Lipolysis and Lipid Oxidation in Weight-Losing Cancer Patients and Healthy Subjects

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Increased lipolysis has been suggested as one of the possible mechanisms underlying cancer cachexia. The study aim was to assess whether lipolysis is increased in weight-losing cancer patients, considering their differences in food intake and body composition. Sixteen healthy subjects and 18 cancer patients with different tumor types and a weight loss of at least 5% in the previous 6 months were included in the study. Food intake was recorded for 4 days. After an overnight fast, [1,1,2,3,3-$^{2}H_5$]glycerol was infused to determine the rate of appearance (Ra) of glycerol as a measure of whole-body lipolysis, and [1-^{13}C]palmitic acid was infused to determine the Ra of palmitate as a measure of adipocyte fatty acid release. Palmitate oxidation was determined by measuring $^{13}CO_2$ enrichment in breath samples, and body composition was measured by bioelectrical impedance analysis. After adjustment for energy intake, whole-body lipolysis was significantly higher in cancer patients versus healthy subjects (6.46 ± 0.63 and 4.67 ± 0.46 μmol/kg ± min, respectively, $P < .05$). The difference in adipocyte fatty acid release did not reach statistical significance. The rate of palmitate oxidation was also significantly higher in patients than in healthy subjects (1.15 ± 0.10 and 0.93 ± 0.07 μmol/kg · min, respectively, $P < .05$). No differences in body composition were observed between groups. In conclusion, whole-body lipolysis (as measured by the Ra of glycerol) and palmitate oxidation were elevated in weight-losing cancer patients, but fatty acid release was not significantly different.

CANCER CACHEXIA is a syndrome of involuntary weight loss, impaired physical performance, and fatigue[1] and is frequently found in patients with malignant tumors.[2,3] Different studies have shown that the weight loss is associated with an increased morbidity, an attenuated response to therapy, a decreased quality of life,[1] and a reduced survival.[4] The beneficial effect of dietary supplementation is modest, and pharmacological agents have failed to improve the condition.[5] Therefore, better knowledge of the mechanisms underlying cancer cachexia is important to develop new treatment strategies.

One of the factors contributing to the development of weight loss is reduced food intake, which may be caused by a decrease in appetite or a tumor treatment,[6,7] mechanical obstruction of the gastrointestinal (GI) tract,[4] or intestinal malabsorption.[7] In addition, metabolic aberrations may contribute to cachexia in cancer patients.[8,9] The combination of reduced energy intake and increased energy expenditure in cancer patients results in substantial weight loss. It has been shown that the weight loss in cancer patients comprises both muscle mass and fat mass (FM).[10] One of the mechanisms that may be involved in the reduction of FM is increased lipolysis. In the literature, several studies have reported elevated lipolysis in cancer patients,[11-13] although one study did not detect any difference in lipolysis between cancer patients and healthy subjects.[14]

The mechanisms responsible for elevated lipolysis in cancer patients are poorly understood. Lipolysis may be stimulated by reduced energy intake, weight loss, or the presence of cancer. In the urine of weight-losing cancer patients, a probably tumor-derived lipolytic material has been detected[15] that stimulates lipolysis[16] and proteolysis[17,18] in vitro and induces weight loss in animals.[19] Furthermore, inflammation mediated by cytokines such as interleukin-6 may affect lipolysis in cancer patients.[20,21] Studies in healthy subjects have demonstrated that the lipolytic rate depends on energy intake[22,23] and the size of the fat-free mass (FFM).[23,24] However, to our knowledge, no data have been reported on lipolysis in cancer patients after adjustment for energy intake or body composition. Therefore, the aim of the present study was to assess whether whole-body lipolysis, adipocyte fatty acid release, and palmitate oxidation are increased in weight-losing cancer patients, considering their differences in food intake and body composition.

