PRELIMINARY REPORT

Abnormal Regulation of Serum Lipid Fatty Acid Profiles in Short Gut Rats Fed Parenteral Nutrition With Lipid

Karen C. McCowen, Pei-Ra Ling, Mario Ollero, Justin A. Maykel, Paola G. Blanco, and Bruce R. Bistrian

Despite absence of essential fatty acid deficiency (EFAD), increases in arachidonic acid to linoleic acid ratios occur in serum phospholipid of patients treated with chronic total parenteral nutrition (TPN). The parenteral lipid component of TPN contains abundant linoleate; thus low phospholipid linoleate may reflect increased conversion to arachidonate. Arachidonic acid excess has been associated with a proinflammatory milieu through increased eicosanoid production and might contribute to the increases in inflammatory markers seen in home TPN patients. We investigated fatty acid metabolism in a rodent model of malabsorption. We hypothesized that short gut rats would metabolize parenteral lipid differently from intact rats. We performed laparotomy and 80% small bowel resection (or sham surgery) in rats. Sixteen sham and 16 short gut rats were randomly assigned to TPN with lipid or fat-free TPN. After 5 days, weight loss was similar in all groups. Analysis of serum phospholipids demonstrated that 20:3ω9 (eicosatrienoic acid) was relatively increased in fat-free TPN groups, irrespective of surgery type, as were distal very long chain ω3 class fatty acids, as anticipated. Uniquely, both nutrition (TPN/lipid *v* fat-free TPN) and surgery type (sham *v* short gut) were significant in determining arachidonic acid levels. Relatively elevated arachidonate occurred in both groups of fat-free rats, suggesting increased Δ6 and/or Δ5 desaturase activity, as expected. In contrast, giving TPN/lipid lowered arachidonate (suggesting appropriately downregulated desaturases) in sham animals, but not in short gut animals. Ratios of arachidonic and di-homo-γ-linolenic to linoleic acids further suggested increased turnover of precursor ω6 to arachidonic acid in short gut rats given lipid compared with the other groups. These preliminary data show that intravenous (IV) lipid gave rise to serum lipid fatty acid profiles that differed in short gut and sham rats. The short gut rat may have a heightened hepatic desaturase activity, inappropriate for the quantity of linoleic acid provided parenterally. Therefore, the short gut rat is an appropriate model to study further arachidonic acid excess in home TPN patients.

ESSENTIAL FATTY acid deficiency (EFAD) is a rare, but important, clinical problem in patients with malabsorption.[1] Classical biochemical findings of EFAD include reductions in the 2 essential fats 18:2ω6 (linoleic acid) and 18:3ω3 (α-linolenic acid), with parallel elevations in 20:3ω9 (eicosatrienoic acid) in serum lipids.[2,3] The diagnosis of EFAD is complete with the finding of a triene/tetraene ratio (20:3ω9/20:4ω6) greater than 0.2. Patients with severe malabsorption who are treated with total parenteral nutrition (TPN) including lipid emulsions should not be at risk of EFAD.[4,5] Lipid emulsions currently in use in the US are derived from soybean oil and contain approximately 50% linoleic acid and 9% α-linolenic acid. Published reports from different countries suggest that home TPN patients receive between 0.3 and 1 g/kg/d of lipid, an amount of essential fats greater than that ingested in a typical Western diet.[6-12]

One poorly understood phenomenon is the near-ubiquitous finding in home TPN patients of elevated serum lipid arachidonic acid concentrations, in association with low linoleic acid, its precursor.[9,11,12] Because linoleic acid supply is not limiting in home TPN, excessive conversion of linoleic acid to arachidonic acid is a potential explanation. However, arachidonic acid is typically extremely tightly regulated, such that increasing its abundance in an enteral diet is not associated with greater arachidonic acid membrane content.[13] Arachidonic acid is not supplied in intravenous (IV) lipid, therefore the excess in home TPN patients is likely to represent a dysregulation in essential fat metabolism. In our home TPN patients, we documented substantial elevations in systemic markers of inflammation, such as soluble tumor necrosis factor (TNF) receptor and interleukin-6.[14] Others have shown that the proportion of fat energy in TPN predicts the future development of TPN-associated liver dysfunction.[10,15] The proinflammatory potential of the excessive arachidonic acid found in serum lipid might contribute to the development of this complication through modulation of eicosanoid production.[16] Notably, it has been clearly documented that lowering of serum lipid arachidonic acid can be associated with reductions in markers of inflammation.[17]

