# Effect of Structured Lipid-Enriched Total Parenteral Nutrition in Rats Bearing Yoshida Sarcoma

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*The efficacy of structured lipid, a triacylglycerol of medium and long chain fatty acids, as an element of nutritional support therapies in cancer cachexia was investigated. Using the Yoshida sarcoma to induce cachexia, male Sprague Dawley rats (90 g) were injected subcutaneously with tumor cells (n = 17) or sterile saline (n = 16). Seven days later, rats were randomized to two intravenous diets for 3 days at 220 kcal/kg body weight/d, including 2 g nitrogen/kg body weight/d and 39% of total calories as either structured lipid or long chain triglyceride. Nitrogen balance, tumor growth rate, energy metabolism, and plasma albumin and free fatty acid levels were measured, and whole-body protein kinetics and liver, muscle, and tumor fractional protein synthetic rates were evaluated by adding $^{14}$C-leucine to the diet during the last 4 hours of feeding. Nitrogen balance improved ($P < .05$) in both tumor and control rats receiving structured lipid-enriched total parenteral nutrition, and was also greater in tumor rats compared with controls. There were no differences in tumor growth or protein kinetics between diet groups. Albumin was lower ($P < .05$) in tumor rats, but significantly higher in both tumor and control rats given structured lipid-enriched total parenteral nutrition. Free fatty acid was significantly higher in tumor rats versus controls. Whole-body protein kinetics were similar among the four groups. Liver weight, liver weight to body weight ratio, and liver protein synthetic rate were higher in tumor rats. Also, liver weight to body weight ratio was lower in tumor and control animals given structured lipid-enriched total parenteral nutrition. Muscle protein synthetic rate was significantly lower in tumor rats, but higher in tumor and control rats given long chain triglyceride-enriched total parenteral nutrition. The nutritional benefits of structured lipid-enriched total parenteral nutrition favor support of host tissue without promoting tumor growth.*

**Keywords:** Structured lipid; parenteral nutrition; protein metabolism; Yoshida sarcoma

## Introduction

Although the development of cancer cachexia has been recognized as a major factor in the death of many cancer patients,[1] the pathogenesis of cancer cachexia is poorly understood. The interaction of several factors may contribute to the development of the syndrome, including mechanical obstruction of the gastrointestinal tract, taste abnormalities, and malabsorption syndromes.[2] Metabolic alterations include changes in energy expenditure; glucose recycling and futile cycles resulting, in part, from predominant anaerobic metabolism of glucose by the tumor; and excessive lipid mobilization.[2]

Reduced dietary intake and progressive weight loss are characteristic of cancer cachexia. Use of total parenteral nutrition (TPN) can overcome the lack of dietary intake and might be expected to improve the nutritional status of the cancer patient and the tolerance of concomitant cancer therapy. However, nutritional support in the cancer cachexia syndrome appears at best to replete fat stores rather than restore lean body mass.[3] Results from randomized clinical trials of TPN in cancer patients undergoing chemotherapy have been disappointing in terms of decreas-

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ing morbidity and increasing survival.[4-6] For this reason, there is continuing research toward identifying the optimal nutritional support therapy for the cancer patient.

Intravenous fat emulsions provide a noncarbohydrate source for fuel and energy while satisfying essential fatty acid requirements. Under conditions of high but physiologic unfusion rates, the traditional fat, long chain triglycerides (LCT), can lead to fat deposition in the liver,[7] impair leukocyte chemotaxis and random migration,[8] and interfere with reticuloendothelial system function.[7] Medium chain triglycerides (MCT) minimize fatty infiltration in the liver and are oxidized more rapidly than LCT.[9] To overcome the disadvantages of LCT while retaining the benefits of MCT, structured lipid (SL) was designed and found to have unique anticatabolic effects.[10] Long chain triglycerides, containing linoleic and/or linoleic fatty acids, and MCT are hydrolyzed and then re-esterified, resulting in rearranged triglycerides having both medium chain and long chain fatty acids in the same triglyceride molecule.[10] Animal studies in burn[11,12] and injury[13] models using SL-enriched diets have demonstrated improved cumulative nitrogen balance and serum albumin levels. Based on these findings, we sought to evaluate the nutritive value of SL-enriched TPN and its impact on certain metabolic alterations in the tumor-bearing host in a model of cancer-associated cachexia.

