Journal of Parenteral and Enteral Nutrition
Volume XX Number X
Month 201X 1–6

DOI: 10.1177/0148607114528360
jpen.sagepub.com
hosted at
online.sagepub.com

Impact of Disease Activity on Resting Energy Expenditure and Body Composition in Adult Crohn's Disease: A Prospective Longitudinal Assessment

Jianfeng Gong, MD[1]; Lugen Zuo, MD[1]; Zhen Guo, MD[1]; Liang Zhang, MD[1]; Yi Li, MD[1]; Lili Gu, MD[1]; Jie Zhao, MD[1]; Lei Cao, MD[1]; Weiming Zhu, MD[1]; Ning Li, MD[1]; and Jieshou Li, PhD[1]

Abstract

Background: There is controversy about nutrition status and calorie needs during phases of active versus inactive adult Crohn's disease (CD). Results have been reported in cross-sectional studies, but longitudinal data are unavailable. Our aim was to explore whether disease activity had an impact on resting energy expenditure (REE) and body composition in adult patients with CD. *Materials and Methods*: Adult patients were studied on 2 occasions with active and inactive CD. REE was measured by indirect calorimetry. Body composition was estimated from bioelectrical impedance analysis. Disease activity was measured using the Crohn's Disease Activity Index (CDAI). Regression analyses of REE with CDAI score, C-reactive protein, and erythrocyte sedimentation rate were also performed. *Results*: Seventy-five patients were included. Patients with active CD had increased REE/body weight compared with patients with inactive disease (28.8 ± 5.4 vs 25.9 ± 4.3 kcal/kg, $P < .001$). Disease behavior and location, but not sex, had an impact on REE/body weight. Body mass index was lower in active disease than in remission (17.4 ± 3.0 vs 18.1 ± 2.6 kg/m^2, $P = .010$). Body composition was not affected by disease behavior or location. *Conclusion*: Patients with remission had a better nutrition status and decreased REE compared with those with active CD. REE could also be affected by disease location and behavior. (*JPEN J Parenter Enteral Nutr*. XXXX;xx:xx-xx)

Keywords

adults; body composition; Crohn's disease; resting energy expenditure

Clinical Relevancy Statement

Determination of the dynamic nutrition needs during the active and inactive phases of adult Crohn's disease (CD) is helpful for guiding nutrition therapy. The impact of disease activity and behavior on energy metabolism and body composition observed in this longitudinal study may be helpful for clinicians in providing appropriate energy substrates and evaluating nutrition status in adult patients with CD.

Introduction

Malnutrition is a common sequela of Crohn's disease (CD). It is estimated that emaciation is found in 20%–75% patients with CD, and ~75% of hospitalized CD patients are undernourished.[1] Malnutrition in CD is associated with decreased quality of life and, more importantly, increased nutrition risk and complications after surgery.

Nutrition therapy is frequently indicated in CD.[2] Exclusive enteral nutrition (EN) is recommended as the primary therapy for induction of remission in childhood CD and adjunctive therapy for adult CD when patients are refractory to corticosteroids or their use is not feasible.[3] Therefore, it is necessary to determine the optimal energy requirement for nutrition therapy. However, the impact of disease activity superimposed on malnutrition relative to energy expenditure is still uncertain. Some work has shown raised resting energy expenditure (REE) in active adult CD,[4,5] but other studies have not found any influence of disease activity on energy metabolism when adjusted for body weight (BW) or fat-free mass (FFM).[6,7] The data concerning body composition in adult CD patients are also heterogeneous, and the effect of disease activity on body composition warrants further investigation.[8]

From the [1]Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, Nanjing, China.

Supplementary material for this article is available on the *Journal of Parenteral and Enteral Nutrition* website at http://jpen.sagepub.com/supplemental.

Financial disclosure: The work was supported by National Natural Science Foundation of China (81270006) and Jiangsu Provincial Special Program of Medical Sciences, China (BL2012006).

