Parenteral nutrition in overweight patients: are intravenous lipids necessary to prevent essential fatty acid deficiency?

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Mobilization of endogenous adipose stores of linoleic acid prevents essential fatty acid deficiency during fasting. However, the dextrose present in standard parenteral nutrition inhibits lipolysis and induces essential fatty acid deficiency unless lipids are administered. It has therefore become standard practice to administer at least 50 grams of intravenous fat per week to patients dependent on parenteral nutrition. This study was undertaken to determine whether hypocaloric feeding would permit sufficient mobilization of linoleic acid from adipose tissue stores to prevent essential fatty acid deficiency in overweight cancer patients receiving fat-free parenteral nutrition. Fifteen patients (mean 127% ideal body weight) received continuous infusions of hypocaloric, fat-free parenteral nutrition for 14 to 58 days (median 30 days). Twelve patients lost weight during the study period, while no patient gained more than 5 kg. Changes in serum albumin were mild. Six patients required insulin for hyperglycemia; however, four of these patients had reductions in their insulin requirement despite continuation of parenteral nutrition. Fatty acid analyses were performed on plasma phospholipids from all 15 patients. No patient developed plasma evidence of essential fatty acid deficiency. In addition, no trend toward the development of essential fatty acid deficiency was observed with increasing durations of fat-free parenteral nutrition. Conclusion: Overweight cancer patients can tolerate prolonged, continuous infusions of hypocaloric, fat-free parenteral nutrition without developing essential fatty acid deficiency. This approach appears to reduce both the toxicity and the expense of parenteral nutrition. (J. Nutr. Biochem. 5:243–247, 1994.)

Keywords: parenteral nutrition; essential fatty acid deficiency

Introduction

Essential fatty acid deficiency (EFAD) is caused by depletion of linoleic acid, a polyunsaturated fatty acid that cannot be synthesized in vivo. It is characterized by impaired growth, skin lesions, and increased cellular membrane fragility and permeability.[1–3] Human adipose tissue contains at least 15%[4,5] linoleic acid and mobilization of these endogenous stores prevents the development of EFAD during brief periods of starvation.[6] Total parenteral nutrition (PN) administered as a continuous infusion can induce sufficient levels of circulating insulin to inhibit lipolysis and predisposes patients to this deficiency syndrome.[6–9]

Alpha linolenic, linoleic, and oleic acids serve as precursors for the synthesis of the n-3, n-6, and n-9 series of polyunsaturated fatty acids (PUFAs), respectively. No conversion takes place among the fatty acids of different series; however, the three families of PUFAs compete for a common system of enzymes for their metabolism. Therefore, when linoleic acid (the precursor of arachidonic acid, 20:4n-6) is absent from the diet, arachidonic acid (a tetraene) is decreased and eicosatrienoic acid, 20:3n-9 (a triene derived from the non-essential oleic acid) is increased. The relative amounts of these fatty acids can be determined chromatographically and a triene to tetraene ratio in excess of 0.2 is indicative of EFAD.[10–13] Numerous case reports have documented the rapid development, i.e., within 2 weeks, of EFAD

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in patients receiving PN without lipids.[10,14–16] It has therefore become standard practice to provide at least 50 to 100 grams of soybean or safflower-based intravenous lipids per week to patients who depend solely on PN to meet their nutritional needs.

When administering intravenous nutrition to obese patients, it is advantageous to utilize a PN regimen that allows for a reduction of body fat while maintaining protein stores. This approach reduces the incidence of hyperglycemia and fluid overload and is especially useful when treating critically ill patients, as such patients are prone to develop these complications. Dickerson et al. demonstrated net protein anabolism in eight obese patients given hypocaloric PN. These patients achieved nitrogen equilibrium or positive balance while losing weight, suggesting that lower rates of glucose infusion do not completely inhibit lipolysis.[17] The present study was designed to determine whether plasma evidence of EFAD develops in overweight cancer patients maintained on prolonged, continuous infusions of hypocaloric, fat-free PN.