## Methods

### *Animal preparation and nutrient infusion*

Thirty-three specific pathogen-free male Sprague-Dawley rats (45 g) were obtained from Taconic Farms (Germantown, NY, USA). The study was conducted under the approval of the Animal Care Committee at the New England Deaconess Hospital and in compliance with their established guidelines. Prior to the experiment, rats were housed for 8 days, two to a cage, and maintained on a 12-hour, light/dark photoperiod at an ambient temperature of 22° ± 1°C. Tap water and rodent chow (Charles River D-3000, Agway Agricultural Products, Minneapolis, MN, USA) were provided ad libitum.

The Yoshida sarcoma cell line was used to induce cancer cachexia over a 10-day period. Previous survival studies revealed that the animals began losing weight 7 days posttumor inoculation, indicating the onset of cachexia, with a median survival time of 12 days. On day 0, 17 animals were inoculated with $10^7$ cells of viable Yoshida sarcoma in the subcutaneous area of the right flank. The non-tumor–bearing rats were given an identical sham injection with sterile saline. The animals were weighed, returned to their cages, and allowed to consume standard laboratory chow and tap water ad libitum. The animals were not pair-fed, and rats bearing rapidly growing tumors had diminished food intake. Parenteral nutrition was given from day 7 to day 10, during which the tumors were in a rapid growth phase.

On day 7, the rats were anesthetized with ether, and a silastic catheter (0.025 in ID × 0.047 in OD; Dow-Corning Laboratories, Corning, NY, USA) was inserted through the internal jugular vein and advanced to the superior vena cava. The catheter was tunneled subcutaneously, exited at the midscapular region, and connected to a flow-through swivel (Instech, Philadelphia, PA, USA) which allowed constant infusion and free movement by the animals. Rats were randomly assigned to two groups and intravenously administered diets with amino acids, dextrose, and fat as either LCTs (Liposyn II, 1:1 ratio of safflower oil to soy oil; Abbott Laboratories, North Chicago, IL, USA), or SL composed of equal amounts (mole/mole) of medium chain and long chain fatty acids (Kabi Vitrum, Stockholm; *Table 1*). The diets were given at one half the planned rate the first night to allow for adaptation to glucose and fat. The animals were given the full calorie diet from day 8 through day 10 using Holter pumps (Critikon Inc., Tampa, FL, USA), and the infusion rates were adjusted so that each animal received 220 calories/kg body weight/d with 2 g amino nitrogen/kg body weight/d. The diets were isonitrogenous, isovolemic, and isocaloric, and were formulated in the hospital pharmacy under aseptic conditions. Twenty-four–hour urine was collected for nitrogen balance determination.

**Isotopic turnover design.** On day 10, (1-$^{14}$C)-L-leucine (50 mCi/mmol; ICN, Irvine, CA, USA) was added to the intravenous diets and a 4-hour constant infusion was conducted to investigate protein kinetics. Each animal received 1.5 μCi/hr of $^{14}$C-leucine at a rate of 1.25 cc/hr through a syringe pump (Harvard Apparatus Co., South Natick, MA, USA).

Total carbon dioxide production, oxygen consumption, respiratory quotient, and resting energy expenditure were determined during the infusion as previously described.[14] At the end of the infusion, the animals were killed by decapitation, and the blood was collected in heparinized tubes and placed on ice. Plasma was separated by centrifugation, then stored at −25°C until the time of analysis. Immediately following decapitation, the body was quickly dissected, and the liver, tumor, and portions of the rectus muscle were removed. The liver was weighed, and two pieces (1 g each) were placed in 10% sulfosalicylic acid, then completely frozen in liquid nitrogen (−180°C) to halt all metabolic processes. Two pieces (1 g each) of muscle were similarly frozen. The tumor was weighed and frozen intact in liquid nitrogen. All samples were stored at −25°C until analysis. The total time between decapitation and sample freezing in liquid nitrogen was 2 to 3 minutes.