In the present study, therefore, we set out to develop a rodent model of malabsorption using small bowel resection. In one published report, short gut rats were noted to have elevated Δ6 desaturase (rate-limiting enzyme for conversion of linoleic acid into arachidonic acid) activity.[18] However, arachidonic acid levels in these rats were not elevated,[19] and the rats had not been given TPN. Therefore, we treated short bowel rats with TPN to examine fatty acid profiles under circumstances where lipid intake is not limiting, as a model for the clinical situation in home TPN. Our principal hypothesis was that short gut and intact rats would demonstrate distinct patterns of distal long chain fatty acids in plasma phospholipids.

MATERIALS AND METHODS

Male Sprague Dawley rats (280 to 300 g) from Taconic Farms (Germantown, NY) were maintained on chow with access to water for

From the Laboratory of Nutrition/Infection, Beth Israel Deaconess Medical Center, Boston, MA.

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Address reprint requests to Bruce R. Bistrian, MD, Laboratory of Nutrition/Infection, Beth Israel Deaconess Medical Center, West Campus, 1 Deaconess Rd, Boston, MA 02215.

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Table 1. Composition of Soybean Oil Lipid Emulsion Used in Parenteral Nutrition

Fatty Acid	%
Linoleic acid	50
Oleic	20
Palmitic	10
α-Linolenic	9
Stearic	3.5

5 days before the study. Animal protocols were in compliance with National Institutes of Health (NIH) guidelines and approved by the Hospital Animal Use Committee. The animals (n = 32) were fasted overnight before the short bowel or sham surgery. For surgery, anesthesia was induced with xylazine 13 mg/kg and ketamine 87 mg/kg. Midline laparotomy in the short gut rats allowed 80% small bowel resection from 3 cm distal to the ligament of Treitz to 2 cm proximal to the ileocecal junction. End-to-end intestinal anastomosis was performed using interrupted 4.0 silk sutures. Sham animals underwent laparotomy, bowel manipulation, and exteriorization for the typical length of time of intestinal resection.

A silicone catheter (0.025 in ID $\times$ 0.047 in OD; Helix Medical, Carpinteria, CA) was placed in the internal jugular vein and tunneled to the interscapular region, then exteriorized and sutured to a swivel (Instech Laboratories, Plymouth Meeting, PA). Four hours postoperatively, TPN was started. Short gut and sham animals (n = 16 per group) were randomized to receive TPN with lipid or fat free TPN. Only tap water was allowed orally. TPN contained amino acids, dextrose, and essential micronutrients at 200 kcal/kg/d with 2 g nitrogen/kg/d, in 210 mL/kg/d. Rats randomized to lipid (n = 8 per group) got 30% nonprotein energy as fat, using 20% Intralipid (Table 1). TPN was continued for 5 days, a time that has been shown to alter desaturase activity in response to dietary changes in rodents.[20,21]

After discontinuation of TPN, animals were sedated, blood samples were drawn into plain tubes by cardiac puncture and immediately placed on ice, and euthanasia was achieved using CO_2. Serum was separated within 1 hour of collection and stored in aliquots at -80°C until analysis.

Lipids from serum were extracted by using 6 vol chloroform-methanol (2:1, vol/vol), centrifuged at 800 $\times$ *g* for 3 minutes, and the resulting lower phase aspirated. Heptadecanoic acid was added to all samples as internal standard in the form of triheptadecanoyl glycerol and diheptadecanoyl phosphatidylcholine [30 μg of each, from chloroform:methanol (1:1, vol/vol) stock solutions] (Nu-Chek Prep, Elysian, MN) prior to extraction. Lipid extracts from the different sample preparations were fractionated into triglycerides and phospholipids by solid phase chromatography using an aminopropyl column, as described elsewhere.[22] The resulting fractions were evaporated to dryness under nitrogen. Fatty acids were transmethylated by alkaline methanolysis using the BF_3 reagent kit (Supelco, Bellefonte, PA). Dry fractions were resuspended in 0.5mL methanolic base, vortexed, and incubated at 100°C for 3minutes. Subsequently, boron trifluoride-methanol (0.5 mL) was added, samples vortexed, and incubated at 100°C for 1 minute prior to addition of hexane (0.5 mL), repeat vortexing, incubation at 100°C for 1 minute, and addition of 6.5 mL saturated NaCl. Samples were finally centrifuged at 800 *g* for 2 minutes. The hexane upper layer was transferred to a new glass tube and an aliquot injected in a Hewlett Packard 5890A gas chromatograph. A Supelcowax column of 30 m length and 0.5 mm internal diameter was used. Initial temperature was 150°C and final temperature 260°C. Detector temperature was 300°C and the total running time 27 minutes. Fatty acid methyl ester peaks were identified by comparison of retention times of standard mixtures (Nu-Chek-Prep) and quantified in comparison with the internal standard (methylheptadecanoate) detector response. Results are expressed as nanomoles percent of total fatty acid content in the sample as well as total nanomoles.

