Original Article

Energy metabolism and nutritional status in hospitalized patients with lung cancer

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This study aimed to investigate the energy metabolism of patients with lung cancer and the relationship between energy metabolism and proinflammatory cytokines. Twenty-eight patients with lung cancer and 18 healthy controls were enrolled in this study. The nutritional status upon admission was analyzed using nutritional screening tools and laboratory tests. The resting energy expenditure and respiratory quotient were measured using indirect calorimetry, and the predicted resting energy expenditure was calculated using the Harris–Benedict equation. Energy expenditure was increased in patients with advanced stage disease, and there were positive correlations between measured resting energy expenditure/body weight and interleukin-6 levels and between measured resting energy expenditure/predicted resting energy expenditure and interleukin-6 levels. There were significant relationships between body mass index and plasma leptin or acylated ghrelin levels. However, the level of appetite controlling hormones did not affect dietary intake. There was a negative correlation between plasma interleukin-6 levels and dietary intake, suggesting that interleukin-6 plays a role in reducing dietary intake. These results indicate that energy expenditure changes significantly with lung cancer stage and that plasma interleukin-6 levels affect energy metabolism and dietary intake. Thus, nutritional management that considers the changes in energy metabolism is important in patients with lung cancer.

***Key Words*: energy metabolism, nutritional status, indirect calorimetry, lung cancer**

Malnutrition is an important problem occurring in patients with cancer and is associated with negative consequences,[1,2] such as poor prognosis and quality of life. Severe weight loss has been found in 30% of newly detected patients with lung cancer.[3] This phenomenon is thought to be caused by a disturbed energy balance. In other words, body weight is reduced by a negative balance between dietary intake and energy expenditure. Certainly, malnutrition results from a decrease in dietary intake and/or increased energy expenditure. There have been numerous studies on energy metabolism in patients with cancer; however, controversial conclusions have been reported. It has been reported that energy expenditure is elevated in patients with lung cancer or pancreatic cancer.[3–5] Furthermore, Hansell *et al.*[6] reported that higher resting energy expenditure (REE) was a poor prognostic indicator in patients with lung cancer. In contrast, it has been reported that energy expenditure is unchanged in patients with gastric cancer or colorectal cancer.[7,8] Recently, Cao *et al.*[9] reported that patients with advanced cancer had elevated energy expenditure, based on a study of 714 patients with cancer and 642 controls. In their report, patients with esophageal cancer, gastric cancer, pancreatic cancer, and non-small cell lung cancer showed elevated energy expenditure, but patients with colorectal cancer did not show any significant differences in energy metabolism from the controls. The type or stage of cancer may affect energy metabolism.

It has been suggested that systemic inflammatory mediators influence the energy metabolism of patients with cancer. In particular, cachexia is most pronounced in end-stage diseases that tend to associate with chronic inflammation, such as in cancer, chronic heart failure, or acquired immune deficiency disease. Proinflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6 must play a key role in cancer cachexia.[10–13] Cytokines are proteins that are predominantly synthesized and released from immune cells. However, changes in the levels of these mediators in peripheral blood do not occur in parallel. Plasma IL-6 levels are reported to be increased in patients with cancer.[14,15] In contrast, conflicting results are reported regarding the plasma levels of TNF-α.[16,17] The paradoxical changes in the levels of these proinflammatory cytokines are recognized to result from differences in their half-lives. Biologically active TNF-α is difficult to detect because of its short half-life and its formation of complexes with soluble TNF-α receptors.[18,19] Agnes *et al.*[20] examined the plasma levels of the soluble TNF-α receptor and clarified that TNF-α had the potential to affect energy expenditure in patients with lung cancer.

Recently, we used indirect calorimetry to examine the energy expenditure of patients with inflammatory bowel disease. Our results clearly showed that IL-6, but not TNF-α, affected the energy metabolism of patients with inflammatory bowel disease.[21] Here, we are the first to describe the nutritional status and REE as well as their relationships with systemic mediators such as proinflammatory cytokines, leptin, and ghrelin in patients with lung cancer.

Subjects and Methods

Patients. Twenty-eight patients with lung cancer (22 men and 6 women; mean age, 69.0 ± 10.9 years) were enrolled in this study. The patients were admitted to the Shiga University of Medical Science Hospital between July 2014 and June 2015. All patients had histologically documented tumors and had not undergone surgery. Sixteen patients who received chemotherapy had passed more than 1 month since their last treatment. All 18 healthy controls (9 men and 9 women; mean age, 65.1 ± 9.7 years) were volunteers; some of them had well-controlled hyperlipidemia or gastric ulcer scar. None of them had malignant or inflammatory disease. The ethics committee of the Shiga University of Medicine approved this study.