SUBJECTS AND METHODS

Subjects

Eighteen patients with histologically proven cancer and a weight loss of at least 5% in the previous 6 months and 16 healthy subjects with stable weight were included in this study. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam, and written informed consent was obtained from all participants prior to the start of the study. The following exclusion criteria were used: treatment with chemotherapy or radiation therapy in the 2 weeks preceding the study, surgery in the previous 2 months, concurrent corticosteroid treatment, insulin-dependent diabetes mellitus, uncontrolled hyperthyroidism or hypothyroidism, edema, and fever. Clinical characteristics of the cancer patients are summarized in Table 1.

Study Protocol

After an overnight fast of about 12 hours, the subjects reported to the outpatient department between 8 and 9 AM for measurement of whole-body lipolysis and lipid oxidation, resting energy expenditure (REE), and body composition. After 15 minutes of absolute rest at the department, Teflon (E.I. du Pont de Nemours, Wilmington, DE) catheters were inserted into the antecubital vein of one arm for infusion of isotopes and the contralateral dorsal hand vein or forearm vein for blood sampling. Baseline blood samples were collected in heparinized vacuum tubes. Four baseline breath samples were collected by exhalation through a straw in 10-mL Exetainer tubes (Labco, Bucks, UK).

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Table 1. Clinical Characteristics of the Weight-Losing Cancer Patients

Age (yr)/ Sex	Tumor Type	Time Since Diagnosis (mo)	Metastases	Prior Treatment	Weight Loss (%/6 mo)
GI					
50/M	Adenocarcinoma of the esophagus	1	None	None	6.9
60/M	Adenocarcinoma of the esophagus	48	Liver, lung	S, C	7.3
69/M	Squamous cell carcinoma of the esophagus	8	Lymph nodes	C	18.1
59/M	Squamous cell carcinoma of the esophagus	22	None	C, R	14.8
49/M	Squamous cell carcinoma of the oropharynx	14	None	C, R	10.7
59/M	Carcinoma of the rectum	24	Liver	S, R	18.0
63/M	Pancreatic cancer (locoregional relapse)	19	None	S, R	14.3
75/M	Pancreatic cancer (locoregional relapse)	7	None	S	7.3
59/M	Gallbladder carcinoma	2	Liver	None	25.0
Other tumors					
74/M	Adenocarcinoma of the lung	12	Liver	S	10.8
55/M	Undifferentiated large-cell carcinoma of the lung	16	Mediastinum	R	5.3
65/M	Mesothelioma of the lung	3	None	None	14.0
73/F	Adenocarcinoma of the mamma	180	Lung, bone	S, H, R	14.4
74/F	Adenocarcinoma of the mamma	1	Bone, lymph nodes	H	7.2
65/F	Carcinoma of the cervix (locoregional relapse)	24	None	S, R	5.3
66/F	Carcinoid	96	Liver, omentum, lymph nodes	None	17.1
65/M	Adenocarcinoma of the kidney	15	Lung	S, I	13.1
65/M	Adenocarcinoma of the unknown primary	1	Liver	None	11.1

Abbreviations: M, male; F, female; S, surgery; R, radiotherapy; C, chemotherapy; H, hormonal treatment; I, interferon treatment.

Blood samples were centrifuged immediately at 1,200 × *g* for 10 minutes at 4°C, and the plasma was stored at −80°C under nitrogen until analysis.