Statistical Analysis

Data are presented as mean $\pm$ SEM. Groups were compared for differences using 2-way analysis of variance (ANOVA), with Bonferroni correction as a post hoc test (SigmaStat 2.0; SSPS, Chicago IL). Significance is defined by the 95% confidence interval (CI).

RESULTS

All groups of rats lost weight after 5 days of IV TPN: short gut TPN/fat-free -33 ± 5 g; sham TPN/fat-free -30 ± 3.5 g; short gut TPN/fat -41 ± 7 g; sham TPN/fat -26 ± 2.8 g (no significant differences between groups).

Fatty acid profiles of serum phospholipids and triglycerides were analyzed as described. Tables 2 and 3 list the phospholipid fatty acid profiles in serum either as nanomoles percent or total nanomoles, which were very similar to the findings in triglyceride fatty acids (not shown).

In animals fed with fat-free TPN for 5 days, irrespective of surgery assignment, palmitic [16:0], palmitoleic [16:1ω7], and eicosatrienoic [20:3ω9] acids were significantly increased on a nanomole percent basis (Table 2). With TPN + lipid, oleic [18:1ω9], and α-linolenic [18:3ω3] acids, which are supplied in TPN (Table 1), were increased. Linoleic acid [18:2ω6], the major polyunsaturated fatty acid provided in parenteral lipid, was similar in serum in all 4 groups, despite fat-free feeding in 2 groups (Table 2).

Examining the distal long chain fatty acids in the ω-3 pathway revealed elevated eicosapentaenoic [20:5ω3], docosapentaenoic [22:5ω3], and docosahexaenoic [22:6ω3] acids in fat-free TPN, irrespective of surgery (Table 2). Similarly, in the ω6 pathway, increases in di-homo-γ-linolenic acid [20:3ω6] were present in fat-free rats compared with TPN + lipid rats, irrespective of surgical assignment. Arachidonic acid [20:4ω6] was affected uniquely by the interaction of surgery and diet: sham surgery rats fed with TPN + lipid had lower arachidonic acid than both groups of rats fed fat-free TPN, in parallel with the findings in the n-3 pathway. However, short bowel rats fed with lipid had similar arachidonic acid to fat-free rats.

In Table 3, total phospholipid fatty acids are listed in nanomoles. As expected, rats fed with lipid have greater total fatty acids than rats fed fat-free TPN. This is principally accounted for by increased amounts of stearic [18:0], oleic [18:1ω9], linoleic [18:2ω6], and α-linolenic [18:3ω3], which were all supplied in the TPN (Table 1). In contrast, metabolites of these fatty acids are similar in all 4 groups (Table 3), suggesting greater endogenous conversion in rats treated with fat-free TPN.

Table 4 lists the relative conversion of fatty acids in serum phospholipids. This was calculated as the ratio of longer chain derivatives to their precursor fatty acids. Feeding rodents a fat-free diet increased the ratios of 20:3ω6/18:2ω6, 20:3ω9/18:1ω9, 20:5ω3/18:3ω3 and triene:tetraene irrespective of surgical assignment. In sham rats, conversion of 18:2ω6 to 20:4ω6 was increased in fat-free TPN versus TPN + fat (as assessed by post hoc Wilcoxon testing, $P < .05$). Short gut rats did not show this difference between diets (similar 20:4ω6/18:2ω6

Table 2. Profile of Plasma Phospholipids (nmol%) in Rats With Short Gut Fed With TPN