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Table 1. Patients characteristics

Characteristics	Healthy control	Lung cancer patient	*p* value
Patients number (male/female)	18 (9/9)	28 (22/6)	
Age (year)	65.1 ± 9.7	69.0 ± 10.9	0.180
Height (cm)	162.0 ± 9.4	161.6 ± 9.05	0.937
Body weight (kg)	61.1 ± 9.8	59.4 ± 13.5	0.451
BMI (kg/m^2)	23.2 ± 2.1	22.6 ± 4.1	0.636
Histology			
AC	—	17	
SCC	—	7	
SCLC	—	1	
NSCLC	—	2	
Carcinoid	—	1	
Staging			
I	—	9	
II	—	1	
III	—	6	
IV	—	12	

BMI, body mass index; AC, adenocarcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer. Each value represents the mean ± SD.

Methods. The following values were measured upon admission.

(1) Nutritional screening: Subjective global assessment (SGA),[22,23] malnutrition universal screening tool (MUST),[24] nutritional risk screening 2002 (NRS2002),[25] and modified Glasgow prognostic score (mGPS).[26]

(2) Anthropometrics: Height (cm), weight (kg), and body mass index (BMI; kg/m^2).

(3) Laboratory tests: Total protein level (g/dl), serum albumin (g/dl), total cholesterol (mg/dl), C-reactive protein (mg/dl), and total lymphocyte count.

(4) Bioelectrical impedance analysis: The percent of body fat (%) and fat-free mass (kg).

(5) Proinflammatory cytokines: Plasma IL-6 levels (pg/dl) and TNF-α levels (pg/dl) were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN).

(6) Appetite-controlling hormones: Plasma leptin levels (ng/ml) were measured using a radioimmunoassay. Plasma acylated ghrelin levels were measured using the active Ghrelin ELISA kit (LSI Medience Corporation, Tokyo, Japan).

(7) Intake: Dietary intake was calculated by an average of the intake over 2 days (kcal/day), and recommended energy need was calculated by multiplying the measured resting energy expenditure (mREE) by the active factor 1.3. The adequacy of energy intake was calculated as (dietary intake/recommended need) × 100 (%).

Indirect calorimetry. The mREE (kcal/kg/day), respiratory quotient (RQ), carbohydrate oxidation, and fat oxidation were measured via computed open-circuit indirect calorimetry (AE-300S, Minato Medical Science Co., Osaka, Japan).[21,27–31] Indirect calorimetry was performed in the hospital room after 8 h of fasting. Period flow and gas calibration were performed prior to all measurements. After resting for 30 min, the patients were assessed in a supine position using a facemask. A pump drew ambient air through a facemask at a constant rate. After equilibrium was reached for 10 min, respiratory exchange was performed continuously over 30 min. The mREE and RQ data were obtained every minute.

The mREE was calculated from the oxygen consumption (VO_2) and carbon dioxide production (VCO_2) using the Weir equation:[32] $mREE = (3.94 \times VO_2 + 1.11 \times VCO_2) \times 1.44$. The RQ measurement was calculated as $RQ = VCO_2/VO_2$. The mREE was then compared with the predicted resting energy expenditure (pREE), which was calculated using the Harris–Benedict equation as follows:[33]

Men: $pREE = 66.47 + 13.75 \times W$ [weight (kg)] $+ 5.0 \times H$ [height (cm)] $- 6.75 \times A$ [age (year)]

Women: $pREE = 665.09 + 9.56 \times W + 1.84 \times H - 4.67 \times A$.

Statistical analyses. The Mann–Whitney *U* test, the one-way analysis of variance, and the chi-squared test were used for the statistical analysis. Correlations were investigated by Spearman rank correlation tests. Values are expressed as the mean and standard deviation. A p value of <0.05 was considered statistically significant.

Results

Patient characteristics. Patient's characteristics are shown in Table 1. Staging of the carcinomas indicated that 9 patients had stage I, 1 patient had stage II, 6 patients had stage III, and 12 patients had stage IV tumors. There were no significant differences in mean age, height, body weight, or BMI between healthy controls and patients with lung cancer.

Nutritional screening. As shown in Table 2, we divided patients with lung cancer into three groups depending on staging; there were 10 patients in stages I and II, 6 patients in stage III, and 12 patients in stage IV. According to the SGA, 8.3% of stage IV patients were considered severely malnourished and 50% of them qualified as moderately malnourished. Stage IV patients tended to be qualified as malnourished more frequently than stage I and II or stage III patients, but there were no significant differences among the patients for these parameters ($p = 0.395$). According to the MUST, 33.3% of stage III patients and 58.4% of stage IV patients were considered at high risk for malnutrition. According to the NRS2002, 16.7% of stage III patients and 50.0% of stage IV patients were considered nutritionally at risk. Stage IV patients were more frequently qualified as high risk by the MUST ($p = 0.022$) and nutritionally at risk by the NRS2002 ($p = 0.023$). According to the mGPS, 33.3% of stage III patients and 50.0% of stage IV patients were considered to belong to the "Alb <3.5 g/dl and CRP ≥0.5 mg/dl" group. These percentages tended to be higher than those of the stage I and II patients ($p = 0.077$).