After baseline sampling, a plasma protein solution (40 g protein/L, albumin ≥85%; CLB, Amsterdam, The Netherlands) was infused that contained the stable isotope–labeled tracers [1,1,2,3,3-$^2H_5$]glycerol (MassTrace, Woburn, MA) and [1-^{13}C]palmitic acid (MassTrace). Labeled glycerol was infused at a rate of about 0.08 μmol/kg · min (prime 1.2 μmol/kg) to determine the rate of appearance (Ra) of glycerol as an index of whole-body lipolysis[25] using a Perfusor Secura pump (Braun, Melsungen, Germany). Labeled palmitate was infused at a rate of approximately 0.04 μmol/kg · min to determine the Ra of palmitate as an index of fatty acid release.[25] The plasma bicarbonate pool was primed with $NaH^{13}CO_3$ (~1.7 μmol/kg) dissolved in saline. The exact amount of tracers infused during the study was determined afterward by measuring the isotope concentration in the infusate. During the isotope infusion, REE was measured for 30 minutes by indirect calorimetry using a ventilated-hood system (Deltatrac MBM-100; Datex Instrumentarium, Helsinki, Finland). The O_2 consumed and CO_2 produced during the last 20 minutes of the measurement were used to calculate REE and the total respiratory quotient. At 50, 60, 70, 80, and 90 minutes after starting the isotope infusion, arterialized venous blood samples[26] were taken with heparinized tubes to measure [$^2H_5$]glycerol and [1-^{13}C]palmitate enrichment. Breath samples were obtained to measure $^{13}CO_2$ enrichment to calculate [1-^{13}C]palmitate oxidation. All blood samples were placed on ice immediately, and centrifuged and stored at the end of the infusion period. To maintain patency, the venflon sampling device was flushed with 2 mL saline containing heparin at low concentration. Heparin-released lipoprotein lipase was verified to be less than 3% of the measured values for total whole-body lipolysis.

Body composition was determined by bioelectrical impedance analysis (Human-IM Scan; Dietosystem, Milan, Italy), using the equation of Deurenberg et al.[27] Body weight (BW) and height were measured. Subjects recorded their dietary intake for 4 days preceding the measurement of lipolysis. Dietary intake was calculated using the nutritional software package Komeet (B.ware Nutrition Software, Arnhem, The Netherlands).

Analysis of Blood Samples

To isolate plasma glycerol, 0.2 mL plasma was deproteinized by subsequently adding and mixing 0.5 mL H_2O, 0.2 mL 0.15-mol/L $CuSO_4$, and 0.2 mL 0.15-mol/L Na_2SWO_4. After centrifugation at 15,000 × *g* and 15°C for 8 minutes, the supernatant was passed through a mixed ion-exchange column (AG50W-X8, AG1-X8, 200-400 mesh, 0.2 g each; Biorad, Richmond, CA). The column was washed with 4 mL H_2O, and the effluent containing glycerol was collected and dried under nitrogen. Derivatives of glycerol were formed during incubation with 0.030 mL pyridine and 0.015 mL *N*-methyl-*N*-(*tert*-butyldimethylsilyl)-trifluoroacetamide ([MTBSTFA] Pierce, Omnilabo, Breda, The Netherlands) for 1 hour at 60°C.

To measure [1-^{13}C]palmitate enrichment, lipids were extracted from 250 μL plasma using chloroform:methanol (2:1 by vol; Merck, Darmstadt, Germany) according to the method of Folch et al[28] in the presence of butylated hydroxytoluene (1 mg/mL) as an antioxidant. Plasma free fatty acids (FFAs) were isolated by thin-layer chromatography (silica plates, Merck no. 5721) using hexane:diisopropylether:acetic acid (60:40:3 by vol; Merck) as a developer. The spots were scraped off, extracted using chloroform:methanol (2:1), dried under nitrogen, and converted to their derivatives by MTBSTFA.

