Metabolic effects of medium chain triglyceride-enriched total parenteral nutrition in rats bearing Yoshida sarcoma

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The ability of medium chain triglyceride-enriched total parenteral nutrition to support host tissue in a model of cancer cachexia was assessed by measuring tumor growth, body weight, nitrogen balance, energy expenditure, leucine kinetics, fractional protein synthetic rate of tumor, liver, and abdominis rectus muscle, and plasma levels of glucose and albumin. Male Sprague–Dawley rats (85–90 gm) received 10^7 cells of viable Yoshida sarcoma subcutaneously on day 0. Control rats received injections of sterile saline. On day 10 rats underwent central venous cannulation and were randomized to one of three isocaloric diets. One group received amino acids and dextrose, while the other two groups were infused with amino acids, dextrose, and fat as either long chain triglyceride or a physical mixture of medium chain triglyceride:long chain triglyceride (3:1). On day 14 L-1-^{14}C-leucine was added to the diet to study protein kinetics, and energy metabolism was measured by indirect calorimetry. Both tumor-bearing and nontumor-bearing rats demonstrated improved nitrogen balance when given medium chain triglyceride-enriched total parenteral nutrition. Tumor-bearing rats had reduced resting energy expenditure vs. nontumor-bearing, while rats receiving total parenteral nutrition without fat had significantly greater respiratory quotients. Tumor-bearing rats had lower total body weight vs. nontumor-bearing on day 10, but body weight of tumor-bearing and nontumor-bearing did not differ on day 14. Whole body protein breakdown decreased and leucine balance increased in tumor-bearing rats as compared to nontumor-bearing. Total liver mass was greater in tumor-bearing rats, but liver protein fractional protein synthetic rate decreased in tumor-bearing rats vs. nontumor-bearing. Tumor growth rate and fractional protein synthetic rate were not altered by the parenteral diet. The data confirm an altered metabolism in the tumor-bearing host, and suggest that medium chain triglyceride can better support host tissue.

Keywords: Yoshida sarcoma; parenteral nutrition; medium chain triglyceride

Introduction

The development of cancer cachexia has long been recognized as a major factor in the death of many patients with cancer.[1] The syndrome of cancer cachexia is characterized by weight loss, anorexia, fatigue, anemia, and hypoalbuminemia, but the etiology of cancer cachexia can not be ascribed to anorexia alone. Even a relatively small tumor can induce both local and systemic changes which impair the absorption and utilization of nutrients.[2] Cancer cachexia bears no simple correlation to tumor burden, tumor cell type, or anatomical site of involvement, and can impair the host's ability to tolerate cancer therapy or respond immunologically.[3] Studies of energy metabolism in cancer patients have yielded inconclusive data regarding changes in reduced energy expenditure (REE) due to presence of tumor.[4] Metabolic studies have shown an increase in glucose production in the tumor-bearing

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(TB) host which is associated with a decrease in whole-body insulin sensitivity and glucose tolerance.[5] Furthermore, Holroyde et al., have proposed that the increase in glucose production can be accounted for by increased Cori cycle activity, in which lactate is reconverted to glucose by anaerobic pathways. This is an energy-requiring process, and may contribute to the cachectic syndrome.[6] Increased plasma free fatty acid (FFA) levels have been observed in TB animals, suggesting greater mobilization of stored fat, or impairment of fat utilization.[6,7]

Cancer cachexia is potentially reversible, in part, by nutritional intervention. However, in both injury[8] and cancer cachexia,[9] nutritional support therapies based on standard parenteral formulations of amino acids and dextrose are less effective at protein repletion of host tissue than in undernutrition alone. Furthermore, under certain conditions tumor growth may be stimulated by forced feeding,[10] and the lean tissue laid down can have an abnormal composition.[9]

Lipid emulsions as a caloric source afford the dual benefit of avoiding excessive glucose administration while providing substantial nonprotein calories in a limited fluid volume.[11] Yet the traditional parenteral fat, long chain triglyceride (LCT), can cause fat infiltration in the liver[12] and impair leukocyte chemotaxis and random migration.[13] Animal studies using medium chain triglycerides (MCT) have proved them uniquely beneficial in the burn[11] and injury[14,15] models. MCT are synthetic triacylglycerols containing fatty acids with 8–10 carbons.[16] Parenterally administered MCT are hydrolyzed by lipoprotein lipase, and oxidized in peripheral and visceral tissues.[17] Compared to LCT, MCT are more ketogenic, do not require carnitine for entry into the mitochondria, and are not re-esterified and stored as fat.[16] MCT products also appear to reduce fatty infiltration of major organ systems and reticuloendothelial system overload syndrome.[11,12,14] In addition, in a N-nitrosomethylurea-induced rat mammary tumor model, Cohen *et al.*, demonstrated a decrease in tumor incidence and an increase in tumor latency when MCT was substituted for LCT in an oral high fat diet.[18]