Laboratory tests, inflammatory cytokines, and appetite-controlling hormones. As shown in Table 3, serum albumin in stage IV patients (3.3 ± 0.8 g/dl) was significantly lower than in stage I and II patients (4.0 ± 0.4 g/dl). Total cholesterol in stage IV

Table 2. Nutritional screening

	Stage I and II	Stage III	Stage IV	*p* value
Patients number	10	6	12	
SGA	(%)	(%)	(%)	
Well nourished	70.0	83.3	41.7	0.395
Moderately malnourished	30.0	16.7	50.0	
Severely malnourished	0	0	8.3	
MUST				
Low risk	100.0	50.0	33.3	0.022
Medium risk	0	16.7	8.3	
High risk	0	33.3	58.4	
NRS2002				
Without nutritional risk	100.0	83.3	50.0	0.023
With nutritional risk	0	16.7	50.0	
mGPS				
Alb ≥3.5 g/dl and CRP <0.5 mg/dl	90.0	50.0	25.0	0.077
Alb <3.5 g/dl and CRP <0.5 mg/dl	10.0	0	8.3	
Alb ≥3.5 g/dl and CRP ≥0.5 mg/dl	0	16.7	16.7	
Alb <3.5 g/dl and CRP ≥0.5 mg/dl	0	33.3	50.0	

SGA, subjective global assessment; MUST, malnutrition universal screening tool; NRS2002, nutritional risk screening 2002; mGPS, modified Glasgow prognostic score.

Table 3. Laboratory tests and proinflammatory cytokines, appetite-controlling hormones

	Stage I and II	Stage III	Stage IV
Laboratory tests			
TP (g/dl)	6.9 ± 0.5	7.0 ± 0.5	6.9 ± 0.6
Alb (g/dl)	4.0 ± 0.4	3.8 ± 0.5	3.3 ± 0.8[a]
T-cho (mg/dl)	206.9 ± 40.2	182.8 ± 31.2	158.1 ± 26.6[a]
CRP (mg/dl)	0.1 ± 0.1	0.7 ± 0.7	3.7 ± 4.2[a,b]
TLC (/μl)	1,588.6 ± 558.7	1,466.5 ± 190.6	1,212.4 ± 525.8
Pronflammatory cytokines			
IL-6 (pg/ml)	14.6 ± 37.8	5.4 ± 5.1	30.3 ± 40.2
TNF-α (pg/dl)	2.2 ± 0.9	1.8 ± 0.7	2.7 ± 2.3
Appetite-controlling hormones			
Leptin (ng/ml)	5.3 ± 7.4	9.5 ± 7.4	10.1 ± 16.5
Acylated ghrelin (fmol/ml)	11.2 ± 10.0	19.0 ± 13.7	23.9 ± 19.5

TP, total protein; Alb, albumin; T-cho, total cholesterol; CRP, C-reactive protein; TLC, total lymphocyte count; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α. Each value represents the mean ± SD. [a]$p<0.05$ compared with lung cancer stage I and II. [b]$p<0.05$ compared with lung cancer stage III.

patients (158.1 ± 26.6 mg/dl) was significantly lower than in stage I and II patients (206.9 ± 40.2 mg/dl). The C-reactive protein level in stage IV patients (3.7 ± 4.2 mg/dl) was significantly greater than in stage I and II patients (0.1 ± 0.1 mg/dl) and stage III patients (0.7 ± 0.7 mg/dl).

The plasma IL-6 level tended to be higher in stage IV patients (30.3 ± 40.2 pg/ml) than in stage I and II patients (14.6 ± 37.8 pg/ml) or in stage III patients (5.4 ± 5.1 pg/ml), but the differences were not significant. There were no significant differences or tendencies in plasma TNF-α, leptin, or acylated ghrelin levels among these three groups.

Energy metabolism. As shown in Table 4, the mREE/body weight and mREE/pREE in healthy controls were 22.0 ± 2.6 kcal/kg/day and 1.05 ± 0.10, respectively. In stage I and II patients, the mREE/body weight was 20.9 ± 2.0 kcal/kg/day and the mREE/pREE was 1.02 ± 0.06. In stage III patients, the mREE/body weight was 21.8 ± 3.7 kcal/kg/day and the mREE/pREE was 1.07 ± 0.13. In stage IV patients, the mREE/body weight was 25.0 ± 5.5 kcal/kg/day and the mREE/pREE was 1.14 ± 0.14. The mean mREE/body weight in stage IV patients was significantly higher than in healthy controls ($p = 0.033$) or than in stage I and II patients ($p = 0.012$). Mean mREE/pREE in stage IV patients was higher than in the healthy controls ($p = 0.059$) or in stage I and II patients ($p = 0.031$). However, there were no significant differences in RQ, glucose, or fat oxidation between the patients with lung cancer and healthy controls.

There were positive correlations between plasma IL-6 levels and mREE/body weight and between plasma IL-6 levels and mREE/pREE. However, there was no significant correlation between plasma TNF-α levels and mREE/body weight or between plasma TNF-α levels and mREE/pREE (Fig. 1).

