Original Article

Changes of energy metabolism, nutritional status and serum cytokine levels in patients with Crohn's disease after anti-tumor necrosis factor-α therapy

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We investigated the effects of treatment with antibodies against tumor necrosis factor (TNF)-α on energy metabolism, nutritional status, serum cytokine levels in patients with Crohn's disease (CD). Twelve patients were enrolled. Resting energy expenditure (REE) levels were measured by indirect calorimetry. Crohn's disease activity index (CDAI) significantly decreased after treatment with anti-TNF-α therapy. Anti-TNF-α therapy did not affect REE, but respiratory quotient (RQ) significantly increased after treatment. Serum interleukin-6 levels were significantly decreased and RQ were significantly increased in high REE (≥25 kcal/kg/day) group as compared to low REE (<25 kcal/kg/day) group. In conclusion, high REE value on admission is a predictive factor for good response to treatment with anti-TNF-α antibodies in active CD patients.

Key Words: **Crohn's disease, energy metabolism, indirect calorimetry, infliximab, adalimumab**

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal (GI) tract of unknown etiology but with pathogenesis likely involving genetic predisposition, alterations of gut microbiota, diet, and other environmental factors.[1–3] CD is associated with symptoms such as abdominal pain and watery diarrhea, and with signs including GI bleeding and perianal fistulas. Endoscopic findings include longitudinal ulcers and mucosal bleeding. Patients often suffer from protein-energy malnutrition caused by malabsorption,[4] and rates of emaciation ranging from 20–75% have been reported in patients with CD.[5,6] Deficiencies of micronutrients such as zinc and selenium occur relatively frequently (25–69%), particularly in CD patients receiving long-term enteral nutrition, and nutritional support is essential in the treatment of this disease, with enteral nutrition (EN) or total parenteral nutrition (TPN) widely accepted as effective therapies for induction or maintenance of remission.[7]

Energy expenditure is reportedly higher in patients with CD than in healthy controls.[8–10] Indeed, we previously demonstrated a marked difference in resting energy expenditure (REE) between CD patients (24.4 ± 2.4 kcal/kg/day) and healthy controls (21.3 ± 1.7 kcal/kg/day) and proposed that nutritional therapy with 25–30 kcal/ideal body weight in kg/day is optimal for patients with active CD.[8] In contrast, Schneeweiss *et al.*[11] found no marked difference in REE values between CD patients and healthy controls but reported that the respiratory quotient (RQ) was significantly lower in patients with active CD. Enteral nutrition has been reported to alter the usage of energy substrates while having no effect on energy expenditure.[11]

Tumor necrosis factor (TNF-α) is a pro-inflammatory cytokine expressed in the inflamed mucosa of patients with active CD. Recently, the anti-TNF-α antibodies infliximab and adalimumab have been recognized as powerful therapeutic tools for remission induction and maintenance in CD patients.[12,13] Patients receiving infliximab experience decreased disease activity, with accompanying lower incidence of relapse and less frequent hospitalization.[14] Further, Hanauer *et al.*[15] reported that adalimumab was superior to placebo in inducing and maintaining remission in patients with moderate-to-severe CD.

Here, we measured changes in energy metabolism, nutritional status, and serum cytokine levels after anti-TNF-α antibody treatment of patients with active CD.

Subjects and Methods

Patients. Twelve patients, admitted with active CD to the Department of Gastroenterology at Shiga University of Medical Science Hospital between June 2011 and July 2012, were enrolled. All patients had been diagnosed with CD using radiological, histological, and clinical criteria. One patient had been treated at an outpatient clinic. Patients who had previously undergone ileostomy or colostomy were excluded.

Methods. The following values were measured before and after treatment with anti-TNF-α antibodies:

1) Anthropometrics: height (cm), weight (kg), body mass index (kg/height in meters squared), percent ideal body weight (body weight in kg × 100/height in meters squared × 22), and percent usual body weight calculated (actual body weight in kg × 100/usual body weight in kg). Usual body weight was taken from a subjective global assessment sheet filled out on admission, or per patients' reports.
2) Laboratory tests: red blood cell count ($\times 10^4$/mm^3), hemoglobin (g/dl), hematocrit (%), white blood cell count (/mm^3), mean corpuscular volume (fl), total lymphocyte count(/mm^3), platelets ($\times 10^3$/mm^3), C-reactive protein (mg/dl), albumin (g/dl).