Plasma enrichment of free [$^2H_5$]glycerol and [1-^{13}C]palmitic acid was analyzed on a Carlo Erba GC8000 gas chromatograph coupled to a Fisons MD800 mass spectrometer (Interscience, Breda, The Netherlands) in electron-impact ionization mode with an interface temperature of 280°C and a source temperature of 200°C. All measurements of isotopic enrichment were made by injecting 1 μL with a split ratio of 50:1 on a fused silica capillary column of 25 m × 0.22 mm coated with 0.11 m HT5 (SGE, Victoria, Australia). Natural glycerol and [$^2H_5$]glycerol (*m/z* 387 and 381) and natural palmitic acid and [1-^{13}C]palmitic acid (*m/z* 313 and 314) were measured by selected ion monitoring. For both [$^2H_5$]glycerol and [1-^{13}C]palmitic acid, the coefficient of variation was 0.2 mol% and no concentration effect was observed for the mol% enrichment. $^{13}CO_2$ in breath samples was measured on an isotope ratio mass spectrometer (ABCA; Europa Scientific, Van Loenen Instruments, Leiden, The Netherlands) with a standard deviation of 0.0002 atom% $^{13}CO_2$. Blood hemoglobin, albumin, prealbumin, and

Table 2. Characteristics of the Study Population (mean ± SEM)

Characteristic	Cancer Patients			Healthy Subjects (n = 16)
	GI (n = 9)	Other (n = 9)	Total Group (n = 18)	
Age (yr)	60 ± 3	67 ± 2*	64 ± 2*	54 ± 2
Sex ratio (M/F)	9/0	5/4	14/4	10/6
Weight (kg)	67.2 ± 3.4	63.8 ± 3.1*	65.5 ± 2.3*	77.0 ± 3.4
Weight loss (%)	13.6 ± 2.1*	10.9 ± 1.4*	12.3 ± 1.2*	0.0 ± 0.0
BMI (kg/m^2)	21.5 ± 1.1†	23.0 ± 1.0	22.2 ± 0.7†	25.3 ± 1.0
%IBW	97.8 ± 4.9*	108.0 ± 5.1	102.9 ± 3.6†	118.2 ± 4.6
Arm circumference (cm)	27.5 ± 1.3*	28.5 ± 1.0†	28.0 ± 0.8*	31.9 ± 0.8
Sum of 4 skinfolds (mm)	33.3 ± 4.6*	45.0 ± 7.7†	39.1 ± 4.6*	69.2 ± 7.4
FFM (kg)	47.6 ± 2.2	44.3 ± 2.5†	45.9 ± 1.7†	54.1 ± 2.9
FM (kg)	20.4 ± 2.4	19.5 ± 1.8	19.9 ± 1.4	23.6 ± 2.2
%FFM	70.6 ± 3.0	69.5 ± 2.2	70.0 ± 1.8	69.8 ± 2.3

*$P < .01$, †$P < .05$: significantly different *v* healthy subjects (*t* test).

C-reactive protein (CRP) levels were measured according to standard clinical chemical methods. The thyroid hormones triiodothyronine (T_3), thyroxine (T_4), and reverse T_3 (rT_3) were analyzed according to the method of Bauer et al.[29] Plasma insulin was determined by radioimmunoassay (Biosource, Fleurus, Belgium).

Calculations

Calculations of the Ra of glycerol and palmitate were made according to Klein and Wolfe[13] using the equation described by Steele,[30] Ra (μmol/kg · min) = $(IE_i/IE_p - 1) \cdot F$, where F is the isotope infusion rate (micromoles per kilogram per minute), IE_i is the isotopic enrichment of the infusate (atom percent excess), and IE_p is the isotopic enrichment in plasma (atom percent excess) during steady-state conditions. The Ra of total FFAs (Ra FFAs) was calculated from the Ra of palmitate assuming that the palmitate concentration was 23% of the total plasma FFA concentration.[31] An index of the relative rates of lipolysis and reesterification was calculated as the ratio of Ra FFA/Ra glycerol.[25]

Palmitate oxidation was calculated according to the equation, palmitate oxidation (micromoles per kilogram per minute) = $(IE_{CO2} \cdot \dot{V}_{CO_2})/(IE_p \cdot BW \cdot k)$, where IE_{CO2} is the isotopic enrichment of expired CO_2 (atom percent excess), $\dot{V}_{CO_2}$ is CO_2 production (micromoles per minute), and k is the bicarbonate correction factor for incomplete recovery of ^{13}C (k = 0.75) according to Wolfe et al.[32]