The effect of a physical mixture of MCT and LCT as an energy source for total parenteral nutrition in a cancer cachexia model with an established tumor has not been explored. We sought to investigate the ability of such lipid emulsions to support host tissues by comparing formulas containing either LCTs or a 3 : 1 physical mixture of MCT and LCT.

Materials and methods

Animal preparation and nutrient infusion

Forty-eight pathogen-free male Sprague–Dawley rats (40–45 gms) were obtained from Taconic Farms Inc. (Germantown, NY, USA). The study was conducted under the approval of the Animal Care Committee at the New England Deaconess Hospital in compliance with their established rules and guidelines. Before the experiment, rats were housed two to a cage for a minimum of 8 days, 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 tumor cell line was used to induce cancer cachexia. Previous characterization of the tumor showed the cachectic period to begin 10 days post inoculation of tumor cells.[19] Therefore, we chose day 10 to day 14 as the optimal study period. On day 0 of the study, 26 animals (85–90 gm) were inoculated with 10^7 cells of viable Yoshida sarcoma into the subcutaneous area of the right flank. The non-tumor-bearing (NTB) 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*. Nontumor-bearing animals were not pair fed with tumor animals because cancer-associated anorexia contributes to the cachectic syndrome. On day 10, rats were anesthetized with ether and a silastic catheter (0.025 in ID × 0.047 in OD; Dow-Corning Laboratories, Midland, MI, USA) was inserted through the internal jugular vein as previously described.[20] The rats were weighed, placed in metabolic units, and intravenously infused with saline (~ 5 ml of 0.9% sodium chloride) for four hours using a Holter pump (Critikon Inc., Tampa, FL, USA). The animals were randomly assigned to three groups (7–9 animals/group) and intravenously administered one of the following intravenous solutions: (1) amino acids and dextrose, (2) amino acids, dextrose, and fat as long chain triglycerides (Travamulsion, Baxter-Travenol, Chicago, IL, USA), and (3) amino acids, dextrose, and fat as a physical mixture of MCT and LCT (*Table 1*). MCT emulsions were generously provided by B. Braun, AG, Melsungen, West Germany. LCT (as Travamulsion) was included in the MCT-enriched solution as this is intended to provide them clinically in order to prevent essential fatty acid deficiency when given over prolonged periods. Over this short period of study essential fatty acid deficiency would not occur. The fat-free solution was primarily provided as an additional control, even though it is well appreciated that glucose is more protein-sparing than fat over short study periods of 4 days or less. The solutions were given at one half the planned caloric intake the first night to allow for adaptation to the glucose and fat. The animals were given the full calorie infusion on day 11 and feeding continued for an additional two days. The infusion rates were adjusted so that each animal received 220 calories/kg body weight/day, including 2 gm amino N/kg body weight/day. The solutions were isonitrogenous, isovolemic, and isocaloric, and were formulated in the hospital pharmacy under aseptic conditions. The rats of infusion were checked gravimetrically twice daily. Twenty-four hour urine was collected for nitrogen balance determination. An additional group of tumor-bearing animals ($N = 9$) did not undergo jugular cannulation, but were allowed to consume laboratory chow *ad libitum*.

Table 1 Dietary composition

Group	Amino acids	Glucose	MCT:LCT 3:1	LCT	Total
	kcal/kg.BW	kcal/kg.BW	kcal/kg.BW	kcal/kg.BW	kcal/kg.BW
GLU	50(22%)	170(78%)	—	—	220
LCT	50(22%)	38(18%)	—	132(60%)	220
MCT	50(22%)	38(18%)	132(60%)	—	220
Additives per 100 ml:					
NaCl	30 mEq				
NaAc	30 mEq				
KCl	30 mEq				
KAc	25 mEq				
KPhos	16 mEq				
Ca+Gluconate	8.4 mEq				
MgSO4	8.0 mEq				
Trace minerals	10.2 mEq				

0.5 ml of MVC 9 + 3 vitamins (Lyphomed Inc., Rosemont, IL, USA) and 0.25 ml of choline chloride 30% w/v were added per 100 ml of solution.
Total calories given were 220 kcal/kg.BW/day including 2 gm amino N/kg.BW/day. The diets were isonitrogenous, isovolumetric, and isocaloric. The GLU diet contained only amino acids and glucose, the LCT diet contained amino acids, glucose, and fat as long chain triglycerides, and the MCT diet contained amino acids, glucose, and fat as medium chain triglycerides and long chain triglycerides.