Methods and materials

From May 1989 to August 1990, all patients at the University of Maryland Cancer Center requiring total parenteral nutrition were screened for inclusion in this study. Patients were considered eligible if they weighed at least 120% of their ideal body weight (IBW),[18] or if lipids were being withheld for a clinical indication, e.g., fluid restriction. Patients who were suitable for tube feeding and those with significant oral intake, i.e., more than clear liquids, were excluded. The study was approved by the University of Maryland Institutional Review Board and all patients signed informed consent.

Patients were initially treated with a 1-L PN regimen containing 70 g of protein and 210 g of carbohydrate. The PN regimen was advanced as tolerated to a formula providing total calories equal to resting energy expenditure − 300 kcal. Resting energy expenditure was defined as basal energy expenditure × 1.1. BEE was calculated by the Harris-Benedict equation[19] using metabolically adjusted weight (MAW) instead of IBW because 20 to 30% of the excess weight in obesity represents fat-free mass.[20–22] If the 24-hour nitrogen balance remained more negative than −5 g per day, the PN regimen was increased as tolerated to provide up to 2.0 g of protein per kg of MAW. Non-protein calories were advanced such that total caloric support (protein plus non-protein calories) did not exceed 25 kcal per kg of MAW. Additional sources of carbohydrates such as infusions of 5% dextrose were closely monitored to avoid excessive caloric intake. Insulin was added to the PN regimen as required to maintain the serum glucose below 220 mg/dL. Laboratory data included a complete blood count, electrolytes, chemistries, and body weight three times a week. Weekly 24-hour urine collections for urinary urea nitrogen (UUN) were obtained. Nitrogen balance was calculated by subtracting the 24-hour UUN plus 4 g from the nitrogen content of the PN.[23] In addition, plasma samples were obtained at baseline and upon removal from the study for fatty acid analysis. Patients were removed from the study when they began to consume more than 5 g of fat in a 24-hour period or when PN was changed to a cyclic regimen, i.e., given discontinuously.

Total kcal given = REE − 300 = (1.1 × BEE) − 300

BEE (males) = 66 + (13.7 × MAW [kg]) + (5 × height [cm]) − (6.8 × age)

BEE (females) = 655 + (9.6 × MAW [kg]) + (1.7 × height [cm]) − (4.7 × age)

MAW = IBW + 20% of the difference between actual and ideal body weight

$$N_2 \text{ balance} = \frac{\text{Protein (gms/day)}}{6.25} - (\text{UUN} + 4)$$

(Legend: REE = resting energy expenditure; BEE = basal energy expenditure; IBW = ideal body weight; MAW = metabolically adjusted weight.)

Fatty acid analysis

All plasma samples were stored under N_2 gas at $< -20°$ C until the time of analysis. Lipids were extracted from plasma using a 2:1 mixture of chloroform/methanol and filtered. L-phosphatidylcholine diheptadecanoyl, the internal standard for phospholipids, was added prior to extraction. The lipid layer containing the total plasma lipids was evaporated until dry using a stream of nitrogen gas. Thin layer chromatography (TLC) was carried out with dried lipid samples dissolved in approximately 120 μL of chloroform. TLC was used to separate the lipid fractions (phospholipids, free fatty acids, triglycerides, and cholesterol esters). The solvent system used to develop the silica gel glass plates was a mixture of petroleum ether/glacial acetic acid (80:20). The bands were visualized under UV light after spraying with a 0.1% solution of 2,7-dichlorofluorescein in methanol. Phospholipids were isolated by scraping the appropriate TLC band into a test tube and were methylated directly using boron trifluoride and methanol.[24] The tubes were capped under an atmosphere of nitrogen and heated in a water steam bath for 45 minutes. After cooling, 1 mL of water was added to each tube and the methyl esters were extracted with 2 to 3 mL of petroleum ether. The ether layer was dried and evaporated under nitrogen to the desired volume of injection.

