Twenty-four-hour energy balance in Crohn disease patients: metabolic implications of steroid treatment

Geltrude Mingrone, Giuseppe Benedetti, Esmeralda Capristo, Andrea De Gaetano, Aldo Virgilio Greco, Pietro Antonio Tataranni, and Giovanni Gasbarrini

ABSTRACT Several hypotheses have been proposed to explain the nutritional deficiencies seen in Crohn disease patients, including inadequate food intake, decreased assimilation and increased loss of nutrients, and increased energy expenditure. To assess the effect of steroid therapy on body composition, energy expenditure, and fuel selection in Crohn disease, we compared 12 patients (6 men and 6 women) with biopsy-proven ileal Crohn disease with 11 healthy volunteers (6 men and 5 women). Five patients [Crohn’s disease activity index (CDAI) = 98.4 ± 3.78] took no medication and seven patients (CDAI = 283.9 ± 22.5) were administered 29 ± 18 mg prednisone/d. Body composition was evaluated by isotopic dilution and bioelectrical impedance analysis, and 24-h energy expenditure and basal metabolic rate were measured in a respiratory chamber. Fat-free mass was not significantly different among groups, whereas fat mass was lower in patients than in control subjects. Energy intake was higher in treated patients than in both untreated patients \((P = 0.004)\) and control subjects \((P = 0.005)\). Fecal losses were not significantly different between untreated patients and control subjects, but were higher (and proportional to the CDAI) in treated patients than in control subjects \((P = 0.001)\). Metabolizable energy was not significantly different among groups, whereas energy balance was significantly higher in treated patients than in both control subjects \((P = 0.0057)\) and untreated patients \((P = 0.018)\). Nitrogen balance was mildly negative in treated patients compared with both control subjects and untreated patients, but not significantly so. In conclusion, prednisone treatment in Crohn disease patients stimulates food intake, promoting an overall positive energy balance despite large fecal nutrient losses. Am J Clin Nutr 1998;67:118–23.

KEY WORDS Crohn disease, respiratory chamber, 24-h energy expenditure, metabolizable energy, energy balance, steroid therapy, body composition, prednisone, humans

INTRODUCTION Several potential mechanisms have been proposed to explain the nutritional and metabolic complications in patients with Crohn disease (1, 2). These include inadequate energy intake (1), decreased assimilation and increased loss of nutrients (3–8), and increased energy expenditure (9). Patients with inflammatory bowel disease may eat less because of the abdominal discomfort or pain and diarrhea often associated with food intake (1). Failure to fully absorb nutrients may occur as a consequence of decreased digestion, resulting from deficient brush border enzyme activity and decreased enterohepatic circulation of bile salts (4). Reports on energy metabolism in patients with Crohn disease have been contradictory. Resting metabolic rate has been found to be increased (9), normal (10), or even reduced (11) in Crohn disease patients compared with healthy control subjects. The only study reporting 24-h energy expenditure measures in Crohn disease patients was designed especially to evaluate substrate oxidation capabilities of patients while they were receiving total parental nutrition, and no comparison was made with a control group (12).

Steroids are used widely for the treatment of inflammatory bowel diseases (13). However, because Crohn disease is characterized by spontaneous remission and relapses, the effect of steroid treatment on the frequency and duration of the remissions is still controversial. The National Cooperative Crohn’s Disease Study (14) found that the number of patients in remission was similar among those who were given placebo and those who were given corticosteroids, azathioprine, or 5-aminosalicylate-sulfonamide. However, with the introduction of newer formulations (such as new 5-aminosalicylates and low-dose, poorly absorbed corticosteroids), it is possible to deliver large amounts of active drug to the bowel and delay the relapse of the inflammatory process (15). Besides their known effects on many events of the inflammatory and immune responses, glucocorticoids have metabolic effects that may strengthen the rationale for their use in the therapy of Crohn disease. Glucocorticoids stimulate food intake (16), promote fat deposition (17, 18), and reduce energy expenditure by the extent of their effect on the inflammatory process (8). On the other hand, long-term treatment with glucocorticoids is associated with increased urinary loss of nitrogen and muscle wasting (19, 20). Therefore, it is relevant to test whether the use of glucocorticoids in patients with Crohn disease is metabolically advantageous.