Dietary intake and the adequacy of energy intake. Dietary intake was 1,600 ± 202 kcal/day in stage I and II patients, 1,391 ± 329 kcal/day in stage III patients, and 1,271 ± 458 kcal/day in stage IV patients. Sixty percent of stage I and II patients, 83% of stage III patients, and 75% of stage IV patients

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Table 4. Energy metabolism

	Healthy controls	Lung cancer patients		
		Stage I and II	Stage III	Stage IV
mREE (kcal/day)	1,335 ± 215	1,260 ± 173	1,413 ± 278	1,343 ± 340
pREE (kcal/day)	1,274 ± 169	1,240 ± 168	1,311 ± 173	1,189 ± 292
mREE/BW (kcal/kg/day)	22.0 ± 2.6	20.9 ± 2.0	21.8 ± 3.7	25.0 ± 5.5[a,b]
mREE/pREE	1.05 ± 0.10	1.02 ± 0.06	1.07 ± 0.13	1.14 ± 0.14[b]
RQ	0.84 ± 0.06	0.80 ± 0.04	0.81 ± 0.05	0.81 ± 0.08
C (g/day)	152.3 ± 78.3	97.5 ± 30.6	128.1 ± 84.4	107.1 ± 71.2
F (g/day)	75.0 ± 30.1	90.6 ± 27.6	93.4 ± 28.9	96.1 ± 50.1

mREE, measured resting energy expenditure; pREE, predicted resting energy expenditure; BW, body weight; RQ, respiratory quotient; C, carbohydrate oxidation; F, fat oxidation. Each value represents the mean ± SD. [a]$p<0.05$ compared with healthy controls. [b]$p<0.05$ compared with lung cancer stage I and II.

