Elevated diet-induced thermogenesis and lipid oxidation rate in Crohn disease¹⁻³

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ABSTRACT
Background: Although malnutrition is frequently observed in Crohn disease (CD), its cause is not clear. Regulation of energy metabolism and diet-induced thermogenesis (DIT) have not been adequately studied in CD.

Objective: The aim was to study DIT and substrate oxidation in patients with inactive ileal CD.

Design: After a test meal providing 50.2 kJ/kg body wt, DIT was assessed by indirect calorimetry performed over 360 min in 18 CD patients and 12 healthy volunteers matched for age, sex, weight, and height. Body composition was evaluated with the labeled-water-bolus injection technique.

Results: Fat-free mass did not differ significantly between groups, but CD patients had markedly lower fat mass than control subjects (13.8 ± 5.63 compared with 19.0 ± 3.49 kg; P < 0.001). Nonprotein respiratory quotient was lower in CD patients than control subjects (0.80 ± 0.04 compared with 0.86 ± 0.03; P < 0.001). Average respiratory quotient between 75 and 150 min after the test meal was 0.85 ± 0.03 in CD patients and 0.91 ± 0.02 in control subjects (P < 0.001). Lipid oxidation rate was higher in CD patients than in control subjects (2.26 ± 1.13 compared with 1.50 ± 0.75 kJ/min; P < 0.05). DIT was higher in CD patients than in control subjects (9.89 ± 1.93% compared with 5.67 ± 0.91% of energy intake; P < 0.001).

Conclusions: Patients with inactive ileal CD had significantly higher DIT and lipid oxidation rate than do healthy volunteers. These results may explain why CD patients have difficulty maintaining adequate nutritional status, and the findings also suggest that a diet relatively rich in fat may attain better energy balance. Am J Clin Nutr 1999;69:325–30.

KEY WORDS: Body composition, Crohn disease, diet-induced thermogenesis, substrate oxidation rates, lipid oxidation, carbohydrate oxidation, indirect calorimetry, labeled-water-bolus injection technique, resting energy expenditure, basal metabolic rate, respiratory quotient, fat mass, fat-free mass.

INTRODUCTION
Malnutrition is frequently observed in Crohn disease (CD), yet its cause is not known. Some authors have hypothesized that CD patients have increased energy expenditure with subsequent weight loss (1, 2), whereas others have concluded that this weight reduction is the consequence of reduced food intake (3). However, in the studies cited above, the patients studied were in a full activity phase of their disease. Therefore, it was impossible to determine whether the increase in energy expenditure was a primary finding or was secondary to the concomitant presence of abscess or fever. Similarly, the reduced food intake observed in CD patients might be a consequence of the nausea and anorexia that are secondary to the disease (3). Elemental enteral diets have been shown to be as effective as total parenteral nutrition (with or without concomitant steroid therapy) in the treatment of active CD (4–10). However, the exact mechanism by which certain diets can improve CD inflammatory indexes is unclear.

To our knowledge, little information is available in the literature regarding diet-induced thermogenesis (DIT) in CD patients, even though this is an interesting area of research with major clinical implications. Increased DIT, with preferential utilization of high-density fuel substrates such as lipids, might be partially responsible for the lower body weight and lower fat mass that are typical in CD patients, even when their chronic inflammatory disease is in remission.

In the present study we evaluated body composition, DIT, and substrate oxidation rates in CD patients whose disease was in remission, and whose body weight had been stable for ≥1 y.

SUBJECTS AND METHODS
Subjects
The CD group included 18 consecutive patients with biopsy-proven CD (10 men and 8 women). These patients were admitted to the Metabolic Diseases Outpatient Clinic of the Catholic University School of Medicine in Rome, and were recruited for the study while they were in clinical remission. The diagnosis of

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²Supported by the Catholic University, Rome.

