± 45	4.50 ± 0.40	12.66 ± 5.74
6	274 ± 16*	104 ± 21*	557 ± 124	4.73 ± 0.14	20.68 ± 5.74*

* $p < 0.05$.

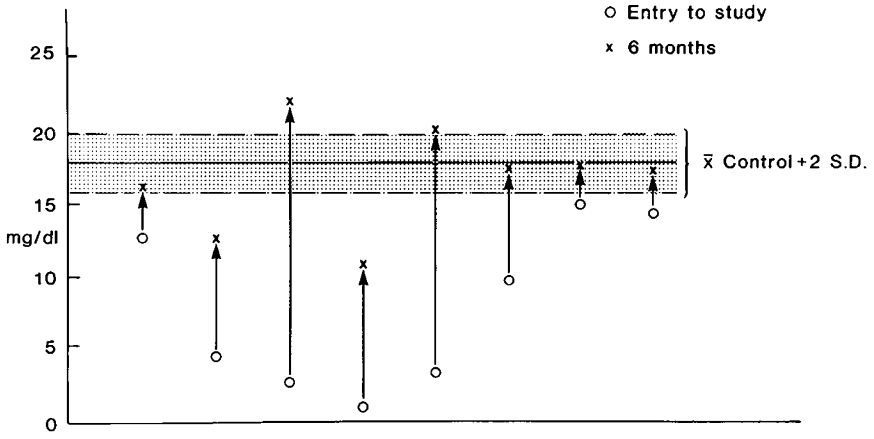

Fig. 2. Plasma phospholipid linoleic acid content (mg/dl) of CF patients on entry and end of study.

provement in body composition the absolute and relative amounts of plasma linoleic acid increased whereas oleic acid decreased. We believe that a longer period of nutritional supplementation would have permitted the achievement of ideal body weight and normalized EFA status.

The plasma fatty acids of the CF patients on entry to the study suggests that the abnormal EFA status is not the result of a pure linoleic acid deficiency. When linoleate is the single nutrient deficiency, its principle metabolite, arachidonic acid (20:4ω6) is low and the triene/tetraene (20:3ω9/20:4ω6) ratio is elevated. The elongation desaturation system that converts linoleic acid to arachidonic acid also converts oleic acid to 5,8,11-eicosatrienoic acid (20:3ω9), but this latter reaction is competitively inhibited by linoleic acid (26). The lack of a significant elevation in the mean triene/tetraene ratio suggests two possible explanations. First, the fall in plasma linoleic acid may not have been large enough to permit conversion of oleic acid to 5,8,11-eicosatrienoic acid. The patient that did have a triene/tetraene ratio of more than 0.4 had the lowest ideal body weight and the lowest plasma linoleic acid level. Second, there are multiple nutritional and hormonal variables that may affect the elongation and desaturation system. For example, in the pure linoleic acid animal model, the expectant rise in 5,8,11-eicosatrienoic acid is delayed and blunted in the presence of a high protein intake (27). Our patients, on entry to the study, were receiving a protein intake well in excess of the RDA. The increased ratio of 20:4ω6/18:2ω6 may be a result of decreased arachidonic acid metabolism and/or a relative increase in the synthesis of arachidonic acid from linoleic acid. Evidence to support the latter hypothesis is the lack of formation of 20:3ω9 in the presence of elevated plasma oleic acid and decreased plasma linoleic acid.

The type of nutrient deficiency has a bearing on the fatty acid profile of malnourished patients. This is not unexpected as fatty acid desaturation and elongation enzyme systems are affected by dietary and hormone changes (28). Desaturation of fatty acids is decreased during fasting and protein deficiency (29, 30), and increased by a high protein intake (30). Patients with kwashiorkor (protein malnutrition) have decreased plasma levels of linoleic

and arachidonic acids and increased levels of palmitoleic and oleic acid (16, 31). Conversely, patients with marasmus (15) and anorexia nervosa (14) (energy deficiency and adequate protein intake) have a similar fatty acid profile with the exception of normal levels of arachidonic acid. The CF patients, initial fatty acid profile, and dietary intake are characteristic of the latter patients. Our findings support previous reports (3, 32–34) of low linoleic with normal arachidonic acids in patients with CF.

Our results suggest that a major cause of the EFA deficiency in malnourished CF patients is a caloric intake that does not meet metabolic requirements. CF patients tend to have a higher oxygen consumption, and therefore a higher basal metabolic rate, than appropriate controls (12). A decreased energy intake coupled with increased energy needs could lead to oxidation of linoleic acid along with other fatty acids to meet energy needs. This would decrease the availability of linoleic acid for use as an EFA. Corn oil, safflower oil, and linoleic acid monoglyceride have been used in long-term linoleic acid supplementation trials in CF patients. Results were variable but most showed minimal (7, 35) or no (36) improvement in EFA status; however, caloric intakes, when reported, were below the RDA for control subjects (7). Improvements of plasma linoleic acid was observed in CF patients when dietary supplementation was directed at increasing calories as well as linoleic acid (9, 37). We attribute the improvement in the EFA status of our CF patients to an improved caloric intake in the presence of a linoleic acid intake in excess of the RDA of 3% of total calories. Although there was not a significant increase in linoleic acid intake during the nutritional rehabilitation, it is apparent that the intake of linoleic acid did increase. Nonetheless, the change in linoleate intake cannot account for the improvement in EFA status in all patients as two subjects improved their EFA status without an increase in the absolute amount of linoleic acid ingested.

Our results also suggest that malabsorption alone is not the sole reason for the EFA deficiency as three of our patients did not have steatorrhea. This finding supports that of McKenna *et al.* (38) who showed that when various linoleic acid-containing lipid preparations were administered with pancreatic enzymes to CF patients, mean maximal increase in percent plasma linoleic was no different than controls.

In summary, we conclude that suboptimal caloric intake is an important factor in the development of EFA deficiency in CF patients. Thus, we would recommend for those CF patients with malnutrition and EFA deficiency: *1*) an energy intake of at least 150% of RDA and *2*) linoleic acid supplementation during the recovery phase of at least 5–7% of total calories—a level two to three times of the RDA—to restore tissue levels (39).

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