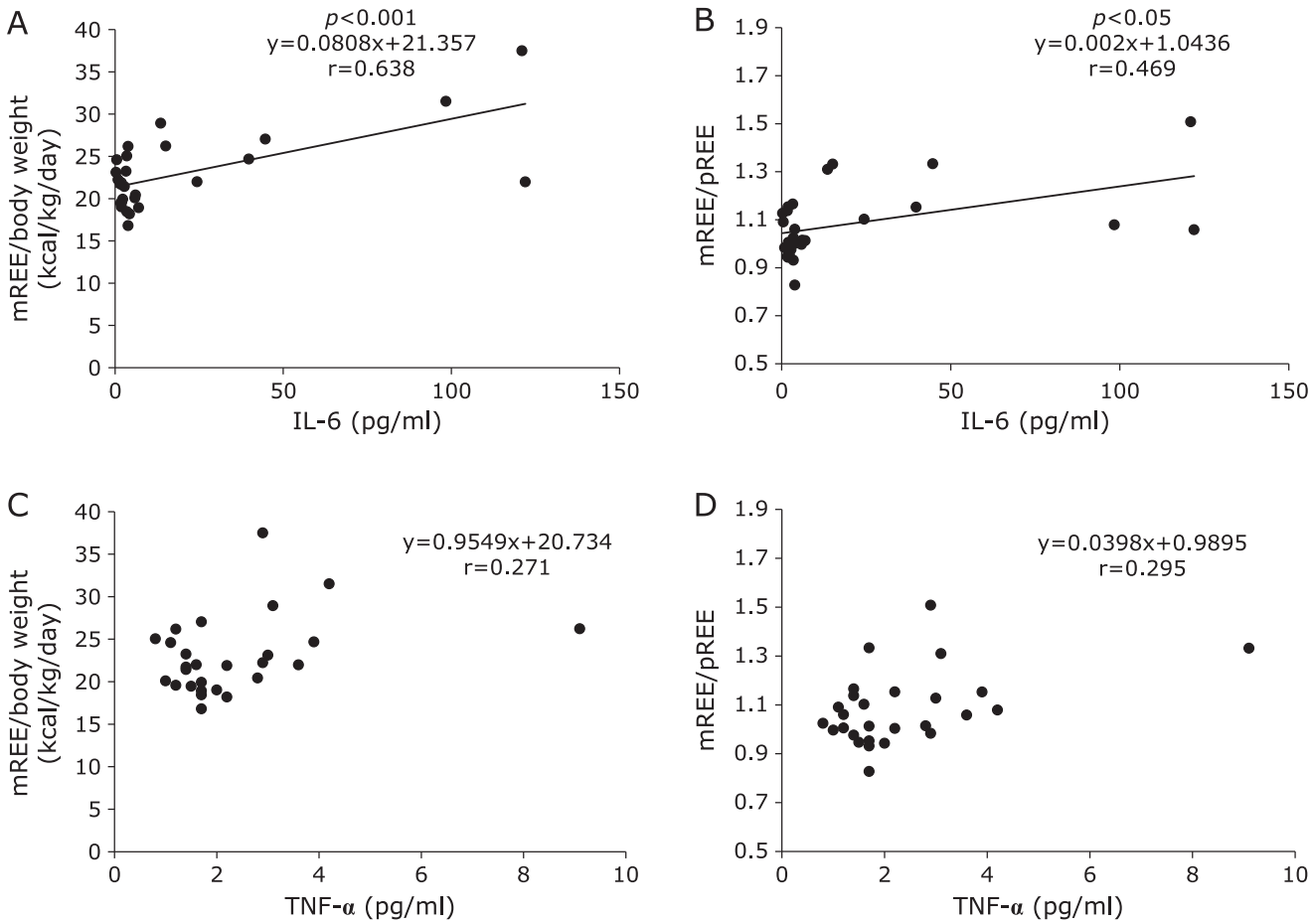

Fig. 1. Correlations between plasma interleukin-6 (IL-6) levels and tumor necrosis factor-α (TNF-α) levels with measured resting energy expenditure (mREE)/body weight or mREE/predicted resting energy expenditure (mREE/pREE) in patients with lung cancer. Plasma IL-6 levels exhibited a positive correlation with mREE/body weight (A) and with mREE/pREE (B). However, there was no significant correlation between plasma TNF-α levels and mREE/body weight (C) or mREE/pREE (D).

eat less than their nutritional need.

As shown in Fig. 2, there were positive correlations between plasma leptin levels and BMI and between plasma leptin levels and percent body fat. However, there was no significant correlation between plasma leptin levels and dietary intake or between plasma leptin levels and the percent of recommended needs.

As shown in Fig. 3, there was a negative correlation between plasma acylated ghrelin levels and BMI. There was also a negative tendency of correlation between plasma acylated ghrelin levels and the percent body fat ($p = 0.090$). However, there were no significant correlations between plasma acylated ghrelin levels and dietary intake or between plasma acylated ghrelin levels and the rate of energy intake.

There were significant negative correlations between plasma IL-6 levels and dietary intake and between plasma IL-6 levels and the rate of energy intake. However, there were no significant

