Energy and Substrate Metabolism in Patients with Active Crohn’s Disease

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ABSTRACT The aim of the study was to evaluate the possible contribution of changes in energy metabolism and substrate oxidation rates to malnutrition in Crohn’s disease and to assess the effect of enteral nutrition on these parameters. Energy metabolism was evaluated by indirect calorimetry in 32 patients with active Crohn’s disease and 19 age- and sex-matched healthy individuals. Measurements were done in the postabsorptive state. Seven out of 32 patients received enteral nutrition via a nasogastric tube. In these patients, resting energy metabolism was determined at d 0 (postabsorptive), 7, 14 (during full enteral nutrition) and 15 (postabsorptive). Resting energy expenditure was not significantly different between patients and controls, whereas the respiratory quotient (RQ) was lower in patients (0.78 ± 0.05 vs. 0.86 ± 0.05; P < 0.05). During enteral nutrition in 7 patients with Crohn’s disease, the RQ increased on d 7 compared with d 0 and remained high even after cessation of enteral nutrition (d 0, 0.78 ± 0.03; d 7, 0.91 ± 0.04; d 15, 0.84 ± 0.05; P < 0.05; d 7 and 15 vs. d 0). No effects of enteral nutrition on resting energy expenditure were found. Active Crohn’s disease is associated with changes in substrate metabolism that resemble a starvation pattern. These changes appear not to be specific to Crohn’s disease but to malnutrition and are readily reversed by enteral nutrition. Enteral nutrition did not affect resting energy expenditure. Wasting is a consequence of malnutrition but not of hypermetabolism in Crohn’s disease. J. Nutr. 129: 844–848, 1999.

KEY WORDS: • Crohn’s disease • humans • energy metabolism • enteral nutrition • substrate oxidation

Crohn’s disease is frequently accompanied by malnutrition and weight loss. The etiology of malnutrition in these patients, however, is not yet completely understood. Anorexia, as a consequence of eating-related symptoms, could lead to malnutrition (Gryboski 1993); this might explain weight loss in some patients. In others, malabsorption and increased intestinal losses have been discussed as a cause of a negative substrate balance as in other catabolic diseases (Stokes 1992). Another etiological factor could be an increased energy expenditure. Increased energy expenditure and changes in substrate oxidation have been found in several diseases and have been linked to weight loss (Wilmore 1991).

Several authors have measured resting energy expenditure in Crohn’s disease with controversial results: Chan et al. (1986) found that patients with Crohn’s disease, without fever and sepsis, did not have increased resting energy expenditure (REE)2, whereas Kushner and Schoeller (1991) found a slight increase in energy needs in stable outpatients with inflammatory bowel disease. These conflicting results could be explained in part by the fact that these authors investigated a rather heterogeneous group of patients with a wide variation of disease activity. In the study of Chan et al. (1986) 43% of patients were receiving prednisone, which influences substrate metabolism (Horber et al. 1991).

Parenteral as well as enteral nutrition are used in active Crohn’s disease although the therapeutic mechanism is not known. Improvement of nutritional status appears to be essential for the anti-inflammatory effect of nutritional therapy as shown in a recent publication (Royall et al. 1994b). In this study, a good correlation between the achievement of a positive nitrogen balance and remission after enteral nutrition in Crohn’s disease was found. Pollicino et al. (1991) studied the effect of cyclic and continuous total parenteral nutrition on energy expenditure and substrate metabolism measured by 24-h whole-body calorimetry. They found that a positive energy balance could easily be achieved in all subjects and demonstrated net lipogenesis from carbohydrate during parenteral nutrition. However, their patients had been in the remission phase of Crohn’s disease, were receiving a low dose oral prednisolone therapy and had already been fed intravenously for at least 1 wk before they were studied (Pollicino et al. 1991).

Therefore, data on the effect of enteral nutrition on energy expenditure and substrate oxidation in active Crohn’s disease are still incomplete.