Statistical Analysis

Data are expressed as the mean ± SEM. Statistical differences between cancer patients and healthy subjects were assessed using linear regression analysis including as covariates (1) a dummy variable to indicate the presence of tumor and (2) energy intake. Pearson correlation coefficients were calculated. Due to the skewed distribution of CRP data, a logarithmic transformation was used for plasma CRP concentrations. *P* values less than .05 were considered statistically significant. Analyses were performed with SPSS software (SPSS for Windows version 6.1.3; SPSS, Chicago, IL).

RESULTS

Characteristics of the cancer patients and healthy subjects are summarized in Table 2. The mean age was significantly higher for the cancer patients versus the healthy subjects, although the age range was comparable, ie, 49 to 75 years in patients and 40 to 75 years in healthy subjects. The BW, body mass index ([BMI] kilograms per meter squared), percentage of ideal BW (%IBW), arm circumference, and sum of 4 skinfolds were significantly lower in cancer patients than in healthy subjects. Absolute values for FFM and FM were reduced in cancer patients, but the percentage of FFM (%FFM) was not different between cancer patients and healthy subjects. Since %FFM was also comparable in patients with GI cancer and patients with other types of tumors (non-GI), %FFM was not included as a covariate in the statistical analyses.

Total energy intake (kilojoules per day) was significantly lower in cancer patients versus healthy subjects, especially in patients with non-GI tumors (Table 3). When expressed per 1 kg BW, energy intake remained 25% lower in patients with non-GI tumors versus healthy controls ($P = .055$). Because of the differences in energy intake between groups, further statistical analyses were adjusted for energy intake. No significant differences in the energy percentage of fat, protein, or carbohydrate intake were observed between any of the groups.

Blood hemoglobin, albumin, and prealbumin were significantly decreased in cancer patients, whereas CRP was significantly increased (Table 4). With regard to thyroid hormones, T_3 was significantly lower and rT_3 significantly higher in cancer patients compared with healthy subjects, whereas T_4 did not show any significant difference between the groups. Urinary creatinine excretion was significantly lower in cancer patients

Table 3. Dietary Intake in Weight-Losing Cancer Patients and Healthy Subjects (mean ± SEM)

Intake	Cancer Patients			Healthy Subjects (n = 16)
	GI (n = 9)	Other (n = 9)	Total Group (n = 18)	
Total (kJ/d)	8,348 ± 902	5,903 ± 568*	7,054 ± 588†	9,081 ± 621
Per 1 kg BW (kJ/kg · d)	128 ± 15	92 ± 8	109 ± 13	122 ± 10
Protein (energy %)	17.8 ± 1.0	17.4 ± 1.0	17.6 ± 0.7	16.9 ± 0.8
Fat (energy %)	34.9 ± 2.0	33.9 ± 1.1	34.4 ± 1.1	36.2 ± 1.5
Carbohydrate (energy %)	44.9 ± 3.1	49.6 ± 1.8	47.4 ± 1.8	46.5 ± 1.3

*$P < .01$, †$P < .05$: significantly different *v* healthy subjects.

Table 4. Biochemical Parameters in Weight-Losing Cancer Patients and Healthy Subjects (mean ± SEM)