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This study was conducted to assess the nutritional status, ie, body composition and daily energy and nutrient balances, of patients with Crohn disease at different stages of activity of the disease and to compare these results with those from healthy adult control subjects. A secondary goal was to investigate the metabolically relevant effects of corticosteroid treatment in patients with Crohn disease.

SUBJECTS AND METHODS

Subjects

Twelve patients, six men and six women, with biopsy-proven ileal Crohn disease were studied. The diagnosis of Crohn disease was based on previously reported clinical, morphologic, and histopathologic criteria (21). The degree of illness was assessed according to the Crohn’s Disease Activity Index (CDAI) described by Best et al (22). Anthropometric characteristics and CDAI scores of subjects are shown in Table 1. Five patients took no medication whereas seven patients received an average daily prednisone dose of 29.0 ± 17.8 mg. Eleven healthy volunteers (six men and five women) matched for age and height were studied as a control group. Control subjects were in good health as assessed by a medical history and physical examination. None of the examined women had their menstrual flow during the study and all were studied in the follicular phase of the menstrual cycle. None of the subjects were habitual smokers.

The nature and purpose of the investigations were explained to each subject before he or she agreed to participate in the study. The protocol followed the guidelines of the hospital ethics committee.

Methods

All subjects were admitted to the hospital the day before the testing and received some orientation on the use of the respiratory chamber and related procedures. Body composition was assessed on admission. Body weight was measured to the nearest 0.1 kg with a beam scale. Body composition was assessed by bioelectrical impedance analysis with a radio frequency current of 800 μA at 50 kHz between a set of electrodes attached to the dorsum of the hand and the foot (Body Composition Analyzer; Medileader, Parma, Italy) (23). In Crohn disease patients only, body composition was also estimated on the basis of total body water measured by isotopic dilution (24). Briefly, 80 μCi tritiated water (100 Ci/L) in 5 mL saline solution was administered as an intravenous bolus injection. Decays per minute were counted in duplicate in 0.5 mL plasma with a Beta-scintillation counter (model 1600TR; Canberra-Packard, Canberra, CT) and were plotted against time. To compute the apparent volume of distribution of the labeled water (equal to total body water), the total amount of tritiated water injected as a bolus was divided by the average concentration of labeled water at the steady state. Fat-free mass (FFM) was calculated as total body water divided by 0.73. Total body water was measured in Crohn disease patients only and not in healthy volunteers for ethical reasons.

Respiratory chamber

At 0800 on the experimental day each subject entered the respiratory chamber to remain for a period of 24 h. Twenty-four-hour energy expenditure and basal metabolic rate were measured as described previously (25, 26). Energy expenditure was calculated according to Ferrannini (27). Protein oxidation was determined from 24-h urinary nitrogen excretion and carbohydrate and lipid oxidation were determined from total energy expenditure and the nonprotein respiratory quotient. Daily oxidation rates of protein, carbohydrate, and lipid were also computed. Calibration procedures and the precision and variability of the respiratory chamber were published previously (25, 26).

Diet

During the day spent in the respiratory chamber, to reproduce their usual eating pattern all subjects were assigned a diet with an energy content computed on the basis of their food diaries, compiled for 7 d before the study. Three meals prepared by a diettian using common foods (meat, fish, vegetables, bread, and fruit) were served to the subjects in the chamber. Served and returned food items were weighed to the nearest gram on a precision scale (KS-01; Rowenta, Berlin). The nutrient content of all food items was calculated by using computerized food tables (Food Processor II; Hesha Research, Salem, OR; modified according to the food tables of the Istituto Nazionale di Nutrizione, Italy). The energy content of food was computed as follows: 18 kJ/g protein, 17.6 kJ/g starch (or starch equivalent), and 38.9 kJ/g fat [4.3 kcal/g protein, 4.2 kcal/g starch (or starch equivalent), and 9.3 kcal/g fat]. Metabolizable energy intake was calculated as the difference between gross energy intake and energy lost in the feces. Energy balance was computed as the difference between daily metabolizable energy intake and energy expenditure. Nitrogen balance was estimated from the difference