In this study, therefore, we investigated energy and substrate metabolism in patients with active Crohn’s disease without corticosteroid therapy. Furthermore, we investigated the effect of enteral nutrition on energy expenditure and substrate
SUBSTRATE METABOLISM IN PATIENTS WITH CROHN’S DISEASE

TABLE 1

Physical characteristics at baseline of healthy controls, patients with Crohn’s disease and patients with Crohn’s disease subsequently receiving enteral nutrition

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Patients with Crohn’s disease</th>
<th>Patients with Crohn’s disease subsequently receiving enteral nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>19</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>7/12</td>
<td>11/21</td>
<td>2/5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64.5 ± 9.9</td>
<td>56.5 ± 13.7**</td>
<td>47.6 ± 10.8***</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.9 ± 8.5</td>
<td>169.2 ± 9.4</td>
<td>165.4 ± 9.5</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.76 ± 0.2</td>
<td>1.64 ± 0.2*</td>
<td>1.5 ± 0.2*</td>
</tr>
<tr>
<td>LBM, kg</td>
<td>48.7 ± 9.4</td>
<td>43.5 ± 10.8*</td>
<td>38.5 ± 9.5*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>21.7 ± 2.3</td>
<td>19.6 ± 3.7*</td>
<td>17.3 ± 3.4</td>
</tr>
<tr>
<td>CDAl</td>
<td>—</td>
<td>296 ± 85</td>
<td>304 ± 117</td>
</tr>
</tbody>
</table>

1 Values are means ± SD.

2 These seven patients are a subgroup of the 32 patients with Crohn’s disease. Significantly different from healthy controls; *P < 0.05; **P < 0.01; ***P < 0.005.

BMI, body mass index; BSA, body surface area; CDAl, Crohn’s disease activity index; LBM, lean body mass.

oxidation rates in these patients. We hypothesized that as in other acute diseases such as infection and trauma, energy expenditure is increased, the respiratory quotient (RQ) is decreased in patients with acute Crohn’s disease and enteral nutrition is able to normalize changes in substrate oxidation rates.

MATERIALS AND METHODS

Subjects. Thirty-two patients with active Crohn’s disease participated in the study. The diagnosis of Crohn’s disease was established by generally accepted criteria in all patients before the study (Malchow et al.1984). Activity of the disease was determined by the Crohn’s Disease Activity Index (CDAI) (Best et al. 1979).

At the beginning of the study, all patients were in an active phase of the disease defined by a CDAI >150. None had a history of chronic liver disease, diabetes mellitus, thyroid dysfunction or other acute or chronic diseases. None of the patients received corticosteroids or other immunosuppressants during the study or within 3 mo before the study. At the time of the study, no patient had a body temperature >37.3°C or any signs of infection.

Nineteen age- and sex-matched healthy subjects served as controls. The clinical data at baseline of controls, patients, and the subgroup of patients subsequently receiving enteral nutrition are presented in Table 1.

The study-protocol was approved by the ethics committee of the University of Vienna, Medical School, and written consent was obtained from all subjects.

Metabolic studies. After an overnight fast, initial resting energy expenditure and substrate oxidation rates were determined in controls and in all patients by indirect calorimetry. Seventy of the 32 patients were treated with enteral nutrition as the sole therapy. In these patients, the effect of enteral nutrition on energy and substrate metabolism was studied by indirect calorimetry before (d 0) during (d 1, 7 and 14) and 12 h after ending enteral nutrition (d 15). Clinical data of these seven patients are presented in Table 1. Enteral nutrition was infused continuously via a nasogastric tube and was started immediately after indirect calorimetry on d 0. Enteral nutrition was started with an infusion rate of 50 mL/h; increasing infusion rates were used to reach the full dose of 100 mL/h (10.042 kJ/d) after 48 h. One patient did not tolerate the full dose and was infused with 80 mL/h. A peptide-based nutrition solution (Salvipeptid, Salvia, Germany) was used; it contained 19 energy% protein, 27 energy% fat, and 54 energy% carbohydrates. The composition of the diet is presented in Table 2.

Indirect calorimetry. Patients and controls were studied on an outpatient status. They were asked not to perform unnecessary activities before entering the metabolic unit. Subjects were lying in bed in a supine position for at least 30 min before starting the measurements. They were instructed to lie quietly until measurements were completed.

Respiratory gas exchange was measured by computerized open-circuit indirect calorimetry using a ventilated hood system (DeltaTrac Metabolic Monitor, Datex Instruments, Finland) as previously described (Schneweis et al.1993). Measurements were done every minute, and the results were averaged over periods of 20 min. Calibrations were performed before and at the end of the measurements.