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Received April 1, 1998.
Accepted for publication July 7, 1998.
CD was based on previously reported clinical, morphologic, and histopathologic criteria (11), and a Crohn’s Disease Activity Index < 150 (12), normal serum α2-globulin concentration (<8 g/L), and erythrocyte sedimentation rate < 20 mm/h, which taken together indicated an inactive phase of disease.

In 12 CD patients, the disease was localized to the terminal ileum, but in the other 6 the disease affected the terminal ileum and first portion of the colon. Disease was not detected in any other portions of the gastrointestinal tract. No intestinal perforations or occlusive episodes were reported in the clinical histories of these patients. Two patients reported the presence of fistulas at the time of CD diagnosis (at 36 and 28 mo before the study), and these fistulas were treated successfully with systemic steroids and antibiotics. At the time of this study, none of the patients had any complications.

The mean duration of CD was 46.4 ± 10.8 mo. The patients had been brought to remission with different medications, including systemic steroids, antibiotics (such as metronidazole), mesalamine, and enemas containing salazopyrin and corticosteroids. None of the patients enrolled in the study had undergone intestinal resection. Twelve patients did not have relapses after the time of diagnosis, whereas 6 patients had an average of 2.4 ± 1.2 relapse episodes. However, no relapses were reported in 6 mo preceding the study, and during this period the patients had not been taking any medications.

Twelve healthy volunteers matched for sex (6 men and 6 women), age, weight, and height were studied as a control group. To exclude the presence of intestinal loop thickness, which is indicative of inflammatory bowel disease, abdominal ultrasonography was performed (13, 14). The body weight of all subjects was stable during the study period. Body weight had not been changed (±2 kg) for ≥1 y before the study.

The subjects studied were clinically euthyroid, had no evidence of renal, cardiac, or hepatic dysfunction, and were not being treated with drugs that affect energy metabolism. All the female subjects were studied during the follicular phase of the menstrual cycle. All the subjects were consuming self-selected diets, none were smokers, and none engaged in regular physical exercise.

**Experimental protocol**

The subjects were admitted to the metabolic ward at 0700, ±24 h before the test meal would be given. Each subject was assigned a diet computed on the basis of the subject’s food diary, which had been compiled over 7 d. The assigned diet was designed to reproduce the usual energy and nutrient intake of the subject. Values for the carbohydrate, lipid, and protein contents of all foods were derived from computerized tables. The calculated average diet composition was 55% of energy from carbohydrate, 30% from fat, and 15% from protein. The mean energy intake, computed from the 7-d food diary, was 7770 ± 340 kJ/d in control subjects and 7450 ± 475 kJ/d (NS) in CD patients.

All the experiments were performed at 0800, after an overnight fast of 10–12 h. After voiding, each subject reclined on a bed and a venous catheter was inserted into an antecubital vein for blood sampling. The line was kept patent with physiologic saline. Respiratory gas exchange measurements were performed for 60 min before ingestion of the test meal to measure resting energy expenditure (REE). Ingestion of the test meal took <3 min. The respiratory gas exchange measurements were continued for 360 min after the meal. The liquid-formula test meal supplied 50.2 kJ/kg body wt (6.25 g protein, 5 g fat, and 20 g carbohydrate in 100 mL), corresponding to 53.3% of energy from carbohydrate, 30% from fat, and 16.7% from protein. DIT was computed by continuous indirect calorimetry using a ventilated hood metabolic monitor (Deltatrac; Datex Instrumentarium, Helsinki) (15) under strictly standardized conditions (16).

Blood samples were drawn every 30 min from the beginning of the study to measure plasma glucose, insulin, and fatty acids. Plasma glucose was measured by the glucose oxidase method using a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured by microparticle enzyme immunoassay (Abbott Imx, Pasadena, CA). Fatty acids were assayed by an enzymatic colorimetric method (NEFA Quick BMY; Boehringer Mannheim, Tokyo).