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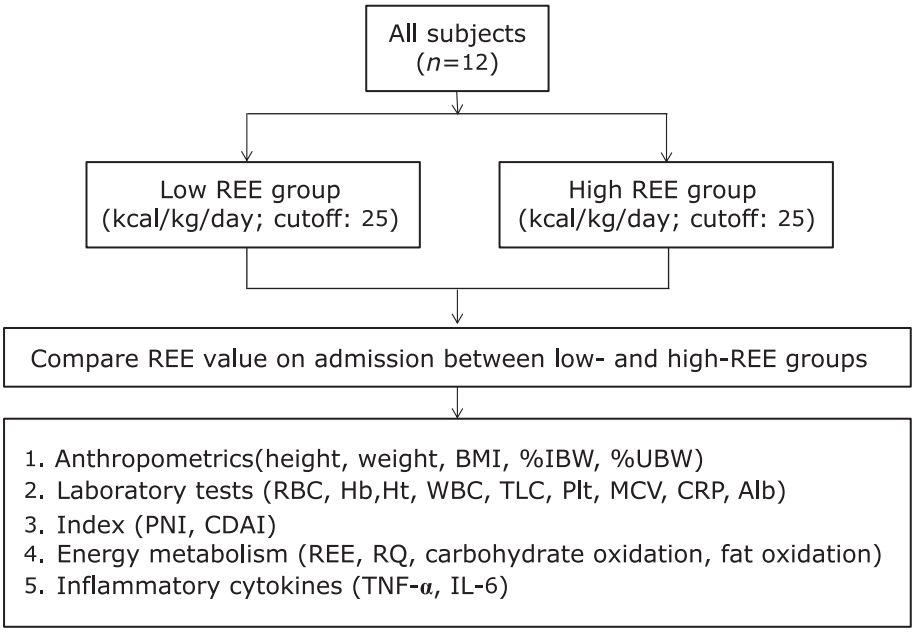

Fig. 1. Evaluated markers. All subjects were divided into two groups according to the REE value of on admission. BMI, body mass index; %IBW, % ideal body weight; %UBW, % usual body weight; RBC, red blood cell count; Hb, hemoglobin; Ht, hematocrit; WBC, white blood cell count; TLC, total lymphocyte count; Plt, platelet count; MCV, mean corpuscular volume; CRP, C-reactive protein; Alb, serum albumin; CDAI, Crohn's disease activity index; PNI, prognostic nutritional index; REE, resting energy expenditure; RQ, respiratory quotient; TNF-α, tumor necrosis factor α; IL-6, Interleukin-6.

3) Indecies: Prognostic nutritional index (PNI) calculated as $10 \times$ albumin (g/dl) $+ 0.005 \times$ total lymphocyte count per cubic mm, Crohn's disease activity index (CDAI).[16,17]
4) Energy metabolism (all measured by indirect calorimetry): REE (kcal/kg/day), RQ, carbohydrate oxidation (kcal/kg/day), and fat oxidation (kcal/kg/day).
5) Inflammatory cytokines: TNF-α (pg/dl) and interleukin-6 (IL-6) (pg/dl) were determined using commercially available ELISA kits (R&D Systems, Minneapolis, MN).

As shown in Fig. 1, subjects were categorized into two groups according to their REE (cutoff: 25 kcal/kg/day) using the values on admission.

Indirect calorimetry. REE (mREE) and non-protein respiratory quotients (np-RQ) were measured using a computed open-circuit indirect calorimeter (AE-300S; Minato Medical Science Co., Osaka, Japan).[8,18–20] Indirect calorimetry (IC) was performed in the same ward room in the hospital after an 8-h fast. Calibration was performed prior to measurements on each patient. After resting at least 30 min, mREEs were assessed in a supine position with a face mask. A pump drew ambient air through the mask at a constant rate. After equilibrating for 10 min, respiratory exchange was performed continuously over 30 min. The mREE and np-RQ data were obtained every minute. The mREE was calculated from oxygen consumption (VO_2) and carbon dioxide production (VCO_2) using the Weir's equation.[21]

$$\text{mREE} = (3.94 \times VO_2 + 1.11 \times VCO_2) \times 1.44$$

Although we were able to evaluate the rates of fat and carbohydrate oxidation, we were not able to analyze the protein oxidation rate, as urine was not collected.

