Malabsorption is a major contributor to underweight in Crohn’s disease patients in remission

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Abstract

Objective: Undernutrition has been reported in 65–75% of patients with Crohn’s disease. The present study aimed at identifying the relative contribution of malnutrition-causing factors in patients with Crohn’s disease in remission.

Methods: Sixteen patients with Crohn’s disease (age 19–57 y) in remission (Crohn’s Activity Disease Index < 150) were included in the study. Their weight was stable for >3 mo and they were off steroids. They all completed 3-d food records and concomitantly collected stools. Self-reported food records were analyzed and energy content in stools was determined by a direct bomb calorimeter. Resting energy expenditure (REE) was studied by indirect calorimetry and body composition by dual-energy X-ray absorptiometry. The study cohort was divided into two groups, with a body mass index (BMI) equal to 18.5 kg/m2 serving as a cutoff point.

Results: Subjects with lower BMIs tended to have less lean body mass (P = 0.006), less bone mineral density (P = 0.006), and lower REE (P = 0.003). No correlation was found between BMI and energy intake but the percentage of malabsorption was negatively correlated with BMI (P = 0.07). When dividing the study based on a BMI of 18.5 kg/m2, no difference was found in caloric intake or REE between groups but subjects with lower BMIs had significant prominent malabsorption compared with the others (21.1 ± 9.8% versus 11.7 ± 3.5%, P = 0.015).

Conclusion: In the presence of similar energy intake, REE does not seem to contribute to lower BMI, although nutrient malabsorption is higher in malnourished patients with Crohn’s disease in remission. We suggest that malabsorption be evaluated in patients with Crohn’s disease who fail to gain weight during disease remission to establish their extra caloric requirements. © 2006 Elsevier Inc. All rights reserved.

Keywords: Crohn’s disease; Resting energy expenditure; Malabsorption

Introduction

Proper nutritional status is the outcome of a diet sufficient to meet an individual’s needs and to keep body composition and function within the normal range [1]. Disease-related malnutrition is a ubiquitous problem, with adverse effects on body structure, function, and clinical outcome [2]. However, nutritional needs may differ according to other parameters, such as energy expenditure, intestinal absorption, and nutrient losses through different organs, mainly the gastrointestinal tract. One of the most widely used indicators of malnutrition is the body mass index (BMI), and a BMI <18.5 kg/m2 has been frequently used as a cutoff point for undernutrition [3]. Increasing nutritional intake may be one of the most effective methods of treating disease-related malnutrition.

Crohn’s disease (CD) is a chronic intestinal disorder of unknown etiology that may involve any part of the gastrointestinal tract. The small bowel is involved in 70% of CD patients [4], and undernutrition has been reported in 65–75% of these patients [5,6]. The pathogenic mechanisms include poor dietary intake, increased energy expenditure, nutrient malabsorption, and intestinal losses. The effect of the interaction of these potential mechanisms has been only
partly investigated. Moreover, most studies were performed on hospitalized patients with active disease; this is especially important because inflammatory processes may affect different metabolic features. The present study aimed at defining the relative contribution of undernutrition-causing factors in CD patients in remission.

Materials and methods

Patients

The study cohort was recruited from the outpatient inflammatory bowel disease clinic at the Tel Aviv Sourasky Medical Center (Tel Aviv, Israel). The diagnosis of CD was based on clinical, morphologic, and histopathologic criteria.

The study inclusion criteria were (1) age $\geq$18 years, (2) disease remission $>3$ mo as determined by a Crohn’s Disease Activity Index score $<150$ [7], (3) no steroid treatment for $>3$ mo, (4) no other chronic diseases, and (5) stable body weight during the 3 mo preceding the study.

Patients with fistulae, ileostomy, or colostomy were excluded. A detailed medical history was taken regarding the disease course, previous surgeries, disease location, clinical symptoms, and medication. BMI was calculated based on weight and height measurements, and a BMI of 18.5 kg/m$^2$ was taken as the cutoff point between undernutrition and a normal nutritional state [3].