Serum tumor necrosis factor α (TNF-α) and interleukin (IL)-2 concentrations were determined by enzyme-linked immunosorbent assays (Predica; Genzyme Corporation, Cambridge, MA). The intraassay variations were 6.06–7.67% for TNF-α and 8.1–10.4% for IL-2. The interassay variations were 6.40–9.64% for TNF-α and 5.6–10.9% for IL-2.

Plasma concentrations of norepinephrine were assayed by using a single-isotope radioenzymatic technique (17). Twenty-four-hour nitrogen elimination was determined with use of the BUN Analyzer II (Beckman Instruments).

Body weight was measured to the nearest 0.1 kg with a beam balance. Body composition was estimated on the basis of total body water (TBW), which was measured by isotopic dilution. Subjects were given 2.96 MBq tritiated water (specific activity: 3.7 TBq/L) in 5 mL saline solution as an intravenous bolus injection on the day preceding the DIT evaluation. The radioactivity was counted in duplicate with a β-scintillation counter (model 1600TR; Canberra-Packard, Meriden, CT) in 0.5 mL plasma, and each point was plotted against time. The amount (in dpm) of the tritiated water bolus was divided by the average concentration of labeled water (dpm/mL) obtained at steady state, which is when the labeled water is homogeneously distributed throughout the body, to compute the apparent volume of labeled water, which equals the TBW. To calculate the fat-free mass (FFM), TBW was divided by 0.73 (18).

The study protocol followed the guidelines of the Catholic University School of Medicine ethics committee, and all subjects gave their written informed consent.

**Respiratory exchange measurements**

Energy expenditure, respiratory quotient (RQ), and substrate oxidation rates were calculated from oxygen consumption, carbon dioxide production (recorded by Deltatrac once per min and averaged over 15 min), and urinary nitrogen excretion, according to the method described by Ferrannini (19). DIT was the cumulative postmeal increase in energy expenditure (during the 360 min after the meal) as compared with the premeal fasting value. The area under the curve was computed by using the trapezoidal rule. DIT was also expressed as a percentage of the meal energy content.

**Statistical analysis**

The results are given as means ± SDs unless specifically stated otherwise. Independent-sample t tests were used to assess the significance of the differences in the examined variables. Fisher’s exact test was used to compare the proportions of men and women in the 2 groups. Linear regression analysis was used...
to evaluate the effect of varying age, fat mass, FFM, sex, and disease on REE, DIT, and RQ. A forward stepwise technique was used, with $P < 0.05$ as the criterion for inclusion of successive variables (20).

**RESULTS**

The subject characteristics, including anthropometric variables, for the 2 groups are shown in Table 1. Body mass index (BMI; in kg/m²) was significantly lower in CD patients than in control subjects (21.6 ± 2.9 compared with 23.8 ± 1.8, respectively; $P < 0.05$). The average FFM (Table 1) and urinary nitrogen loss in 24 h (0.158 ± 0.02 and 0.150 ± 0.02 g/kg body wt in CD patients and control subjects, respectively) did not differ significantly between groups. On the contrary, fat mass was markedly lower in CD patients than in control subjects (13.8 ± 5.63 compared with 19.0 ± 3.49 kg, respectively; $P < 0.001$). For REE, no significant difference was found between patients with CD and control subjects (Table 2).

The time course of energy expenditure in the fasting period (the 60 min before the test meal) and in the postmeal period (360 min) in healthy control subjects and in patients with CD is shown in Figure 1. DIT, as a percentage of the energy content of the test meal, was significantly higher in CD patients than in control subjects (9.89 ± 1.93% compared with 5.67 ± 0.91%, $P < 0.001$).