Statistical analysis. The Wilcoxon signed rank test was used to analyze differences between two statuses (pre- and post-treatment). A p value <0.05 was considered to be statistically significant. Results were expressed in median (25% quartile, 75% quartile).

Results

Patients' characteristics are shown in Table 1. Among them, three patients had disease confined to the ileal while nine had ileo-colitic involvement. Infliximab was used in five patients, and adalimumab in seven. One patient receiving each treatment underwent infliximab and one of adalimumab[7] after surgery of ileo-cecal resection during their hospital stay. Nine patients received TPN (eight of whom were shifted to elemental diet therapy while still in hospital), and three patients received elemental diet therapy (in combination with peripheral parenteral nutrition in two patients). Seven patients were also treated with mesalazine and four with azathioprine.

As shown in Table 2, values for white blood cell (WBC) numbers, CDAI, and fat oxidation significantly decreased after treatment with anti-TNF-α antibodies, while serum albumin levels, PNI, RQ, and carbohydrate oxidation significantly increased. No significant changes in REE were noted after treatment ($p = 0.084$). The significant increases in RQ were supported by the findings of concomitant significant decreases in fat oxidation ($p<0.01$) and significant increases in carbohydrate oxidation ($p<0.01$).

We divided the patients into two groups according to REE at admission, with a cutoff of 25 kcal/kg/day. While CDAI decreased significantly in both groups ($p<0.05$) (Fig. 2), RQ significantly increased in the high-REE group ($p<0.05$) (Fig. 3). WBC numbers and C-reactive protein (CRP) levels also significantly decreased($p<0.05$, respectively), while albumin significantly increased in patients in the high-REE group ($p<0.05$) (Table 3). Serum IL-6 levels were significantly decreased in the high-REE patients (Fig. 4). Platelet counts underwent a significant decrease in the high-REE group but remained in normal ranges before and after treatment.

Discussion

Recently introduced, infliximab and adalimumab are powerful tools for the treatment of CD. Nutritional therapy is also consid-

Table 1. Characteristics of CD patients (n = 12)

Characteristics	
Age (y)	27 (24, 36)
Gender (male/female)	9/3
BMI (kg/m^2)	
Pre-treatment	17.7 (16.6, 21.2)
Post-treatment	18.3 (17.1, 20.9)
Type of CD (ileal/ileocolitic)	3/9
Treatments	
Anti-TNF-α (infliximab and adalimumab)	5/7
Nutritional therapy	
TPN (TPN shifted to ED therapy)	9 (8)
Elemental diet therapy(ED therapy in combination with PPN)	3 (2)

CD, Crohn Disease; BMI, body mass index; TPN, total parenteral nutrition; ED, elemental diet; PPN, peripheral parenteral nutrition. Values are expressed as median (25% quartile, 75% quartile).

Table 2. All values before and after treatment (n = 12)