Parameter	Cancer Patients			Healthy Subjects (n = 16)
	GI (n = 9)	Other (n = 9)	Total Group(n = 18)	
Blood				
Hemoglobin (mmol/L)	7.7 ± 0.4†	7.1 ± 0.3*	7.4 ± 0.3*	8.6 ± 0.2
Albumin (g/L)	39 ± 2*	39 ± 1*	39 ± 1*	48 ± 1
Prealbumin (g/L)	0.19 ± 0.02*	0.17 ± 0.01*	0.18 ± 0.01*	0.28 ± 0.01
T_3 (nmol/L)	1.22 ± 0.15*	1.52 ± 0.13†	1.39 ± 0.11*	1.89 ± 0.10
T_4 (nmol/L)	93 ± 8	112 ± 9	102 ± 6	90 ± 4.0
rT_3 (nmol/L)‡	0.54 ± 0.14†	0.36 ± 0.11†	0.48 ± 0.09*	0.25 ± 0.02
CRP (mg/L)‡	25 ± 13†	17 ± 15†	21 ± 10*	1 ± 1
Urine				
Creatinine excretion (g/24 h)	0.14 ± 0.01†	0.13 ± 0.02	0.14 ± 0.01†	0.17 ± 0.01

*$P < .01$, †$P < .05$: significantly different *v* healthy subjects (*t* test).
‡Median ± SEM.

versus healthy subjects. Again, no significant difference in any biochemical parameter was detected between cancer patients with GI tumors versus other types of tumors.

Whole-body lipolysis as measured by the Ra of glycerol was 38% higher after correction for energy intake in cancer patients versus healthy subjects ($P < .05$; Table 5). When the 2 subgroups of cancer patients were considered separately, a 50% elevation in the Ra of glycerol was observed in patients with non-GI cancer ($P < .05$), whereas the elevation in the Ra of glycerol did not reach statistical significance in GI patients. Although adipocyte fatty acid release as measured by the Ra of palmitate also tended to be higher in cancer patients versus healthy subjects, this difference failed to reach statistical significance ($P < .10$). Reesterification, as indicated by the ratio Ra FFA/Ra glycerol, did not differ significantly between cancer patients and healthy subjects, although values tended to be lower in cancer patients. Palmitate oxidation was significantly elevated in the total group of cancer patients ($P < .05$), as well as the subgroup of non-GI cancer patients ($P < .05$). REE per 1 kg BW was significantly elevated in patients with GI cancer and patients with other tumor types ($P < .01$).

Palmitate oxidation ($r = .52$, $P < .05$) and REE ($r = .65$, $P < .01$), but not lipolysis or fatty acid release, were significantly correlated with the logarithm of the plasma CRP concentration.

DISCUSSION

Increased lipolysis is one of the factors that may contribute to weight loss in cancer cachexia.[33] However, it is not known whether lipolysis is increased in cancer patients when alterations in energy intake and body composition are considered. In the present study, we investigated whether lipolysis is higher in weight-losing cancer patients versus healthy subjects considering their differences in food intake and body composition. Since no differences in %FFM were observed, this factor was not included in the statistical analyses. However, energy intake showed substantial differences between groups and was therefore included in the statistical analyses as a covariate. Whole-body lipolysis was assessed using infusion of $^2H_5$-labeled glycerol, whereas adipocyte fatty acid release was measured using ^{13}C-labeled palmitate. Whole-body lipolysis and palmitate oxidation were significantly higher in cancer patients than in healthy subjects, but the difference in fatty acid release between the 2 groups failed to reach statistical significance.

Lipolysis is the hydrolysis of triglycerides into free glycerol and fatty acids. For every triacylglycerol molecule hydrolyzed, 1 molecule of glycerol is released into the plasma. The Ra of glycerol is therefore a direct reflection of the rate of lipolysis.[25] In contrast, the Ra of palmitate may be affected by other factors such as reesterification within the tissue[25] and differential mobilization of different fatty acids from adipose tissue.[34] The index for reesterification, calculated as the ratio Ra FFA/Ra glycerol, did not differ significantly between groups in the present study.

Several studies have shown that lipolysis expressed per 1 kg BW does not differ significantly between younger and older subjects.[35-37] Based on these observations and the fact that age did not correlate with lipolysis in the present study, we conclude that the slight difference in age between cancer patients and healthy subjects in the present study did not affect the study outcome.