Isotopic turnover design

On day 14, (1-^{14}C)-L-leucine (50 mCi/mmol, ICN Pharmaceuticals, Inc., Irvine, CA, USA) was added to the solutions and a 4 hour constant intravenous infusion was conducted to investigate protein kinetics. Each animal received 1.5 uCi/hr of ^{14}C-leucine at a rate of 1.25 cc/hr from a syringe pump (Harvard Apparatus Co., Inc., South Natick, MA, USA).

During the infusion, room air was circulated through the metabolic chambers at a rate of 1.6 liters/min using a Masterflex pump (Cole-Parmer Instruments Co., Chicago, IL, USA). At half hour intervals the ^{14}C-carbon dioxide from each animal was trapped in 5 ml of an absolute ethanol, phenolphthalein (0.1% wt/vol), and hyamine hydroxide solution (Packard Instruments Co., Inc., Downers Grove, IL, USA) 23:1:1, respectively. Ten ml of commercial scintillant (Betafluor, National Diagnostics, Somerville, NJ, USA) was added to the sample after saturation was attained as determined by color change of phenolphthalein and the samples were analyzed for total ^{14}C radioactivity in a Beckman LS-8000 liquid scintillation spectrometer (Beckman Instruments, Fullerton, CA, USA). Quenching was corrected by internal standardization (Amhersham Corporation, Arlington Heights, IL, USA).

Total carbon dioxide production (VCO_2), oxygen consumption (VO_2), respiratory quotient (RQ), and resting energy expenditure (REE) were determined during the infusion. Rate of air flow through the metabolic chambers was determined using a Collins gasometer (Warren Collins Inc., Braintree, MA, USA). Air entering and exiting the chambers was measured for O_2 and CO_2 content using a polarigraphic O_2 analyzer and an infrared CO_2 sensor (Beckman Instruments, Fullerton, CA, USA). VO_2 and VCO_2 were calculated from the change in gas concentration multiplied by the air flow rate (corrected for standard temperature and pressure). REE was derived from the Weir equation.[21]

At the end of the infusion, the animals were sacrificed by decapitation and mixed arteriovenous blood was collected in heparinized tubes. Plasma was separated by centrifugation and 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 abdominis rectus muscle removed. The liver was weighed and two pieces of approximately 1 g each was placed in 5 ml of 10% sulfosalicylic acid (SSA) or 5 ml of saline and then completely frozen in liquid nitrogen (−180°C) to halt all metabolic processes. Two 1 g pieces 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 sacrifice and sample freezing in liquid nitrogen was 2–3 minutes.

Analytical methods

To determine free leucine specific radioactivity in the plasma pool, plasma was deproteinized with sulfosalicylic acid. Following centrifugation, the supernatant was carefully removed and leucine concentration (μmol/ml) was determined on a reverse phase column (C_{18} uBondapack, Waters Associates, Milford, MA, USA) by high performance liquid chromatography using gradient elution with acetate/phosphate buffer and 65% methanol, pre-column derivitization with ophthaldialdehyde (Sigma Chemical Co., St. Louis, MO, USA), and fluorescence detection. To remove radiolabeled ketoisocaproic acid from the sample, an aliquot of the supernatant was incubated with 30% H_2O_2.[22] Following centrifugation, a commercial scintillant (Beckman MP, Beckman Instruments, Fullerton, CA, USA) was added and the samples were analyzed for ^{14}C radioactivity.

Albumin concentration was determined by the bromocreosol green method (Albustrate, General Diagnostics, Morris Plains, NJ, USA). Plasma glucose concentrations were determined photometrically using a hexokinase/glucose-6-P-dehydrogenase single reagent kit (Sigma Diagnostics, St. Louis, MO, USA). Total urinary nitrogen was determined following a micro-Kjeldahl digestion.