Nutritional assessment

Resting energy expenditure measurements.

Resting energy expenditure (REE) was measured by an open-circuit, indirect calorimeter (Deltatrac, Helsinki, Finland). Patients fasted (water drinking was allowed) from 2000 h the night before the test until the next morning. Patients lied supine for 30 min before commencing the study at 0800 h. After calibration with standardized oxygen and carbon dioxide gas concentrations (95% O$_2$ 5% CO$_2$), a plastic canopy was placed over the patient’s head and REE was measured for 1 h. There was a 10-min washout period before starting data collection. The interindividual coefficient of variation in our laboratory is $<3\%$. The results were compared with the Harris-Benedict prediction equations [8]. The normative values of our laboratory are within 90% to 110% of that predicted by the above equations.

Body composition measurements.

Lean body mass (LBM) and body fat mass were measured by dual-energy X-ray absorptiometry (Lunar, Madison, WI, USA). These measurements and those of REE were taken after an overnight fast and after voiding.

Food intake records, stool collection, and caloric intake.

Patients were instructed to keep 3-d food records and to collect stools throughout the same 3 d. The food records were analyzed according to the Israeli food composition tables. Patients were fed activated charcoal at the beginning of the first and fourth days to delineate the stool collection period. The collected stools were stored at $-20^\circ C$ until analysis. Fecal gross energy was determined on lyophilized aliquots of stools using ballistic bomb calorimetry (Parr, Moline, IL, USA). Fat content was determined gravimetrically after acid hydrolysis [9]. The percentage of malabsorption was calculated by dividing the caloric content of the stools by the concomitant 3-d caloric intake.

Statistical analysis

Pearson’s correlation coefficients were calculated to examine the association between BMI and other continuous parameters. Subjects were also assigned to one of two groups based on BMI (BMI $\geq$18.5 kg/m$^2$) and comparison between groups of patients in terms of demographic and clinical factors was performed with the Mann-Whitney and Fisher’s exact tests, as applicable. The difference between groups with respect to all clinical parameters adjusted for gender was examined using one-way analysis of covariance, with gender as a covariate based on ranks. Pearson’s partial correlation, controlled for gender, was also computed for BMI and energy expenditure measurements. The statistical significance level was set at 0.05. SPSS software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Sixteen patients who met the predefined inclusion criteria were recruited. The group consisted of 6 women and 10 men, with an age range of 21–50 y and a BMI range of 14.7–24.8 kg/m$^2$. Subjects were also categorized into two groups based on BMI ($<18.5$ versus $\geq$18.5 kg/m$^2$). Each group consisted of eight patients. The group with normal BMI levels included two women compared with four in the underweight group. Seven patients in each group had ileocecal and ileocolonic involvement and one patient in each group had Crohn’s colitis. Four patients in the underweight group and one patient in the normal BMI group underwent an ileocecal resection.

Patients’ characteristics, including body composition parameters, are presented in Table 1.

In the entire group, BMI was positively correlated with LBM ($P = 0.006$), bone mineral density ($P = 0.006$), REE ($P = 0.003$), and REE as a percentage of that predicted by the Harris-Benedict equations (REEPP; $P = 0.017$). No correlation was found between daily energy intake and BMI, but percentage of malabsorption was negatively correlated with BMI ($P = 0.07$). As expected, REE was positively correlated with LBM ($P = 0.0001$), which itself was positively correlated with protein intake ($P = 0.05$). A significant negative correlation was found between malabsorption and REEPP.

