Effect of malnutrition and short-term refeeding on peripheral blood mononuclear cell mitochondrial complex I activity in humans[1–3]

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ABSTRACT

Background: Previous investigations in rats have shown that the first enzyme of the mitochondrial electron transport chain (complex I) is altered in peripheral blood mononuclear cells (PBMCs) and muscle by dietary manipulations.

Objective: We hypothesized that similar changes would occur in human PBMCs as a result of dietary malnutrition and short-term refeeding irrespective of the presence or absence of active inflammatory bowel disease (IBD).

Design: Fourteen malnourished patients with active IBD, 13 malnourished patients without IBD, and 42 healthy subjects were investigated. Complex I activity, body mass index, body composition, energy and protein intakes, and resting energy expenditure were measured. Five patients without IBD and 6 patients with IBD were investigated after 7 d of refeeding.

Results: In patients without IBD, weight loss was mainly due to a loss of fat mass. In contrast, weight loss in IBD patients was due to a loss of both fat-free mass and fat mass. Complex I activity was reduced to the same degree in both groups of patients and was significantly lower than that observed in healthy subjects. In both groups of patients, complex I activity correlated significantly with body weight, body mass index, percentage weight loss, and fat mass. Complex I activity increased significantly after 1 wk of refeeding in both groups of patients before observed changes of measured nutritional assessment indexes.

Conclusion: Our study showed that mitochondrial complex I activity measured in PBMCs seems to be a specific marker of dietary malnutrition and responds rapidly to refeeding. *Am J Clin Nutr* 2003;77:1304–11.

KEY WORDS Malnutrition, refeeding, inflammatory bowel disease, peripheral blood mononuclear cells, mitochondria, complex I

INTRODUCTION

Malnutrition is the result of a disturbance in the equilibrium between dietary intake and nutrient needs (1). The consequences of prolonged malnutrition are sequentially altered cellular metabolism, impaired function, and finally, loss of body tissues (2). Clinically, malnutrition is often associated with muscular dysfunction and weakness and altered immunity resulting in an increased risk of infection (3–5). Weight loss is common in patients with inflammatory bowel disease (IBD) (6–8). The main causes of weight loss are reduced nutrient intake, maldigestion, malabsorption, elimination of nutrients as a result of oxidative stress, and enteric loss of nutrients (7, 9). In active IBD patients, the metabolic disturbances associated with malnutrition may be caused by malnutrition itself or by inflammation. It is well known that the prevalence and degree of malnutrition are markedly influenced by the activity and extent of the disease (10). Furthermore, disease activity with bowel inflammation could cause weight loss by increasing energy expenditure (11), which may be related to altered cellular metabolism.

Mitochondria occupy a pivotal position in aerobic ATP production. All of the energy-producing reactions generate reducing equivalents that are ultimately oxidized by oxygen through a chain of oxidoreduction reactions occurring in complexes I–IV residing in the inner mitochondrial membrane (electron transport chain). These processes create a proton gradient across the inner mitochondrial membrane, which is used to drive ATP synthesis by complex V (F0F1 ATPase; EC 3.6.1.3) (12). Previous studies suggest that muscle cell energetics are altered by protein-energy restriction, showing a slower rephosphorylation of ADP in the skeletal muscle of malnourished rats (13, 14). Consistent with this observation, we recently observed that malnutrition impaired the activity of mitochondrial electron transport chain in muscle (complexes I–III) as well as in the peripheral blood mononuclear cells (PBMCs) (complex I) of rats (15). Furthermore, in another study, the reduction of complex I and III activities was proportional to a reduction in the oxidative phosphorylation rate in the muscle of malnourished rats (16).

Muscle function responds earlier to refeeding than do traditional indicators of body composition (17, 18) and could be profoundly influenced by protein restriction despite an adequate energy intake (19). In this context, it is of interest that protein refeeding, but not glucose refeeding, restored the electron transport chain in the soleus muscle and PBMCs of rats without any associated gain in body weight (15).