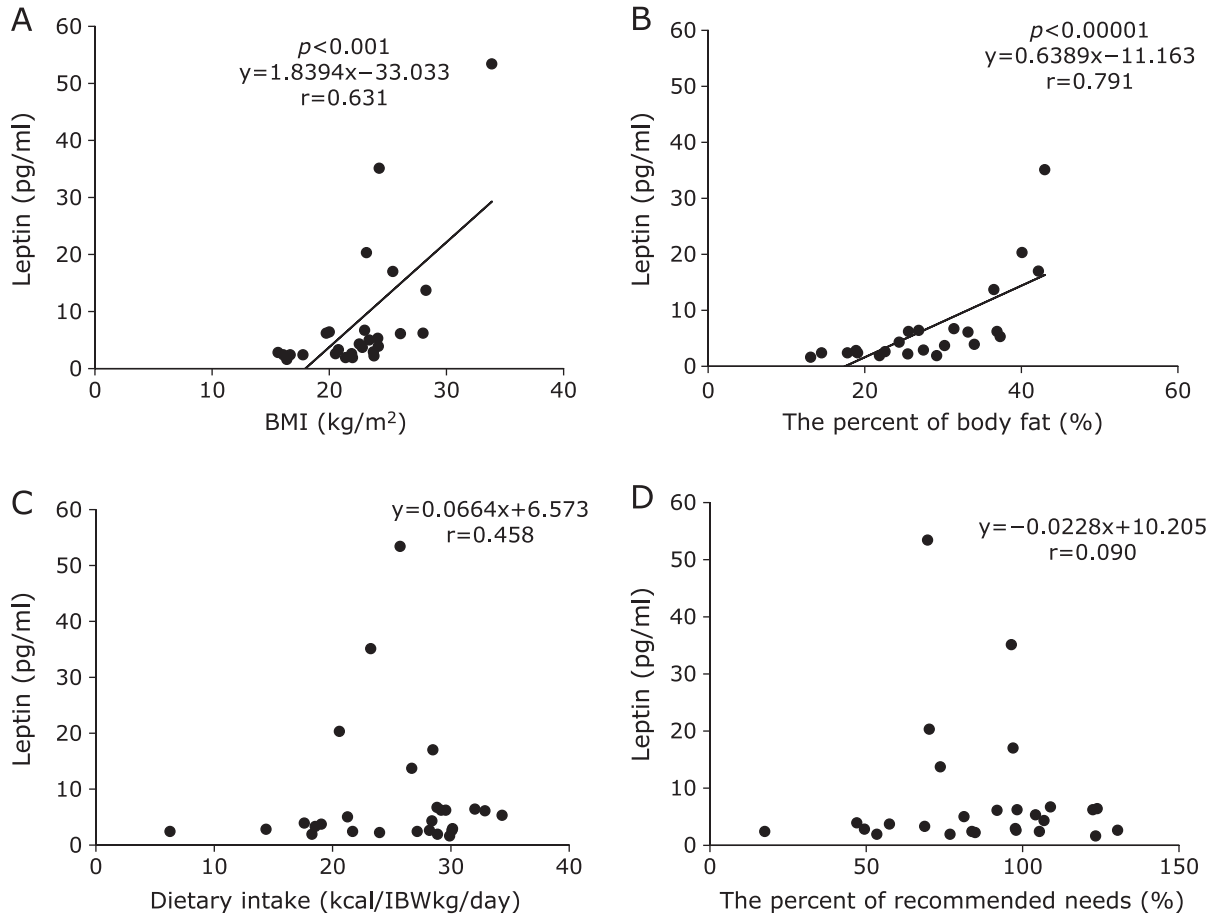

Fig. 2. Correlations between plasma leptin levels and body mass index (BMI), the percent of body fat (%FAT), intake, and the percent of recommended needs in patients with lung cancer. Plasma leptin levels exhibited a positive correlation with BMI (A) and %FAT (B). However, there was no significant correlation between plasma leptin levels and intake (C) or percent of recommended needs (D).

correlations between plasma TNF-α levels and dietary intake or between plasma TNF-α levels and the rate of energy intake (Fig. 4).

Discussion

In this study, we demonstrated that REE was elevated in patients with advanced lung cancer and that this change in energy metabolism was significantly associated with plasma levels of the proinflammatory cytokine IL-6. It has been generally accepted that the proinflammatory cytokines IL-1β, IL-6, and TNF-α are connected with malnutrition in patients with cancer.[34] Furthermore, these cytokines play important roles in the pathogenesis of cachexia.[13] DeJong *et al.*[35] showed that plasma levels of the systemic inflammatory mediators IL-6 and soluble TNF-α receptor correlated with an increased ubiquitin level, which played an important role in muscle wasting in cachexia.

Thus, proinflammatory cytokines certainly induce muscle wasting in patients with cancer. In particular, increased plasma IL-6 levels were reported in patients with lung cancer,[36] and there are some reports of a significant relationship between systemic inflammation and REE.[37] Previously, Kotani *et al.*[38] reported that mREE/pREE exhibited a significant correlation with IL-6 level but was not correlated with TNF-α levels in surgical trauma. In the present study, we clearly demonstrated that IL-6, but not TNF-α, played a main role in the negative balance of energy metabolism in patients with lung cancer. This phenomenon is quite similar to our recent report concerning energy metabolism in patients with inflammatory bowel disease.[21] Certainly, TNF-α has been reported to be a strong inducer of IL-6 production,[39] and at least some of the elevation of serum IL-6 levels depends upon TNF-α. However, it has been reported that biologically active TNF-α is difficult to detect because of its short half-life and the formation of complexes with soluble TNF-α receptors.[20] These characteristics of TNF-α may impact the serum levels of IL-6 and TNF-α in our present study.

Körber *et al.*[40] reported that lipid utilization was increased in patients with cancer who were losing weight. We recently reported similar results in patients with Crohn's disease receiving anti-TNF-α therapy.[29] Glucose oxidation may be inhibited by proinflammatory cytokines such as IL-6 or TNF-α.[41,42] However, in our present study, there were no significant differences in glucose or fat oxidations between patients with lung cancer and healthy controls.

In this study, we examined the levels of leptin and ghrelin in patients with lung cancer. We demonstrated that the plasma leptin level significantly correlated with BMI in patients with lung cancer. Tas *et al.*[43] also reported that plasma leptin levels were significantly lower in patients with lung cancer than in healthy controls and that the plasma leptin level significantly decreased after chemotherapy. Leptin is derived from the adipose tissue and plays a role in inhibiting energy intake. We speculate that reduced leptin secretion may represent a compensatory mechanism during energy imbalance. In contrast, ghrelin is derived from the stomach