The intracellular (acid soluble) and protein-bound leucine specific activities in liver, abdominis rectus muscle, and tumor were analyzed by methods previously described by our laboratory.[23]

Rates of whole body leucine appearance (flux), oxidation, percentage of flux oxidized, incorporation into protein (synthesis), release from protein (breakdown), and leucine balance (synthesis minus breakdown) were estimated from the equations of Waterlow.[24] It was assumed that a plateau labeling (steady state) of the plasma compartment was achieved when the maximum specific activity was reached in the expired breath. The protein fractional synthetic rates in liver, abdominis rectus muscle, and tumor were derived from the equations of Garlick *et al.*[25]

Estimates of fractional tumor growth, Kg, were derived from tumor volume measurements on days 10 and 14. Tumor volumes were estimated from measurements of tumor length, width, and depth in millimeters as previously described.[20] These measurements bear a close relationship to tumor weight. Tumor protein degradation rates, Kd, were estimated as the difference between tumor protein fractional synthesis rate, measured isotopically, and tumor growth rate. This relationship is expressed by the following equation:

$$Kd = Ks - Kg,$$

where Kd, Ks, and Kg are fractional rates of degradation, synthesis, and growth respectively.

Statistical analysis

Data are presented as mean ± standard error (SEM). The data were compared for statistical differences using two-way and one-way analysis of variance (ANOVA) using BMDP Statistical Software (BMDP, Los Angeles, CA, USA). The Student's t-test using separate variance T tests was applied only when the ANOVA was found to be significant ($p < .05$). When only interaction was significant by ANOVA the more rigid Bonferroni correction for T test was employed.

Results

Cumulative (3½ day) nitrogen balance during the parenteral infusion was significantly improved in both the TB and NTB rats receiving solutions enriched with MCT (ANOVA, $p < .05$ by diet) (*Figure 1*), implying that MCT can effectively support host tissue in both normal and cachectic subjects. Both TB and NTB rats receiving LCT demonstrated near zero or even negative nitrogen balance, while MCT-enriched and fat-free parenteral feeding allowed the rats to achieve positive nitrogen balance. However, nitrogen balance was significantly improved in TB and NTB rats receiving MCT compared to NTB rats receiving LCT by *t*-test.

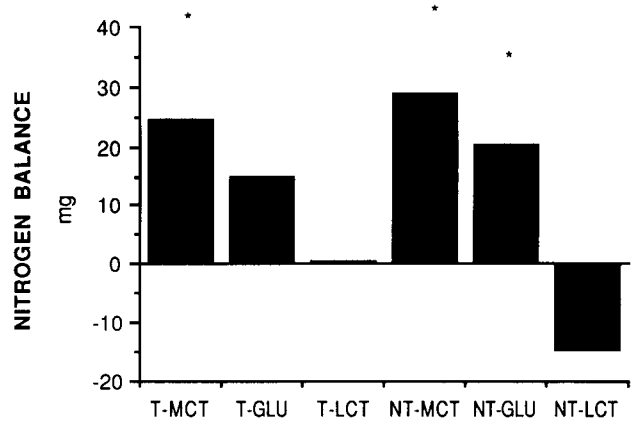

Figure 1 Cumulative nitrogen balance. Cumulative nitrogen balance was significantly improved in both the tumor and normal animals receiving MCT-enriched infusions ($p < 0.05$ by diet, ANOVA). The nontumor animals receiving the LCT diet showed marked negative nitrogen balance, and the tumor-bearing animals receiving LCT diet showed near zero nitrogen balance. Data are mean ± S.E.M.* = $p < 0.05$, Student's *t*-test vs. nontumor LCT.

Table 2 Tumor kinetics

	GLU	LCT	MCT
Franctional			
Synthetic Rate	56.7 ± 14.6	100.6 ± 26.7	57.8 ± 17.3
Degradation Rate	54.5 ± 16.2	76.2 ± 16.0	58.1 ± 5.8
Growth Rate	1.7 ± 6.6	3.5 ± 5.8	−4.3 ± 5.4

Mean ± S.E.M. (%/day)
There were no significant differences in tumor kinetics, but tumor regression was seen in the animals infused with MCT-enriched diet.

Tumor growth rate, degradation rate, and fractional protein synthesis rate are presented in *Table 2*. There were no significant trends, but tumor regression was seen in the animals infused with MCT-containing solutions. Tumor growth rate in chow-fed animals did not differ from that of TPN-fed animals. (*Table 3*) Thus, the administration of TPN did not significantly stimulate or retard tumor growth in this experiment.

