Differences in essential fatty acid requirements by enteral and parenteral routes of administration in patients with fat malabsorption[1,2]

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ABSTRACT

Background: Essential fatty acid (EFA) requirements of patients receiving home parenteral nutrition (HPN) are uncertain.

Objective: The objective was to evaluate the influence of the route of administration (enteral compared with parenteral) on plasma phospholipid EFA concentrations.

Design: Intestinal absorption, parenteral supplement of EFAs, and plasma phospholipid EFA concentrations were investigated in balance studies in 4 groups (A, B, C, and D) of 10 patients with short-bowel syndrome and a fecal loss of >2000 kJ/d. Groups A (fat malabsorption <50%) and B (fat malabsorption >50%) did not receive HPN, whereas group C received HPN containing lipids (7.5 and 1.2 g/d linoleic and linolenic acids, respectively) and group D received fat-free HPN.

Results: Intestinal absorption of linoleic and linolenic acids was 8.9 and 1.3 g/d and 2.6 and 0.4 g/d in groups A and B, respectively, whereas EFA absorption was negligible in groups C and D. Thus, intestinal absorption of EFAs in group A corresponded to parenteral EFA supplements in group C, whereas group D was almost totally deprived of EFAs. The median plasma phospholipid concentration of linoleic acid decreased by 21.9%, >16.3%, >13.8%, 11.0%, and >7.7% and linolenic acid by 0.3%, 0.2%, 0.2%, >0.2%, and 0.1%, respectively, in 10 healthy control subjects and groups A, B, C, and D ($P < 0.001$).

Conclusions: Intestinally absorbed EFAs maintained plasma EFA status better than did an equal quantity of parenterally supplied EFAs. Intravenous requirements of EFAs in patients with negligible absorption of EFAs are probably higher than the amounts recommended to patients with preserved intestinal absorption of EFAs. *Am J Clin Nutr* 1999;70:78–84.

KEY WORDS Essential fatty acid deficiency, plasma phospholipids, linoleic acid, linolenic acid, intestinal absorption, home parenteral nutrition, HPN, short-bowel syndrome, humans

INTRODUCTION

The precursor essential fatty acids (EFAs) of the n−6 and n−3 families, linoleic (18:2n−6) and linolenic (18:3n−3) acids and their derivatives, cannot be synthesized de novo in humans; therefore, enteral or parenteral administration of these fatty acids or their conversion products is necessary to prevent the development of EFA deficiency (EFAD). Severe malabsorption (1), low dietary intake (2), and increased requirements of EFAs (3) may lead to EFAD. A relation between increasing intestinal fat malabsorption and the development of biochemical signs of EFAD has been shown in patients with short-bowel syndrome who manage without parenteral nutrition (4). As the degree of malabsorption increases, a condition of intestinal failure—defined as the inadequate ability to ingest, digest, or adequately absorb nutrients and fluids—necessitates parenteral support to avoid progressive dehydration and malnutrition. When fat-free total parenteral nutrition was introduced in patients with intestinal failure in the 1970s, clinical signs of EFAD occurred, primarily the dermatitis characteristic of EFAD (5). However, since then a wide range of clinical manifestations has been related to EFAD: increased water permeability of the skin (6), increased susceptibility to infection (2), lowered resistance to irradiation injury and impaired wound healing (7, 8), hematologic disturbances (9), fat infiltration of the liver (10), impaired chylomicron synthesis, and aggravated fat malabsorption (11). More recent studies have focused on the effects of EFAs on cholesterol metabolism and eicosanoid synthesis, thereby proposing EFAD as a cause of atherosclerotic disease and compromised immune system status (12–14).

In an attempt to prevent these manifestations, patients with intestinal failure are supplemented with EFAs via parenteral nutrition. Uncertainty remains, however, regarding the optimum amount of EFAs to provide parenterally. Some studies have focused on requirements of EFAs in patients in intensive care units with a temporary need for parenteral supplements (15–17). Because these patients have been exposed to trauma or surgery, the demand for EFAs may be increased as a result of their hypercatabolic condition. Other studies have focused on biochemical signs of EFAD in patients with short-bowel syndrome receiving home parenteral nutrition (HPN), but, in these studies, intestinal fat absorption and thereby the absorption of EFAs was not evaluated (18–21).

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To describe the relation between the intestinal absorption and the parenteral supply of EFAs and the presence of biochemical signs of EFAD, the intestinal absorption of EFAs was measured by using a balance technique in 4 stable groups of patients with increasing degrees of fat malabsorption and known risk factors for EFAD. Two of the groups managed without parenteral support (non-HPN), whereas 2 groups had intestinal failure evidenced by the long-term need for HPN. Patients in one of the HPN groups received parenteral lipids.