After dividing the group by a BMI of 18.5 kg/m$^2$ and after adjusting for gender based on ranks, it emerged that
Energy intake, resting energy expenditure, and energy malabsorption in 16 patients with Crohn’s disease

<table>
<thead>
<tr>
<th>BMI ≥ 18.5 kg/m²</th>
<th>BMI &lt; 18.5 kg/m²</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily caloric intake (kcal/d)</td>
<td>2097 ± 575</td>
<td>2197 ± 845</td>
</tr>
<tr>
<td>REE (kcal/d)</td>
<td>1750 ± 224</td>
<td>1432 ± 297</td>
</tr>
<tr>
<td>REEPP (%)</td>
<td>110.6 ± 5.2</td>
<td>104.2 ± 5.6</td>
</tr>
<tr>
<td>RQ</td>
<td>0.83 ± 0.04</td>
<td>0.82 ± 0.04</td>
</tr>
<tr>
<td>Malabsorption (%)</td>
<td>11.7 ± 3.5</td>
<td>21.1 ± 9.8</td>
</tr>
<tr>
<td>Fat excretion/intake (%)</td>
<td>9.01 ± 4.05</td>
<td>6.48 ± 12.05</td>
</tr>
</tbody>
</table>

*BMI, body mass index; REEPP, resting energy expenditure based on Harris-Benedict equations; RQ, respiratory quotient
* Analysis of covariance adjusted for gender based on ranks.

Our results indicate that nutrient malabsorption seemed to be the most important contributor to underweight in our patients. Different quantities of caloric intake did not seem to cause the difference in BMI and neither did an increased REE because REE was lower in patients with lower BMI.

Underweight is a frequent finding in patients with CD and is usually attributed to the above-mentioned factors. Decreased caloric intake of patients with CD may be attributed to several factors, such as anorexia, abdominal pain, nausea, vomiting, and intestinal obstruction. Anorexia associated with inflammation appears to be a major contributor [10] and decreased caloric intake is frequently observed in patients with CD with high disease activity [11]. Our patients were all in remission for >3 mo before study entry and had a Crohn’s Disease Activity Index score <150. This may explain why we found no significant differences in caloric intake between the low and normal BMI groups. Our results are in accordance with previous studies, such as those by Geerling et al. [12] and Lanfranchi et al. [13] who found no differences in caloric intake in patients with CD during remission.

It has long been hypothesized that increased energy expenditure contributes to weight loss in patients with CD. However, studies on energy metabolism in these patients have been contradictory [14]; some have indicated that energy expenditure is not significantly different between patients and healthy controls [15,16], whereas others demonstrated an increased [17–19] or even decreased [20] REE. Our study suggests that REE is within normal range when expressed as REEPP. Moreover, a significantly positive correlation was found between BMI and REE and between BMI and REEPP, meaning that the more malnourished subjects have lower REE. After categorizing two groups based on BMI, REEPP in the better nourished subjects was in the upper limits of the normal range and four of eight subjects had an REEPP >110%. In the undernourished group, only two subjects had an REEPP above normal, and as a group undernourished subjects tended to have a significantly lower expense. Nevertheless, we have demonstrated a significant difference in REEPP between patients with normal BMI and those who are underweight. This difference may explain some of the contradictory findings in the literature with respect to energy expenditure of these patients.

Malabsorption in patients with CD was mainly found in patients after ileal resection, affecting fat and vitamin B12 absorption [21,22] and other vitamins and trace elements [23]. Filipsson et al. [21] studied fecal excretion in patients with CD before intestinal resection and found predominantly mild steatorrhea in 24% of patients with ileal disease, 26% of those with ileocolonic involvement, and 17% of those with Crohn’s colitis. After resection of the ileum and ileocecal valve, fecal fat excretion increased. The frequency and severity of steatorrhea correlated with the extent of ileal resection and was infrequent and mild when resections were <30 cm in length. In our study, a marginally negative significant correlation was found between BMI and malabsorption (p < 0.07). After categorizing the study population...
into two groups, both groups had increased malabsorption, but underweight subjects had a statistically significant increased malabsorption compared to the well-nourished subjects \( (P < 0.007) \). Fat malabsorption was increased but not statistically different between groups. Increased protein losses may have also contributed to the difference in total energy malabsorption between groups.