The nonprotein RQ was significantly ($P < 0.001$) lower in CD patients (0.80 ± 0.04) than in control subjects (0.86 ± 0.03). Fasting carbohydrate oxidation rate was found to be 2.50 ± 0.63 kJ/min in control subjects, compared with 1.55 ± 0.63 kJ/min in CD patients ($P < 0.001$). Fasting lipid oxidation rate was 1.50 ± 0.75 kJ/min in control subjects, compared with 2.26 ± 1.13 kJ/min in CD patients ($P < 0.05$).

Average RQ values between 75 and 150 min postmeal were significantly ($P < 0.001$) lower in CD patients (0.85 ± 0.03) than in control subjects (0.91 ± 0.02). Consequently, the average postmeal lipid oxidation rate was higher (2.26 ± 0.75 compared with 1.13 ± 0.38 kJ/min, $P < 0.001$) and the carbohydrate oxidation rate was lower (2.97 ± 0.79 compared with 3.76 ± 0.79 kJ/min, $P < 0.001$) in CD patients than in control subjects.

Multiple linear regression analysis of REE on FFM, fat mass, age, sex, and disease did not show any significant influence of sex or disease, FFM, fat mass, and age explained 75% of the interindividual variance in REE. For DIT and RQ, the only significant predictor was the presence of the disease ($R^2 = 0.629$ and $R^2 = 0.405$, respectively) (Table 3).

For plasma concentrations of glucose, insulin, fatty acids, and norepinephrine, no significant differences were detected between CD patients and control subjects, either during fasting or after the meal. Serum TNF-α and IL-2 concentrations did not differ significantly between CD patients and control subjects.

**DISCUSSION**

Little research has been done regarding the effect of food ingestion on energy expenditure and substrate utilization in CD patients. DIT, measured by 24-h whole-body calorimetry in 8 patients receiving total parenteral nutrition while in remission from CD, was 6.1 ± 3.1% of energy intake (21). However, these patients were receiving drugs such as prednisolone and sulfasalazine. Substrate utilization and nutrient balance were followed by Müller et al (22) in 10 patients with CD in remission. The patients were receiving low-dose steroid treatment and were studied during an 8-d period of continuous enteral nutrition that provided a supply of protein that was first constant and then

**Figure 1.** Time course of resting (–60 to 0 min) and postmeal (0–360 min) energy expenditure in 18 CD disease patients (solid line) and 12 control subjects (dashed line). $x \pm SE$.  

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Crohn disease patients</th>
<th>Control subjects</th>
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<tr>
<td></td>
<td>($n = 10$, M, 8 F)</td>
<td>($n = 6$, M, 6 F)</td>
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<tr>
<td>Age (y)</td>
<td>35.3 ± 9.1</td>
<td>35.6 ± 12.5</td>
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<tr>
<td>Height (cm)</td>
<td>169 ± 8.2</td>
<td>167 ± 5.3</td>
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<tr>
<td>Weight (kg)</td>
<td>61.8 ± 11.3</td>
<td>66.7 ± 5.86</td>
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<tr>
<td>Fat-free mass (kg)</td>
<td>48.0 ± 7.07</td>
<td>47.7 ± 6.09</td>
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<tr>
<td>Fat mass (kg)</td>
<td>13.8 ± 5.63</td>
<td>19.0 ± 3.49</td>
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1/ $x \pm SD.$

2/ Significantly different from Crohn disease patients, $P < 0.001$.