Fatty Acid	Short Gut Fat-free	Short Gut + Fat	Sham Fat-free	Sham + Fat
16:0*	29.71 ± 1.12	25.48 ± 0.74	28.76 ± 0.69	27.47 ± 0.29
16:1 (n-7)*	0.56 ± 0.12	0.14 ± 0.01	0.86 ± 0.25	0.16 ± 0.01
18:0†	24.24 ± 1.07	26.03 ± 0.83	23.54 ± 0.73	22.79 ± 0.4
18:1 (n-9)*	2.42 ± 0.2	6.31 ± 1.31	2.22 ± 0.27	8.02 ± 0.7
18:2 (n-6)	14.6 ± 1.03	14.81 ± 1	14.81 ± 1.14	17.86 ± 0.77
18:3 (n-3)*†	0.03 ± 0.01	0.08 ± 0.01	0.01 ± 0.01	0.11 ± 0.01
20:3 (n-9)*	0.2 ± 0.03	0.09 ± 0.01	0.22 ± 0.02	0.12 ± 0.01
20:3 (n-6)*‡	0.71 ± 0.08	0.48 ± 0.02	0.72 ± 0.06	0.58 ± 0.01
20:4 (n-6)§	19.64 ± 1.07	20.1 ± 1.1	21.91 ± 0.62	17.78 ± 0.84
20:5 (n-3)‖	0.46 ± 0.07	0.34 ± 0.1	0.48 ± 0.11	0.21 ± 0.05
22:4 (n-6)	0.26 ± 0.02	0.26 ± 0.02	0.26 ± 0.03	0.24 ± 0.01
22:5 (n-6)	0.18 ± 0.02	0.14 ± 0.02	0.14 ± 0.04	0.15 ± 0.01
22:5 (n-3)*	0.68 ± 0.04	0.5 ± 0.05	0.65 ± 0.03	0.51 ± 0.03
22:6 (n-3)*†	6.3 ± 0.26	5.31 ± 0.33	5.43 ± 0.47	4 ± 0.24

NOTE. Data are mean ± SEM, n = 32.
*$P < .01$, ‖$P < .05$, fat-free *v* + fat.
†$P \leq .05$, sham + fat *v* short gut + fat.
‡$P = .087$, sham + fat *v* short gut + fat.
§$P < .05$, sham + fat *v* other 3 groups.

ratios), such that desaturation/elongation of linoleic acid (18:2ω6) to arachidonic acid (20:4ω6) in both groups of short gut rats resembled that seen in fat-free shams, and was not reduced by presence of fat in the TPN. In parallel, the data suggest that desaturation of 20:3ω6 to 20:4ω6 was more active in short gut rats fed fat, so that this step represented the source of the difference between short gut and sham rats fed identical diets (TPN + fat). Post hoc analysis by Wilcoxon testing of sham versus short gut rats fed TPN + lipid showed a significant differences in ratios of 20:4ω6 to 20:3ω6 ($P < .05$). Triene: tetraene ratios did not rise above 0.2, confirming absence of EFAD as it has been defined for humans.

DISCUSSION

This study of different nutritional treatments in short gut versus sham rat demonstrates that rats with malabsorption appear to metabolize linoleic acid abnormally when it is provided as a component of TPN. Similar findings have been widely published in human home TPN cohorts and are of considerable concern to nutrition support specialists.[16,23] Here we have developed a hypothesis to explain the increases in arachidonic acid and have created an animal model of short bowel to recapitulate the problem and study the future development of alternative nutritional approaches. For model simplicity, our rats were maintained *nil per os*, unlike human patients with short gut, who all eat.