Received for publication October 8, 2013; accepted for publication February 25, 2014.

Corresponding Author:
Weiming Zhu, MD, Department of General Surgery, Jinling Hospital, Medical School of Nanjing University, East Zhongshan Road, Nanjing 210002, China.
Email: juwiming@aliyun.com.

Previous studies were predominantly cross-sectional, and individual variations and small sample sizes often interfered with results; thus, it is necessary to examine the dynamic change of energy metabolism and body composition in the same patient with active or quiescent CD. The purpose of this longitudinal study was to observe the effects of disease activity, location, and behavior on REE and body composition in a prospectively followed cohort of adult CD patients.

Materials and Methods

Patients

All CD patients, aged ≥17 years (Montreal classification A2/A3), who attended the outpatient clinics or were admitted to the Inflammatory Bowel Disease Center at Jinling Hospital, Nanjing, China, were eligible for enrollment in this prospective cohort, regardless of disease activity level. Patients were enrolled from January 2010 to October 2012. Baseline measurements were completed within 1 week after enrollment. Eligible patients were followed up until their disease status changed (active vs remission) or to the end of the study (February 2013). The follow-up interval was a maximum of 3 months. During follow-up, patients were routinely assessed for disease activity according to CD Activity Index (CDAI) score, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). If disease activity changed, indirect calorimetry and anthropometry were performed again.

For final inclusion in the current study, patients must have had 2 disease activity statuses: active (with CDAI score 150–450) and remission (with CDAI score <150) during follow-up. Patients who declined to participate, were lost to follow-up, died, or did not reach or left remission were excluded. Pregnant patients or patients with a history of chronic liver disease, diabetes mellitus, thyroid dysfunction, or other acute or chronic diseases were also excluded.

For patients with active disease on entry, remission could be induced either medically (by 5-aminosalicylic acid, EN, corticosteroid, or infliximab [IFX]) or surgically. For patients receiving medical therapy, repeated evaluation was performed after a minimum interval of 6 weeks after initiation of therapy.[9] For those undergoing surgery, reevaluation was carried out at least 3 months after the operation to eliminate the potential influence of surgical stress on metabolism.[10] For patients who had remission on entry and acute flare-up later, protocols for maintenance therapy were recorded.

The study was approved by the Ethical Committee of Jinling Hospital. Informed consent was obtained from all patients.

Disease Activity and Classification

Disease activity was scored using the CDAI,[11] which consisted of 8 factors, each summed after adjustment with a weighting factor. Serum CRP level was included in the routine clinical tests via a modified latex-enhanced immunoturbidimetric assay using a CRP latex kit (Hitachi 7600-020, Hitachi, Japan) according to the manufacturer's instructions. ESR as a clinical marker of systemic inflammation was also recorded.

Disease was classified according to the Montreal criteria on the basis of age of onset (A) (≤16 years [A1], 17–40 years [A2], and ≥40 years [A3]), location (L) (terminal ileum [L1], colon [L2], ileum–colon [L3], and isolated upper disease [L4]), or behavior (B) (nonstricturing nonpenetrating [B1], stricturing [B2], and penetrating [B3]).[12] L4 was a modifier that could be added to L1–L3 when concomitant upper gastrointestinal (GI) disease was present. P was added to B1–B3 when concomitant perianal disease was present.

REE

REE was measured using indirect calorimetry that measured oxygen consumed and carbon dioxide produced. Measurements were made in the morning after an overnight fast. REE was determined by open circuit indirect calorimetry using a ventilated hood system. The measurement was carried out over 20 minutes, with the patient in the supine position under standard conditions of rest, immobility, thermoneutrality (22°C–24°C), and mental relaxation. The system was calibrated for each patient, and the flow rate of air was adjusted according to the size of the patient. The calorimeter produced a measurement of REE every minute, and the final figure was the average of all measurements. All calorimetry measures were done at steady state.