### *Analytic methods*

Resting energy expenditure was derived from the equation of Weir.[15] Total urinary nitrogen was determined following a micro-Kjeldahl digestion.[14] Plasma free fatty acid levels were determined by the method

**Table 1** Dietary composition

| Group | Amino acids (kcal/kg body weight) | Glucose (kcal/kg body weight) | Lipid (kcal/kg body weight) | Total (kcal/kg body weight) |
|---|---|---|---|---|
| LCT (%) | 50 (22) | 85 (39) | 85 (39) | 220 |
| SL (%) | 50 (22) | 85 (39) | 85 (39) | 220 |
| | | Additives per 1,000 ml | | |
| | | NaCl: 30 mEq | | |
| | | NaAc: 30 mEq | | |
| | | KCl: 30 mEq | | |
| | | KAc: 25 mEq | | |
| | | KPhos: 16 mEq | | |
| | | Ca++ gluconate: 8.4 mEq | | |
| | | $MgSO_4$: 8.0 mEq | | |
| | | Trace minerals: 10.2 ml | | |

A total of 0.5 ml of MVC 9+3 (Lyphomed, Rosemont, IL, USA) vitamins and 0.25 ml of choline chloride (30% wt/vol) were added per 100 ml of hyperal solution.

*Fatty acid composition*

| Fatty acid | Structured lipid (% composition) | Long chain triglyceride (% composition) |
|---|---|---|
| 8:0 | 22.0 | — |
| 10:0 | 12.6 | — |
| 12:0 | 0.2 | 0.3 |
| 14:0 | 0.6 | 0.2 |
| 16:0 | 7.0 | 9.4 |
| 18:0 | 2.3 | 3.2 |
| 18:1w9 | 14.6 | 19.8 |
| 18:2w6 | 33.4 | 61.2 |
| 18:3w3 | 5.1 | 0.5 |
| 20:0 | — | 0.5 |
| Others | 2.2 | 2.2 |
| Total | 100.0 | 100.0 |

Total calories given were 220 kcal/kg/d, with 2 gm nitrogen/kg/d, and contained amino acids, glucose, and fat as either SL or LCT. Fatty acid composition was determined in our laboratory by gas-liquid chromatography.

of Ho and Meng.[16] Albumin concentration was determined by the bromocresol green method (Albustrate, General Diagnostics, Morris Plains, NJ, USA). The specific radioactivity of free leucine in the plasma pool was determined as previously described.[14]

To assure homogeneous sampling of the tumor, the tumors were immersed in liquid nitrogen, then pulverized with a hammer. The tissue samples, liver, rectus muscle, and tumor were thawed and homogenized (Brinkmann Polytron, Westbury, NY, USA). Tissue nitrogen content was determined by micro-Kjeldahl digestion. The free intracellular (Si) and protein-bound (Sb) leucine-specific radioactivities were determined as previously described.[14]

Rates of whole body leucine appearance, oxidation, percentage of leucine oxidized, synthesis, breakdown, and leucine balance were estimated from the equations of Waterlow et al.[17] It was assumed that a plateau labeling (steady state) of the plasma compartment was achieved when the specific activity maximum was reached in the expired breath. The protein fractional synthetic rates in the liver, rectus muscle, and tumor were derived from the equations of Garlick et al.[18] Tumor protein breakdown rates were estimated as the difference between tumor protein synthetic rate, measured isotopically, and tumor growth rate.

Estimates of fractional tumor growth were derived from tumor volume measurements on days 7 and 10. Tumor volumes were estimated from measurements of tumor length, width, and depth in millimeters. These measurements bear a close relationship to tumor weight.

### *Statistical analysis*

Data are presented as mean ± SD. The data were compared for statistical differences using two- and one-way analysis of variance (ANOVA) using BMDP Statistical Software (BMDP, Los Angeles, CA, USA).

## Results

### *Body weight*

The tumor-bearing animals weighed significantly less than the non-tumor–bearing animals on day 7, indicating their cachectic state (*Table 2*). The tumors on day 7 were small and estimated at less than 1% of body weight, so the weight of the animal on day 7 includes the weight of the tumor. On day 10, the tumor weight was 2% to 10% of body weight, so the tumor weight was subtracted from the body weight on day 10 to obtain the net body weight. The net body weight of the tumor-bearing animals on day 10 was significantly lower than the non-tumor–bearing animals, reflecting

**Table 2** Body weight

| | Structured lipid tumor | Long chain triglyceride tumor | Structured lipid non-tumor | Long chain triglyceride non-tumor |
|---|---|---|---|---|
| Body weight[a] (day 7) | 151.5 ± 8.1 | 146.8 ± 9.3 | 156.1 ± 10.1 | 154.4 ± 6.1 |
| Body weight (day 10) | 140.5 ± 10.2 | 134.3 ± 6.8 | 140.5 ± 10.6 | 137.0 ± 4.7 |
| Tumor weight (day 10) | 6.7 ± 3.8 | 5.1 ± 2.2 | | |
| Tumor weight/body weight (day 10) | 4.8 ± 2.7 | 3.8 ± 1.6 | | |
| Net body weight[a] (day 10) | 133.8 ± 10.4 | 129.1 ± 7.3 | 140.5 ± 10.6 | 137.0 ± 4.7 |
| Net weight change (day 10–day 7) | −17.7 ± 5.1 | −17.7 ± 3.2 | −15.6 ± 2.7 | −17.4 ± 2.5 |