Because we found that nutritional manipulations in animals influenced the electron transport chain, we decided to investigate the first enzyme of the mitochondrial electron transport chain (complex I) in human PBMCs. Our objectives were to *1*) compare

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TABLE 1
Physical and clinical characteristics of the malnourished patients without inflammatory bowel disease[1]

	Patients
	n
Age (y)	
≤25	1
50–64	5
≥65	7
Sex	
Male	7
Female	6
Diagnosis	
Dumping syndrome	2
Gastrointestinal motility disorder	3
Intestinal obstruction	2
Ischemic colitis	1
Radiation enteritis-enteral tube feeding problem	1
Short-bowel syndrome	1
Depression-anorexia	1
Intestinal lymphangiectasia[2]	1
Noninfected progressive bronchiectasis	1
Therapeutic medication	
Estrogen and progesterone[3]	2
BMI (kg/m^2)	
≤14	3
15–18	4
≥19	6
%WL	
≤−30	3
−29 to −10	8
≥−9	1
Duration of weight loss (mo)	
≥12	2
11–6	3
≤5	7

[1] *n* = 13; %WL, percentage weight loss at the time of the study.
[2] This patient had ascites; therefore, it was not possible to estimate the %WL at the time of the study or the duration of weight loss.
[3] Treatment for menopausal symptoms.

TABLE 2
Physical and clinical characteristics of the malnourished patients with inflammatory bowel disease (IBD)[1]

	Active Crohn disease	Ulcerative colitis disease
	n	
Age (y)		
≤25	3	2
26–50	6	2
≥65	1	0
Sex		
Male	4	3
Female	6	1
Disease duration (y)		
≥10	3	2
5–9	4	0
≤1	0	1
New diagnosis	3[2]	1
Previous small-bowel resection	6	1
Localization of IBD		
Small intestine	6	1
Small intestine and colon	3	1
Stomach and colon	1	0
Colon	0	2
Ulceration	8	2
Therapeutic medication		
Pentasa	0	1
Steroids, oral	4	2
Steroids, intravenous	3	1
Imuran	1	0
Imuran + steroid	1	0
Methotrexate	1	0
BMI (kg/m^2)		
≤14	1	0
15–18	7	3
≥19	2	1
%WL		
−20 to −10	9	4
≥−9	1	0
Duration of weight loss (mo)		
6–12	4	0
≤5	6	4

[1] *n* = 14. %WL, percentage weight loss at the time of the study.
[2] One patient had edema.

complex I activity in malnourished patients with and without active IBD with that in the healthy subjects, *2*) evaluate the relation between complex I activity and nutritional assessment indexes and metabolic rate in both groups of patients, and *3*) determine whether the provision of nutritional support has the same effect on complex I activity in both groups of patients.

SUBJECTS AND METHODS

The Ethics Committee of St Michael's Hospital (Toronto) approved the study protocol, and all subjects gave their informed consent before the start of the study.

Patients

Because rapid weight loss is a predictor of nutrition-related complications (20, 21), we selected patients who had lost 10% of their usual body weight (ie, their premorbid body weight) in the previous 6 mo or less and who had received no prior nutritional intervention. Patients were excluded if they had neurologic disease, bone marrow disorder, renal dysfunction, sepsis, cancer, or metabolic disease (eg, diabetes). Fourteen malnourished patients with IBD [7 women and 7 men with a mean (±SD) age of 37 ± 14 y] and 13 malnourished patients without IBD (6 women and 7 men aged 63 ± 18 y) were recruited after admission to the Gastroenterology Service of St Michael's Hospital. IBD was diagnosed on the basis of clinical, endoscopic, radiologic, and histologic criteria. Ten IBD patients had Crohn disease and 4 patients had ulcerative colitis. Because diarrhea due to extensive intestinal resection can spuriously alter the Crohn's disease activity index (CDAI) (22), the CDAI was formally assessed in the 4 Crohn disease patients who did not have extensive resection of the small intestine, colon, or both. In all 4 patients, the CDAI was markedly elevated at 338 ± 18 (normal < 150). However, the other 10 patients with IBD had active inflammation on the basis of the clinical criteria of their attending physician. All patients received medical treatment during the study, including corticosteroids. The characteristics of the patients without and with IBD are shown in **Tables 1** and **2**, respectively.

Three patients without IBD and 1 patient with IBD refused to have indirect calorimetry performed. It was not possible to measure body composition in 1 patient without IBD because of the presence of ascites, and 1 IBD patient and 4 other patients without IBD refused consent for the body composition-measurement.

Control subjects

Forty-two healthy volunteers (23 women and 19 men aged 40 ± 15 y) participated in this study as control subjects. They were recruited from the hospital staff of St Michael's Hospital.

Refeeding study

Five of 13 patients without IBD and 6 of 14 patients with IBD were investigated 7 d after nutritional support had commenced. Nutritional support was defined as parenteral nutrition, enteral nutrition, nutritional supplements, or a combination of methods. The nutritional prescription for each patient was determined by a clinical dietitian in conjunction with the medical team.

Methods

In control subjects and patients before and after 7 d of refeeding, all measurements were performed after an overnight fast.