	Pre-	Post-	p
Body weight			
BMI (kg/m^2)	17.7 (16.6, 21.2)	18.3 (17.1, 20.9)	0.265
%IBW (%)	80.3 (75.6, 96.2)	82.8 (77.8, 95.1)	0.23
%UBW (%)	86.8 (83.3, 97.0)	89.6 (86.6, 95.4)	0.213
Laboratory tests			
RBC ($\times 10^4$/mm^3)	386 (330, 469)	398 (377, 440)	0.308
Hb (g/dL)	11.3 (9.4, 11.9)	11.6 (11.1, 12.0)	0.1
Ht (%)	35.0 (28.2, 36.8)	35.1 (33.7, 36.7)	0.136
WBC (/mm^3)	6700 (6100, 8900)	5000 (4000, 5700)	0.041
MCV (fL)	85.3 (78.4, 86.7)	87.7 (82.0, 89.0)	0.117
TLC (/mm^3)	1530 (1134, 2089)	1837 (1636, 2113)	0.099
Plt ($\times 10^3$/mm^3)	438 (404, 496)	311 (244, 345)	0.062
CRP (mg/dL)	2.36 (1.07, 5.14)	0.12 (0.04, 0.23)	0.06
Alb (g/dL)	3.0 (2.8, 3.3)	3.6 (3.5, 3.8)	0.004
Index			
PNI	38.7 (34.6, 43.1)	46.1 (45.7, 47.8)	0.012
CDAI	221 (163, 286)	138 (115, 166)	0.002
Energy metabolism			
REE (kcal/kg/day)	26.6 (23.4, 30.6)	24.9 (21.8, 26.6)	0.084
RQ	0.82 (0.80, 0.85)	0.86 (0.84, 0.95)	0.003
Fat oxidation (kcal/kg/day)	14.7 (13.3, 16.9)	9.4 (4.3, 12.2)	0.002
Carbohydrate oxidation (kcal/kg/day)	8.7 (7.5, 14.8)	13.2 (9.2, 21.5)	0.008
Inflammatory cytokines			
TNF-α (pg/dL)	2.1 (1.8, 2.5)	2.2 (1.4, 3.8)	0.185
IL-6 (pg/dL)	10.7 (6.2, 14.7)	3.0 (2.1, 4.1)	0.091

BMI, body mass index; %IBW, % ideal body weight; %UBW, % usual body weight; RBC, red blood cell count; Hb, hemoglobin; Ht, hematocrit; WBC, white blood cell count; MCV, mean corpuscular volume; TLC, total lymphocyte count; Plt, platelets; CRP, C-reactive protein; Alb, albumin; CDAI, Crohn disease activity index; PNI, prognostic nutritional index; REE, resting energy expenditure; RQ, respiratory quotient; TNF-α, tumor necrosis factor α; IL-6, interleukin-6. Values are expressed asmedian (25% quartile, 75% quartile).

ered to be indispensable. The current study suggests that anti-TNF-α therapy has positive effects on both nutritional and inflammatory status, as demonstrated by the significant decrease in CDAI and increase in serum albumin levels, RQ, and PNI values after treatment. While the usefulness of PNI as a nutritional and inflammatory marker has been reported in patients with colon cancer,[17] it has not yet been validated in CD patients. Potential availability and feasibility to evaluate the clinical activity and nutritional status of CD seems to be interesting, and further studies should be performed to validate its utility.

The treatment-related increase in RQ levels in the high-REE group might be due to decreases in lipolysis and recovery from starvation state induced by calming down the inflammation. Findings concerning the effects of anti-TNF-α therapy on energy metabolism in CD patients are controversial. Wiese *et al.*[22] reported that RQ tended to increase after infliximab therapy (p = 0.07), whereas no increase was detected in the REE value. In contrast, Steiner *et al.*[23] working with pediatric patients reported a significant reduction in RQ during parenteral nutrition after infliximab therapy. To our knowledge, ours is the first report demonstrating that RQ values are significantly increased after treatment with anti-TNF-α therapy in patients with active CD.

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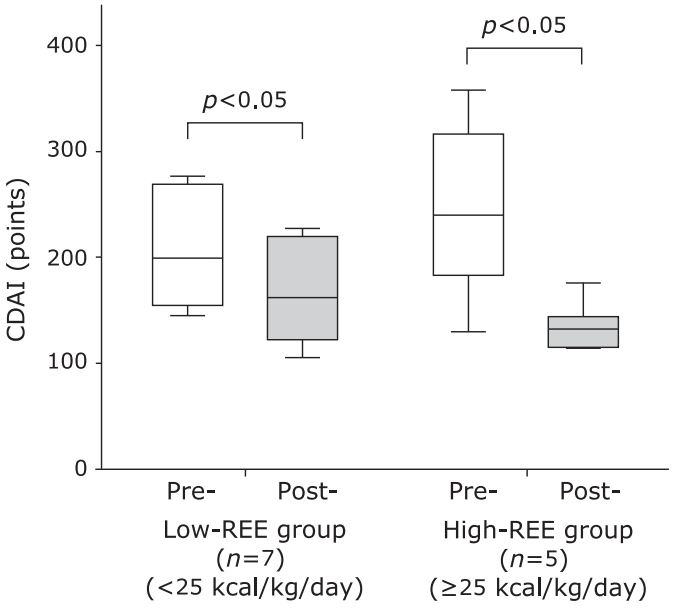

