Changes in body composition, substrate oxidation, and resting metabolic rate in adult celiac disease patients after a 1-y gluten-free diet treatment[1,2]

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ABSTRACT

Background: The incidence of celiac disease has been on the rise in both Europe and the United States. Celiac disease patients are at high risk of undernutrition because of nutrient malabsorption.

Objective: The aim of the present study was to evaluate changes in body composition and energy metabolism in a group of patients with celiac disease before and after consumption of a gluten-free diet (GFD).

Design: Body composition (by anthropometry and isotopic dilution), resting metabolic rate (RMR), and substrate oxidation rates (by indirect calorimetry) were assessed in 39 adult celiac disease patients (16 men and 23 women) with a mean (±SD) age of 29.9 ± 7.6 y, weight of 58.3 ± 6.6 kg, and percentage body fat of 20.1 ± 6.7%, and in 63 (29 men and 34 women) age- and height-matched control subjects (age: 33.2 ± 8.1 y; weight: 66.8 ± 6.6 kg; and percentage body fat: 25.4 ± 3.7%). Celiac disease patients were studied twice, at diagnosis and 1 y after treatment with a GFD.

Results: Before treatment, celiac disease patients had a lower body weight ($P < 0.05$) and a higher carbohydrate oxidation rate ($P < 0.01$) than did control subjects. Carbohydrate oxidation rates correlated positively with fecal lipid loss in untreated celiac disease patients ($r = 0.80$, $P < 0.0001$). After the GFD, percentage body fat was higher in celiac disease patients than in control subjects ($P < 0.01$), and lipid intakes tended to be higher than before treatment.

Conclusions: This longitudinal study showed that the GFD treatment significantly increased body fat stores. Untreated patients preferentially utilized carbohydrates as a fuel substrate, probably as a consequence of both lipid malabsorption and a high carbohydrate intake, and lipid utilization increased with the restoration of the intestinal mucosa. *Am J Clin Nutr* 2000;72:76–81.

KEY WORDS Celiac disease, fat mass, fat-free mass, resting metabolic rate, substrate oxidation, body composition, gluten-free diet

INTRODUCTION

Celiac disease is characterized by histologic lesions that may vary from partial to total atrophy of the small-bowel mucosa, induced by ingestion of gluten-containing products. Treatment with a gluten-free diet (GFD) is associated with a marked improvement or restoration of the intestinal mucosa (1, 2). The prevalence of celiac disease in Europe is high: 1.8 cases/1000 individuals in a sample of 2237 Italian subjects aged 25–87 y (3) and 2.7 cases/1000 individuals in a Finnish population aged ≥15 y (4). In the United States, a prevalence of 4.0 cases/1000 individuals in a large sample of healthy adult blood donors was reported recently (5), suggesting that celiac disease might have been underdiagnosed in previous surveys (6, 7). Therefore, increasing interest has been devoted to the clinical features and long-term complications of celiac disease.

Untreated patients affected by the classic form of celiac disease, characterized by diarrhea, abdominal pain, and weight loss, are at high risk of malnutrition because of nutrient malabsorption secondary to intestinal atrophy. Several studies have shown that osteopenia occurs in adult patients with celiac disease and that a GFD can improve, if not normalize, bone mineral density (8–10). The effect of dietary interventions on body composition and nutritional status in celiac disease patients is less well established, which may be due to the clinical heterogeneity of the disorder, ranging from oligosymptomatic to classic forms (11). As a consequence, celiac disease patients have been described as having either a normal (12) or an impaired nutritional status (13). In addition, energy expenditure or energy loss, both major determinants of normal and stable body weights (14), have not been studied extensively in celiac disease patients.

In a case-control study, body composition and energy metabolism in both treated and untreated patients with a new diagnosis of the classic form of celiac disease were evaluated. Body weight and substrate oxidation rates of treated and untreated patients were significantly different from those of an age-, sex-, and height-matched group of healthy subjects (15).

To the best of our knowledge, no longitudinal study of the metabolic features of celiac disease patients after strict adherence to a

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Received July 27, 1999.

Accepted for publication December 22, 1999.