Body Composition Analysis

Body composition was measured by bipolar bioelectrical impedance analysis (BIA). A multifrequency BIA with 8-point tactile electrodes (InBody 3.0, Biospace, Seoul, Korea) was used. This analyzer used an alternating current of 250 mA with multiple frequencies of 5, 50, 250, and 500 kHz. Like the single-frequency BIA with 8 electrodes, 2 electrodes were built in each grip and plate. The multifrequency analyzer measured segmental impedance in the right arm, left arm, right leg, left leg, and trunk for all frequencies and automatically displayed measurements of FFM, fat mass (FM), body cell mass, skeletal muscle mass, bone mineral content, internal cell water, external cell water, and segmental fluid distribution. All indirect calorimetry and anthropometry measurements were made by well-trained nursing staff.

Triceps skinfold thickness (TSF) of the right mid-arm was measured using a conventional skinfold caliper with standard techniques. The arm circumference (AC) was measured with a plastic tape. Arm muscle circumference (AMC) was calculated as follows: $AMC = AC - 3.142 \times TSF$ (all in centimeters).[13]

Statistical Analysis

Results were expressed as mean and standard deviation. Student *t* test for paired data was applied to compare the main variables of interest (observed REE and anthropometry

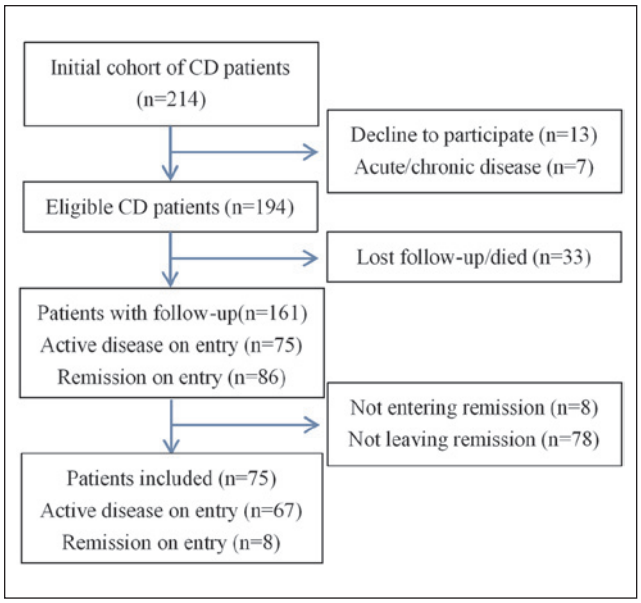

Figure 1. Flow chart of the patient inclusion process.

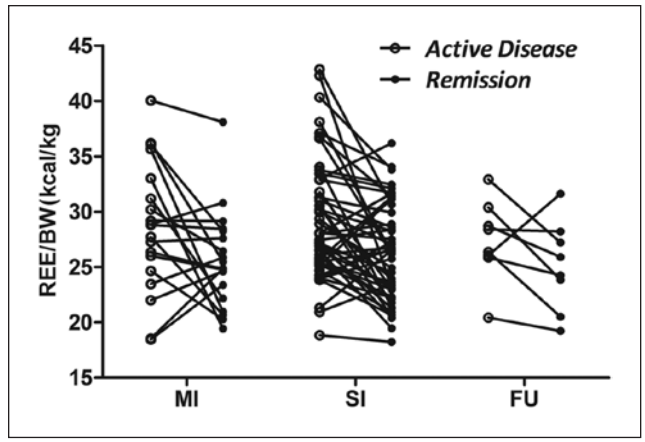

Figure 2. Resting energy expenditure in adult patients with active and inactive Crohns' disease after medically induced remission (MI), surgically induced remission (SI), or patients with disease flare-up (FU).

parameters) in active and inactive disease. For comparison of variables in different subgroups, one-way analysis of variance (ANOVA) followed by Newman–Keuls multiple comparison test was used. Correlations between continuous variables were assessed by correlation coefficients and regression analyses. Statistical analysis was performed using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA). Results were considered significant at $P < .05$.