Body composition

Height was measured to the nearest 0.1 cm and body weight to the nearest 0.1 kg with a beam scale. Body mass index (BMI; in kg/m^2) was calculated from weight and height. Whole-body bioimpedance spectroscopy measurements were performed with Xitron 4000B (Xitron Technologies, San Diego). Briefly, one set of electrodes was placed at the wrist and a second set at the ankle. All measurements were performed on the left side of the body after the subject had been in a supine position for 10–15 min. Total body resistance, reactance, and impedance were obtained over a frequency range of 1 kHz to 1.2 MHz. A computer program supplied by the manufacturer calculated total body water. The assessment of total body water with this method was previously validated in healthy subjects (23). Fat-free mass (FFM) was calculated by using a hydration constant of 0.73, and fat mass (FM) was calculated as the difference between body weight and FFM (24).

Indirect calorimetry

After an overnight fast, REE was determined by indirect calorimetry. Subjects were asked to avoid any exercise from the evening before the measurement and then to lie quietly in the supine position for ≥ 30 min before and during the REE measurements.

Respiratory gas exchange (oxygen consumption and carbon dioxide production) was measured by computerized open-circuit indirect calorimetry with a ventilated-hood system (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki). The oxygen and carbon dioxide sensors were calibrated for accuracy before each analysis. Measurements were done each minute, and the results were averaged over periods of 15–20 min when a steady state was reached. REE was calculated by using the Weir equation (25).

Diet history

For all patients, diet composition and energy intake before admission were assessed by a 3-d recall dietary history. A record was kept of all intakes, including enteral and parenteral nutrition over the next week for the 11 patients receiving nutritional supplementation.

All healthy volunteers were instructed by the dietitian on how to keep food records and were asked not to change their habitual food intakes. The participants were asked to record, in as much detail as possible, all food and beverages consumed over a 3-d period, including at least one weekend day.

The data on the food records were used to calculate intakes of energy and protein with a computer program based on food tables and analyzed by using NUTRIWATCH, a nutrient analysis program (WINDOWS version 320; based on the 1997 Canadian Nutrient File).

PBMC analyses

For PBMC isolation, a venous blood sample (24 mL) was obtained from each subject and delivered to the laboratory within 1 h of sampling. The PBMCs were isolated by density gradient centrifugation (26), and all procedures were performed at ambient room temperature (20–25 °C). After gentle agitation to mix the blood, an 8-mL aliquot was layered onto a percoll-saline solution. The solution was prepared as described by the supplier (Amersham Pharmacia Biotech, Baie d'Urfé, Canada): 56.25% Percoll, 37.50% Hank's Balance Salt Solution, and 0.80% NaCl (vol:vol) to a final density of 1.06–1.08 kg/L. The layered blood and percoll solution was centrifuged at 1600 × *g* for 30 min. The mononuclear cells were collected at the interface, washed 3 times with phosphate-buffered saline (PBS; 20 mmol/L, pH 7.5), and spun at 480 × *g* for 10 min as described previously (15). The cell pellet was suspended in 200 μL PBS (20 mmol/L, pH 7.2), sonicated for 15 s (3 bursts of 5 s each) at 300 W on ice, and stored at −70 °C until analyzed (15).

The protein concentration of the cell suspension was determined by using the biuret method, and the mononuclear cell suspension was diluted with PBS (20 mmol/L, pH 7.2) to a protein concentration of 5 g/L and then the samples were frozen and thawed 3 times to disrupt the mitochondrial membrane.

Enzyme activity was measured spectrophotometrically under conditions of maximal reaction velocity at an optimal pH and at room temperature as described below. All assays were performed in duplicate in a final volume of 1 mL by using a double-beam spectrophotometer (Spectrophotometer DU Series 600; Beckman Instruments, Fullerton, CA).

Complex I activity

Complex I activity was measured by following the oxidation of NADH, determined by the slope of the change in optical density at 340 nm (27). Briefly, mononuclear cell suspension was added to a buffer containing PBS (25 mmol/L, pH 7.2), 5 mmol $MgCl_2$/L, 2 mmol KCN/L, 2.5 g bovine serum albumin/L (fraction V), 2 mg antimycin A/L, 0.13 mmol NADH/L, and 65 mmol ubiquinone 1/L. The NADH-ubiquinone oxidoreductase activity was measured for 4 min. Then, 2 mg rotenone/L was added, after which the activity was measured for an additional 3 min. The specific complex I activity is the rotenone-sensitive NADH:ubiquinone oxidoreductase (EC 1.6.5.3) activity and is expressed as nmol · min^{-1} · mg PBMC protein^{-1} (15).