Urea nitrogen appearance rate (UNP) was calculated from 12-h urinary nitrogen excretion and changes in the body urea nitrogen pool (Maroni et al. 1985).

Body composition. Lean body mass (LBM) was determined by anthropometry according to Durnin and Womersley (1979). Triceps-, biceps-, subscapular- and suprailiac-skinfolds were measured by a Lange caliper (Cambridge Scientific, Cambridge, MD) and used to determine body density. Body fat and LBM were calculated from density using Siri’s equation (Durnin and Womersley 1974).

TABLE 2

Composition of the nutrient solution administered to seven patients with Crohn’s disease

<table>
<thead>
<tr>
<th>Contents</th>
<th>unit/L</th>
<th>Contents</th>
<th>unit/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, g</td>
<td>47.5</td>
<td>Retinol, mg</td>
<td>0.5</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>135</td>
<td>Cholecalciferol, µg</td>
<td>5</td>
</tr>
<tr>
<td>Fat, g</td>
<td>30</td>
<td>Vitamin E, mg</td>
<td>7</td>
</tr>
<tr>
<td>Energy, kJ</td>
<td>4250</td>
<td>Vitamin K, µg</td>
<td>40</td>
</tr>
<tr>
<td>Water, mL</td>
<td>800</td>
<td>Vitamin C, mg</td>
<td>37.5</td>
</tr>
<tr>
<td>Sodium, mmol</td>
<td>45</td>
<td>Thiamin, mg</td>
<td>0.75</td>
</tr>
<tr>
<td>Potassium, mmol</td>
<td>45</td>
<td>Riboflavin, mg</td>
<td>0.9</td>
</tr>
<tr>
<td>Chloride, mmol</td>
<td>45</td>
<td>Nicotinamide, mg</td>
<td>9.5</td>
</tr>
<tr>
<td>Calcium, mmol</td>
<td>10</td>
<td>Vitamin B-6, mg</td>
<td>1</td>
</tr>
<tr>
<td>Phosphorus, mmol</td>
<td>12.9</td>
<td>Folic acid, mg</td>
<td>0.13</td>
</tr>
<tr>
<td>Magnesium, mmol</td>
<td>7.4</td>
<td>Pantothenate, mg</td>
<td>4</td>
</tr>
<tr>
<td>Iron, mmol</td>
<td>143</td>
<td>Vitamin B-12, µg</td>
<td>2.5</td>
</tr>
<tr>
<td>Zinc, µmol</td>
<td>114.5</td>
<td>Biotin, µg</td>
<td>75</td>
</tr>
<tr>
<td>Copper, µmol</td>
<td>22</td>
<td>Choline, mg</td>
<td>200</td>
</tr>
<tr>
<td>Fluoride, µmol</td>
<td>9.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manganese, µmol</td>
<td>34.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iodide, µmol</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromium, µmol</td>
<td>1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molybdenum, µmol</td>
<td>1.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Calculations. REE and substrate oxidation rates were calculated from measured VO₂, VCO₂, and UNP according to Ferranini (1989) and Frayn (1983). For this purpose, protein oxidation was estimated from UNP (1 g urea nitrogen = 6.25 g protein). UNP was calculated from urine urea nitrogen concentration and urine volume per day:

\[
\text{Glucose oxidation (g/min) (CHO) = 4.55} \\
\times \text{VCO₂ (L/min)} - 3.21 \times \text{VO₂ (L/min)} - 2.87 \times \text{UNP (g/min)}. \\
\text{Fat oxidation (g/min) (FAT) = 1.67} \\
\times \text{VO₂ (L/min)} - 1.67 \times \text{VCO₂ (L/min)} - 1.92 \times \text{UNP (g/min)}. \\
\text{Protein oxidation (g/min) (PRO) = 6.25 \times UNP (g/min)}. \\
\text{REE (kJ/min) = 16.4 \times VO₂ + 4.61 \times VCO₂ - 13.98 \times UNP.}
\]