SUBJECTS AND METHODS

Patients

Four groups of 10 patients each with known risks of EFAD were selected from a group of 46 HPN and 45 non-HPN patients admitted on an elective basis to the Department of Gastroenterology, Rigshospitalet, Copenhagen, for diagnosis and evaluation of malabsorption. Patients, who had known fat malabsorption and a fecal energy loss of >2.0 MJ/d as a consequence of intestinal resection were recruited for the study by mail. Two of the groups did not receive HPN and 2 groups did. One group of patients had mild-to-moderate fat malabsorption (0–50%; non-HPN group A), whereas another group had severe fat malabsorption (>50%; non-HPN group B). Both non-HPN groups had sufficient food and fluid intakes and absorption to manage without HPN. Seventeen of the non-HPN patients had an intestinal resection because of Crohn disease, 2 had short-bowel syndrome as a result of complications after intraabdominal surgery, and 1 had an intestinal resection because of a mesenteric infarction. Patients in the remaining 2 groups had intestinal failure because of a reduced food intake or severe malabsorption and were dependent on parenteral support. Patients in one of these groups received HPN supplemented with EFAs (HPN group C), whereas patients in the other group received HPN without lipids (HPN group D).

Lipids were infused once or twice a week in separate 500-mL bottles along with a standard HPN solution containing glucose, amino acids, and electrolytes. Lipids were provided to the patients in whom energy requirements were not met by the energy content of the standard 3-L bags (6.8 MJ), mainly to patients with severe intestinal malabsorption and problems maintaining body weight. Lipid infusion is not routine in the Danish HPN regimen (22, 23); therefore, the exclusion of lipids in group D was not due to intolerance or adverse effects. Eleven of the patients in the HPN groups had intestinal resections because of Crohn disease, 5 had short-bowel syndrome as a result of complications after intraabdominal surgery, 3 had an intestinal resection because of radiation enteritis, and 1 had an intestinal resection because of a mesenteric infarction. The plasma fatty acid status of the patients was compared with that of 10 control subjects (laboratory and hospital staff members: 3 men and 7 women aged 33–60 y; median age of 50 y). The study was approved by the Ethical Committee for Medical Research in Copenhagen and was conducted according to the Helsinki II Declaration.

Study protocol

Before admission, patients were contacted by phone and informed about the procedures of the study. Patients were instructed to bring any special foods in duplicate (snacks, candy, soft drinks, etc) that they might desire that could not be provided by the hospital. Patients were admitted for 2.5 d. On the first afternoon of their hospital stay, patients were given 3 containers and an electronic precision balance. Two of the containers were for collection of feces and urine, respectively, and the third container was for collection of a duplicate of the patients' peroral intake (all food and beverages). With the precision balance, which had a scale in grams, patients were instructed to weigh individual food items and beverages separately, one portion for themselves and an equal portion for the container. Patients were instructed that they could eat ad libitum from a continental-style breakfast, lunch, and supper buffet containing a wide range of food items. Beverages included water, tea, coffee, milk products, soft drinks, and juice. Sandwiches, biscuits, and beverages were available in the kitchen between meals, and patients were allowed to use the hospital cafeteria as long as double portions of the diet were collected. It was emphasized to the patients that they were obliged to consume everything they selected so that a true estimate of their intake could be determined. The patients were requested to fast starting at midnight on the day of admission. During hospitalization, the patients receiving parenteral nutrition received their usual supplements, except lipids. Patients were instructed not to take lipid emulsions 48 h before the fasting whole-blood sample (10 mL collected into EDTA-containing tubes for fatty acid analysis) was taken at 0800 on the morning of the second day of hospitalization. At this time, the study and collection period began and patients were requested to urinate and defecate or empty their stoma bags. During the next 48 h, patients collected feces, urine, and the duplicate diet into each of the 3 containers, respectively. The feces were collected on ice and immediately frozen at −20°C until analyzed. The blood samples for fatty acid analysis were immediately centrifuged at 1000 × *g* for 10 min at room temperature and plasma was stored at −20°C until analyzed.

Patients were interviewed about the composition and volume of their parenteral support, and information regarding daily medication use was recorded. Patients received their usual parenteral supplements and medications during admission, but were told not to place duplicate medication in the diet container.

Analytic methods

Fasting body weight and height were measured during admission. Body composition was measured during or before admission by dual-energy X-ray absorptiometry (XR-26 DXA densitometer; Norland Corp, Fort Atkinson, WI) as part of the ambulatory follow-up in these patients. Weight and energy contents of the parenteral supplements were calculated from information given by manufacturers. The parenteral lipid used was Intralipid (Pharmacia and Upjohn, Copenhagen). Intralipid 10% and 20% contained 52% 18:2n−6 and 8% 18:3n−3, 115 and 230 mmol triacylglycerol/L, 52.6 and 105.2 g trilinoleate/L, and 8.0 and 16.1 g trilinolenate/L, respectively. The energy contents of the 2 emulsions were 4600 and 8400 kJ/L, respectively.