We previously showed the linearity of our PBMC complex I measurement at low and high levels (15). To evaluate the reproducibility, PBMC complex I activity was measured in 3 patients on 3 occasions at intervals of 1 wk at a time. During this period the subjects did not receive any nutritional supplementation. The mean ± SD of the PBMC complex I activity of these 9 measurements was 1.97 ± 0.41 nmol · min^{-1} · mg PBMC protein^{-1}. The CV

TABLE 3
Comparison of total energy and protein intakes, fat-free mass (FFM), fat mass (FM), and resting energy expenditure (REE) between malnourished patients with and without inflammatory bowel disease (IBD), and the respective age-matched control group[1]

	Age-matched control group	Patients without IBD	Age-matched control group	Patients with IBD
Total energy intake (MJ/d)	10.6 ± 2.7 [14]	3.6 ± 2.3[2] [13]	10.8 ± 3.6 [28]	3.9 ± 1.9[2] [14]
Protein intake (g/d)	111 ± 32 [14]	31 ± 24[2] [13]	123 ± 54 [28]	42 ± 25[2] [14]
FFM (kg)	47 ± 11 [14]	34 ± 7 [8]	49 ± 13 [28]	35 ± 9[2] [13]
FM (kg)	30 ± 7 [14]	12 ± 6[2] [8]	21 ± 78[3] [28]	13 ± 7[2] [13]
REE (MJ/d)	6.8 ± 1.1 [14]	5.5 ± 1.0 [10]	7.5 ± 1.6 [28]	6.0 ± 1.2[2] [13]

[1] $\bar{x}$ ± SD; n in brackets.
[2] Significantly different from the respective age-matched control group, $P < 0.001$ (Mann-Whitney U test and Bonferroni correction).
[3] Significantly different from the other age-matched control group, $P < 0.02$ (Mann-Whitney U test and Bonferroni correction).

of complex I activity over 3 wk was 13 ± 6%, indicating that our measurements were reproducible.

Statistical analysis

All results are presented as means ± SDs. The mean ages of the patients with and without IBD were 37 ± 14 and 63 ± 18 y, respectively, whereas the mean age of the control subjects was 40 ± 15 y. To match the age of the patients and the healthy control subjects, 14 healthy control subjects (9 women and 5 men) aged 59 ± 11 y were selected from the 42 healthy control subjects to match the older age range of the patients without IBD, and the younger control subjects were compared with those with IBD. The nonparametric Mann-Whitney U test was used to compare data between the 2 groups of healthy control subjects and between patients and the respective control group. For multiple pairwise comparisons, P values obtained after use of the Mann-Whitney U test were Bonferroni corrected. The nonparametric Wilcoxon signed-rank test was used to compare patient data before and after refeeding. The Spearman correlation was used to determine the relation between complex I activity and other variables. The STATISTICA 5.0 program for WINDOWS was used for the statistical analyses (Statsoft, Tulsa, OK).

RESULTS

Body composition, REE, energy and protein intakes, and PBMC complex I activity in the 2 age-matched control groups

Older control subjects (59 ± 11 y of age), who were age-matched to patients without IBD, had a significantly higher BMI than did the younger control subjects (32 ± 7 y of age), who were age-matched to the IBD patients (28 ± 4 compared with 24 ± 4; $P < 0.04$). This higher BMI was due to the fact that the older control subjects had a greater FM than did the younger control subjects (30 ± 7 compared with 21 ± 7 kg; $P < 0.02$; **Table 3**). Measured REE and energy and protein intakes were not significantly different between the 2 groups of control subjects (Table 3). Moreover, PBMC complex I activity was not significantly different between the 2 groups of control subjects (**Figure 1**).

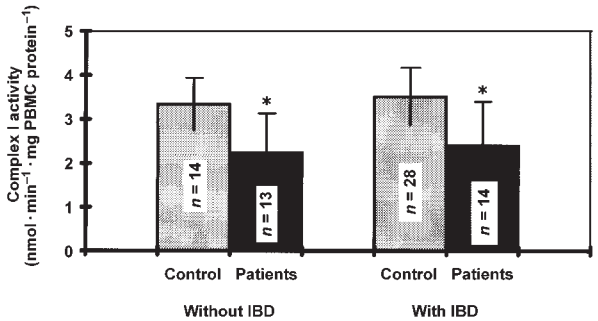


FIGURE 1. Mean (± SD) complex I activity of peripheral blood mononuclear cells (PBMCs) in patients with and without inflammatory bowel disease (IBD) and in the respective age-matched healthy control group. *Significantly different from the respective age-matched control group $P < 0.001$ (Mann-Whitney U test and Bonferroni correction).