The respiratory quotients were significantly higher in animals given dextrose and amino acids (*Table 4*). RQ was significantly lower in TB rats given MCT-containing solutions in comparison to all other groups. The TB rats had significantly lower resting energy expenditure compared to the normal rats (*Table 4*).

The body weights of the TB animals before nutrient administration were lower ($p < .001$) than those of the NTB animals, reflecting weight loss characteristic of the cachectic syndrome (*Table 5*). All of the animals in the study lost weight during the parenteral infusion. The tumor animals lost significantly less weight than the normal animals, in agreement with the observed decrease in resting metabolic expenditure in TB animals. Nutritional regimen did not greatly influence

Table 3 Tumor size on day 10 and day 14: TPN vs. ad libitum

	Tumor volume day 10 (mm^3)	Tumor volume day 14
GLU	4720 ± 925	5009 ± 1317
LCT	4853 ± 798	6564 ± 2064
MCT	5594 ± 1494	5541 ± 1582
Ad libitum	4412 ± 367	6154 ± 1214

Mean ± S.E.M.
The tumor growth rate of chow-fed animals was not significantly different from that of TPN-fed animals, nor were there significant differences by TPN solution.

Table 4 Indirect calorimetry

	*RQ	** REE kcal/kg/day
Tumor GLU	1.10 ± .03[a,b]	138.7 ± 16.2[b]
Tumor LCT	0.93 ± .01[c,d]	160.0 ± 15.4
Tumor MCT	0.87 ± .02[d,e,f]	183.4 ± 12.6[d]
Nontumor GLU	1.05 ± .02[g,h]	186.9 ± 6.8[i]
Nontumor LCT	0.93 ± .02	178.1 ± 5.9
Nontumor MCT	0.93 ± .01	186.5 ± 15.8

Mean ± S.E.M.
* $p < .001$ by diet and $< .05$ interaction (ANOVA).
** $p < .05$ by tumor treatment (ANOVA).
[a] = $p < .01$ (*t*-test) vs. Tumor LCT and Non tumor MCT.
[b] = $p < .001$ (*t*-test) vs. Tumor MCT.
[c] = $p < .05$ (*t*-test) vs. Tumor MCT.
[d] = $p < .001$ (*t*-test) vs. Nontumor GLU.
[e] = $p < .05$ (*t*-test) vs. Nontumor LCT.
[f] = $p < .05$ (*t*-test) vs. Nontumor MCT.
[g] = $p < .001$ (*t*-test) vs. Nontumor LCT.
[h] = $p < .001$ (*t*-test) vs. Nontumor MCT.
[i] = $p < .05$ (*t*-test) vs. Tumor GLU.
Respiratory quotient was higher in rats receiving fat-free TPN, while RQ was significantly lower in tumor-bearing rats receiving MCT-enriched TPN. Tumor animals had significantly lower resting energy expenditure compared to the normal animals.

weight change, although TB animals receiving GLU did lose significantly less weight than each of the NTB groups.

Whole-body leucine kinetics are shown in *Table 6*. There were no significant differences in whole-body leucine flux, percentage of flux oxidized, oxidation, or synthesis. Whole body protein breakdown was significantly lower and leucine balance was higher in tumor rats as compared to normals. This was particularly evident in NTB animals receiving LCT which had significantly greater breakdown than each of the TB groups by *t*-test.

The tumor rats had significantly greater liver weight vs. normal rats ($p < .05$), and the liver comprised a significantly greater ($p - .01$) proportion of total body weight in TB rats (*Table 7*). The liver protein fractional synthetic rates in the TB animals were significantly lower than in NTB animals, and were lowest in rats receiving solutions enriched with MCT (*Table 7*). There were no differences in percent protein (gm protein per gm of tissue) in liver. The protein fractional synthetic rate and percent protein in the rectus muscle were not altered by nutritional manipulation or tumor presence (*Table 8*).

There was a significant interaction of tumor and type of feeding on plasma albumin levels by ANOVA with the level in tumor bearing animals receiving LCT significantly higher than tumor bearing animals receiving glucose by Bonferroni test (*Table 9*). Plasma glucose levels were higher in tumor vs. nontumor rats but this did not reach statistical significance ($p > .07$ by ANOVA) (*Table 9*). Animals given solutions containing MCT had the lowest plasma glucose levels among the TB animals.