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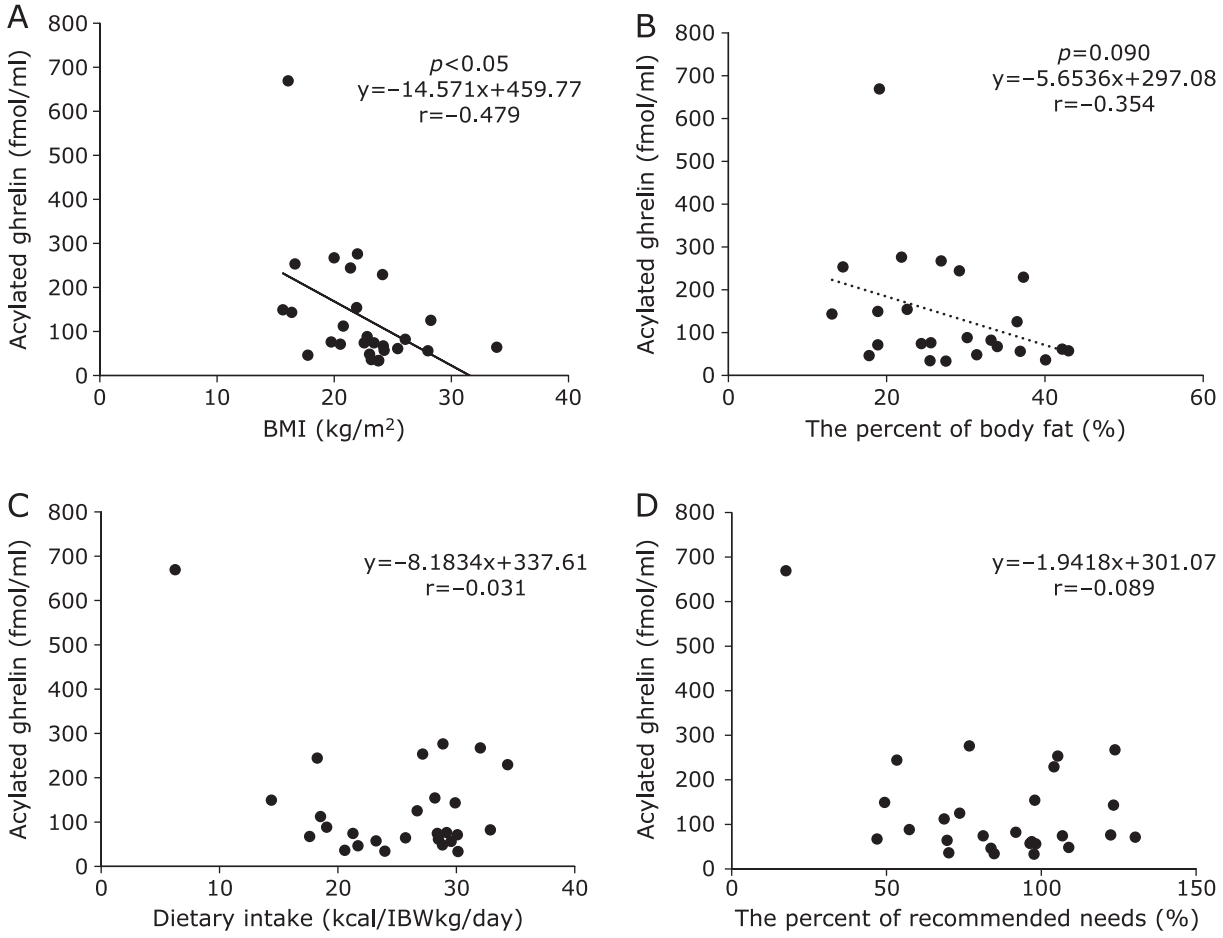

Fig. 3. Correlation between acylated ghrelin levels and body mass index (BMI), the percent of body fat (%FAT), intake and the percent of recommended needs. Acylated ghrelin levels exhibited negative correlation with BMI (A) and %FAT ($p = 0.090$) (B). However, there was no significant correlation between acylated ghrelin levels and intake (C) or the percent of recommended needs (D).

and is one of the hormones involved in controlling body weight, insulin secretion, and appetite regulation. Of the two circulating forms of ghrelin, acylated and des-acylated, the acylated form is thought to be essential for the biological activity of ghrelin. Previously, Shimizu *et al.*[44] reported that plasma ghrelin levels were significantly higher in patients with lung cancer cachexia than in healthy controls or in patients with non-cachexia lung cancer. Furthermore, we demonstrated that the plasma acylated ghrelin level negatively correlated with BMI. From these results, increased acylated ghrelin may also represent a compensatory mechanism during energy imbalance. Similar findings have been reported in patients with chronic obstructive pulmonary disease. Takabatake *et al.*[45] also reported significant correlations between plasma leptin levels (log transformed) and BMI or the percent of fat in patients with chronic obstructive pulmonary disease. Itoh *et al.*[46] reported that plasma ghrelin levels were significantly higher in underweight patients with chronic obstructive pulmonary disease. Changes in plasma leptin and acylated ghrelin levels follow the same pattern in patients with lung cancer that they do in those with chronic obstructive pulmonary disease. Leptin has been reported as a candidate factor of increasing REE.[47] However, no significant relationship between mREE and plasma leptin or ghrelin levels was seen in this study. We could not demonstrate that these signals affected energy expenditure itself in patients with lung cancer. The number of patients in this study was not large, and only two patients revealed cachexic findings. Recently, Fearon *et al.*[48] defined and classified cancer cachexia into three stages of clinical relevance: pre-cachexia, cachexia, and refractory cachexia. It may be necessary to investigate energy metabolism in a large number of patients with advanced lung cancer according to these three stages.

Anorexia and reduced food intake are among the host physiologic responses to tumors, and anorexia is an important symptom in patients with advanced cancer. In patients with cancer, anorexia contributes to the development of malnutrition or cachexia. Multiple factors, such as proinflammatory cytokines, eicosanoids, and hormones, have been connected with cancer anorexia. Our results confirm that plasma IL-6 correlates with reduced food intake, and proinflammatory cytokines play a significant role in energy imbalance. Trikha *et al.*[49] reported that anti-IL-6 monoclonal antibody therapy decreased the incidence of cancer-related anorexia and cachexia. This therapy may be useful in treating malnutrition in patients with lung cancer. The usefulness of fish oil for patients with pancreatic or colorectal cancer has recently been reported.[50,51] Fish oils, such as eicosapentaenoic acid, may inhibit the function of proinflammatory cytokines.[52–54] Some nutritional factors, such as eicosapentaenoic acid, may be useful in the nutritional management of patients with lung cancer.