Previous studies have shown that REE is higher in cancer

Table 5. Ra of Glycerol and Palmitate and the Ratio Ra FFA/Ra Glycerol in Plasma, Rate of Palmitate Oxidation, and REE in Weight-Losing Cancer Patients and Healthy Subjects (mean ± SEM)

Parameter	Cancer Patients			Healthy Subjects (n = 16)
	GI (n = 9)	Other (n = 9)	Total Group (n = 18)	
Ra glycerol (μmol/kg · min)	5.88 ± 0.60	7.04 ± 1.12*	6.46 ± 0.63†	4.67 ± 0.46
Ra palmitate (μmol/kg · min)	4.23 ± 0.41	4.38 ± 0.55	4.30 ± 0.33	3.59 ± 0.23
Ra FFA/Ra glycerol (ratio)	3.23 ± 0.25	2.82 ± 0.17	3.03 ± 0.16	3.75 ± 0.37
Palmitate oxidation (μmol/kg · min)	1.14 ± 0.16	1.16 ± 0.14*	1.15 ± 0.10*	0.93 ± 0.07
REE (kJ/kg · 24 h)	97 ± 4‡	96 ± 4‡	97 ± 3‡	84 ± 2

*$P = .05$, †$P < .05$, ‡$P < .01$: significantly different *v* healthy subjects after adjustment for energy intake.

patients with an acute-phase response versus patients without this response.[38,39] This finding was confirmed in the present study, where REE was significantly correlated with the plasma CRP concentration. However, whole-body lipolysis was not correlated with plasma CRP in cancer patients, although it has been suggested that cytokines and inflammation may mediate changes in lipid metabolism.[21] Rather, the presence of a lipolytic factor[15,16] or lipolytic hormones may have stimulated whole-body lipolysis in cancer patients.

We observed that the Ra of glycerol was higher in patients with non-GI cancer versus GI cancer patients, which may be explained by the fact that a higher proportion of non-GI patients had metastatic disease compared with GI patients. A previous study in GI cancer patients showed a positive correlation between tumor bulk and the rate of net protein catabolism and glucose oxidation, but the rate of lipolysis was not measured in that study.[40] Another study reported a significant increase of glucose turnover in rats with a large tumor burden but not in rats with a small tumor burden,[41] whereas the observed trend for increased lipid cycling in tumor-bearing animals did not reach statistical significance.

With regard to the high degree of weight loss in our cancer patients, it is likely that most of the patients were in negative energy balance at the time of the measurements, which may have affected the study outcome. Although the effect of energy imbalance on lipolysis in cancer patients is not known, several studies on the effects of weight reduction on lipolysis in obese subjects have been reported. In one study, the Ra of glycerol did not change significantly during 28 days of weight reduction. In two other studies,[42,43] lipolytic measurements were performed before and after weight reduction, although BW was stable at the time of the measurements. These studies showed that the basal rate of adipocyte lipolysis in vitro decreased about 50% after weight reduction,[42,43] and fat oxidation also decreased significantly.[43] In the present study, since whole-body lipolysis and palmitate oxidation were elevated instead of reduced in weight-losing cancer patients, it is unlikely that the observed differences in lipolysis between healthy subjects and cancer patients can be explained by a negative energy balance in these patients.

It may be noted that our values for the Ra of glycerol and palmitate in cancer patients and healthy subjects are higher than those reported in comparable studies.[11-14] Although there is no simple explanation for this, it should be emphasized that the differences between our values and those reported in the literature did not affect the comparison between patients and healthy subjects in our study, since identical methodology was used for all subjects.

We conclude that lipolysis and palmitate oxidation are elevated in weight-losing cancer patients when energy intake is considered. Body composition did not differ between patients and healthy subjects, so adjustment for this potential confounder was not needed. Differences in fatty acid release and reesterification between cancer patients and healthy subjects did not reach statistical significance. Prospective studies are needed to assess the role of increased lipolysis and fat oxidation in the etiology of weight loss in cancer patients.

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