TABLE 1
Body-composition variables of the control subjects and treated and untreated celiac disease patients by sex[1]

	Control subjects		Untreated patients		Treated patients	
	Women (n = 34)	Men (n = 29)	Women (n = 23)	Men (n = 16)	Women (n = 23)	Men (n = 16)
Age (y)	32.8 ± 7.0	33.6 ± 9.3	31.4 ± 7.8	27.8 ± 7.0	32.4 ± 7.8	28.8 ± 7.0
Weight (kg)	63.1 ± 4.5	71.5 ± 5.7	55.9 ± 5.9[2,3]	61.6 ± 6.4[2,3]	58.7 ± 5.5[2]	64.0 ± 5.9[2]
Height (cm)	165 ± 4.8	172 ± 4.7	164 ± 4.7	170 ± 5.8	164 ± 4.7	170 ± 5.8
Fat mass						
(kg)	16.9 ± 2.8	17.0 ± 3.3	13.9 ± 3.0[2,4]	8.4 ± 2.7[2]	15.9 ± 2.6[5]	10.7 ± 2.7[2]
(%)	26.8 ± 3.8	23.7 ± 3.5	24.7 ± 3.8[3,5]	13.5 ± 3.9[2,3]	27.1 ± 2.9	16.7 ± 4.0[2]
Fat-free mass						
(kg)	46.3 ± 4.5	54.7 ± 4.6	42.0 ± 4.2[5]	53.3 ± 5.9[5]	42.8 ± 4.1[5]	53.3 ± 5.6[5]
(%)	73.4 ± 4.3	76.4 ± 3.5	75.3 ± 3.8[5]	86.5 ± 3.9[2]	73.0 ± 2.9	83.3 ± 3.9[2]

[1] $\bar{x}$ ± SD.
[2,5] Significantly different from control subjects: [2] $P < 0.01$, [5] $P < 0.05$.
[3,4] Significantly different from treated patients: [3] $P < 0.05$, [4] $P < 0.01$.

GFD has been conducted. Thus, the aim of the present study was to investigate changes in body composition and energy metabolism in a group of adult patients with a new diagnosis of the classic form of celiac disease before and after a GFD treatment.

SUBJECTS AND METHODS

Subjects

Of the entire adult celiac disease patient population attending the outpatient clinic of the Department of Internal Medicine at the Catholic University in Rome between June 1995 and October 1998 (234 patients), 43 adult patients with the classic form of celiac disease were consecutively enrolled in the study. The diagnosis was based on previously reported histologic evidence of subtotal or total duodenal villous atrophy (1, 16).

Four patients did not complete the study protocol, 3 because of low compliance with the GFD diet and 1 because of relocation to another country. A final group of 39 patients was studied before and after consumption of a GFD for 12.4 ± 0.3 mo. After 3 mo of a GFD treatment, the patients' duodenal mucosa was normal or markedly improved on the basis of a biopsy obtained endoscopically. Afterward, a blood sample was obtained every 3 mo to determine anti-gliadin and anti-endomysium antibodies. Sixty-three healthy volunteers (29 men and 34 women) matched for age (33.2 ± 8.1 y; range: 18–55 y) and height (168 ± 6.2 cm; range: 158–176 cm) constituted a control group.

The baseline anthropometric characteristics of the 2 groups of subjects examined separately by sex are reported in **Table 1**. All subjects underwent a clinical and laboratory examination before enrollment. Exclusion criteria were as follows: secondary causes of intestinal atrophy, endocrine disorders, consumption of drugs able to influence data collection, evidence of intestinal bacterial overgrowth (assessed by a lactulose breath-hydrogen test), impairment of glucose and lipid metabolism, hepatic or renal disease, fever, pregnancy, smoking >10 cigarettes daily, and intensive physical activity, as assessed by the Harvard Alumni Health Questionnaire (17). Because of the influence of the menstrual cycle on body composition and energy metabolism (18), women were examined during the follicular phase of the menstrual cycle, which was determined by medical questionnaire, ultrasound examination, and hormonal assessment. All control subjects had no history of gastrointestinal disease and for ethical reasons did not undergo intestinal biopsy. The study was approved by the Ethics Committee of the Catholic University of Rome and all subjects gave their informed consent before enrollment.

Analytic measurements

A blood sample was collected after an overnight fast, immediately centrifuged at 1500 × g for 15 min at 25°C, and stored at −20°C until analyzed. Samples were collected at baseline from both patients and control subjects and from celiac disease patients after a GFD was consumed for 12 mo. Anti-igliadins were assessed with a microenzyme-linked immunosorbent assay technique and anti-endomysium antibodies were detected by using an indirect immunofluorescence technique. Total protein, albumin, hemoglobin, iron, ferritin, transferrin, retinol binding protein, and fibrinogen concentrations and iron binding capacity, hematocrit, and white and red blood cell counts were measured by using standard laboratory techniques. Vitamin B-12 and folic acid were simultaneously determined from the same sample with a radioimmunologic kit (Quantaphase II B12/Folate RadioAssay; Bio-Rad, Hercules, CA). Reference ranges for vitamin B-12 and folic acid were determined by analyzing blood samples from 299 healthy donors, which were 96–570 and 3.4–46.7 nmol/L, respectively.