The fatty acid methyl esters were separated and quantified using a Perkin-Elmer Sigma 2000 gas chromatograph equipped with a 30-meter fused silica capillary column (0.32 mm I.D., 0.20 μ film thickness, Supelco, Bellefonte, PA USA) and a flame ionization detector. Helium was the carrier gas with a flow rate of 1.03 mL/min. The split ratio used was 50:1 with injector and detector temperatures were set at 240° C. Oven temperature was programmed to start at 70° C and then rise to 165° C at a rate of 30° C/min, then to 168° C at a rate of 0.5 C/min, then to 205° C at a rate of 2° C/min, with a final hold of 7 minutes. Peaks were identified by comparison with authentic standards (Nu-Check Prep, Elysian, MN USA) using a Perkin-Elmer LCI-100 computing integrator.[25] Triene to tetraene ratios were determined by dividing the area of 20:3n9 (eicosatrienoic acid) by that of 20:4n6 (arachidonic acid).

Results

Fifteen patients received at least 2 weeks of hypocaloric, fat-free PN during the study period *(Table 1)*. The indication for parenteral nutrition generally fell into one of four categories: severe anorexia due to chemotherapy, mucositis prohibiting adequate oral intake, severe diarrhea requiring bowel rest, or respiratory compromise requiring intubation. All patients received intensive chemotherapy utilizing high doses of cytotoxic drugs such as Ara-C, daunorubicin, cyclophosphamide, and etoposide. The median time on the study was 30 days with a range from 14 to 58 days. Nearly all the patients were severely myelosuppressed and required aggressive supportive care with transfusions, broad spectrum antibiotics, and amphotericin B. Six patients required insulin; three patients required more than 50 units per day, while four patients (nos. 5, 13, 14, 21) had reductions in their insulin requirements during PN. The mean weight (± SD)

Table 1 Patient characteristics

Patient no.	Diagnosis	% IBW pre-PN	Δ Weight (post-pre study) (kg)	Δ Albumin (post-pre study) (gm/dL)	Insulin requirement (μ/day)
1	AML	135	+2.5	−0.2	40
2	ALL	138	−21.1	0	0
3	Large Cell Lymphoma	154	−2.7	−0.2	0
4	AML	130	−4.1	0	0
5	AML	106	−7.6	+0.3	25
6	AML	115	−2.8	+0.2	0
7	AML	174	−3.0	−1.3	0
8	AML	116	−2.1	−0.2	0
9	AML	120	−6.6	−0.5	0
10	AML	136	−4.8	+0.5	85
11	AML	115	+1.1	0	0
12	AML	124	+4.6	0	100
13	AML	130	−5.0	+0.1	0
14	ALL	126	−8.6	−1.0	10
15	AML	126	−0.9	−1.0	80

AML, acute myeloid leukemia.
ALL, acute lymphocytic leukemia.

of the patients (expressed as a percentage of IBW) before beginning PN was 127 ± 17. Twelve patients lost weight while receiving hypocaloric PN, while three patients gained less than 5 kg each. The change in serum albumin from the time of entry to longest follow up was ≤ 0.5 gm/dL in 12 of the 15 patients. Nitrogen balance data are available for 13 patients: eight had at least one positive nitrogen balance study, and 12 had at least one nitrogen balance more positive than −5 grams per day.

Fatty acid analysis was performed on plasma phospholipids from all 15 patients at baseline and upon removal from the study. Eleven patients received continuous, hypocaloric, fat-free PN with negligible oral intake for at least 3 weeks (range 21–58 days), while four patients remained on study for 2 to 3 weeks. The fatty acid composition of plasma phospholipids at baseline and at longest follow-up are shown in *Table 2*. The triene to tetraene ratios obtained by dividing the weight % of the triene (elcosatrienoic acid) by the tetraene (arachidonic acid) are shown in *Table 3*. No patient developed biochemical evidence of EFAD (triene to tetraene ratio > 0.2), and no trend toward the development of EFAD was observed with increasing durations of fat-free PN.

One patient (no. 6) initially had an elevated triene to tetraene ratio of 0.35. This "baseline" value was obtained after the patient received 13 days of a PN regimen providing 1590 kcal or REE − 98 kcals. The PN regimen was adjusted on day 14 to provide 1349 kcals or REE − 339 kcals. Repeat fatty acid analyses on days 20, 27, and 34 revealed triene to tetraene ratios of 0.32, 0.10, and 0.06, respectively.