Fig. 2. Comparison of changes in RQ according to REE on admission (cutoff, 25 kcal/kg/day). Data are expressed as the median and interquartile ranges. CDAI, Crohn's disease activity index; REE, resting energy expenditure.

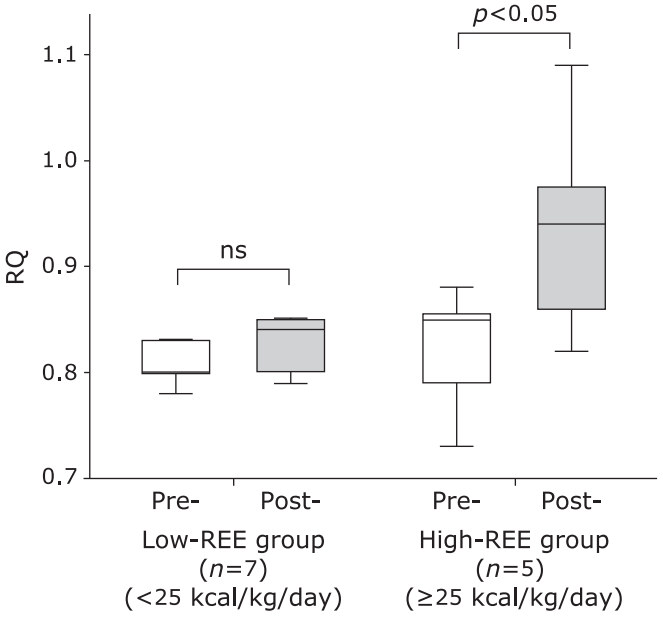

Fig. 3. Comparison of changes in CDAI according to REE on admission (cutoff, 25 kcal/kg/day). Data are expressed as the median and interquartile ranges. RQ, respiratory quotient; REE, resting energy expenditure; ns, not significant.

Table 3. Comparison of pre- and post-treatment changes based on REE atadmission

	Pre-	Post-	*p*
High REE group (*n* = 7)			
WBC (/mm^3)	8000 (7100, 10000)	5100 (4500, 6200)	0.018
Plt ($\times 10^3$/mm^3)	440 (434, 498)	320 (291, 342)	0.018
CRP (mg/dL)	2.36 (1.21, 4.58)	0.05 (0.03, 0.09)	0.018
Alb (g/dL)	3.2 (2.9, 3.3)	3.7 (3.6, 3.9)	0.028
Low REE group (*n* = 5)			
WBC (/mm^3)	5750 (5525, 6025)	4200 (4000, 4625)	0.686
Plt ($\times 10^3$/mm^3)	263 (225, 384)	202 (199, 339)	1.000
CRP (mg/dL)	3.07 (1.15, 7.49)	0.95 (0.25, 1.67)	0.893
Alb (g/dL)	2.9 (2.9, 3.1)	3.6 (3.5, 3.6)	0.066

REE, resting energy expenditure; WBC, white blood cell count; Plt, platelet; CRP, C-reactive protein; Alb, albumin. Values are expressed asmedian (25% quartile, 75% quartile).

The reduced fat stores in CD patients can be explained by an increase in fat oxidation.[9] Glucose oxidation may be inhibited by pro-inflammatory cytokines such as TNF-α and IL-6,[24,25] and the principal metabolic substrate may shift from fat to carbohydrate oxidation after anti-TNF-α therapy. This suggests that RQ is a useful marker in the assessment of disease activity and the prediction of response to anti-TNF-α therapy.