**Table 2**

<table>
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<th>Control subjects</th>
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<tr>
<td></td>
<td>($n = 18$)</td>
<td>($n = 12$)</td>
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<tr>
<td>Resting energy expenditure (kJ/min)</td>
<td>4.60 ± 0.602</td>
<td>4.527 ± 0.389</td>
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<td>Nonprotein respiratory quotient</td>
<td>0.80 ± 0.04</td>
<td>0.86 ± 0.03²</td>
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<tr>
<td>Fasting carbohydrate oxidation rate (kJ/min)</td>
<td>1.55 ± 0.63</td>
<td>2.50 ± 0.63²</td>
</tr>
<tr>
<td>Fasting lipid oxidation rate (kJ/min)</td>
<td>2.26 ± 1.13</td>
<td>1.50 ± 0.75³</td>
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<tr>
<td>Carbohydrate oxidation rate between 75 and 150 min postmeal (kJ/min)</td>
<td>2.97 ± 0.79</td>
<td>3.76 ± 0.79²</td>
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<tr>
<td>Lipid oxidation rate between 75 and 150 min postmeal (kJ/min)</td>
<td>2.26 ± 0.75</td>
<td>1.13 ± 0.38²</td>
</tr>
<tr>
<td>Diet-induced thermogenesis over 360 min (%)</td>
<td>9.89 ± 1.93</td>
<td>5.67 ± 0.91²</td>
</tr>
</tbody>
</table>

1/ $x \pm SD.$

2/ Significantly different from Crohn disease patients: ²$P < 0.001$, ³$P < 0.05$.  

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**Figure 1.** Time course of resting (–60 to 0 min) and postmeal (0–360 min) energy expenditure in 18 Crohn disease patients (solid line) and 12 control subjects (dashed line). $x \pm SE$.  

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**Table 3**

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<thead>
<tr>
<th></th>
<th>Crohn disease patients</th>
<th>Control subjects</th>
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<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>2.9 compared with 23.8</td>
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</table>
| Fasting lipid oxidation rate (kJ/min) | 1.8, respectively | 0.63 kJ/min in  
| Fast-                  |                        | control subjects |
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increasing. These authors found an accumulation of tissue carbohydrates and protein but a depletion of body fat. DIT was 8.5% when the energy infusion rate was 1.5 times the REE, and it rose progressively as energy intake increased. The major difference between our investigation and the studies reported previously is that all patients in the previous studies were receiving steroid treatment and were also receiving either total parenteral nutrition (21) or medium-chain triglyceride (MCT)-rich enteral nutrition (22), whereas the CD patients in our study were not receiving any of these treatments.

Our data show that FFM was well maintained in patients with inactive ileal CD, as compared with healthy volunteers. In contrast, fat mass was significantly lower in CD patients than in control subjects. The multiple regression analysis showed that, although REE was similar in the 2 groups, both DIT and RQ were significantly influenced by the presence of the disease.

Recently, we used a calorimetric chamber to carry out a 24-h study of CD patients with and without steroid treatment, but we did not compute the DIT because it has been shown that DIT has a low reproducibility when determined with use of a respiratory chamber (23). The poor reliability of DIT when measured with this apparatus (24, 25) was attributed to the large variability of the terms used in the computation, such as the REE and the intercept of the regression line between 24-h energy expenditure and spontaneous physical activity.

The present study showed significantly higher DIT in patients with inactive ileal CD, compared with control subjects. Furthermore, as previously shown by our group (26), the fasting RQ seems to be significantly lower in CD patients than in control subjects, with a corresponding elevation of the fasting lipid oxidation rate in CD patients. In a study performed over 24 h in CD patients, these data were confirmed in subjects not receiving steroid treatment. However, the steroid-treated patients in this study showed a significantly higher 24-h RQ, probably as a consequence of the high carbohydrate-to-lipid ratio of their diets after correction for nutrient losses in feces (23). Our current data suggest that elevated lipid utilization may be characteristic of CD and may occur independently of the degree of disease activity. These results agree with those reported by Müller et al (22), who observed that fat rather than glucose is the major energy source during chronic, continuous, 24-h enteral infusion of a liquid-formula diet. The diet used by these authors (45% of energy from carbohydrate, 35% from fat, and 20% from protein) was different from the diet we used, because their formula was richer in lipids, of which 50% were MCTs. Furthermore, Müller et al (22) found that CD patients failed to reach positive fat balance, and thus they hypothesized that these patients cannot preserve or replete their fat stores.