Results

Patient Demographics

From January 2010 to October 2012, 214 patients were screened for eligibility. As shown in Figure 1, 75 patients (57 male) were finally included in the current study. Patients' median age was 33 (range, 17–68) years. Forty-two had ileocolonic disease (L3), 5 of whom had upper GI involvement (L3+L4); 8 patients had colonic disease (L2); 23 patients had ileal involvement (L1), and 2 of them had upper GI involvement (L1+L4); and 2 patients had upper GI disease only (L4).

Among the 75 patients, 15 had nonstricturing, nonpenetrating disease (B1, 2 with perianal lesion [P]), 22 had stricturing disease (B2, 2 with P), and 38 had penetrating disease (B3, 4 with P).

Sixty-seven patients had active disease on entry, and remission was induced by medical therapy in 19 patients, 5 of whom had IFX therapy, 1 received corticosteroids, and 13 achieved remission with EN. Forty-eight patients had surgically or surgically/medically induced remission. Eight patients had disease recurrence during follow-up. Among them, 6 were maintained on azathiopurine (2–2.5 mg/kg/d) and 2 were maintained on other immunosuppressants. Overall, the patients were followed up for a median of 5.0 months, with a range of 1.5–25.8 months.

Change and Impact of Therapy on REE

REE adjusted for BW (REE/BW) decreased from 28.8 ± 5.4 kcal/kg at active disease to 25.9 ± 4.3 kcal/kg at remission, with a mean decrease of 2.9 ± 5.3 kcal/kg ($P < .001$) and a percentage of 8.3% ± 17.0%. As shown in Figure 2, for patients with medically and surgically induced remission, REE/BW decreased from 28.6 ± 5.9 to 25.6 ± 4.4 kcal/kg ($P < .001$) and from 29.1 ± 5.4 to 26.1 ± 4.4 kcal/kg ($P < .001$), respectively. For 8 patients with disease flaring up, the ratio of REE/BW increased from 25.1 ± 4.1 to 27.4 ± 3.7 kcal/kg ($P < .001$). Similarly, the ratio of REE/FFM reduced from 33.6 ± 6.2 to 30.6 ± 5.3 kcal/kg from active to inactive status ($P < .001$).

REE and Markers of Inflammation

A regression model was used to evaluate the effect of inflammatory markers on REE. REE/BW did not have a linear relationship with intestinal inflammation measured by CRP ($r^2 = 0.0001$, $P = .931$), ESR ($r^2 = .002$, $P = .737$), or CDAI score ($r^2 = 0.023$, $P = .195$) in active disease. In remission, there was no association of REE/BW with CRP ($r^2 = 0.040$, $P = .084$), ESR ($r^2 = 0.0002$, $P = .895$), or CDAI ($r^2 = 0.003$, $P = .650$; Figure 3).

To examine whether the change in inflammation markers correlated with REE change, regression analysis was performed again. There was no linear regression between ΔREE/BW and ΔCRP ($r^2 = 0.004$, $P = .581$), ΔESR ($r^2 = 0.00002$, $P = .969$), or ΔCDAI ($r^2 = 0.00003$, $P = .965$). Similarly, there