In patients in whom the remnant small bowel was not measured at surgery, the remaining length was calculated as the difference between the normal small-bowel length (ie, 350 cm) and the length of resection. The numbers of patients who had their remnant small-bowel length calculated were as follows: 5 in non-HPN group A (small intestinal resections of 0, 50, 50, 95, and 150 cm), 4 in non-HPN group B (small intestinal resections of 85, 100, 110, and 170 cm), and 1 each in HPN groups C and D (small intestinal resections of 210 and 50 cm, respectively). The length of the colon was expressed as the percentage of the

TABLE 1
Patient characteristics[1]

Groups	Control subjects (n = 7 F, 3 M)	non-HPN patients: Group A: FMal ≤ 50% (n = 6 F, 4 M)	non-HPN patients: Group B: FMal > 50% (n = 4 F, 6 M)	HPN patients: Group C: iv lipids (n = 8 F, 2 M)	HPN patients: Group D: no iv lipids (n = 8 F, 2 M)	P^2
Age (y)	50 (33–57)	47 (43–49)	46 (34–64)	39 (31–53)	57 (45–60)	0.42
Weight (kg)	68 (62–73)	64 (55–73)	58 (56–64)	54 (49–63)	58 (52–72)	0.26
Height (cm)	175 (165–177)	169 (160–177)	176 (164–178)	170 (163–176)	165 (161–167)	0.57
BMI (kg/m^2)	21.9 (20.7–23.5)	22.2 (19.1–25.4)	19.3 (18.5–21.1)	19.3 (18.4–21.5)	21 (19–25)	0.14
Lean body mass (kg)	—	40 (38–56)[a]	48 (37–49)[a]	34 (28–39)[a]	35 (32–37)[a]	0.04
Fat mass (kg)	—	16 (10–19)[a]	11 (6–14)[a]	18 (11–23)[a]	19 (17–21)[a]	0.04
Bone mass (kg)	—	2.8 (2.6–3.1)	2.8 (2.6–2.9)	2.2 (1.8–2.9)	2.3 (2.1–2.7)	0.05
Remnant small intestine (cm)	—	200 (165–300)[a]	190 (155–240)[a]	53 (30–120)[b]	128 (60–145)[b]	0.002
Remnant colon (%)	—	43 (0–86)	29 (0–57)	28 (0–86)	0 (0–28)	0.33
Time since last resection (y)	—	12 (4–20)[a]	14 (7–16)[a]	5 (1–13)[b]	3 (2–5)[c]	0.006

[1] Median; 25th–75th percentiles in parentheses. Medians with different superscript letters are significantly different, $P < 0.05$ (all pairwise multiple-comparisons procedure, Tukey's test). HPN, home parenteral nutrition; FMal, fat malabsorption; iv, intravenous.
[2] Differences across groups by Kruskal-Wallis one-way ANOVA on ranks.

usual length according to the method of Cummings et al (24). Remnant intestinal lengths were used only for descriptive purposes. Fasting blood samples were taken from the 10 control subjects, in whom weights and heights were also measured.

Dietary and fecal analyses

Intestinal absorption was calculated as the difference between dietary intake and fecal excretion. The weight of the 48-h oral intake and fecal losses was measured. Analyses of the diet and feces were done with homogenized and freeze-dried samples as described previously (25). Dietary and fecal energy were determined by bomb calorimetry in an IKA adiabatic calorimeter (model C 4000 A; IKA-Analysentechnik, Heitersheim, Germany). Fatty acids were determined by combined gas-liquid chromatography and mass spectrometry. In general, the peaks were identified from their retention time. However, in some instances, especially in the feces of patients with a preserved colon, the fatty acid peaks were hard to separate and identify by retention time; therefore, mass spectrometry was used for definitive identification. To convert fatty acids from grams to kilojoules, the values were multiplied by 39.1. Because <10% of unsaturated fatty acids in the diet was recovered as hydroxy fatty acids in the feces, bacterial hydroxylation of EFAs was not corrected for (26, 27). Less than one-third of the unsaturated fatty acids in the diet was EFAs.

Plasma fatty acid analysis

Fatty acid analysis was performed as described earlier (4). The total lipid fraction from plasma samples was extracted according to the method of Folch et al (28). The phospholipid fraction was isolated by thin-layer chromatography and saponified and methylated with boron trifluoride (29). Fatty acid methyl esters were analyzed by using a Hewlett-Packard 5890 (series II; Birkerod, Denmark) gas chromatograph equipped with a fused silica column (SP2380, 60 m, 0.25 mm internal diameter; Supleco Inc, Bellefonte, PA).

Statistics

Nonparametric testing was performed because observations were not sampled from a population with a normal distribution and the assumptions of equal variances for a parametric test between groups were not met. Differences between groups were assessed by nonparametric Kruskal-Wallis one-way analysis of variance on ranks. A Tukey's test with adjustment for multiple comparisons was used as the post hoc test for multiple pairwise comparisons. P values <0.05 indicated significant differences between groups. Calculations were performed by using the SIGMASTAT statistical package (Jandel Corp, Erkrath, Germany).