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td>Physical characteristics of the subjects</td>
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<tr>
<td><strong>Control subjects</strong></td>
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<tr>
<td>(n = 6M, 5F)</td>
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<tr>
<td><strong>Age (y)</strong></td>
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<tr>
<td><strong>Height (cm)</strong></td>
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<td><strong>Weight (kg)</strong></td>
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<td><strong>BMI (kg/m²)</strong></td>
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<tr>
<td><strong>FFM (kg)</strong></td>
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<td><strong>FM (kg)</strong></td>
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<td><strong>CDAI</strong></td>
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1x ± SD. $P_1$, control subjects compared with untreated Crohn disease patients; $P_2$, treated Crohn disease patients compared with untreated Crohn disease patients; $P_3$, control subjects compared with treated Crohn disease patients; FFM, fat-free mass; FM, fat mass; CDAI, Crohn’s Disease Activity Index.
between dietary nitrogen intake and the sum of urinary and fecal nitrogen losses.

**Analysis of lipids and carbohydrates in feces**

Feces were collected in a covered tank located in the respiratory chamber over 24 h and were weighed. A specimen of 1–2 g was taken and proteins precipitated with 5–10 mg trichloroacetic acid. Lipids were extracted twice with eight volumes of chloroform:methanol (2:1, by vol), with the solutions stirred at 60 °C for 15 min. The combined extracts were dried in a GyroVap apparatus (GV1; Gio DeVita, Rome) operating at 60 °C and coupled with a vacuum pump and a gas trap (FTS System, Stone Ridge, NY). The dry weight of lipid extracts was obtained by weighing the sample tube before and after drying the extracts. Water extracts for starch analysis were obtained from 1–2 g of the same feces sample after precipitation of proteins with 5–10 mg trichloroacetic acid. To remove inorganic salts, ion-exchange resin (Dowex 50 W-X4, 100–200 mesh, H⁺; Sigma Chemical Co, St Louis) was used. Aqueous extracts were treated with cation-exchange resin (Dowex 50 W-X4, 100–200 μm mesh, H⁺; Sigma Chemical Co, St Louis) to remove salts, concentrated under reduced pressure, and filtered through an HV filter (0.45 μm; Millipore, Molsheim, France). The samples were evaporated in the GyroVap as described previously. Samples were then hydrolyzed in 0.3 mL of 2 mol HCl/L in a vacuum-sealed tube for 2 h. The hydrolysate was evaporated to dryness under a vacuum (<1 mm Hg) over KOH pellets. Carbohydrates were separated and measured by HPLC with a cation-exchange column according to the method described by Togami et al (28).

**Statistical analysis**

All data are presented as means ± SDs unless specifically stated otherwise. The reliability of the bioelectrical impedance analysis estimate of FFM was established by a Bland-Altman analysis of the subjects (those with Crohn disease) whose FFM was estimated by both bioelectrical impedance analysis and labeled water. Intergroup comparisons were by Kruskal-Wallis nonparametric analysis of variance, followed by pairwise Mann-Whitney U tests corrected for simultaneous inference with the Bonferroni inequality. The linear correlation between prednisone dose and metabolic indicators (such as energy expenditure or substrate oxidation) was assessed by the Spearman rank technique. Linear regression analysis was used to assess the independence between quantitative variables. For the purposes of regression, the CDAI was assimilated to a continuous, rational variable, given the large number of possible values it can take and its near-normal distribution.

**RESULTS**

The first 12 of 20 new clinical patients who came under our observation in 1996 were enrolled in the present study; the patients represented, therefore, ~60% of our total new clinical population for 1 y. Five of these patients did not require medication because they had a low CDAI score, whereas seven patients received an average daily prednisone dose of 29.0 ± 17.8 mg at the time of the investigation.