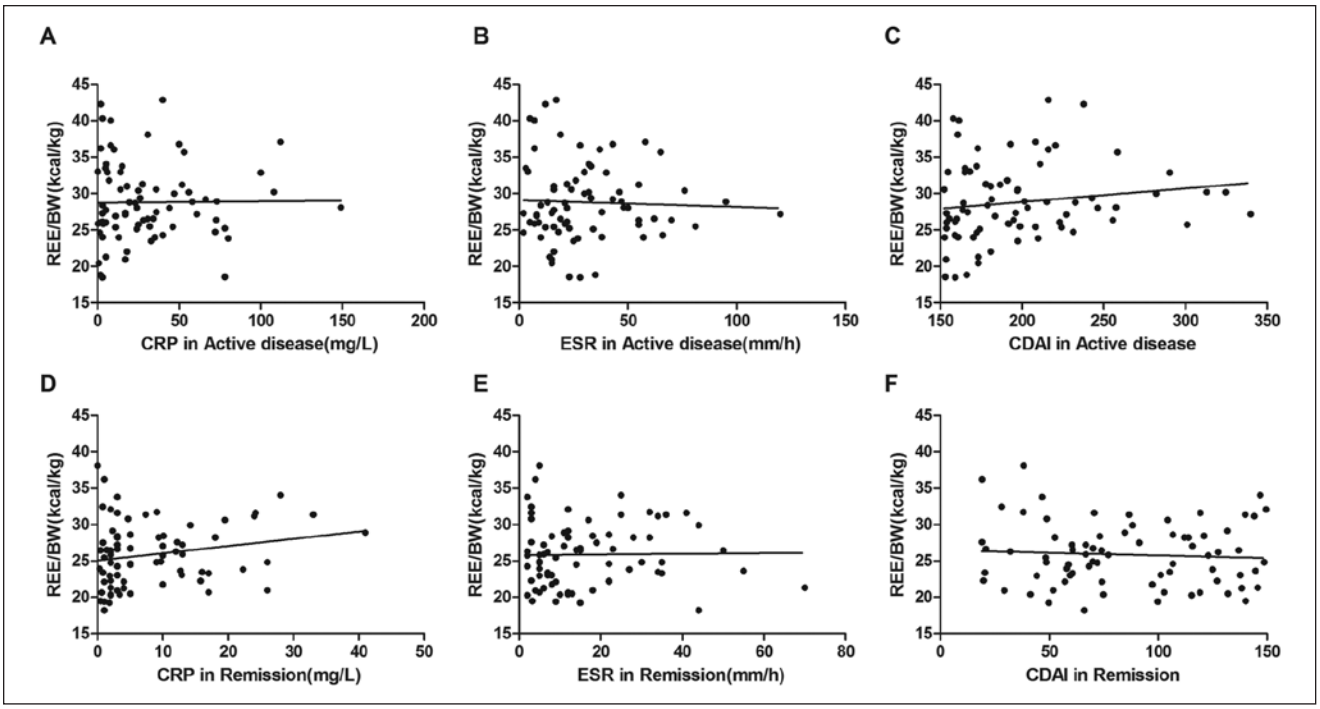

Figure 3. Linear regression analysis between resting energy expenditure/body weight and C-reactive protein (A), erythrocyte sedimentation rate (B), and Crohn's Disease Activity Index score (C) in active disease or in remission (D–F).

was no correlation of ΔREE/FFM with ΔCRP (r^2 = 0.013, P = .326), ΔESR (r^2 = 0.042, P = .079), or ΔCDAI (r^2 = 0.010, P = .376).

Impact of Sex, Disease Location, and Behavior on REE

Sex did not influence REE/BW either in active (P = .394) or inactive (P = .073) disease. A similar result was observed for REE/FFM (P = .145 and P = .129, respectively).

As shown in Supplementary Figure S1-A, REE/BW differed significantly among patients with different disease behavior (B) at remission (P = .011 for 1-way ANOVA) but not in active disease (P = .094). At remission, REE/BW in B1 (23.0 ± 2.6 kcal/kg) was significantly lower when compared with B2 (27.2 ± 4.4 kcal/kg, P < .05) and B3 (26.3 ± 4.4 kcal/kg, P < .05).