RESULTS

Patient characteristics are shown in **Table 1**. There were no significant differences in age, weight, height, body mass index (in kg/m^2), or the sex ratio between groups. There was a trend toward a lower lean body mass and a higher fat mass in the HPN patients. HPN groups C and D had significantly shorter remnant small bowels (53 and 128 cm, respectively) than patients in non-HPN groups A and B (200 and 190 cm, respectively). Time since the last resection was significantly shorter in HPN patients than in non-HPN patients ($P < 0.006$).

Diet and parenteral supplements

Results of the dietary analyses and composition of the parenteral supplements are shown in **Table 2**. Total energy intake was significantly lower in HPN group C than in non-HPN group B. When parenteral energy supplements were accounted for, the total energy supply was equivalent in the 4 groups. HPN group C had a significantly lower dietary fat intake than non-HPN groups A and B. Dietary intakes of 18:2n−6 and 18:3n−3 were significantly lower in HPN patients than in non-HPN patients. Parenteral supplements of 18:2n−6 and 18:3n−3 in HPN group C was 7.5 and 1.2 g/d. The total supplies of 18:2n−6 and 18:3n−3 were not significantly different between HPN group C and non-HPN group A, the patients with light-to-moderate fat malabsorption, but were significantly higher in HPN group C than in non-HPN group B and HPN group D. These differences were significant between all groups except between non-HPN group B and HPN group C.

Intestinal absorption

Intestinal absorption (calculated as the difference between dietary intake and fecal excretion) in the 4 groups is shown in **Table 3**. Absolute energy absorption was significantly lower in

TABLE 2
Diet analysis and parenteral supply[1]

	non-HPN patients		HPN patients		
	Group A: FMal ≤ 50% (n = 10)	Group B: FMal > 50% (n = 10)	Group C: iv lipids (n = 10)	Group D: no iv lipids (n = 10)	P^2
Dietary energy intake (MJ/d)	11.0 (9.5–11.8)[a,b]	12.9 (8.4–15.9)[a]	6.7 (5.3–8.8)[b]	9.5 (7.6–10.7)[a,b]	0.007
Parenteral energy supply (MJ/d)	—	—	5.0 (4.1–7.4)	3.6 (1.9–5.3)	—
Total energy supply (MJ/d)	11.0 (9.5–11.8)	12.9 (8.4–15.9)	11.4 (10.7–16.4)	13.0 (9.6–16.0)	0.46
Dietary fat energy (MJ/d)	3.4 (2.6–3.9)[a]	3.0 (2.4–3.7)[a]	1.4 (1.0–2.2)[b]	2.8 (2.1–3.0)[a,b]	0.004
Dietary fat weight (g/d)	87 (66–99)[a]	76 (60–94)[a]	35 (25–56)[b]	71 (52–78)[a,b]	0.004
Dietary 18:2n−6 (g/d)	10.9 (10.4–12.0)[a]	7.2 (3.9–12.0)[a]	2.8 (2.2–5.7)[b]	2.9 (1.0–5.4)[b]	<0.001
Dietary 18:3n−3 (g/d)	1.4 (1.3–1.6)[a]	0.7 (0.5–1.2)[b]	0.2 (0.0–0.4)[c]	0.0 (0.0–0.2)[c]	<0.001
Parenteral 18:2n−6 (g/d)	—	—	7.5 (7.5–7.5)	—	—
Parenteral 18:3n−3 (g/d)	—	—	1.2 (1.2–1.2)	—	—
Total 18:2n−6 (g/d)	10.9 (10.4–12.0)[a]	7.2 (3.9–12.0)[b]	10.3 (9.7–15.0)[a]	2.9 (1.0–5.4)[c]	<0.001
Total 18:3n−3 (g/d)	1.4 (1.3–1.6)[a]	0.7 (0.5–1.2)[b]	1.4 (1.2–1.5)[a]	0.0 (0.0–0.2)[c]	<0.001

[1] Median; 25th–75th percentiles in parentheses. Medians with different superscript letters are significantly different, $P < 0.05$ (all pairwise multiple-comparisons procedure, Tukey's test). HPN, home parenteral nutrition; FMal, fat malabsorption; iv, intravenous.
[2] Differences across groups by Kruskal-Wallis one-way ANOVA on ranks.

HPN groups C and D than in non-HPN patient groups A and B. When parenteral energy supplements were accounted for, there were no significant differences in total energy supply between the 4 groups. As expected, relative enteral fat absorption was significantly lower in non-HPN group B than in non-HPN group A, on the basis of the criteria of inclusion. A similar difference in relative fat absorption was not observed between HPN group C and HPN group D or non-HPN group B. The absorption of 18:2n−6 and 18:3n−3 was significantly higher in non-HPN group A than in non-HPN group B and significantly higher in non-HPN groups A and B than in HPN groups C and D. The parenteral supplement of 7.5 g 18:2n−6/d in HPN group C increased the total supply to an amount corresponding to the intestinal absorption in non-HPN group A. The parenteral supplement of 1.2 g 18:3n−3/d in HPN group C only increased the total supplement to ≈75% of the intestinal absorption in non-HPN group A.