Body-composition analysis

Body weight was measured to the nearest 0.1 kg with a beam scale, and height was measured to the nearest 0.5 cm with a wall-mounted stadiometer while the subjects were wearing light clothes and no shoes. Total body water (TBW) was measured with an isotopic dilution technique, as described previously (19, 20), by using an intravenous bolus injection containing 3700 kBq (100 μCi) tritiated water and 370 GBq/L (100 mCi/mL) in 5 mL of a saline solution. The decays per minute counted with a β-scintillation counter (model 1600TR; Canberra-Packard, Meriden, CT), in duplicate on 0.5 mL plasma for each point was plotted against time (min). The amount (dose per minute) of the tritiated water bolus was divided by the average concentration of labeled water (dose per minute per milliliter) obtained at the steady state, ie, when the labeled water was homogeneously distributed throughout the body, to compute the apparent volume of distribution of the labeled water equal to TBW. Fat-free mass

TABLE 2
Biochemical variables of the control subjects and untreated and treated celiac disease patients[1]

	Control subjects (n = 63)	Untreated patients (n = 39)	Treated patients (n = 39)
Iron (mmol/L)	18.4 ± 3.6	7.6 ± 4.8[2,3]	12.6 ± 5.4[2]
Transferrin (g/L)	2.86 ± 0.9	2.19 ± 1.0[2]	2.32 ± 1.1[4]
Vitamin B-12 (pmol/L)	401 ± 106	294 ± 137[4]	311 ± 124[4]
Folic acid (nmol/L)	29.7 ± 7.0	11.8 ± 9.3[2,5]	17.0 ± 10.4[2]
Hematocrit	0.431 ± 0.018	0.409 ± 0.016[2]	0.412 ± 0.016[4]
Albumin (g/L)	43 ± 12	40 ± 12[2,5]	42 ± 11

[1] $\bar{x}$ ± SD. Reference values (15, 27) are as follows: iron, 9–27 mmol/L; transferrin, 1.85–3.50 g/L; vitamin B-12, 96–570 pmol/L; folic acid, 3.4–46.7 nmol/L; hematocrit, 0.4; albumin, 35–50 g/L.
[2,4] Significantly different from control subjects: [2] $P < 0.01$, [4] $P < 0.05$.
[3,5] Significantly different from treated patients: [3] $P < 0.01$, [5] $P < 0.05$

(FFM; in kg) was calculated by multiplying TBW by 0.732, and fat mass (FM; in kg) was computed as the difference between body weight and FFM; FFM and FM are also expressed as percentages of body weight (%FFM and %FM) (19).

Energy expenditure and substrate oxidation assessment

All the indirect calorimetry measurements were performed at 0830 after an overnight fast. Respiratory gas exchange measurements were performed over 60 min by continuous indirect calorimetry with an open-circuit ventilated-hood system (monitor MBM-100; Deltatrac, Datex Instrumentarium Corp, Helsinki) under strictly standardized conditions (18). After voiding, the subject entered a quiet room in which the air temperature and the humidity level were kept constant at 24–26°C and 35–40%, respectively. Then, the subject was placed in a semisupine position on a bed and remained awake and motionless for almost 30 min before and during the experimental session. The system was calibrated immediately before each measurement by using standard gases of known concentration. The CV for resting metabolic rate (RMR) in our laboratory is 3.6% (21). RMR and substrate oxidation rates were calculated from oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and urinary nitrogen excretion according to Ferrannini (22) and the nonprotein respiratory quotient (npRQ) was calculated as the ratio of np $\dot{V}CO_2$ to np $\dot{V}O_2$ ratio. Twenty-four–hour urine samples were collected the day before the calorimetric study to determine urinary nitrogen excretion with a blood urea nitrogen analyzer (Beckman Instruments, Fullerton, CA). The theoretically calculated energy expenditure value for each subject examined was computed by using the Harris-Benedict equation (23) and was then compared with the value determined by indirect calorimetry.