Discussion

Human adipose tissue contains approximately 15% linoleic acid, thus representing a major source of essential fatty acid.[4,5] Mobilization of these endogenous stores prevents the development of EFAD during complete starvation in patients with adequate adipose reserves.[6] However, during PN, lipolysis is inhibited by the insulin response to the infusion of dextrose at or above the rate of metabolic energy needs.[6–8] Wene et al. initially reported the development of EFAD in healthy adults within 2 weeks of beginning continuous, nasogastric or intravenous, fat-free diets. However, during a 24-hour fast, and during intermittent feeding, plasma linoleic acid levels increased to normal due to mobilization of adipose tissue stores.[25] In a study involving seven patients, Mascioli et al. extended this observation to individuals receiving PN without lipids and showed that EFAD can be prevented or reversed by the cyclic administration of PN wherein patients received a glucose-free formula for 12 hours each day.[9] During the glucose-free periods, insulin levels decreased, allowing access to the essential fatty acids stored in adipose tissue.

The rapid development of EFAD in patients receiving PN without lipids has been well documented.[10,14–16] Two requirements for this phenomenon have been emphasized: a fat-free PN regimen and the continuous infusion of glucose. However, based on the data presented here, a third requirement appears to be the administration of a sufficient carbohydrate load to inhibit adipose tissue lipolysis completely.

We studied 15 cancer patients with negligible oral intake who were maintained on hypocaloric, fat-free PN for 14 to 58 days. No patient developed plasma evidence of EFAD. One patient (no. 6) had inadvertently received 13 days of PN providing 200 kcal/day in excess of the defined hypocaloric goal before the baseline fatty acid profile was obtained. This "baseline" study revealed a triene to tetraene ratio of 0.35, indicating EFAD. The PN regimen was subsequently reduced to provide REE − 339 kcals and the triene to tetraene ratios normalized over the next 3 weeks. No other patient had biochemical evidence of EFAD, and no trend toward the development of this deficiency was observed with increasing durations of fat-free PN. In fact, seven patients had a lower triene to tetraene ratio after receiving ≥

Table 2 Weight percent of fatty acids

Pt. no.	16:0	18:0	18:1n-9	18:2n-6	18:3n-3	20:3n-9*	20:4n-6**	20:5n-3	22:6n-3
1B	21.3	12.9	11.7	11.2	1.0	0.2	8.1	0.1	1.5
1F	25.3	13.3	10.7	12.4	0.2	ND	6.6	0.1	1.0
2B	26.1	6.6	11.1	13.9	4.0	ND	5.5	ND	ND
2F	9.0	5.1	4.8	6.4	2.8	ND	2.1	1.1	ND
3B	25.7	10.8	10.0	11.0	0.1	0.1	7.7	ND	1.8
3F	20.6	9.9	6.5	8.8	1.1	ND	6.2	ND	1.3
4B	23.0	13.3	16.5	3.2	0.5	1.3	11.5	0.4	2.5
4F	23.4	12.2	16.2	1.8	1.6	1.4	9.3	0.3	4.3
5B	30.5	10.4	18.6	11.6	0.4	0.7	4.3	0.2	0.6
5F	31.1	11.8	16.2	10.3	0.4	0.3	7.3	0.5	1.1
6B	25.0	16.2	15.0	2.5	0.2	4.3	13.0	0.2	2.3
6F	29.6	12.8	7.5	8.0	0.3	0.9	11.8	0.6	2.2
7B	25.6	8.7	9.9	10.1	1.1	0.1	5.5	0.2	3.0
7F	29.7	11.1	12.7	8.3	1.4	0.2	9.5	0.2	2.1
8B	22.8	6.2	12.3	10.1	10.2	ND	6.3	0.2	2.8
8F	26.2	10.4	9.2	7.0	0.2	1.0	5.8	0.2	1.4
9B	31.9	12.0	14.4	6.3	1.1	0.4	6.4	0.2	1.2
9F	25.0	12.0	14.1	4.7	1.7	0.2	8.6	0.1	1.6
10B	19.1	11.4	7.9	7.3	1.4	0.01	6.8	0.2	5.4
10F	20.1	9.8	5.9	6.9	2.0	ND	6.2	ND	7.0
11B	19.4	10.0	9.0	10.1	2.1	0.2	4.3	0.1	7.8
11F	19.5	8.9	10.3	5.4	3.3	0.2	5.1	0.1	12.7
12B	25.1	10.4	9.7	8.7	3.2	0.1	4.2	0.2	9.0
12F	25.3	7.9	12.7	7.3	3.0	0.1	3.5	0.1	8.2
13B	21.4	10.0	7.0	12.1	1.7	ND	6.8	0.8	5.2
13F	24.8	11.3	12.7	10.3	1.1	ND	5.3	1.2	3.7
14B	28.3	8.3	11.3	14.6	0.8	ND	5.8	0.3	2.6
14F	25.9	12.0	16.6	10.7	0.8	0.2	6.0	0.2	3.1
15B	35.7	9.5	12.1	11.1	0.1	0.1	4.8	ND	0.2
15F	31.4	7.5	10.7	11.0	0.8	0.1	6.6	ND	1.6