Note that CD patients share some physical characteristics with patients who have anorexia nervosa. Both groups have a very low fat mass compared with control subjects (26). Studies of DIT in anorexic patients have yielded conflicting results. DIT in these patients was found to be higher than (27), similar to (28), or even lower than (29–31) that of control subjects. However, an earlier study reported an impressive thermogenic response after a mixed meal administered by nasogastric tube in anorexia nervosa patients (27). This response amounted to 24% and 41% of the energy input, respectively, in semistarvation and refeeding conditions. In our study, CD patients had significantly higher DIT than healthy control subjects, but DIT was not elevated as much as has been described in anorexia nervosa. Another similarity to anorexic patients (27) is the preferential use of lipids as an energy source in our CD patients after the test meal.

In attempts to explain the elevated DIT in CD patients, catecholamines and cytokines have been assayed. However, we failed to show either increased sympathetic nervous system activity or a rise in plasma concentrations of cytokines (IL-2 and TNF-α), both of which could be responsible for the altered metabolic response to feeding observed in the CD patients in our study. The lack of increases in the above-mentioned factors, which are commonly recognized as stimulating the energy response to food intake, suggests that other possible causes, such as altered release of metabolic regulatory peptides or impaired efficiency of energy processing in lean tissue, may play a role in the increased DIT in CD. Reduced efficiency of energy production might be due, at least to some extent, to depletion of glycogen stores in muscle and liver coupled with an enhancement of futile cycles as proposed by Newsholme (32).

Flatt et al (33) found that in normal control subjects, the fat content of a mixed meal did not influence either the glycemic or the insulinelmic postprandial responses. Furthermore, the time course of the changes in the RQ after meal ingestion is not affected by its fat content, suggesting that the mixture of nutrients oxidized after the meal is independent of the amount of fat ingested. In another study, in which the oxidation rates of nutrients were measured over 24 h in a respiratory chamber (34), the addition of 106 ± 6 g fat to a balanced, weight-maintenance diet failed to promote the use of fat as a metabolic fuel in 7 healthy volunteers. The authors of this study concluded that the entire fat supplement was stored, because there was no evidence of fat malabsorption. The experimental observation that CD patients have higher fasting and postmeal lipid oxidation rates than control subjects suggests that CD patients may have a peculiar metabolic characteristic. The lower glucose oxidation rate in association with the higher lipid oxidation rate found in CD patients compared with control subjects suggests that glucose is actively stored as glycogen, possibly as a consequence of depletion of tissue glycogen. However, no data are available on the glycogen content of skeletal muscle in patients with CD. The preferential oxidation of fat as an energy substrate in the fasting state might be of strategic importance for the conservation of body protein in these patients.

In fact, it has been shown that preservation of body protein and
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reduced nitrogen excretion during prolonged starvation depends on the continued availability of lipids as fuel (35, 36).

Finally, the elevated lipid oxidation rate was not correlated with elevated plasma fatty acid concentrations. A correlation between the plasma concentration and turnover rate of fatty acids has been reported in the literature, and it has also been suggested that the plasma fatty acid concentration might be used as an indicator of the fatty acid turnover rate (37). However, our data, together with the findings of other authors, do not appear to substantiate this claim (38–42). Because plasma fatty acid concentration only reflects the equilibrium between lipolysis and cellular utilization, it is possible that plasma concentration alone may not be a suitable indicator of fatty acid turnover. Hence, if skeletal muscle of CD patients takes up fatty acids from the circulation at a rate exceeding that of fatty acid production from lipolysis, we should find even lower plasma concentrations of fatty acids in CD patients than in healthy control subjects.

In conclusion, the elevation of DIT observed in CD patients with inactive ileal disease can partially explain their difficulty in gaining weight. Furthermore, the finding that a greater proportion of energy is derived from fat than from carbohydrate after a mixed liquid-formula meal may account for the low storage of fat in CD patients, which is revealed by their typically low fat mass.

REFERENCES