Very few studies have investigated concomitantly energy intake, energy absorption, and energy expenditure in patients with CD. Rigaud et al. [11] studied these parameters in two groups of patients. One group kept a stable weight over the 3 mo before being studied, whereas the others lost weight during this period. These groups were mixed with regard to disease activity and patients with malabsorption were excluded. No differences were observed between groups regarding REE and energy malabsorption. Therefore, the researchers concluded that decreased energy intake is the main contributor to weight loss. Our study is different because all our patients had a stable weight. We also asked a different clinical question and chose a different set of patients. Our question, which is frequently being encountered in the clinic, is: Why are some patients in remission underweight despite our efforts to rehabilitate them? Therefore, our patients who were had a low disease index, and malabsorption was not an exclusion criterion. Moreover, in our setting, malabsorption was found to be the main contributor to the difference between groups.

Stable weight is achieved when net digestible energy (energy intake minus energy malabsorption) equals energy expenditure. Our patients kept a stable weight for the last 3 mo before the study and were, therefore, in energy balance. Nevertheless, undernourished patients had significant malabsorption. What are the possible compensating mechanisms that enable them to keep a stable weight? In the past, undernutrition was found to decrease REE [24]. Because our underweight patients with CD suffer most probably from undernutrition, they may experience a relative reduction in REE. This is supported by the negative correlation between REEPP and malabsorption in our study \( (P < 0.037) \). This may also explain why the REEPP of our undernourished patients was significantly lower than that of the well-nourished subjects. Reduced REE may be a compensatory response for the caloric deficit due to malabsorption and may help to maintain a stable weight. In contrast to undernourished subjects, patients with normal BMI levels consume, most probably, enough calories and absorb enough to keep a stable weight and REE within the upper limit of the normal range. To study this hypothesis, we classified our patients into those who had a normal REE (REEPP \( < 110\% \)) and those who had above normal expense \( (>110\%) \). Subjects with the lower REEPP had more malabsorption than did those with above normal values \( (443 \pm 360 \) versus \( 232 \pm 136 \) kcal/d, respectively; \( P = 0.069 \)). Another possible compensating mechanism for malabsorption is an increased energy intake. The difference between groups did not reach a significant level.

How can we then increase weight in our patients? Nutritional rehabilitation was found to increase REE in healthy and diseased undernourished patients [25]. Moreover, in undernourished patients with cystic fibrosis and significant malabsorption, nutritional rehabilitation increased REE beyond the expected increase that was attributed to the increase in LBM [25]. This increase was suggested to indicate a loss of the compensating mechanism. If this is the case, we may speculate that, when nutrition intervention overcomes malabsorption in our patients, an increase in their REE will take place. This should be taken into account when planning nutritional support.
There are a few limitations to our study. The study population was rather small due to difficulties in recruiting subjects, mainly due to the inconvenience of the 72-h fecal collections. The second limitation of this study is the fact that other components of daily energy expenditure, i.e., physical activity and diet-induced thermogenesis, were not measured, whereas REE comprises only 70% of daily energy expenditure. Because none of our patients had active disease during the 3 mo (at least) before study entry, and they were all working and maintaining a normal lifestyle, a significant difference between groups in terms of this energy component is not very likely. The third limitation has to do with the fact that the undernourished group had a larger number of individuals who underwent intestinal resection, and this created some unbalance between groups. However, this most probably reflects the higher percentage of undernutrition in patients who had resection of the ileocecal valve. Whether the results would be the same if individuals with intestinal resection had been excluded from the study cannot be determined due to the small size of the groups. We are also aware that we did not have a formal healthy control group because the main purpose of the study was to compare well-nourished with undernourished patients with CD in remission. The REE of healthy subjects measured in our energy laboratory was within the normal range based on the Harris-Benedict equation (90–110%) and the norms of our laboratory for energy and fat malabsorption are 11% and 8%, respectively.

In conclusion, we have demonstrated that malabsorption of nutrients is most probably the most significant contributor to underweight in patients with CD in remission because REE was found to be positively correlated with BMI and energy intake did not correlate significantly. We suggest, therefore, measuring intestinal absorption in patients with CD who fail to gain weight during disease remission in addition to REE whenever possible and, accordingly, to look for alternative routes to increase net caloric intake.

Acknowledgments

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References