Substrate oxidation rates were expressed as a percentage of total energy expenditure. Energy balances were calculated on d 7 and 14 in the seven patients receiving enteral nutrition, from 24-h energy expenditure based on REE, taking into account activity factor of 12% of resting energy expenditure and a diet-induced thermogenesis of 6% energy intake (Acheson et al. 1982, Pollicino et al. 1991, 12% of resting energy expenditure and a diet-induced thermogenesis of 6% energy intake (Acheson et al. 1982, Pollicino et al. 1991, Frayn 1983). For this purpose, protein oxidation was estimated from UNP (1 g urea nitrogen = 6.25 g protein). UNP was calculated from urine urea nitrogen concentration and urine volume per day:

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\text{REE (kJ/min) = 16.4 \times VO₂ + 4.61 \times VCO₂ - 13.98 \times UNP.}
\]

Statistical analysis. All results are presented as means and SD. To compare data between patients and controls, the Wilcoxon-test was used. The relationship between REE and RQ, and UNP and total body mass existed in patients (r = 0.75; P < 0.0001) and controls (r = 0.6; P < 0.01). The regression line for patients was on a slightly higher REE level; however, the slopes of the lines and the y-intercepts were not significantly different (Fig. 2).

Disease activity as reflected by the CDAI ranged from 188 to 542. Different disease activities did not influence energy expenditure as indicated by the lack of a correlation between CDAI and REE (r = −0.09, P = 0.61). The RQ was significantly lower in patients than in healthy controls (Table 3), indicating a lower oxidation rate for carbohydrate and a higher oxidation rate for fat in patients (Fig. 1). Due to the reduced LBM (Table 2), UNP and protein oxidation rate (Fig. 1), calculated from UNP, also were significantly lower in patients.

A correlation between UNP and body weight existed in both patients (r = 0.45, P < 0.05) and healthy controls (r = 0.52, P < 0.05). No such correlation existed between RQ and body weight.

No change was observed in REE over the 15 d. UNP, RQ, and non-protein RQ increased significantly on d 7 and 14 relative to d 0 and, except for the non-protein RQ, remained elevated even after cessation of enteral nutrition (Table 4). These changes were caused by a profound increase in carbohydrate oxidation and protein oxidation, accompanied by a decrease in fat oxidation (Fig. 3). All of these changes (except for carbohydrate oxidation rates) were gradually reversed when enteral nutrition was discontinued on d 15 but remained at a lower level.

![FIGURE 1](https://example.com/figure1.png)

**TABLE 3** Metabolic studies at baseline of patients with Crohn’s disease and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Patients with Crohn’s disease</th>
<th>Patients with Crohn’s disease subsequently receiving enteral nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>19</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>REE, kJ/min</td>
<td>4.10 ± 0.6</td>
<td>4.12 ± 0.7</td>
<td>4.01 ± 0.8</td>
</tr>
<tr>
<td>RQ</td>
<td>0.86 ± 0.05</td>
<td>0.78 ± 0.05*</td>
<td>0.78 ± 0.03*</td>
</tr>
<tr>
<td>UNP, mg/min</td>
<td>6.50 ± 2.3</td>
<td>3.73 ± 3.0*</td>
<td>1.75 ± 1.04*</td>
</tr>
<tr>
<td>Non-protein RQ</td>
<td>0.87 ± 0.06</td>
<td>0.78 ± 0.05*</td>
<td>0.79 ± 0.03*</td>
</tr>
</tbody>
</table>

1 Values are expressed as means ± SD.
2 These seven patients are a subgroup of the 32 patients with Crohn’s disease. Significantly different from healthy controls; *P < 0.001.

REE, resting energy expenditure; RQ, respiratory quotient; UNP, urea nitrogen appearance rate.
formed by Lavoisier at the end of the 18th century. Body parameters should be used as the denominator of metabolic rates has been normalized by the active body mass (Ferranini 1989). What should be made on the status of energy metabolism during physical activity.

To compare data from groups of patients with different body size and body composition, metabolic parameters have to be normalized by the active body mass (Ferranini 1989). What should be used as the denominator of metabolic rates has been discussed since the early studies on energy metabolism per-should be proven to apply to a wider population before it could be applied to all malnourished individuals’’ (Royall et al.1994a).