Energy and protein intakes, nutritional assessment variables, and metabolic rate in malnourished patients with and without IBD

The mean energy intake was one-third as great in both groups of patients than in their respective control group (Table 3). Similarly, the mean protein intake was significantly lower in both groups of patients (Table 3). The energy and protein intakes were not significantly different between the 2 groups of patients (Table 3).

The degree of malnutrition assessed on the basis of BMI, body weight, percentage weight loss (%WL), and body composition was not significantly different between the 2 groups of patients (Table 3 and **Table 4**). Compared with the respective control group, absolute FFM and FM were significantly lower in the IBD patients (Table 3). In the malnourished patients without IBD, FFM and FM were also lower than in the respective control group, but significantly so for FM only. The relative loss of FM and FFM were different between patients with and without IBD. Percentage FFM was significantly higher (75 ± 10% compared with 61 ± 7%; $P < 0.001$) and percentage FM was significantly lower (25 ± 11%

TABLE 4
Nutritional assessment indexes in malnourished patients with and without inflammatory bowel disease (IBD)[1]

	Patients without IBD	Patients with IBD
Weight (kg)	49 ± 14 [13]	48 ± 9 [14]
BMI (kg/m^2)	18 ± 4 [13]	17 ± 2 [14]
Usual body weight (kg)	61 ± 13 [13]	59 ± 9 [14]
%WL[2]	−20 ± 11 [12]	−19 ± 6 [14]
%WL/ht^2 [2,3]	−7.6 ± 4.3 [12]	−6.9 ± 2.9 [14]
Duration of weight loss (mo)[2]	11 ± 16 [12]	5 ± 4 [14]

[1] $\bar{x}$ ± SD; n in brackets. %WL, percentage weight loss at the time of the study. There were no significant differences between the groups (Mann-Whitney U test).
[2] Not estimated in one patient because of the presence of ascites.
[3] %WL related to height squared.