The Bland-Altman plot of the difference between the FFM estimates obtained with labeled water and with bioelectrical impedance analysis and the average estimated for each subject is shown in Figure 1. No systematic error component or appreciable heteroscedasticity was present. The two methods presented a mean difference (bias) of 0.25 kg. The maximum likely error, therefore, taken to be twice the SD of the difference, was 5.25 kg. These results indicate that the two methods of body-composition assessment were in excellent average agreement, with an acceptable random scatter of the differences in estimates. Therefore, only body-composition results by bioelectrical impedance analysis are used in the rest of the paper. FFM values in Crohn disease patients were not statistically different from those observed in control subjects. In contrast, fat mass was significantly lower in Crohn disease patients than in healthy volunteers (Table 1). The direct (uncorrected for simultaneous inference) comparison of fat mass between Crohn disease patients who did and did not receive steroid therapy was also nominally significant (P = 0.042); the patients who did not receive steroid therapy had the lowest fat mass among the three groups.

The energy profile for each group of subjects examined is reported in Table 2. Crohn disease patients receiving steroid treatment had significantly higher energy intakes than did control subjects. A positive correlation between food intake and daily prednisone dose (mg) was found (r = 0.93, P = 0.0025; Spearman nonparametric correlation) (Figure 2). No significant difference in energy intake was found between untreated Crohn disease patients and control subjects.

Crohn disease patients receiving steroids had higher total energy, carbohydrate, and lipid fecal losses than both untreated Crohn disease patients and control subjects (Table 2). In these patients, lipid fecal losses accounted for 87.1% of total fecal losses. Lipid fecal losses in Crohn disease patients with active disease were positively associated with the CDAI (r = 0.96, P = 0.0004) (Figure 3). These patients had significantly higher carbohydrate intakes than both untreated Crohn disease patients and control subjects.

Twenty-four-hour energy expenditure and basal metabolic rate were similar in Crohn disease patients and control subjects. Subjects with a higher FFM expended more energy than those with a lower FFM: linear regression analysis showed a positive correlation between 24-h energy expenditure and FFM in control subjects and in the two groups of Crohn disease patients studied (Spearman r = 0.83, P = 0.0017 in control subjects; Spearman r = 0.90, P = 0.037 in untreated Crohn disease patients; and Spearman r = 0.86, P = 0.014 in treated Crohn disease patients).

![Figure 1](https://example.com/figure1.png)  
**FIGURE 1.** Bland-Altman plot of the differences in fat-free mass estimated by bioelectrical impedance analysis (FFM-BIA) and by the labeled water technique (FFM-H2O) versus the average estimate obtained with the two methods on the same subject (n = 12). The solid line indicates the average difference (0.25 kg) and the broken lines indicate the average difference ± 2 SDs of the difference (SDD = 2.62 kg).
Metabolizable energy content of the food was not significantly different among the three groups, whereas energy balance was significantly higher in treated Crohn disease patients than in both untreated Crohn disease patients and control subjects (\(P = 0.028\) and \(P = 0.001\), respectively), as shown in Table 2.

The nitrogen profile for each group is reported in Table 3. Nitrogen balance was mildly negative in patients receiving steroid therapy compared with both healthy control subjects and untreated Crohn disease patients; however, the difference was not significant, most likely because of the high interindividual variability.

The fasting basal respiratory quotient was 0.816 ± 0.018 in treated Crohn disease patients, 0.784 ± 0.053 in untreated Crohn disease patients, and 0.825 ± 0.041 in control subjects, and was not significantly different among groups. The 24-h respiratory quotient was significantly higher in treated Crohn disease patients than in control subjects (0.906 ± 0.022 compared with 0.854 ± 0.033; \(P = 0.003\)), but was similar in untreated Crohn disease patients and control subjects (0.834 ± 0.065 compared with 0.854 ± 0.033; NS). No significant differences in 24-h urinary nitrogen excretion were found among groups.