Fatty acid composition of plasma phospholipids

The fatty acid composition of plasma phospholipids is given in **Table 4**. The percentage by weight of 18:2n−6 was highest in the control group and next highest as follows: non-HPN group A > non-HPN group B > HPN group C > HPN group D. These differences were significant between all groups except between non-HPN group B and HPN group C. The percentage of 18:2n−6 was 11.0% in HPN group C despite parenteral supplementation with lipids and was 7.7% in HPN group D, who did not receive parenteral lipids. The distribution of values for 18:3n−3 was as follows: control group > non-HPN group A = non-HPN group B = HPN group C > HPN group D. However, the only differences that were significant were those between the control group and HPN groups C and D.

As shown previously, a low percentage by weight of essential n−6 and n−3 fatty acids is often concomitant with elevated concentrations of nonessential n−7 and n−9 fatty acids (4, 18). A characteristic sign of EFAD is a high concentration of eicosatrienoic acid (20:3n−9), the decisive component of the Holman index (30). The amount of 20:3n−9 was 13 times higher in HPN group D than in the control subjects. Similarly, the concentration of 16:1n−7 was 5 times higher in HPN group D than in the control group.

TABLE 3
Intestinal absorption[1]

	non-HPN patients		HPN patients		
	Group A: FMal ≤ 50% (n = 10)	Group B: FMal > 50% (n = 10)	Group C: iv lipids (n = 10)	Group D: no iv lipids (n = 10)	P^2
Energy (MJ/d)	7.9 (7.6–9.9)[a]	8.1 (5.8–8.8)[a]	3.0 (2.0–5.0)[b]	3.8 (3.0–5.3)[b]	<0.001
Relative energy absorption (%)	80 (75–81)[a]	60 (54–71)[b]	42 (29–76)[b]	46 (36–51)[b]	<0.001
Enteral energy absorption + parenteral energy supply (MJ/d)	7.9 (7.6–9.9)	8.1 (5.8–8.8)	8.6 (7.4–9.6)	8.0 (6.8–6.6)	0.62
Enteral fat energy (MJ/d)	2.4 (2.0–2.7)[a]	0.6 (0.3–1.1)[b]	0.1 (−0.2–0.7)[b]	0.5 (0.3–0.7)[b]	<0.001
Enteral fat weight (g/d)	61 (50–69)[a]	17 (7–29)[b]	3 (−6–19)[b]	14 (7–18)[b]	<0.001
Relative fat absorption (%)	72 (65–83)[a]	21 (7–34)[b]	8 (−10–30)[b]	22 (14–26)[b]	<0.001
Weight of 18:2n−6 (g/d)	8.9 (8.4–9.7)[a]	2.6 (1.4–4.2)[b]	0.4 (-1.2-1.6)[c]	0.2 (−0.6–1.4)[c]	<0.001
Weight of 18:3n−3 (g/d)	1.3 (1.1–1.5)[a]	0.4 (0.3–0.5)[b]	−0.1 (-0.4–0.)[c]	−0.3 (−0.5–0.0)[c]	<0.001
18:2n−6 absorption + parenteral supplement (g/d)	8.9 (8.4–9.7)[a]	2.6 (1.4–4.2)[b]	7.9 (5.7–9.1)[a]	0.2 (−0.6–1.4)[b]	<0.001
18:3n−3 absorption + parenteral supplement (g/d)	1.3 (1.1–1.5)[a]	0.4 (0.3–0.5)[b]	0.9 (0.8–1.3)[a]	−0.3 (−0.5–0.0)[c]	<0.001

[1] Median; 25th–75th percentiles in parentheses. Medians with different superscript letters are significantly different, $P < 0.05$ (all pairwise multiple-comparisons procedure, Tukey's test). HPN, home parenteral nutrition; FMal, fat malabsorption; iv, intravenous.
[2] Differences across groups by Kruskal-Wallis one-way ANOVA on ranks.