The measurement of individual REE is essential for planning optimal nutritional treatment regimens in CD patients in order to prevent overfeeding and the resultant Refeeding syndrome.[26] In the present study, REE values did not show significant change during anti-TNF-α treatment. Our observations are compatible with the findings of some recent reports. For example, Wiese *et al.*[22] reported no significant changes in REE values after 6 weeks and 6 months of infliximab therapy in adult CD patients, and another study in pediatric patients found no significant changes in REE after 2 weeks of infliximab therapy.[23,27] However, Kushner *et al.*[10] reported that REE increased with increasing clinical disease activity. These conflicting findings may indicate a complicated energy status in patients with active disease, due to starvation from reduced dietary intake and superimposed hypermetabolic status associated with the inflammation.

In the high-REE group, serum IL-6 levels significantly decreased after anti-TNF-α therapy, but this was not observed in the low-REE group. This finding is compatible with the recent report that IL-6 is one of several factors contributing to the REE value and that serum IL-6 levels correlate with severity of malnutrition.[28,29] These suggest that higher IL-6 levels before treatment can be used to predict efficacy of anti-TNF-α therapy and thereby improve nutritional status as well as inflammatory status.

TNF-α has been reported to be a strong inducer of IL-6 production in many cell types,[30,31] suggesting that at least some of the elevation of serum IL-6 levels is dependent on TNF-α. TNF-α likely played a role in the elevation of serum IL-6 levels in the high-REE patients in the present study, and neutralization of TNF-α by anti-TNF-α antibodies may improve TNF-α-dependent IL-6 elevation and any part of the REE value that is IL-6-dependent.

In contrast, in the low-REE patients, IL-6 levels were not

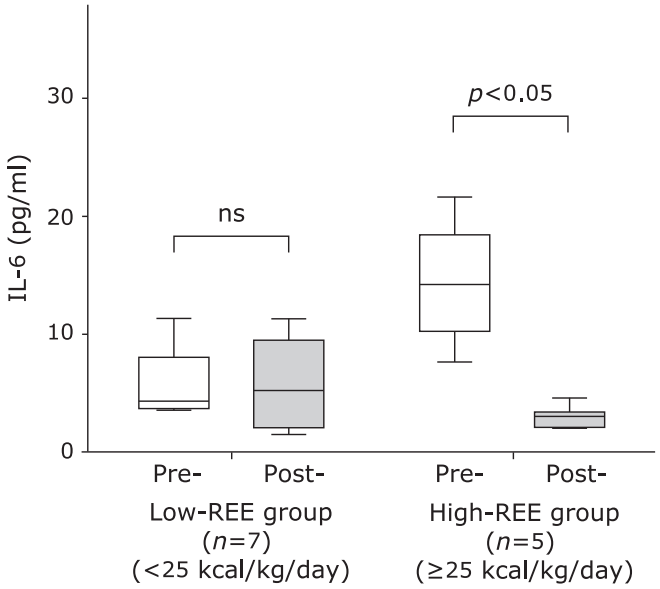

Fig. 4. Comparison of changes in IL-6 levels with REE on admission (cutoff, 25 kcal/kg/day). Data are expressed as the median and interquartile ranges. IL-6, Interleukin-6; REE, resting energy expenditure; ns, not significant.

elevated at admission, and anti-TNF-α antibodies revealed no significant effects, indirectly suggesting that TNF-α may not play a role in the pathophysiology of low-REE patients. Previous studies have indicated that protein malnutrition induces a suppression of the general immune response.[32] A recent study by Hashimoto *et al*.[33] clearly demonstrated that lack of a single amino acid in the diet impairs intestinal immunity and enhances the susceptibility to gastrointestinal infections. Based on these observations, low serum IL-6 levels coupled with low REE values in CD patients may be associated with a malnutrition-induced reduction of immune response.

In conclusion, active CD patients showed a significant decrease in fat oxidation after initiation of anti-TNF-α antibody treatment, indicating that the substrate of energy metabolism shifted from fat to carbohydrate after treatment, and thereby suggesting that a decrease in RQ value may be a predictor of the efficacy of anti-TNF-α antibody therapy. In addition, measurement of REE values is important not only predicting response to anti-TNF antibodies, but also determining a definitive nutritional treatment for patients with active CD.

Conflict of Interest

No potential interests of conflict were disclosed.

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