The impact of disease location on REE/BW was investigated (Supplementary Figure S1-B). Although patients with different disease location had similar REE/BW on remission (P = 1.000), in active disease, the difference was significant (P = .035). Isolated colonic disease (L2, n = 8; 33.6 ± 4.0 kcal/kg) had the most prominent increase as compared with isolated ileal disease (L1, n = 21; 28.3 ± 5.6 kcal/kg, P < .05) or ileocolonic disease (L3, n = 37; 28.5 ± 5.0 kcal/kg, P < .05).

Impact of Disease Activity, Location, and Behavior on Body Composition

For patients with active disease, body mass index (BMI) was 17.4 ± 3.0 kg/m^2, compared with 18.1 ± 2.6 kg/m^2 in remission (P = .010), indicating that patients with quiescent disease had better nutrition status than those with active disease.

As shown in Figure 4, subsequent analysis revealed that FFM had a trend of increase in inactive disease (43.5 ± 7.9 vs 42.4 ± 8.8 kg, P = .071), as well as FM (6.9 ± 4.8 vs 7.6 ± 4.5 kg, P = .187) and protein mass (8.7 ± 1.8 vs 8.4 ± 1.8, P = .092). However, skeletal muscle mass (23.4 ± 5.3 vs 23.2 ± 5.4 kg, P = .609), body cell mass (28.3 ± 5.4 vs 28.0 ± 5.9 kg, P = .358), and bone mineral content (2.6 ± 0.8 vs 2.6 ± 0.6 kg, P = .625) were comparable in different disease states.

AC (26.0 ± 5.1 vs 25.8 ± 4.9 cm, P = .760) and AMC (23.0 ± 5.3 vs 23.3 ± 4.7 cm, P = .611) also did not differ between groups.

The effect of disease behavior or location on the percentage fat mass (PFM) and percentage skeletal muscle mass (PSMM) in patients with active or inactive CD was examined. Neither disease behavior nor location (ileal, ileocolonic, or colonic) affected PFM or PSMM (Supplementary Figure S2).

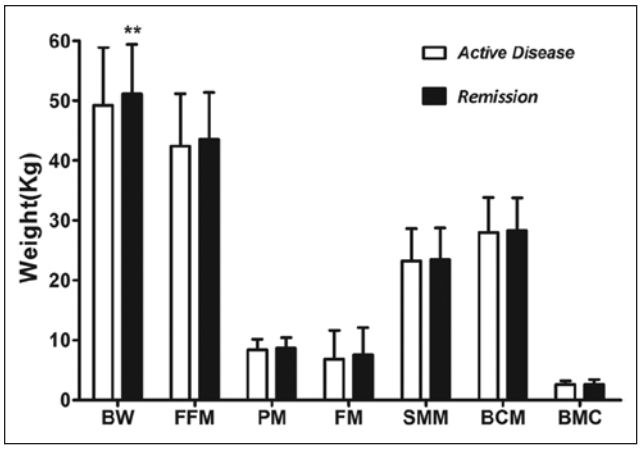

Figure 4. Changes of anthropometry parameters in patients with active disease and remission. BCM, body cell mass; BMC, bone mineral content. BW, body weight; FFM, fat-free mass; FM, fat mass; PM, protein mass; SMM, skeletal muscle mass. $^{**}P < .01$ versus active disease.

Discussion

The current prospective longitudinal study provided direct evidence that disease activity had a significant impact on energy expenditure and anthropometric parameters in adult CD. Furthermore, REE was affected by disease location and behavior.

The relationship between energy expenditure and disease activity in adult CD is uncertain. Previous studies comparing the REE in CD patients with healthy controls, or active versus inactive CD, were almost exclusively cross-sectional in design. The current self-comparison longitudinal study that was adequately corrected for biologically important confounders was helpful for determining the effect of disease activity on REE. It was found that patients with active disease had an 8.3% increase in REE compared with patients in remission in the current study. The result is consistent with previous data reporting REE/FFM changes in pediatric CD patients undergoing surgery-induced remission.[10]

The present study failed to find a linear relationship between REE/BW or REE/FFM and CDAI, CRP, or ESR. The results agree with the cross-sectional observation of Wiskin et al.[14] The explanation might be the heterogeneity of REE among individuals and the way that REE is adjusted for body size and composition. Expressing energy expenditure as REE/FFM might result in higher values for those with the lowest FFM.[14] Wiskin et al showed that REE/kg $FFM^{0.52}$ might be able to adjust for the variance of REE attributable to body composition or BW in children,[15] but whether it is suitable for adults is unknown.