[a] $P < .05$ ANOVA (tumor versus non-tumor).
Mean ± SD (g). Tumor-bearing animals weighed significantly less on day 7 and day 10, reflecting their cachectic state. All animals lost weight, but there was no difference in weight change. Tumor weight and percentage of body weight did not differ between the diet groups.

**Table 3** Liver and muscle kinetics

| | Structured lipid tumor | Long chain triglyceride tumor | Structured lipid non-tumor | Long chain triglyceride non-tumor |
|---|---|---|---|---|
| Liver weight[a] (g) | 6.0 ± 0.8 | 6.0 ± 0.6 | 5.4 ± 0.5 | 5.7 ± 0.4 |
| Liver weight/body weight[b] (%) | 4.3 ± 0.3 | 4.5 ± 0.4 | 3.9 ± 0.2 | 4.2 ± 0.2 |
| Liver FSR[a] (%/d) | 18.6 ± 4.9 | 23.9 ± 12.0 | 14.9 ± 7.0 | 14.4 ± 5.5 |
| Muscle FSR[b] (%/d) | 1.6 ± 0.5 | 2.4 ± 0.5 | 2.8 ± 0.5 | 3.4 ± 1.2 |
| Muscle % protein (%) | 19.7 ± 4.6 | 20.0 ± 2.1 | 19.2 ± 5.6 | 20.2 ± 4.0 |

[a] $P < .05$ (ANOVA), tumor versus non-tumor.
[b] $P < .05$ (ANOVA), tumor versus non-tumor and SL versus LCT.
Mean ± SD. Liver weight, percentage of body weight, and protein synthetic rate were higher ($P < .05$) in tumor-bearing rats. Liver as percent of body weight was lower in animals given SL diet. Muscle protein synthetic rate was lower in tumor-bearing rats, but was higher in rats given LCT diet.

their original cachectic state. All of the animals in the study lost weight, but there were no significant differences in net weight change. The weight loss may be partly explained by the stress response to anesthesia and central venous catheterization, and administration of one half the planned calories on day 7.

### *Tumor growth and protein kinetics*

There were no significant differences in tumor growth rate or protein kinetics due to the administration of SL or LCT-enriched TPN. Initial and final tumor volume, final tumor weight, percent protein, and fractional protein synthetic and catabolic rate were similar between the dietary regimens (data not shown).

### *Protein kinetics in the host*

**Whole-body protein kinetics.** During a constant infusion of L-1-$^{14}$C-leucine, radioisotope excretion in the expired breath reached a steady state within 2 to 4 hours. Whole-body protein kinetics showed no significant differences due to the effects of diet manipulation or tumor presence (not shown).

**Liver kinetics.** Liver weight, liver weight as a percentage of body weight, and liver protein fractional synthetic rates were significantly higher in tumor-bearing animals (*Table 3*). However, liver weight as a percentage of body weight was significantly lower in both tumor- and non-tumor–bearing animals receiving SL-enriched TPN compared with those given LCT-enriched TPN.

**Muscle kinetics.** Muscle protein fractional synthetic rates were significantly lower in the tumor-bearing animals, reflecting the catabolic state induced by the presence of the tumor (*Table 3*). Muscle protein fractional synthetic rates were significantly higher in tumor- and non-tumor–bearing animals infused with LCT-enriched diets. The percentage of protein in the muscle was unchanged by diet manipulation.

### *Nitrogen balance*

Structured lipid-enriched diets significantly improved cumulative nitrogen balance in both tumor and non-tumor–bearing rats, suggesting that SL spares host protein (*Figure 1*). Also, nitrogen balance in the

tumor-bearing animals was significantly higher compared with the non-tumor–bearing animals.

### *Albumin concentration*

Plasma albumin levels were significantly lower in the tumor-bearing animals, but were higher in both the tumor- and non-tumor–bearing animals infused with SL-enriched TPN (*Table 4*). The lower albumin levels in the tumor-bearing rats reflect the malnourished state of the cachectic animals, but the SL-enriched infusions improved net plasma albumin concentration.