TABLE 4
Fatty acid composition of plasma phospholipids[1]

Fatty acid	Control subjects (n = 10)	non-HPN patients: Group A: FMal ≤ 50% (n = 10)	non-HPN patients: Group B: FMal > 50% (n = 10)	HPN patients: Group C: iv lipids (n = 10)	HPN patients: Group D: no iv lipids (n = 10)	P^2
	% by wt of total fatty acids	*% by wt of total fatty acids*		*% by wt of total fatty acids*		
Saturated						
14:0	0.3 (0.3–0.4)[a]	0.4 (0.4–0.5)[b]	0.5 (0.4–0.6)[b]	0.4 (0.4–0.5)[a,b]	0.4 (0.4–0.5)[a,b]	0.006
16: 0	29.3 (28.6–30.0)[a]	31.8 (30.6–32.3)[a]	30.9 (29.5–31.8)[a]	29.6 (29.3–32.6)[a]	32.2 (30.0–33.8)[a]	0.026
18:0	16.1 (15.1–16.8)[a]	13.3 (12.6–14.1)[b]	13.1 (12.5–13.5)[b]	15.9 (14.5–17.0)[a]	13.7 (11.3–15.9)[b]	0.001
Total	46.6 (45.8–46.7)	46.1 (45.8–46.8)	46.0 (44.5–46.5)	47.2 (45.5–48.1)	46.2 (45.5–47.6)	0.45
n−7						
16:1	0.5 (0.4–0.5)[a]	0.9 (0.7–1.3)[b]	1.5 (1.2–1.9)[b,c]	1.7 (1.6–1.9)[c,d]	2.3 (1.6–3.0)[d]	<0.001
18:1	1.6 (1.5–1.7)[a]	1.7 (1.6–2.2)[b,c]	2.4 (2.1–3.0)[c]	3.2 (2.5–4.5)[d]	3.2 (3.0–3.8)[d]	<0.001
Total	2.5 (2.4–2.6)[a,b]	2.8 (2.7–3.9)[b,c]	4.1 (3.5–5.3)[c,d]	5.2 (4.2–6.7)[d]	6.1 (5.2–6.6)[d]	<0.001
n−9						
18:1	12.2 (11.8–12.4)[a]	12.0 (11.0–13.7)[a]	14.7 (13.4–15.6)[a,b]	13.0 (11.2–14.4)[a]	17.5 (15.3–20.6)[b]	<0.001
20:1	0.4 (0.4–0.4)[a]	0.4 (0.3–0.4)[a,b]	0.4 (0.2–0.5)[a,b]	0.2 (0.2–0.3)[b]	0.2 (0.2–0.3)[b]	0.003
20:3	0.2 (0.2–0.2)[a]	0.2 (0.2–0.3)[a]	0.2 (0.2–0.3)[a]	0.6 (0.4–1.1)[a,b]	2.6 (1.1–4.1)[c]	<0.001
Total	13.2 (12.7–13.5)[a]	13.1 (12.0–14.5)[a]	15.9 (14.2–16.6)[a]	14.6 (12.1–16.8)[a]	20.9 (17.2–26.6)[b]	<0.001
n−7 + n−9	15.8 (15.2–16.0)[a]	16.5 (14.8–17.7)[a,b]	19.6 (18.3–22.4)[a,b]	20.3 (16.9–22.4)[b]	26.5 (22.0–33.1)[c]	<0.001
n−6						
18:2	21.9 (20.4–23.7)[a]	16.3 (15.0–18.9)[b]	13.8 (12.0–15.5)[c]	11.0 (9.6–14.2)[c,d]	7.7 (5.6–8.9)[e]	<0.001
18:3	0.0 (0.0–0.0)[a]	0.2 (0.1–0.2)[b]	0.2 (0.1–0.2)[b]	0.2 (0.1–0.3)[b]	0.2 (0.1–0.2)[b]	0.001
20:3	2.3 (2.0–2.4)[a]	3.3 (2.9–4.2)[b]	3.4 (2.8–4.0)[b]	4.1 (3.7–4.4)[b]	3.2 (2.4–4.0)[b]	<0.001
20:4	7.8 (7.1–8.2)[a]	10.4 (9.3–10.8)[b]	8.1 (7.5–10.2)[a]	11.7 (9.4–12.7)[b]	8.3 (6.7–9.5)[a]	0.003
22:4	0.0 (0.0–0.0)[a]	0.0 (0.0–0.0)[a]	0.0 (0.0–0.0)[a]	0.0 (0.0–0.1)[b]	0.0 (0.0–0.0)[a]	0.01
22:5	0.0 (0.0–0.0)[a]	0.2 (0.1–0.2)[b]	0.2 (0.2–0.4)[b]	0.3 (0.0–0.4)[b,c]	0.3 (0.3–0.5)[c]	<0.001
Total	32.3 (31.7–32.9)[a]	31.1 (31.1–32.7)[a,b]	27.9 (25.4–29.6)[b,c]	28.2 (25.6–30.9)[b,c]	21.0 (16.5–24.1)[d]	<0.001
n−3						
18:3	0.3 (0.2–0.3)[a]	0.2 (0.2–0.3)[a,b]	0.2 (0.2–0.3)[a]	0.2 (0.1–0.2)[b]	0.1 (0.0–0.1)[b]	<0.001
20:5	1.1 (0.8–1.4)[a,b]	1.3 (1.1–1.6)[a,b]	1.4 (0.9–1.6)[a]	0.8 (0.6–0.9)[b]	0.8 (0.6–1.1)[a,b]	0.01
22:5	0.7 (0.6–0.9)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	0.9 (0.8–1.0)	0.9 (0.7–1.2)	0.08
22:6	3.1 (2.8–3.7)[a]	3.1 (2.7–3.4)[a]	3.0 (2.2–3.5)[a]	2.6 (2.0–2.9)[a]	2.3 (1.8–2.7)[a]	0.03
Total	5.3 (4.5–6.3)[a]	5.7 (5.4–5.8)[a]	5.5 (4.8–6.4)[a]	4.3 (3.7–5.1)[a]	4.0 (3.4–5.1)[a]	0.006
n−6 + n−3	37.6 (37.3–38.2)[a]	36.8 (36.4–37.8)[a,b]	33.3 (30.2–35.0)[a,b]	32.6 (29.3–36.3)[b]	25.1 (20.4–29.4)[c]	<0.001
Total unsaturated	53.0 (52.7–53.5)	53.3 (52.6–53.7)	53.1 (52.8–54.6)	52.1 (51.4–53.9)	53.1 (51.5–53.8)	0.59
n−7 + n−9/ n−6 + n−3	0.42 (0.41–0.43)[a]	0.45 (0.39–0.48)[a]	0.59 (0.54–0.76)[a]	0.64 (0.47–0.76)[a]	1.07 (0.74–1.62)[b]	<0.001
Holman index (30)	0.028 (0.026–0.024)[a,b]	0.024 (0.020–0.025)[a]	0.024 (0.021–0.028)[a]	0.058 (0.029–0.088)[b]	0.318 (0.106–0.532)[c]	<0.001