The effects of a fat-free diet on fatty acid profiles are not surprising. In the sham surgery rats fed without exogenous lipid, elevations were noted in palmitic and palmitoleic acids, which are abundant in fat stores or easily synthesized through de novo lipogenesis and therefore are not essential nutrients. These changes in serum lipid fatty acids occurred in parallel

Table 3. Profile of Plasma Phospholipids (nmol) in Rats With Short Gut Fed With TPN

Fatty Acid	Short Gut Fat-Free	Short Gut + Fat	Sham Fat-Free	Sham + Fat
Total*	397 ± 28	512 ± 43	416 ± 38	482 ± 20
16:0	117.3 ± 8.3	130.5 ± 11	119.3 ± 10.9	132.3 ± 5.8
16:1 (n-7)*	2.2 ± 0.5	0.7 ± 0.1	3.9 ± 1.2	0.8 ± 0.05
18:0[1]	96 ± 8.3	132 ± 10.6	97.7 ± 8.4	109.6 ± 4.6
18:1 (n-9)*	9.4 ± 0.7	34.6 ± 8.6	9.3 ± 1.5	38.6 ± 3.4
18:2 (n-6)*	57.5 ± 5.4	76.2 ± 8	60.5 ± 6.4	85.6 ± 4.5
18:3 (n-3)*	0.1 ± 0.05	0.4 ± 0.08	0.05 ± 0.03	0.5 ± 0.03
20:3 (n-9)*	0.8 ± 0.2	0.4 ± 0.06	1 ± 0.2	0.6 ± 0.06
20:3 (n-6)	2.9 ± 0.4	2.1 ± 0.3	3.1 ± 0.5	2.8 ± 0.1
20:4 (n-6)	79 ± 9.6	101.5 ± 9	91.7 ± 8.8	86.2 ± 6.2
20:5 (n-3)	1.9 ± 0.3	1.8 ± 0.7	2.1 ± 0.5	1 ± 0.2
22:4 (n-6)	1 ± 0.1	1.3 ± 0.1	1.1 ± 0.2	1.2 ± 0.06
22:5 (n-6)	0.7 ± 0.09	0.7 ± 0.2	0.6 ± 0.2	0.7 ± 0.05
22:5 (n-3)	2.7 ± 0.3	2.5 ± 0.3	2.8 ± 0.4	2.4 ± 0.2
22:6 (n-3)	25.2 ± 2.3	27.2 ± 3	23.4 ± 3.4	19.3 ± 1.6

NOTE. Data are mean ± SEM, n = 32.
*$P < .01$ fat-free *v* + fat.

Table 4. Ratios of Serum Phospholipid Fatty Acids

Fatty Acids	Short Gut Fat-Free	Short Gut + Fat	Sham Fat-Free	Sham + Fat
ω6 Family				
20:3ω6/18:2ω6*	0.051 ± 0.007	0.03 ± 0.006	0.052 ± 0.007	0.033 ± 0.001
20:4ω6/18:2ω6†	1.44 ± 0.15	1.43 ± 0.17	1.56 ± 0.15	1.02 ± 0.1
20:4ω6/20:3ω6	34.1 ± 6.6	42.2 ± 1.9	32.5 ± 3.8	31 ± 1.8
22:4ω6/20:4ω6	0.014 ± 0.001	0.013 ± 0.001	0.012 ± 0.001	0.014 ± 0.001
22:5ω6/22:4ω6‡	0.67 ± 0.06	0.52 ± 0.088	0.49 ± 0.1	0.64 ± 0.03
ω9 Family				
20:3ω9/18:1ω9*	0.088 ± 0.02	0.017 ± 0.03	0.104 ± 0.01	0.015 ± 0.01
ω3 Family				
20:5ω3/18:3ω3*	0.19 ± 0.03	0.092 ± 0.04	0.23 ± 0.05	0.03 ± 0.01
22:5ω3/20:5ω3	2.18 ± 0.5	2.2 ± 0.46	2.2 ± 0.7	2.86 ± 0.38
22:6ω3/22:5ω3§	9.67 ± 0.74	11.18 ± 0.1	8.33 ± 0.65	8.03 ± 0.45
Triene/tetraene*	0.01 ± 0.002	0.004 ± 0.001	0.01 ± 0.001	0.007 ± 0.001

NOTE. Data are mean ± SEM, n = 32.

*$P < .01$, fat-free *v* + fat.

†$P = .07$, sham + fat *v* other 3 groups.

‡$P < .05$, for interaction of nutrition and surgery assignments.

§$P < .01$, short gut *v* sham.

with an increase, although not to pathologic levels, in both eicosatrienoic acid and the triene:tetraene ratio. When nutritional inadequacy of essential fatty acids (linoleic and α-linolenic acids) is sensed by mammals, hepatic Δ6 and Δ5 desaturase activities increase to defend cell membrane arachidonic acid concentrations.[20,21] Among other polyunsaturated fatty acids, arachidonate is critically important as a key regulator of cell signaling functions and also governs expression of a wide array of genes. The hepatic desaturases also convert fatty acid precursors in the ω3 and ω9 pathways, which accounts for the elevations seen in distal end products of these ω3 and ω9 pathways in fat-free diet.