### *Free fatty acid concentration*

Plasma free fatty acid levels were significantly higher in the tumor-bearing animals compared with the controls (*Table 4*). This observation is consistent with other animal studies,[19,20] and implies greater fat utilization in tumor-bearing animals.

### *Energy expenditure*

Respiratory quotient was similar among the treatment groups, but the tumor-bearing animals had significantly lower resting energy expenditure (*Table 5*) compared with the controls (*Table 6*). Recognizing that resting energy expenditure under these conditions represents resting plus active expenditure, this finding can be largely explained by the observed reduction in spontaneous activity of the tumor-bearing animals.

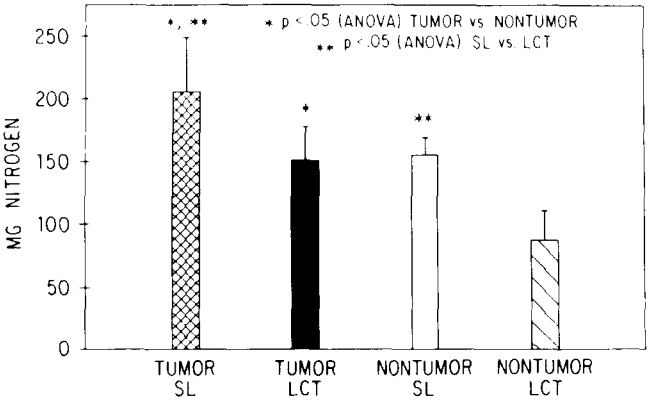


**Figure 1** The cumulative nitrogen balance was significantly higher in the tumor-bearing animals and in both tumor- and non-tumor–bearing animals receiving SL-enriched TPN.

**Table 4** Plasma albumin and free fatty acid levels

| | Plasma albumin levels[a] (g/dl) | Plasma free fatty acid levels[b] (mEq/L) |
|---|---|---|
| SL tumor | 2.76 ± 0.28 | 1.09 ± 0.46 |
| LCT tumor | 2.48 ± 0.19 | 0.74 ± 0.21 |
| SL non-tumor | 3.20 ± 0.21 | 0.54 ± 0.18 |
| LCT non-tumor | 2.98 ± 0.18 | 0.54 ± 0.22 |

[a] $P < .05$ (ANOVA), tumor versus non-tumor and SL versus LCT.
[b] $P < .05$ (ANOVA), tumor versus non-tumor.
Mean ± SD. Plasma albumin level was lower in tumor-bearing rats, but was significantly improved in both tumor-bearing and control rats given SL-enriched diets. Plasma free fatty acid was significantly higher in tumor-bearing rats versus controls.

**Table 5** Energy expenditure

| | Respiratory quotient | Resting energy expenditure[a] (Kcal/kg/d) |
|---|---|---|
| SL tumor | 0.98 ± 0.03 | 162 ± 26 |
| LCT tumor | 0.94 ± 0.05 | 171 ± 25 |
| SL non-tumor | 0.95 ± 0.02 | 194 ± 18 |
| LCT non-tumor | 0.95 ± 0.02 | 193 ± 17 |

[a] $P < .02$ (ANOVA), tumor versus non-tumor.
Mean ± SD. Tumor-bearing rats had reduced energy expenditure ($P < .05$). Respiratory quotient was unchanged.

**Table 6** Energy expenditure

| | Respiratory quotient | Resting energy expenditure[a] (Kcal/kg/d) |
|---|---|---|
| SL tumor | 0.98 ± 0.03 | 162 ± 26 |
| LCT tumor | 0.94 ± 0.05 | 171 ± 25 |
| SL non-tumor | 0.95 ± 0.02 | 194 ± 18 |
| LCT non-tumor | 0.95 ± 0.02 | 193 ± 17 |

[a] $P < .02$ (ANOVA), tumor versus non-tumor.
Mean ± STD. Tumor-bearing rats had reduced energy expenditure ($P < .05$). Respiratory quotient was unchanged.

## Discussion

Babayan first suggested that the metabolism of SLs composed of long chain and medium chain fatty acids was different from that of a physical mixture of the component triglycerides.[21] The ability of the structured triglyceride to deliver abundant quantities of free fatty acids to undergo B-oxidation to acetyl CoA, thereby sparing protein oxidation while efficiently providing linoleic acid for cell membrane maintenance and prostaglandin biosynthesis (by way of conversion to arachidonic acid), may represent a major advantage of the SL versus a physical mixture of MCT and LCT. How SLs accomplish the reduction in protein oxidation, whether by more efficient digestion, absorption, or preferential intracellular uptake by peripheral tissues, is uncertain.