*elcosatrienoic acid (triene).
**arachidonic acid (tetraene).
B, baseline fatty acid analysis, F, final, ND, none detected.

Table 3 Fatty acid analysis

Patient no.	$T:T_B$ Triene:Tetraene (Baseline)	$T:T_F$ Triene:Tetraene (Follow up)	Duration of hypocaloric PN without lipids (days)
1	0.02	0.01	58
2	0.01	0.01	50
3	0.01	<0.01	42
4	0.11	0.15	36
5	0.16	0.04	36
6	0.35	0.06	34
7	0.02	0.02	30
8	<0.01	0.02	30
9	0.06	0.02	26
10	0.01	<0.01	21
11	0.04	0.04	21
12	0.01	0.04	20
13	<0.01	<0.01	16
14	<0.01	0.03	14
15	0.01	0.02	14
mean ± SD	mean 0.05 ± 0.09	mean 0.03 ± 0.04	30 ± 13

$T:T_F$ is not significantly different from $T:T_B$ ($P = 0.53$).
$T:T_F$ is significantly less than 0.2 ($P > 0.0001$).
Wilcoxon test used for statistical analysis.

3 weeks of TPN without lipids than at baseline. Four patients weighed less than 120% IBW, including one patient weighing 106% IBW. These patients also tolerated fat-free PN (range 21–36 days) without developing EFAD.

Ten of the 15 patients in this study weighed more than 120% of their IBW. Given this fact and the severity of the patients' underlying illnesses, PN was tolerated remarkably well. Hyperglycemia and fluid overload were infrequently observed and rarely severe. While six patients required insulin to maintain their serum glucose below 220 mg/dL, only three patients required more than 50 units of insulin per day, and four patients actually had a reduction in insulin requirement despite continued intravenous feeding. Weight gain, presumably due to fluid retention, was only observed in three patients and no patient gained as much as 5 kg.

An additional benefit to the utilization of a hypocaloric, fat-free PN regimen in the appropriate setting is reduced cost. Most PN patients receive lipids daily, regardless of their weight, to provide non-carbohydrate calories as well as to prevent EFAD. At the University of Maryland Cancer Center, the cost to the patient is $33.50 per bottle of Intralipid (Kabi Pharmacia, Piscataway, NJ). This does not take into account the costs associated with the need for additional infusion pumps, IV tubing, and laboratory monitoring of serum triglycerides. Thus, the potential savings of this approach exceeds $1,000 per month.

In summary, overweight cancer patients can tolerate prolonged, continuous infusions of hypocaloric, fat-free PN without developing EFAD. Although adequate amounts of amino acids (~ 1.5 gm/kg MAW) are required to support protein synthesis, a low carbohydrate PN regimen allows access to endogenous stores of polyunsaturated fatty acids and prevents linoleic acid deficiency. This approach helps to minimize the fluid retention and glucose intolerance that are often associated with PN in highly stressed, overweight patients.

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