In the ω6 pathway, 20:3 and 20:4 were increased in fat-free shams compared with fat-fed shams. However, the short gut rat phospholipid ω6 fatty acid profile was quite different from that in the sham rat. The short gut rat fed IV fat had an arachidonic acid concentration similar to fat-free rats and significantly higher than TPN + fat shams. In contrast, the immediate precursor of arachidonic acid, di-homo-γ-linolenic acid, was similar in sham and short gut and was elevated in fat-free nutrition irrespective of surgical assignment. Because resection results in greater metabolic stress than sham surgery, this might be one contributing factor to the differences between the 2 groups of rats receiving TPN with lipid. Although the enzyme activity was not measured directly, the fatty acid profile differences suggest that Δ5 desaturase, which converts di-homo-γ-linolenic acid to arachidonic acid, is upregulated in the short gut rat, independent of type of TPN. An alternative interpretation of these fatty acid profiles is that short gut rats receiving lipid were not able to downregulate the desaturases to the same extent as rats with normal functioning gut receiving lipid. Because the fat was given parenterally, malabsorption per se cannot be implicated.

There are similarities between findings in our short gut rats and in patients with severe malabsorption who require home TPN, although the presence of reasonable oral intake in most of these patients may contribute to the many differences. Increases in arachidonic acid compared with normal subjects and reductions in linoleic acid were documented in home TPN patients receiving lipid (an average 0.4 g/kg/d), which were independent of the presence of short bowel, suggesting that malabsorption was the key underlying feature.[12] These findings are almost identical to those in our recent publication[11] and are similar to many prior reports, although consideration has not before been given to potential mechanisms, because an appropriate animal model had not been fully investigated.

In rats studied after 6 weeks of short bowel syndrome without nutrition support, hepatic Δ5 and Δ6 desaturase activities were increased in proportion to the degree of small intestine removed.[18] At the time of study, both 50% and 75% small bowel resected rats were significantly undernourished, however, and neither 20:3ω9 levels nor triene:tetraene ratios were reported. Arachidonic acid was lower in 75% resected than sham surgery, although this might have been caused by frank EFAD.[19] In this situation, reduction of dietary linoleic acid would increase hepatic desaturase activity to accelerate conversion of linoleic acid to arachidonic acid. Only with the development of EFAD with very low levels of linoleic acid would this activity be unable to maintain normal arachidonic acid in serum lipids. This might suggest that to achieve arachidonic acid levels in humans with short gut syndrome similar to those seen in normal subjects, very low levels of parenteral linoleic acid need to be provided. This model[19] does not resemble the human condition of short bowel, and thus these findings are of uncertain relevance.

Minich et al[24] used a different model of malabsorption to study polyunsaturated fatty acid metabolism. Bile-diverted rats had substantial fat malabsorption, but net fat absorption was maintained through marked hyperphagia. Although full fatty acid profiles were not reported, ratio of arachidonic to linoleic acid was greatly increased in rats with malabsorption. In addition, the investigators did note a probable increased turnover of linoleate to arachidonate using an oral ^{13}C-linoleate bolus. Because the focus of the work was in absorptive function of bile, little speculation on the mechanism for this finding was entertained. This model also fails to recapitulate the human

condition of malabsorption, because hyperphagia is usually not a typical consequence, as it results in diarrhea.

Therefore, this preliminary report shows that a unique abnormality is present in the short gut rat, whereby even a high-fat diet fails to prevent an increase in arachidonic acid unlike in control rats. These findings closely resemble those seen in serum lipid fatty acid profiles in humans with diverse causes of malabsorption. Whereas upregulation of arachidonic acid production in a fat-free diet is appropriate, it is likely a maladaptive phenomenon in short gut patients receiving TPN containing lipid and may contribute to proinflammatory-associated conditions, such as liver dysfunction. The short gut rat fed TPN with lipid can serve as a model for investigation of a number of therapies that might lower arachidonic acid without causing EFAD, such as nutritional supplementation with fish oil.

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