**DISCUSSION**

The incidence of Crohn disease seems to have increased greatly in Europe in the past decades. A study of Scottish children showed that the number of new cases per year increased from 6.6 per million in 1968 to 29 per million in 1988 (29). Furthermore, the European Group for the Study of Inflammatory Bowel Diseases found recently that the average incidence of Crohn disease in the European population aged 15–64 y is ≈5 cases per 100,000 persons/y (30), with a higher incidence in northern than in southern Europe. Unfortunately, no data are available on the incidence or prevalence of this disease in Rome; the incidence in Milan is <1.4 per 100,000 persons/y and that in Palermo is 7.4 per 100,000 persons/y (30).

The present study confirms our previous report of an altered nutritional status in patients with Crohn disease (31). Although FFM seems to be preserved, a low fat mass is a peculiar feature of Crohn disease. Fat mass was slightly higher in Crohn disease patients treated with prednisone than in patients who did not receive steroids, suggesting a possible positive effect of steroid treatment on nutritional status in patients with Crohn disease. As

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**TABLE 2**

<table>
<thead>
<tr>
<th>Control subjects (n = 11)</th>
<th>Untreated Crohn disease patients (n = 5)</th>
<th>Treated Crohn disease patients (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kJ/d)</td>
<td>7762 ± 518 NS</td>
<td>7449 ± 548 0.004</td>
</tr>
<tr>
<td>Energy fecal loss</td>
<td>68 ± 2 NS</td>
<td>67 ± 3 0.004</td>
</tr>
<tr>
<td>Metabolizable energy intake (kJ/d)</td>
<td>7694 ± 506 NS</td>
<td>7382 ± 539 NS</td>
</tr>
<tr>
<td>Energy expenditure</td>
<td>7632 ± 900 NS</td>
<td>7145 ± 646 NS</td>
</tr>
<tr>
<td>Energy balance</td>
<td>50 ± 10 NS</td>
<td>237 ± 170 0.028</td>
</tr>
<tr>
<td>Carbohydrate intake</td>
<td>3964 ± 259 NS</td>
<td>3808 ± 277 0.004</td>
</tr>
<tr>
<td>Carbohydrate fecal loss</td>
<td>10 ± 1 NS</td>
<td>11 ± 2 0.004</td>
</tr>
<tr>
<td>Lipid intake</td>
<td>2254 ± 147 NS</td>
<td>2243 ± 163 NS</td>
</tr>
<tr>
<td>Lipid fecal loss</td>
<td>58 ± 6 NS</td>
<td>56 ± 3 0.004</td>
</tr>
</tbody>
</table>

\(x \pm SD.\) Metabolic variables were measured over 24 h. Metabolizable energy intake was calculated as the difference between gross energy intake and energy fecal loss. Energy balance was calculated as the difference between metabolizable energy intake and energy expenditure. \(P_1\), control subjects compared with untreated Crohn disease patients; \(P_2\), treated Crohn disease patients compared with untreated Crohn disease patients; \(P_3\), control subjects compared with treated Crohn disease patients.
indicated by the energy metabolism data, this may be due to the stimulatory effect of steroids on food intake, which in turn promotes a positive energy balance.

The reasons for the poor nutritional status of Crohn disease patients compared with normal control subjects are not immediately evident from our results. In line with some studies (32, 33), but not all (10), we found no differences in metabolizable energy intake among groups. Also, 24-h energy expenditure was comparable in all three groups. As a consequence, all three groups had a slightly positive energy balance, with the untreated Crohn disease patients having values that were intermediate between normal control subjects (lower values) and treated Crohn disease patients (higher values). This finding is surprising given the lower fat mass of untreated Crohn disease patients and can be explained only as an occasional finding or as the result of the measurement being performed during a day of remission of the disease, when the bowel inflammatory process was not affecting food intake or energy expenditure.

Glucocorticoids are known to promote positive balance and to favor energy storage. Tataranni et al (16) showed recently that compared with placebo a 4-d administration of therapeutic methylprednisolone (40 mg/d) to healthy volunteers induces a significant increase in food intake. Our study not only confirms an increased food intake in Crohn disease patients receiving prednisone, but also indicates that this increase is proportional to the steroid dose administered.