The results of the present study showed that patients with B1 behavior had a lower REE/BW compared with patients with B2 or B3 behavior, which has not been reported previously. There is a possibility that complicated (penetrating or stricturing) diseases are prone to have infections or abscess formation, which increase energy expenditure. The different REE during disease flare-up with colonic versus ileocolonic or ileal disease may reflect the burden of inflammation. Severe colonic disease is usually pancolitis (5/8 in the cohort) and therefore represents a large burden of inflammation compared with that of segmental ileal or ileocolonic disease.

Body composition was assessed by BIA in the current study. The use of BIA in malnourished patients with CD has been validated, and its accuracy is comparable to dual-energy X-ray absorptiometry.[16] The present data revealed that CD patients in remission had a better nutrition outcome than those with active disease. This is consistent with a previous cross-sectional study by Rocha et al,[17] which showed a higher percentage of malnutrition (BMI <18.5 kg/m^2) in active CD versus remission. Vadan et al[18] also found that in patients with moderate to severe CD treated with IFX, clinical remission was the principle factor with weight gain. In the present study, there was no association between disease location or behavior and PFM or PSMM, which was in contrast with the results of Capristo et al.[19] In another population-based study, Jahnsen et al[20] found that disease location did not have a significant effect on body composition variables.

There were limitations to the current study. First, there was no healthy population as a control group. Although it is believed that adults with CD have higher REE than the general population,[21] a recent study by Filippi et al[22] showed that adults with CD in remission had similar REE/FFM to healthy controls. Second, remission was induced by various therapeutic approaches, such as EN,[23] prednisolone, IFX,[18] or surgery,[10] which might have a different impact on REE and body composition. However, the strength of the current study was that it was the first to examine dynamically the change of metabolism and body composition in different disease states of adult CD. Third, a conundrum was that only BMI but no individual components of body composition increased significantly during remission. Both FFM and FM had a trend of increase during remission; thus, their cumulative effect might explain the statistically significant increase in BMI.

In summary, the present study demonstrated that active adult CD was associated with an 8.3% increase in REE compared with inactive CD, and the increase was more prominent in complicated (stricturing or penetrating) and colonic CD. Body composition was also affected by disease activity, and patients in remission had a higher BMI than those with active disease.

Acknowledgments

The authors thank Yingchun Huang and Sitong Liu for performing indirect calorimetry and BIA assessment.

Author Contributions

Jianfeng Gong, data acquisition, analysis, interpretation, and manuscript drafting/revision; **Lugen Zuo** and **Zhen Guo**, data acquisition, interpretation, and statistical analysis; **Liang Zhang**, **Yi Li,**

Lili Gu, Jie Zhao, and **Lei Cao**, patient enrollment and data acquisition; **Weiming Zhu**, design and coordination, interpretation of data, manuscript drafting/revision; **Ning Li** and **Jieshou Li**, study concept, supervision and consultation, manuscript revision. All authors read and approved the final manuscript.