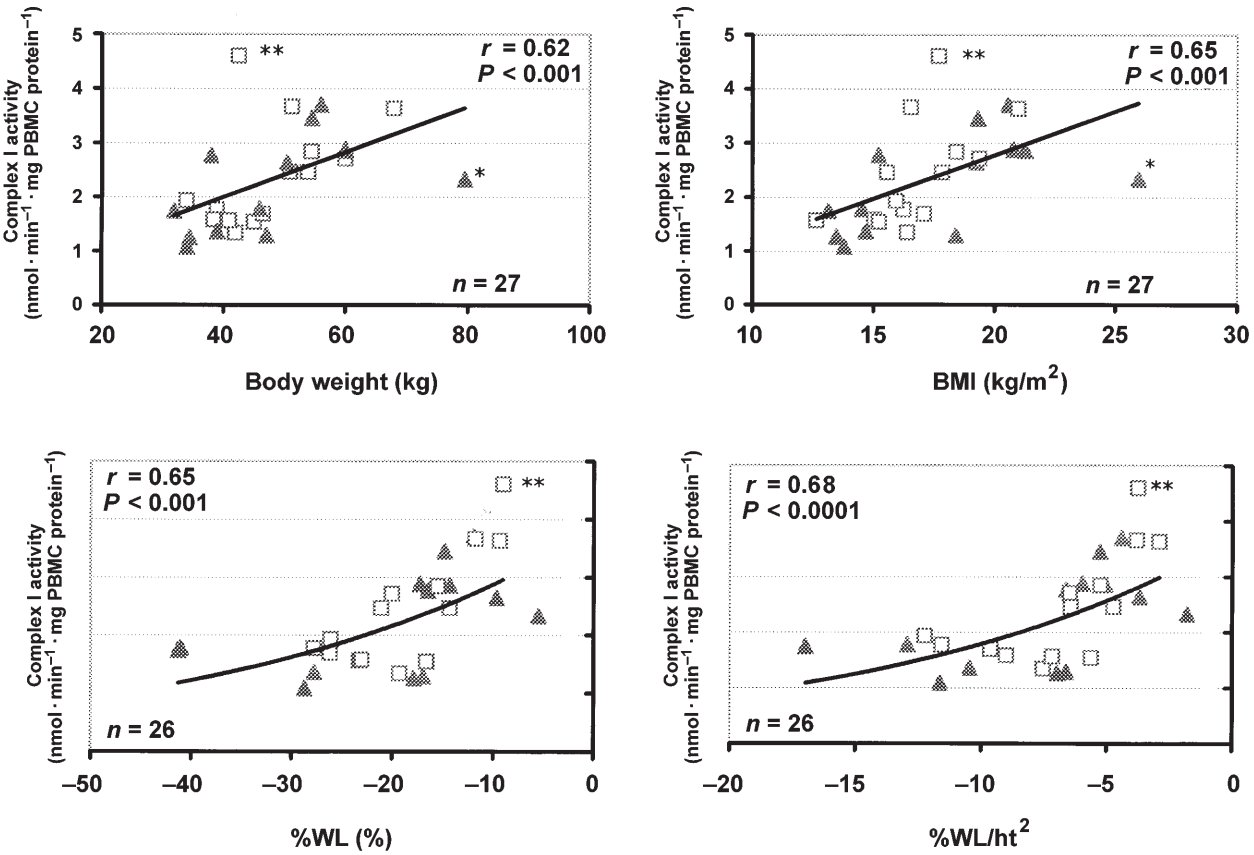


FIGURE 2. Relation between complex I activity of peripheral blood mononuclear cells (PBMCs) and body weight, BMI, percentage weight loss (%WL) and %WL relative to height squared (%WL/ht^2) in patients with (□) and without (▲) inflammatory bowel disease (all patients combined). *Patient with ascites for whom it was not possible to estimate %WL at the time of the study or the duration of weight loss. **Patient with a normal albumin concentration.

compared with 39 ± 7%; $P < 0.001$) in patients without IBD than in the age-matched control subjects. In contrast, percentage FFM (73 ± 10% compared with 69 ± 9%; NS) and percentage FM (28 ± 14% compared with 31 ± 9%; NS) were not significantly different between the IBD patients and the age-matched control subjects.

Measured REE (MJ/d) was lower in both groups of patients than in their respective control group (Table 3), but only the comparison between IBD patients and age-matched control subjects was significant. Moreover, REE related to the FFM was significantly higher in the IBD patients than in the age-matched control subjects (180 ± 30 compared with 156 ± 30 MJ/kg FFM; $P < 0.03$) and was not significantly different between patients without IBD and age-matched control subjects (159 ± 21 compared with 152 ± 24 MJ/kg FFM; NS).

Effect of malnutrition on PBMC complex I activity

PBMC complex I activity was significantly lower in both groups of patients when compared with their age-matched control groups ($P < 0.001$) but was not significantly different between the 2 groups of patients (Figure 1).

Correlation between PBMC complex I activity and nutritional assessment parameters in malnourished patients

The PBMC complex I activity of all patients taken as a single group was directly correlated with body weight ($r = 0.62$, $P < 0.001$) and BMI ($r = 0.65$, $P < 0.001$) and inversely related with %WL ($r = 0.65$, $P < 0.001$) and %WL/ht^2 ($r = 0.68$, $P < 0.001$; **Figure 2**). In addition, these relations were maintained when patient groups were analyzed separately (data not shown).

PBMC complex I activity did not correlate with FFM but increased significantly with FM ($r = 0.52$, $P < 0.02$; **Figure 3**). In contrast, there was no relation between FFM and FM ($r = 0.24$, NS). Furthermore, PBMC complex I activity did not correlate with intakes of energy and protein and REE expressed as MJ/kg body weight or as MJ/kg FFM.

Effect of 7 d of refeeding on body composition, REE, and complex I activity

Before nutritional support, the degree of malnutrition evaluated on the basis of body composition was not significantly different between the 2 subgroups of patients. After 1 wk of refeeding, energy and protein intakes increased significantly in both groups of patients: by ≈72% for energy and protein in patients without IBD ($P < 0.05$) and by ≈92% and ≈99% for energy and protein, respectively ($P < 0.03$), in patients with IBD.

Correspondingly, complex I activity increased significantly in both groups of patients after 1 wk of nutritional support (**Figure 4**). Compared with the respective control group, complex I activity was still significantly lower in malnourished patients without IBD after short-term refeeding. At that time, there were no significant changes in body composition from day 0 to day 7 (FFM: 34 ± 8 compared with 33 ± 6 kg; FM: 9 ± 4 compared with 10 ± 5 kg) or