Discussion

Cancer cachexia is the proximate cause of death in a significant number of patients with cancer.[1] Recent

Table 5 Body weight and tumor weight

	Initial *final day 10 body weight	** Weight change	Tumor weight	Tumor % of body wt
Tumor GLU	127.0 ± 6.9[a,b,c]	−12.6 ± 4.9[e]	5.4 ± 1.6	4.5 ± 1.3
Tumor LCT	140.3 ± 4.4[b,d]	−24.5 ± 6.8	7.0 ± 1.3	5.7 ± 1.0
Tumor MCT	143.6 ± 8.3	−23.8 ± 4.7	6.1 ± 2.0	4.6 ± 1.2
Nontumor GLU	154.8 ± 5.3	−26.8 ± 2.5		
Nontumor LCT	160.6 ± 3.7	−32.6 ± 4.7		
Nontumor MCT	152.9 ± 3.7	−27.6 ± 1.8		

Mean ± S.E.M. (grams)
* $p < .001$ (ANOVA) by tumor treatment.
** $p < .05$ (ANOVA) by tumor treatment.
[a] = $p < .01$ (*t*-test) vs Tumor GLU.
[b] = $p < .01$ (*t*-test) vs Nontumor LCT.
[c] = $p < .01$ (*t*-test) vs Nontumor MCT.
[d] = $p < .05$ (*t*-test) vs Nontumor MCT.
[e] = $p < .05$ (*t*-test) vs Nontumor GLU, LCT and MCT.
The tumor-bearing animals weighed significantly less than the nontumor animals at the beginning of the parenteral infusion. Final body weights were similar, but the tumor animals lost less weight as compared to the nontumor animals.

Table 6 Whole body leucine kinetics

Flux	% Flux oxidized	Oxidation	Synthesis	* Breakdown	* Isotope balance
Tumor-bearing					
GLU 31.1 ± 3.5	57.6 ± 7.4	17.1 ± 1.9	14.0 ± 3.6	12.1 ± 3.5[a]	1.9 ± 2.2
LCT 38.0 ± 4.8	35.4 ± 2.1	13.7 ± 2.0	24.3 ± 3.1	19.9 ± 4.2[a]	4.4 ± 1.8
MCT 36.2 ± 4.4	41.1 ± 4.4	15.1 ± 2.3	21.1 ± 3.1	18.6 ± 4.0[a]	2.6 ± 1.7
Nontumor-bearing					
GLU 37.5 ± 7.1	48.6 ± 4.1	17.6 ± 3.4	19.9 ± 4.5	18.9 ± 7.0	1.0 ± 3.1
LCT 54.3 ± 8.0	52.2 ± 7.4	31.9 ± 8.8	22.4 ± 3.0	38.7 ± 7.2	−16.2 ± 7.8
MCT 42.0 ± 5.3	40.2 ± 3.5	16.2 ± 1.9	25.8 ± 4.1	25.8 ± 5.8	0.1 ± 2.4

Mean ± S.E.M.
Flux, Oxidation, Synthesis, Breakdown, and Isotope Balance in units of umol/hr/100gm.
% Flux Oxidized in units of percent.
* $p < .05$ (ANOVA) by tumor treatment.
[a] $p < .05$ by Student's t test vs Nontumor LCT.
Tumor-bearing animals had significantly lower whole-body protein breakdown rate and higher leucine balance as compared to normals.

Table 7 Liver weight and protein data

	* Liver wt	** Liver/body	Protein	* Fractional prot synth
	gm	%	%	%/day
Tumor GLU	6.4 ± 0.4[a]	5.4 ± 0.4[a]	21.3 ± 0.3	59 ± 16
Tumor LCT	5.9 ± 0.3	4.9 ± 0.3	19.6 ± 0.9	82 ± 7
Tumor MCT	5.8 ± 0.3	4.7 ± 0.3	17.8 ± 0.8	31 ± 5[bcd]
Nontumor GLU	5.2 ± 0.2	4.1 ± 0.2	18.9 ± 0.9	86 ± 12
Nontumor LCT	5.7 ± 0.6	4.4 ± 0.2	19.6 ± 0.8	70 ± 13
Nontumor MCT	5.2 ± 0.2	4.02 ± 0.2	18.9 ± 0.7	89 ± 13

Mean ± S.E.M.
* = $p < .05$ by tumor treatment (ANOVA).
** = $p < .01$ by tumor treatment (ANOVA).
[a] = $p < .05$ by t-test vs. Nontumor GLU and MCT.
[b] = $p < .001$ by t-test vs. Tumor LCT.
[c] = $p < .01$ by t-test vs. Nontumor GLU and MCT.
[d] = $p < .05$ by t-test vs. Nontumor LCT.
The tumor rats had significantly greater liver weight and liver weight as a percentage of body weight vs. the normal rats. Liver protein fractional synthetic rates were lower in tumor animals, and lowest in those animals given MCT-enriched infusions.