In conclusion, REE was increased in patients with advanced lung cancer, and the proinflammatory cytokine IL-6 affected this change in energy metabolism. Leptin and acylated ghrelin were secreted as a compensatory mechanism during energy imbalance.

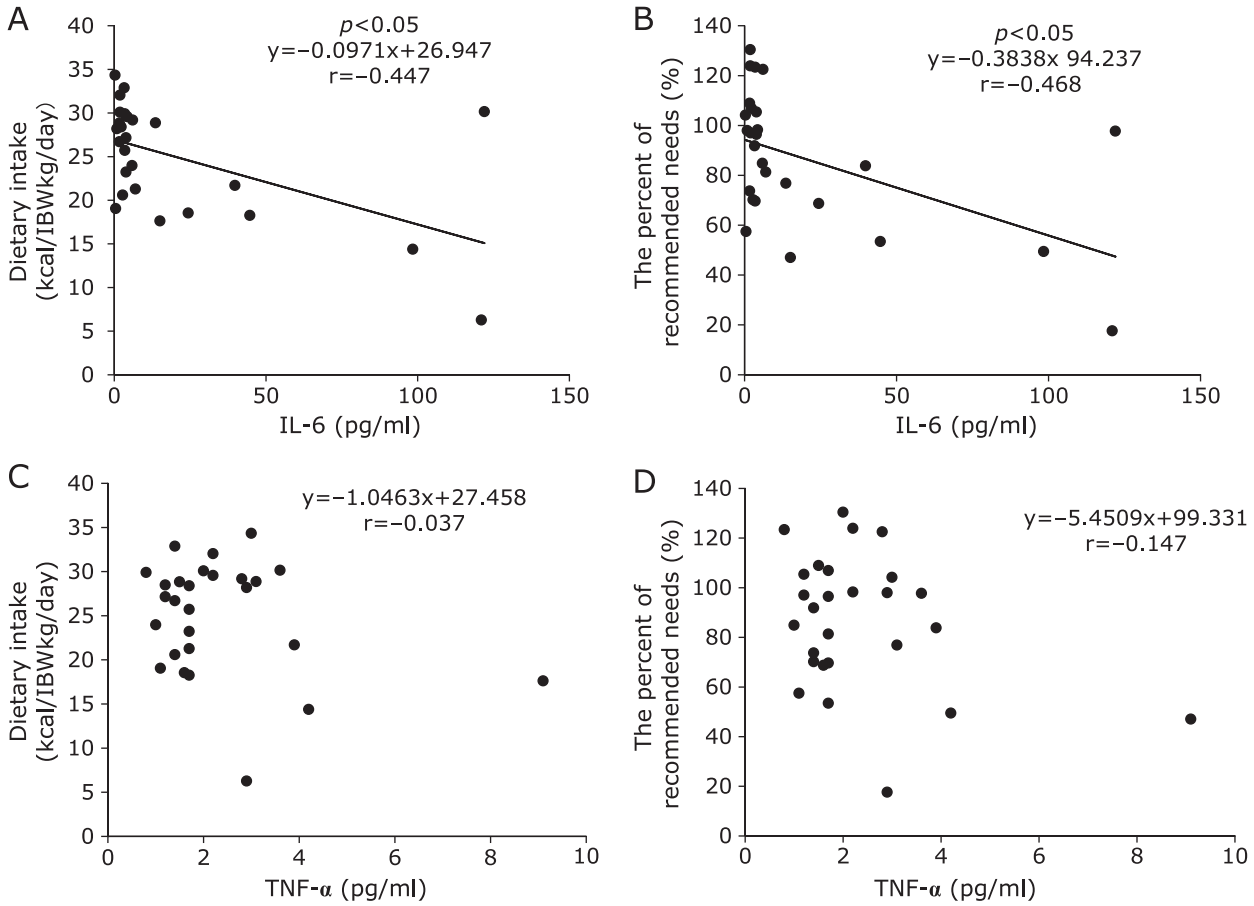

Fig. 4. Correlation between plasma interleukin-6 (IL-6) levels and tumor necrosis factor-α (TNF-α) levels or intake or the percent of recommended needs. Plasma IL-6 levels exhibited negative correlation with intake (A) and the percent of recommended needs (B). However, there was no significant correlation between plasma TNF-α levels and intake (C) or the percent of recommended needs (D).

Nevertheless, reduced appetite was seen in advanced patients with lung cancer. From our results, IL-6 may also affect this cancer-related anorexia. Therefore, nutritional management that considers the changes in energy metabolism is important in patients with lung cancer.

Conflict of Interest

No potential interests of conflict were disclosed.

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