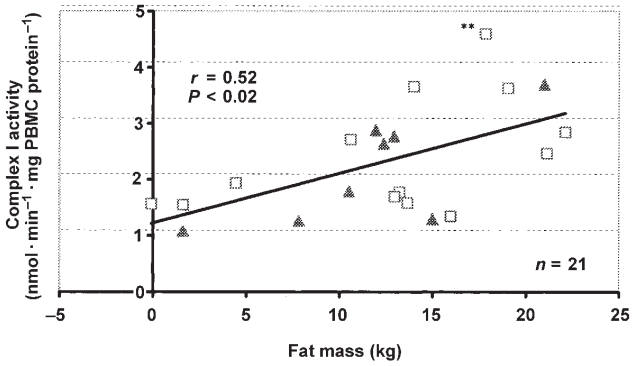


FIGURE 3. Relation between complex I activity of peripheral blood mononuclear cells (PBMCs) and fat mass in patients with (□) and without (▲) inflammatory bowel disease (all patients combined). **Patient with a normal albumin concentration.

in serum albumin (27 ± 9 compared with 26 ± 7 g/L). On the other hand, the change in complex I activity during the 7-d refeeding period correlated with the change in energy and protein intakes in both groups of patients (**Figure 5**).

DISCUSSION

Effect of malnutrition on PBMC complex I activity

This study is the first to show that clinical protein-energy malnutrition in humans reduces PBMC complex I activity (Figure 1) and confirms the results observed previously in malnourished rats (15). Moreover, PBMC complex I activity is directly and quantitatively related to the degree of malnutrition evaluated by changes in body composition (Figures 2 and 3).

An important question is whether complex I activity is related purely to reduced dietary intake or reflects the effects of energy deficit on body metabolism. It is unlikely to be related to reduced dietary intake per se because complex I activity was only partially restored by short-term refeeding. Moreover, it was not correlated with energy and protein intakes on admission, despite the fact that there was a marked decrease in energy and protein intakes in both

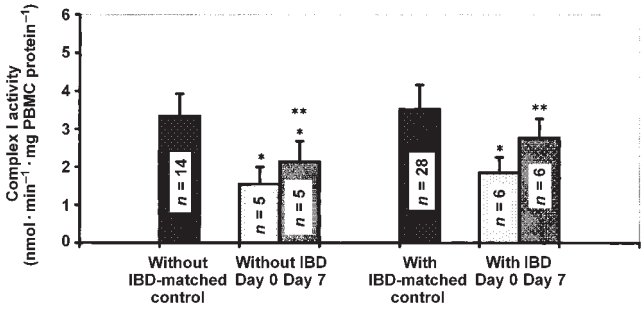
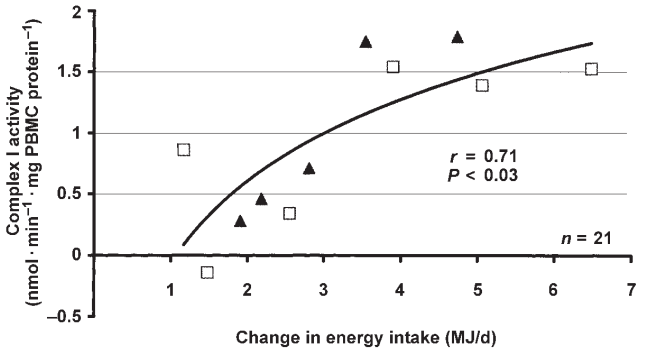


FIGURE 4. Mean (± SD) complex I activity of peripheral blood mononuclear cells (PBMCs) in patients with and without inflammatory bowel disease (IBD) and in the respective age-matched healthy control group before (day 0) and after 7 d of refeeding. *Significantly different from the respective age-matched control group, $P < 0.001$ (Mann-Whitney U test and Bonferroni correction). **Significantly different from day 0, $P < 0.05$ (Wilcoxon signed-rank test).



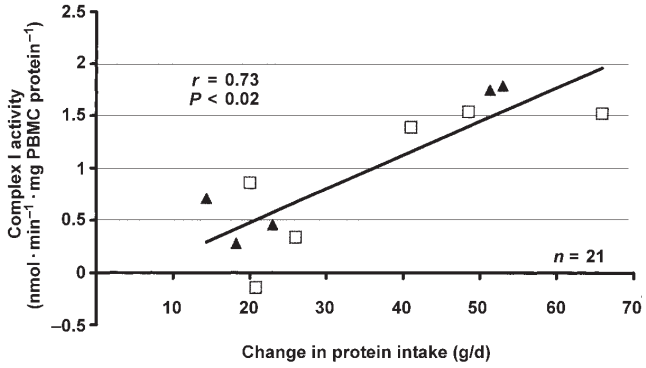


FIGURE 5. Relation between change in complex I activity of peripheral blood mononuclear cells (PBMCs) and change in total energy and protein intakes after 7 d of refeeding in patients with (□) and without (▲) inflammatory bowel disease (all patients combined).

groups of patients at that time. Furthermore, complex I activity correlated with changes in FM (Figure 3), which is an excellent index of energy balance, in relation to requirements (deficit or surfeit) (28).