[1] Median; 25th–75th percentiles in parentheses. Medians with different superscript letters are significantly different, $P < 0.05$ (all pairwise multiple-comparisons procedures, Tukey's test). HPN, home parenteral nutrition; FMal, fat malabsorption; iv, intravenous.

[2] Differences across groups by Kruskal-Wallis one-way ANOVA on ranks.

DISCUSSION

Biochemical signs of EFAD were evident in the 4 groups of patients with fat malabsorption. In these patients, intestinal absorption of the precursors 18:2n−6 and 18:3n−3 was determined in short-term balance studies by measuring the fatty acid content of their self-selected diet and subsequently in their feces. Even in patients with mild-to-moderate fat malabsorption (<50% of daily fat intake), ie, non-HPN group A, biochemical signs of EFAD were observed. The percentage of 18:2n−6 was significantly lower in non-HPN group A than in the control subjects, whereas the percentage of 18:3n−3 was not significantly different between these 2 groups. Compensatory differences evidenced by a significantly higher concentration of 16:1n−7 were shown between patients in non-HPN group A and the control subjects. Intestinal absorption of 18:2n−6 in non-HPN group A was 8.9 g/d, corresponding to 0.13 g/kg body wt, or ≈4% of their energy absorption. Intestinal absorption of 18:3n−3 in this group was 1.3 g/d, corresponding to ≈0.6% of their energy absorption. In patients with severe fat malabsorption, ie, non-HPN group B, the percentage by weight of 18:2n−6 was 13.8%. There were no significant differences in 18:3n−3 or 20:3n−9 between non-HPN group B and the control group; however, 16:1n−7 was significantly higher in the control subjects. Intestinal absorption of 18:2n−6 in non-HPN group B was 2.6 g/d, corresponding to 0.05 g/kg body wt or ≈1.4% of their energy absorption. Intestinal absorption of 18:2n−6 in non-HPN group B was 0.4 g/d, corresponding to ≈0.2% of their energy absorption. These findings agree with the generally accepted view that daily dietary requirements of 18:2n−6 and 18:3n−3 are a minimum of 4% (31) and 0.3%, respectively, of total energy intake (32, 33).

In patients in HPN group C, the intestinal absorption of both 18:2n−6 and 18:3n−3 was negligible (0.4 and −0.1 g/d, respectively), but the patients had a parenteral supply of 18:2n−6 and 18:3n−3 of 7.5 and 1.2 g/d, respectively, whereby the total sum of intestinal absorption and parenteral supply of 18:2n−6 and 18:3n−3 were ≈8 and 1.2 g/d, respectively. Thus, the total

supply of 18:2n−6 was ≈0.15 g/kg body wt, corresponding to ≈4% of the total energy requirements of the patients, just as in patients in non-HPN group A, but the supply of EFAs was mainly by the parenteral route. Nevertheless, the concentration of 18:2n−6 in plasma phospholipids was only 11% and the classic signs of EFAD, as evidenced by an increase in the Holman index and as a consequence of the elevated concentrations of 20:3n−9 and 16:1n−7, were more pronounced. The route of administration (enteral or parenteral), therefore, seems to be important when supplementing with EFAs.