Our studies focusing on the metabolic parameters associated with malnutrition and malignancy revealed alterations due to the administration of SL-enriched TPN. Improved cumulative nitrogen balance ($P < .05$) was demonstrated in both tumor- and non-tumor–bearing animals receiving SL-enriched TPN. This finding is consistent with previous studies of traumatic injury[11-13] and suggests that SL is uniquely able to promote nitrogen retention in comparison to other fat energy sources in a tumor-bearing host. Nitrogen bal-

ance was also significantly higher in tumor-bearing animals compared with controls. Fenninger and Mider concluded that a tumor could act as a "nitrogen trap," sequestering host proteins in competition for nutrients and limiting systemic re-entry of amino acids.[22] More importantly, the greater nitrogen balance in tumor-bearing animals likely reflects the increased liver size, a component of the host response to tumor presence.

Hypoalbuminemia, due to a reduction in net synthetic activity and translocation into the interstitial space, usually reflects the metabolic response to injury and infection. The significantly lower plasma albumin seen in the tumor-bearing rats may be due to decreased synthetic activity in the presence of the tumor. The improvement in plasma albumin seen in both tumor- and non-tumor–bearing rats receiving SL correlates well with previous studies in traumatic injury,[11-13] and with the improved nitrogen retention seen in these animals.

Our study demonstrated an increase in plasma free fatty acid concentration in tumor-bearing animals. During fat mobilization, triglyceride stores are hydrolyzed by tissue lipase yielding free fatty acid and glycerol.[23] As first postulated by Nakahara and Fukuoka,[24] a lipid mobilizing factor released by the tumor has been isolated in the serum of tumor-bearing mice[25] and in the ascites of cancer patients, but not in non-cancerous ascites fluids.[26] However, Mays was unable to detect a lipid-mobilizing factor in the serum of patients with various cancers.[27] Clinical investigations have noted increased free fatty acid mobilization and oxidation in cancer patients before significant weight loss.[28,29] Elevated plasma free fatty acid levels have been found in tumor-bearing animals,[19,20] but there is conflicting data in humans.[19,28] A correlation between plasma free fatty acid levels and fatty acid turnover has been demonstrated in normal patients,[30,31] but this relationship has been shown to dissolve in trauma and sepsis.[32] Assuming there is a direct relationship between free fatty acid concentration and free fatty acid turnover in a tumor-bearing rat, these data suggest greater fat mobilization due to the presence of the tumor. This would be consistent with the other metabolic characteristics of tumor growth that resemble the general injury response.

The increase in liver protein fractional synthetic rates in the tumor-bearing animals can be taken as further evidence that the metabolic abnormalities induced by the tumor resemble those found in the response to injury. It has been noted in cancer cachexia that the livers tend to enlarge while all other tissues and organs tend to lose weight.[33] Our data confirmed this finding, as the tumor-bearing animals had significantly higher liver weights as a percentage of body weight. It is interesting to note that the animals given SL-enriched TPN had significantly lower liver weights as a percentage of body weight, suggesting that SL-enriched infusions oppose the effect of the tumor on the liver.

The decreased muscle fractional synthetic rates in the tumor-bearing animals reflect the net breakdown of muscle protein to support tumor growth. Long chain triglyceride-enriched TPN administration increased muscle protein fractional synthesis; however, the net body weight was not improved with LCT administration, suggesting a compensatory increase in fractional catabolism with no net benefit for the skeletal muscle.

Since there were no significant differences in tumor growth or kinetics due to the administration of SL-enriched or LCT-enriched TPN, the nutritional benefits of SL-enriched TPN (i.e., improved nitrogen balance and plasma albumin and reduced liver size in relation to body weight) support the potential value of these emulsions. This preferential repletion of host tissue suggests that SL may be an improved fat energy source in TPN for patients with cancer-associated cachexia. Structured lipid is considered a GRAS ("generally regarded as safe" by the Food and Drug Administration) food item similar to MCT; therefore, its exploratory use in human cancer when provided enterally could be rapidly undertaken. Its parenteral use in humans will require more extensive evaluation as drugs, similar to other parenteral lipid emulsions.

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