The mechanism of reduced PBMC complex I activity may have been due to either a decrease in the number of mitochondria per PBMC or to a decrease in complex I activity, mitochondrium, or both. Our study and other studies did not clearly distinguish between these 3 possibilities. However, a previous animal study (15), which showed that complex I activity was restored within 24 h by protein feeding, suggests that altered mitochondrial enzyme synthesis or catabolism, rather than mitochondrial proliferation, is likely to be the mechanism of nutritional effects. More work is required to elucidate the cause of changes in mitochondrial complex I activity with malnutrition.

Effect of inflammation on the PBMC complex I activity

Because inflammation causes hypermetabolism (29) and accelerates the loss of tissue mass (7), it is possible that in malnourished patients with IBD, PBMC complex I activity may be differently affected and may not reflect the degree of malnutrition.

The patients with IBD were admitted to the hospital for uncontrolled activity of their disease and showed metabolic phenomena associated with inflammation. They had a proportionate reduction in FM and FFM due to the well-known effect of cytokines on muscle wasting (30) and a high REE even when adjusted for FFM (11, 31). Despite these differences between the 2 patient groups,

PBMC complex I activity decreased to the same extent in both groups of patients (Figure 1), indicating that IBD does not alter mitochondrial complex I activity disproportionate to the degree of malnutrition.

Effect of short-term refeeding on complex I activity

In patients with and without IBD, PBMC complex I activity increased significantly (> 50%) after only 1 wk of refeeding (Figure 4), but it did not reach the level observed in control subjects. These data support previous results observed in malnourished rats, in which we showed that mitochondrial complex I activity in muscle and PBMCs increased significantly after 1 d of refeeding (15). Moreover, the increase in complex I activity was independent of the traditional nutritional assessment variables, which did not change after 1 wk of refeeding in either group of patients.

Because complex I activity increases but does not reach normal levels with short-term refeeding, the question arises as to whether longer-term refeeding and normalization of body composition is necessary for complete restoration of complex I activity. The results of the current study and other available data do not allow us to answer this question conclusively. However, 2 lines of evidence favor the conclusion that function and complex I activity can be normalized before complete restoration of body composition. We previously observed normalization of muscle function after 4 wk of refeeding, at which time body weight was 71% of ideal body weight and body nitrogen was 78% of normal (17). Because we have shown that the effect of protein-energy deficit on muscle function is due to a slowing of the ATP resynthesis rate in stimulated muscle, a mitochondrial function (13). Consequently, the observation given above in relation to the restoration of muscle function suggests an improvement in mitochondrial activity. In addition, 7 malnourished patients with different pathologies were also investigated for 1 mo (before and after 7, 14, and 30 d of refeeding) (32). These preliminary observations indicate that complex I activity is restored to normal after 1 mo of refeeding. At that time, there was an improvement in BMI and in other variables of body composition measured by bioimpedance spectroscopy, but these variables were still significantly different between the patients and control subjects. Taken together, these observations suggest that mitochondrial function may be restored before restoration of body composition. To convincingly support the dominant role of protein and energy intakes as being responsible for the normalization of complex I activity, it will be necessary to study a larger population of malnourished patients at various stages of response to refeeding.

Finally, our study showed a response in complex I activity similar to that of nutritional supplementation, irrespective of the presence of inflammation (Figures 4 and 5). In our clinical study, we showed a significant correlation between the increase in macronutrient intake, specifically of energy and protein, and the increase in complex I activity after short-term refeeding (Figure 5). These results are consistent with previous investigations showing a defect of the peripheral blood leukocyte function (endogenous pyrogen synthesis) in nonstressed and stressed malnourished patients. An improvement of the host's metabolic response was also observed after a short period of refeeding, which may have been related to protein intake (33, 34). It seems that the rapid improvement in mononuclear mitochondrial activity with refeeding may have important therapeutic implications. These findings suggest that reduced mononuclear function with malnutrition, which increases the risk of sepsis, may respond rapidly to nutritional support. Furthermore, our previous observation that protein feeding seems to especially improve mitochondrial function (15) suggests that protein feeding might be especially important in reducing the risk of sepsis. Several previous studies are consistent with this possibility (35–39).

Conclusion

Our study is the first to show a quantitative relation between PBMC complex I activity and the degree of malnutrition. We also showed that there is a rapid though incomplete improvement in PBMC complex I activity after 1 wk of refeeding. Moreover, the presence of active IBD does not seem to significantly influence these relations.

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