There is skepticism about the use of short-term balance studies because some of the feces excreted during at least the first 24 h of a study is a reflection of intake before the beginning of the study. However, because the patients in the present study had no dietary restrictions, their intakes may have resembled their intakes before admission. The availability in this study of certain foods that are difficult to prepare, expensive and thus not normally purchased by the subjects, or otherwise more desirable than foods normally consumed by the subjects, may have led to a transient increase in certain nutrients beyond what the subjects generally consumed. Although not measured in all patients, the intestinal transit time was short in patients receiving HPN and in non-HPN patients with severe malabsorption; fat absorption was negligible in all groups, except in non-HPN group A, also minimizing the problem.

The limited effect of the parenteral supply of 18:2n−6 on the presence of biochemical signs of EFAD may have been related to the unphysiologic bolus administration of lipids once or twice a week. Because lipids are infused together with glucose and amino acids as part of HPN, and thus the insulin concentration is presumably high, it seems unlikely that lipids are immediately β-oxidized. However, it is possible that the bolus administration of EFAs leads to a deposition in adipose tissue of fatty acids more readily β-oxidized than the intestinally absorbed fatty acids during periods of fasting. Furthermore, the load of glucose and amino acids may lead to synthesis of nonessential fatty acids, thereby displacing the balance between essential and nonessential fatty acids.

The effect of the parenteral supply of EFAs was evident when the intestinal absorption of 18:2n−6 and 18:3n−3 was compared in HPN groups C and D. Both HPN groups C and D had negligible intestinal absorption of 18:2n−6 and 18:3n−3, but they did not receive parenteral lipids. HPN group D had the most profound biochemical signs of EFAD, as evidenced by an 18:2n−6 plasma phospholipid content of 7.7% and a distinctive elevation in the Holman index to 0.32 because of the high plasma phospholipid content of 20:3n−9 (2.6%). Furthermore, the content of 18:3n−3 (0.1%) was lower in HPN group D than in the control group.

Parenteral EFA supplements appear to reduce the classic biochemical signs of EFAD, but a normalization of plasma phospholipids seems to require larger lipid supplements or a more regular administration. Mascioli et al (21) investigated the effect of intravenous lipids on the triene-tetraene ratio (Holman index). By increasing the biweekly doses of lipids delivered in total nutrient admixtures, they found that most patients required ≥1 g lipid · kg body $wt^{-1} \cdot wk^{-1}$ to correct the serologic signs of EFAD, defined as a Holman index > 0.2. This would correspond to a dose of 250 mL 20% Intralipid/wk. In a recent study of a total cohort of patients receiving HPN, it was found that 500 mL 20% Intralipid once a week was sufficient in all patients to prevent a Holman index > 0.2, even in patients with minimal oral dietary intake and in those with severe small-intestinal failure due to small-bowel resection (18). Jeejeebhoy et al (34), however, found that the fatty acid composition of phospholipids of membranes was deficient in linoleate when EFAs were provided in an infusion of 350 mL 10% lipid emulsion/d; therefore, they advocated daily lipid infusions of ≈500 mL 10% lipid. This would correspond to a daily supply of ≈26 g 18:2n−6 and 4 g 18:3n−3, or ≈15% and 7% of total energy, respectively. Ito et al (35) measured the adipose tissue fatty acid composition in recipients of long-term total parenteral nutrition. Similarly, they suggested that normal adipose tissue stores of 18:2n−6 and 18:3n−3 were maintained when 11–20% and 4–12%, respectively, of total energy were supplied as 18:2n−6 and 18:3n−3.

The definition of EFAD is controversial. In the present study, claims of biochemical EFAD in group A were based solely on a low plasma phospholipid content of 18:2n−6. On the basis of the Holman index, commonly used to determine EFAD, only groups C and D had biochemical EFAD. In our opinion, a low plasma phospholipid content of the precursor EFAs 18:2n−6 and 18:3n−3 may be as justifiable an indicator of EFAD as other indicators (eg, the Holman index and n−3 + n− 6/n−7 + n−9). However, this study mainly focused on differences in the maintenance of plasma phospholipid EFAs via the enteral and parenteral supply of EFAs.

This study showed low amounts of 18:2n−6 in plasma phospholipids even in patients who met 4% of their daily energy requirements by intestinal absorption of 18:2n−6. Hence, such a requirement may be too low for patients with fat malabsorption to maintain their fatty acid status and should be regarded as a minimum requirement. When the effects of enteral and parenteral supplementation with EFAs on the fatty acid status in plasma phospholipids were compared, EFAs supplied intestinally maintained fatty acid status better than did EFAs supplied parenterally. Therefore, intravenous EFA requirements may be even higher in patients with negligible intestinal fat absorption who are dependent on HPN. Adjustments in the amount of parenteral lipid supplements can be made reliably on the basis of repeated blood tests, but the clinical benefits and cost-effectiveness of lipid supplementation should be considered before attempting to normalize the fatty acid status of HPN patients.

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