To determine whether different methods have all been used to calculate the”metabolic active tissue mass. Azcue et al. (1997) recently published a paper on energy expenditure and body composition in children with Crohn’s disease. They normalized energy expenditure by total body weight and LBM, calculated by bioelectrical impedance analysis, total body potassium and the difference of total body water (measured with H218O) and extracellular water (determined with bromide space study). They found that the REE of patients with Crohn’s disease was not different from controls whether expressed as calories per kilogram body weight or per kilogram LBM. Royall et al. (1994a) showed that determination of lean body mass by bioelectric impedance analysis and by total body potassium is of limited validity in malnourished patients. They found an underestimation of free fat mass with wide scatter of values for hydration of free fat mass when total body potassium was used, with several values outside of the accepted biological limits. Data obtained by bioelectric impedance analysis resulted in an overestimation of free fat mass. The authors concluded that both methods and dual-energy X-ray absorptiometry “should be proven to apply to a wider population before it could be applied to all malnourished individuals” (Royall et al.1994a).

Because there are no accurate methods available for met-
suring the metabolically active body mass until now, we tried to overcome the problems related to the determination of lean body mass by normalization of metabolic data by comparing the slopes of the regression lines between REE and LBM or total body mass. This approach has been used in comparative physiology for years (Schmidt-Nielsen 1984). Calculating the regression between total body weight and measured REE in both patients and healthy controls, a significant correlation between these variables was found in our study (patients: $r = 0.75$, $P < 0.0001$; controls: $r = 0.6$, $P < 0.01$). The slopes were virtually identical. Because the regression lines between body weight and REE were not different among the study groups, the same conclusion concerning energy expenditure in Crohn’s disease would be expected, even if controls and patients were matched on the basis of body weight and body composition. Our data are consistent with the data of Azcue et al. (1997) in children with Crohn’s disease. They also found that there was no difference in the slope of the relation between REE and LBM.

The changes in substrate metabolism found in our patients resemble those of starvation. In this condition, the RQ and urinary nitrogen appearance rate are reduced, calculated oxidation rates for glucose and protein are lowered and the oxidation rate for fat is elevated (Cahill et al. 1966). Factors such as a lowered food intake due to anorexia and raised intestinal losses of nutrients may lead to this alteration of substrate metabolism. These changes are completely dependent on substrate availability. After only 1 d of enteral nutrition, substrate oxidation rates were almost normalized in our study. This normalization remained even after completion of enteral nutrition and may reflect the availability of replenished glycogen stores. Although the duration of enteral nutrition and the study period were too short to show significant effects on body weight, body composition and Crohn’s disease activity, patients were in positive energy balance. This has been linked to the efficiency of nutritional therapy in patients with Crohn’s disease (Royall et al. 1994b).

It is surprising that we did not observe a decline in the metabolic rate in these patients who obviously were malnourished. The fact that energy expenditure is not lowered in Crohn’s disease does not exclude the possibility that a reduction in the metabolic rate, caused by starvation, is masked by an elevation of energy expenditure by the inflammatory bowel disease, thus, no net effect on energy expenditure could be observed.

From our findings, we have to conclude that weight loss in patients with Crohn’s disease is not due to an elevation in energy expenditure, but the consequence of malnutrition caused by anorexia, malabsorption and increased intestinal losses (Gryboski 1993, Stokes 1992).

In earlier studies, it was shown that enteral nutrition as well as parenteral nutrition improved the nutritional status of patients with Crohn’s disease (Lochs et al. 1991, Pollicino et al. 1991). Our data also support the importance of enteral nutrition for these patients by demonstrating that infused substrates are utilized.

Furthermore, energy balance was positive in our study (~1.8 kJ/min on d 7 and 14). If we were to assume that the energy balance remains in this range, over the 14-d feeding period, a weight gain of 1–2 kg, depending on the nutrient stored, could be expected. However, we found an increase in body weight of only 0.7 kg. The reason for this discrepancy can be explained by stool losses, possible changes in hydration status and the fact that we did not measure total energy expenditure directly. Rather, we calculated it from REE, an activity index of 12% of REE and a diet-induced thermogenesis of 6% (Pollicino et al. 1991).

In summary, patients with active Crohn’s disease show changes in substrate oxidation similar to those in starvation, whereas energy expenditure is not altered as in cachectic diseases. Wasting, therefore, is a consequence of malnutrition but not of hypermetabolism in Crohn’s disease. Refeeding normalized the observed changes in substrate metabolism, underlining the importance of enteral nutrition in this disease.

**LITERATURE CITED**