References

1. Alastair F, Emma G, Emma P. Nutrition in inflammatory bowel disease. *JPEN J Parenter Enteral Nutr*. 2011;35:571-580.
2. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2007:CD000542.
3. Lochs H, Dejong C, Hammarqvist F, et al. ESPEN guidelines on enteral nutrition: gastroenterology. *Clin Nutr*. 2006;25:260-274.
4. Rigaud D, Cerf M, Angel Alberto L, Sobhani I, Carduner MJ, Mignon M. Increase of resting energy expenditure during flare-ups in Crohn disease. *Gastroenterol Clin Biol*. 1993;17:932-937.
5. Kushner RF, Schoeller DA. Resting and total energy expenditure in patients with inflammatory bowel disease. *Am J Clin Nutr*. 1991;53:161-165.
6. Al-Jaouni R, Hebuterne X, Pouget I, Rampal P. Energy metabolism and substrate oxidation in patients with Crohn's disease. *Nutrition*. 2000;16:173-178.
7. Schneeweiss B, Lochs H, Zauner C, et al. Energy and substrate metabolism in patients with active Crohn's disease. *J Nutr*. 1999;129:844-848.
8. Bryant RV, Trott MJ, Bartholomeusz FD, Andrews JM. Systematic review: body composition in adults with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2013;38:213-225.
9. Azcue M, Rashid M, Griffiths A, Pencharz PB. Energy expenditure and body composition in children with Crohn's disease: effect of enteral nutrition and treatment with prednisolone. *Gut*. 1997;41:203-208.
10. Varille V, Cézard JP, de Lagausie P, et al. Resting energy expenditure before and after surgical resection of gut lesions in pediatric Crohn's disease. *J Pediatr Gastroenterol Nutr*. 1996;23:13-19.
11. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology*. 1976;70:439-444.
12. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut*. 2006;55:749-753.
13. Allen BJ, Blagojevic N, Delaney I, et al. The role of body protein studies in clinical trials. *Basic Life Sci*. 1990;55:155-169.
14. Wiskin AE, Wootton SA, Cornelius VR, Afzal NA, Elia M, Beattie RM. No relation between disease activity measured by multiple methods and REE in childhood Crohn disease. *J Pediatr Gastroenterol Nutr*. 2012;54:271-276.
15. Wiskin AE, Wootton SA, Culliford DJ, Afzal NA, Jackson AA, Beattie RM. Impact of disease activity on resting energy expenditure in children with inflammatory bowel disease. *Clin Nutr*. 2009;28:652-656.
16. Thibault R, Genton L, Pichard C. Body composition: why, when and for who? *Clin Nutr*. 2012;31:435-447.
17. Rocha R, Santana GO, Almeida N, Lyra AC. Analysis of fat and muscle mass in patients with inflammatory bowel disease during remission and active phase. *Br J Nutr*. 2009;101:676-679.
18. Vadan R, Gheorghe LS, Constantinescu A, Gheorghe C. The prevalence of malnutrition and the evolution of nutritional status in patients with moderate to severe forms of Crohn's disease treated with infliximab. *Clin Nutr*. 2011;30:86-91.
19. Capristo E, Addolorato G, Mingrone G, Greco AV, Gasbarrini G. Effect of disease localization on the anthropometric and metabolic features of Crohn's disease. *Am J Gastroenterol*. 1998;93:2411-2419.
20. Jahnsen J, Falch JA, Mowinckel P, Aadland E. Body composition in patients with inflammatory bowel disease: a population-based study. *Am J Gastroenterol*. 2003;98:1556-1562.
21. Capristo E, Mingrone G, Addolorato G, Greco AV, Gasbarrini G. Metabolic features of inflammatory bowel disease in a remission phase of the disease activity. *J Intern Med*. 1998;243:339-347.
22. Filippi J, Al-Jaouni R, Wiroth JB, Hébuterne X, Schneider SM. Nutritional deficiencies in patients with Crohn's disease in remission. *Inflamm Bowel Dis*. 2006;12:185-191.
23. Gerasimidis K, Talwar D, Duncan A, et al. Impact of exclusive enteral nutrition on body composition and circulating micronutrients in plasma and erythrocytes of children with active Crohn's disease. *Inflamm Bowel Dis*. 2012;18:1672-1681.