However, despite the high doses of steroids administered, a marked lipid malabsorption was still observed in our patients. It is possible that the steroid dose used was insufficient to control the disease. Because the average daily ratio of steroid dose to the CDAI score was high, it is possible that the lipid malabsorption in these patients was due to pathologic mechanisms that are independent of the degree of inflammation of the small intestine.

Because of fecal energy loss, metabolizable energy intake was not different among the three groups. In contrast, energy balance was significantly higher in treated Crohn disease patients than in the other groups. This finding needs to be evaluated with caution because energy balance was calculated on a single day and experimental conditions as well as other factors may have affected the measurement. However, it is possible that the increased energy intake induced by steroid administration compensates for the fecal energy losses and promotes a positive energy balance. In the presence of excess energy, glucocorticoids have been shown to induce fat deposition as a result of promoting preadipocyte differentiation and increasing the activity of lipoprotein lipase (34, 35). This may be the explanation for the slightly better nutritional status of treated compared with untreated Crohn disease patients in our study.

Few data are reported in the literature on the nitrogen-wasting effects of corticosteroids; in particular, high-dose (1000 mg), short-term (3 d) intravenous administration of methylprednisolone in patients with rheumatoid arthritis showed a strong protein catabolic effect (20). However, no information on nitrogen balance is available for the dose of steroids used in our study. Our data seem to indicate that a moderate, although not significant, negative nitrogen balance is present in treated Crohn disease patients. Because nitrogen balance was evaluated only over a 24-h period and because treated Crohn disease patients did not have reduced FFM compared with control subjects, this information needs to be interpreted with caution. In any case, clinicians should be aware of the risk of inducing negative nitrogen balance when administering steroids in high doses or for prolonged periods of time. However, whether the effect of steroid treatment on energy metabolism can be sustained for a prolonged period of time without incurring muscle wasting (19, 20) remains to be evaluated in longitudinal studies.

A trend toward a lower respiratory quotient (basal and 24-h) was observed in the group of untreated Crohn disease patients. This suggests that these patients oxidize more lipids than healthy control subjects and confirms our previous report (31). On the contrary, steroid-treated patients had a significantly higher 24-h respiratory quotient, which was probably the consequence of the high carbohydrate-to-lipid ratio of their diet after correction for nutrient losses in feces. In conclusion, our study confirms that the nutritional status of patients with Crohn disease is compromised and suggests that prednisone treatment may favor a certain degree of fat mass recovery by promoting an overall positive energy balance, mostly via a stimulation of food intake, although also by promoting a mildly negative nitrogen balance.

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 11)</th>
<th>Untreated Crohn disease patients (n = 5)</th>
<th>Treated Crohn disease patients (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein energy intake (kJ/d)</td>
<td>1554 ± 101</td>
<td>1400 ± 101</td>
<td>2294 ± 658</td>
</tr>
<tr>
<td>Nitrogen intake (g·kg body wt⁻¹·d⁻¹)</td>
<td>0.201 ± 0.023</td>
<td>0.239 ± 0.018</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrogen urinary loss (g·kg body wt⁻¹·d⁻¹)</td>
<td>0.153 ± 0.019</td>
<td>NS</td>
<td>0.167 ± 0.033</td>
</tr>
<tr>
<td>Nitrogen fecal loss (g·kg body wt⁻¹·d⁻¹)</td>
<td>0.032 ± 0.012</td>
<td>NS</td>
<td>0.035 ± 0.008</td>
</tr>
<tr>
<td>Total nitrogen loss (g·kg body wt⁻¹·d⁻¹)</td>
<td>0.185 ± 0.023</td>
<td>NS</td>
<td>0.203 ± 0.041</td>
</tr>
<tr>
<td>Nitrogen balance (g·kg body wt⁻¹·d⁻¹)</td>
<td>0.015 ± 0.015</td>
<td>NS</td>
<td>0.037 ± 0.026</td>
</tr>
</tbody>
</table>

*Note: *All values are mean ± SD. Metabolic variables were measured over 24 h. P₁, control subjects compared with untreated Crohn disease patients; P₂, treated Crohn disease patients compared with untreated Crohn disease patients; P₃, control subjects compared with treated Crohn disease patients.
REFERENCES