Table 8 Muscle protein

	Protein %	Fractional synthesis rate %/Day
Tumor GLU	23.4 ± 2.2	4.6 ± 1.2
Tumor LCT	21.8 ± 2.2	7.6 ± 2.5
Tumor MCT	19.1 ± 1.1	4.0 ± 1.2
Nontumor GLU	20.8 ± 0.6	5.3 ± 0.9
Nontumor LCT	21.6 ± 0.9	5.5 ± 1.4
Nontumor MCT	19.1 ± 1.1	4.6 ± 0.6

Mean ± S.E.M.
Percent protein (gm protein/gm tissue) and fractional protein synthetic rate were similar for all groups.

Table 9 Plasma glucose and albumin levels

	Plasma glucose mg/dL	*Plasma albumin gm/dL
Tumor GLU	225.6 ± 50.6	2.84 ± .11
Tumor LCT	201.2 ± 32.4	3.41 ± .17**
Tumor MCT	148.6 ± 34.3	2.94 ± .11
Nontumor GLU	163.7 ± 36.1	3.03 ± .12
Nontumor LCT	140.2 ± 9.8	2.99 ± .13
Nontumor MCT	135.4 ± 7.8	3.22 ± .06

Mean ± S.E.M.
* Interaction significant by ANOVA, $p < .02$.
** Significantly different from Tumor GLU by Bonferroni, $p < .05$.
Plasma glucose level was numerically higher in tumor-bearing vs. normal rats ($p < 0.07$). Animals given MCT-enriched infusions had the lowest plasma glucose levels among the tumor-bearing animals. Plasma albumin levels were significant for interaction by ANOVA.

recognition that lack of dietary intake and cachexia, to some degree, could be overcome by aggressive use of enteral and parenteral nutrition has focused attention on new nutritional support therapies. Metabolic limitations to the infusion of large quantities of dextrose in the critically ill patient led to the consideration of fat as means to provide substantial amounts of dietary energy in limited volumes of low osmolarity.[26] The traditional fat choice, LCT, is metabolized slowly when provided both enterally and parenterally[27] and may cause fatty infiltration of the liver when provided by the latter route. We have investigated the nutritional utility of an alternative fat source, MCT.

Cumulative nitrogen balance increased ($p < 0.05$) in both TB and NTB animals receiving infusions enriched with MCT. Nitrogen balance was significantly lower ($p < 0.05$, t-test) in NTB rats given LCT-enriched solutions vs. NTB and TB rats given MCT (*Figure 1*). The poor nitrogen balance of both the tumor and normal rats given LCT can most likely be attributed to the fact that the nutrient intake contained 78% of nonprotein calories as fat. Evidently this is an excessive amount of fat when the fat source is LCT, although in man this amount is considered clinically acceptable. Sobrado demonstrated that LCT diets at 75% of nonprotein calories results in reticuloendothelial system overloading in normal and burned guinea pigs, but RES function was unhindered in animals receiving MCT-enriched solutions at this caloric level.[11] Here, both tumor and normal rats receiving MCT or glucose-based TPN achieved positive nitrogen balance. Thus MCT-enriched infusions supported host tissue in both TB and normal animals, suggesting that MCT-enriched TPN spares lean body mass more effectively than LCT-enriched or fat-free TPN.

Investigations into the characteristics of energy metabolism and the assessment of energy requirements in cancer patients are limited. Some investigators have reported increased REE in weight-losing cancer patients as compared to controls, while others have reported no increase in REE.[4] Animals receiving solutions of amino acids and dextrose in this study had significantly higher respiratory quotients than rats given TPN with fat, in accordance with expected RQs for the respective diets.[28] The RQ of TB rats receiving MCT-diets was significantly lower ($p < 0.05$, t-test) as compared to all other groups, implying that fat was the predominant energy substrate in these animals. The resting energy expenditure of the TB animals was significantly lower as compared to that of normals. Recognizing that measured energy expenditure under these conditions represents resting plus activity expenditure, this finding may be explained, in part, by the clinically observed reduction in spontaneous activity of the TB animals. The REE in the tumor animals given MCT-enriched infusions was similar to that of the normal animals, but the RQ was decreased, suggesting that MCT-enriched TPN may allow utilization of endogenous fat for metabolic energy more efficiently than LCT-enriched TPN in TB rats, thus sparing body protein. MCT emulsions can give a "calorie burst effect" with calories becoming more rapidly available for metabolic use than calories from LCT.[27] This thermogenic effect is accompanied by a net increase in energy expenditure, reflecting greater net fat oxidation. Several studies suggest that MCT are oxidized more rapidly than LCT because they do not require carnitine to enter the mitochondria for oxidation.[29,30,31] This thermogenic effect of MCT was suggested in the tumor animals but not in the normals.

The significantly reduced body weight loss in the TB versus the normal animals may be due to the lower resting energy expenditure and lower whole-body protein breakdown rate of the TB animals. The weight loss itself can be attributed to the effects of surgical stress and the administration of only half the planned calories during the first night of feeding as well as the net loss of intestinal contents with parenteral feeding. Here, the animals were given TPN at 220 kcal/kg/day because in our experience TB rats are unable to tolerate the fluid volume necessary to deliver more than 220 kal/kg/day. Although measured energy expenditure in the NTB rats was 180 to 190 kcal/kg/day, this level of caloric intake may be insufficient. Another possibility is that our flow-through breath collection system for indirect calorimetry may not adequately measure total caloric expenditure. Although previous studies have demonstrated an effect of MCT administration to produce weight loss,[32,33] the choice of diet did not alter weight change in the present study except that the TB animals receiving glucose did lose significantly less weight than any of the NTB groups.

Whole-body leucine kinetics revealed a significantly decreased protein breakdown and increased leucine balance in the TB animals, which is in agreement with the TB animals losing less weight than the NTB animals. There was a marked decrease in leucine balance in the NTB animals receiving LCT-enriched infusions, which was consistent with their negative nitrogen balance and loss of body weight. Thus there is a reasonable correlation between dynamic protein assessment and more traditional nutritional assessment techniques.

During TPN administration, development of hepatic dysfunction is a common complication.[26] In a model of liver insufficiency, Pomposelli *et al.*, found abnormal hepatic morphology in animals given solutions containing dextrose, dextrose and amino acids, and dextrose, amino acids, and fat as long chain triglycerides, yet this effect was not seen with a solution containing dextrose, amino acids and fat as a 3:1 physical mixture of MCTs and LCTs.[12] Because parenterally administered MCT are hydrolyzed by lipoprotein lipase more quickly than LCT and are not easily elongated or stored, fat deposition in the liver may be decreased in animals given MCT-enriched solutions. Here, the protein nutritional status of specific tissues was affected by the nutritional support regimen. The TB animals receiving MCT-enriched infusions showed significantly lower protein fractional synthetic rates in the liver than any of the other groups except TB animals receiving glucose. In his work on protein and fat

metabolism during protein repletion with TPN, Stein suggested that elevations in liver synthetic rates were characteristic of metabolic stress and not necessarily indicative of improved nutritional status.[34] Recognizing that net protein content in the liver is dependent upon the balance between synthetic and catabolic rate, it is reasonable to conclude that the increased liver mass in tumor animals is achieved through a reduction in the rate of catabolism. Among the tumor animals there was no difference in liver weight or percent protein; therefore the decreased protein fractional synthetic rate seen in TB animals receiving MCT-enriched TPN must be accompanied by a decreased catabolic rate.

Although not statistically significant ($p < 0.07$), the tumor animals had higher plasma glucose levels than normal animals. This marginal difference does support evidence for an altered glucose metabolism in the cachectic syndrome, in agreement with previous studies.[35] There was a significant interaction of tumor presence and nutrient intake on plasma albumin, with plasma albumin significantly greater in TB animals receiving LCT vs. those receiving GLU.

In summary, we found that parenteral solutions enriched with MCT preferentially spare body protein in the TB host. The normal animals receiving MCT-enriched solutions demonstrated improved nitrogen balance, but the unique aspects of MCT were most evident in the TB animal. Nitrogen balance improved and liver fractional synthetic rate decreased. Furthermore, tumor growth rate was at least numerically lower in the TB animals given MCT-enriched diets. Thus, MCT-enriched parenteral nutrition supported host protein metabolism without acceleration in tumor growth in a cancer cachexia model and may be useful as a potential energy source in nutritional support regimens for cachectic patients.

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