Energy intake analysis

All subjects participating in the study compiled a 7-d food diary, which was analyzed by an expert dietitian. The subjects were carefully instructed about the modalities for recording the food diary, with the recommendation that they report the amount and the brand of gluten-free products consumed. The nutrient content of all food items was then calculated by using computerized food tables (Food Processor II; ESHA Research, Salem, OR) modified according to the food tables of the National Institute of Nutrition (Rome). The energy content of the gluten-free food items was carefully determined according to the manufacturer's directions.

Fecal output

A 3-d sample of feces was collected in a covered tank and weighed. After homogenization, a 1–2-g specimen was taken and proteins were precipitated with 5–10 mg trichloroacetic acid. Lipid and starch were analyzed as described previously (20, 24).

Statistical analysis

All results are reported as means ± SDs, unless otherwise stated. A two-tailed P value < 0.05 was considered significant. A chi-square analysis was performed to check for differences in sex distribution. Bonferroni-corrected Wilcoxon tests were used to compare pre- and posttreatment differences in celiac disease patients. Mann-Whitney U tests were used to compare variables between groups. Linear regression analysis was used to evaluate the effect of age, sex, FM, and FFM on metabolic variables, and a forward stepwise technique was used with a P value < 0.05 as a criterion for inclusion of successive variables. Spearman correlation coefficients were calculated for the estimates of the level of association between 2 variables (25).

RESULTS

Clinical evaluation

There was no significant difference in sex distribution among groups. The mean duration of symptoms in celiac disease patients before diagnosis was 14.2 mo (range: 2–28 mo). Major symptoms reported by untreated celiac disease patients at enrollment were as follows: >3 daily bowel movements in 28 patients (71.8%), 19 of whom (48.7%) reported diarrhea; abdominal pain in 27 patients (69.2%); and asthenia in 31 patients (79.5%). Minor symptoms reported by untreated celiac disease patients at enrollment were nausea, constipation, and depression (26). At the 12-mo follow-up visit, 3 of 39 patients (7.7%) who consumed the GFD reported occasional episodes of diarrhea, and 4 of 39 patients (10.2%) reported persistent abdominal pain.

Laboratory indexes

Anti-gliadin and anti-endomysium antibodies were detected in all untreated patients at baseline but in none of the patients after 1 y of a GFD. None of the subjects enrolled had an immunoglobulin (Ig) A deficiency. Celiac disease patients, both at diagnosis and after the GFD, had lower blood iron, transferrin, vitamin B-12, and folic acid concentrations than did control subjects, whereas no significant differences were found between groups in the other investigated biochemical indexes. GFD treatment significantly increased blood folic acid and iron concentrations (**Table 2**).

Body composition

The body-composition variables of the subjects examined are shown in Table 1. Both untreated and treated celiac disease patients had a lower body weight than did control subjects, regardless of treatment, and celiac disease patients had lower FFM and FM values than did control subjects. %FFM was significantly higher in untreated male and female celiac disease patients than in control subjects, whereas there were no significant differences between patient subgroups. %FM was significantly lower in untreated patients, independently of sex, and in

TABLE 3
Energy metabolism and energy intakes in control subjects and untreated and treated celiac disease patients[1]

	Control subjects (n = 63)	Untreated patients (n = 39)	Treated patients (n = 39)
RMR (kJ/d)	6670 ± 760	6770 ± 680	6810 ± 690
npRQ	0.83 ± 0.03	0.87 ± 0.03[2,3]	0.81 ± 0.04
Carbohydrate oxidation (kJ/d)	2840 ± 560	3500 ± 680[2,3]	2440 ± 670
Lipid oxidation (kJ/d)	2550 ± 540	2000 ± 810[2,3]	3030 ± 540[4]
Energy intake (kJ/d)	8100 ± 800	8300 ± 700	8400 ± 750
Carbohydrate intake (kJ/d)	4400 ± 100	4600 ± 100[2,5]	4500 ± 150
Lipid intake (kJ/d)	2200 ± 150	2150 ± 150[3]	2300 ± 100[4]
Protein intake (kJ/d)	1500 ± 100	1500 ± 200	1500 ± 150

[1] $\bar{x}$ ± SD. RMR, resting metabolic rate; npRQ, nonprotein respiratory quotient.
[2,4] Significantly different from control subjects: [2] $P < 0.01$, [4] $P < 0.05$.
[3,5] Significantly different from treated patients: [3] $P < 0.01$, [5] $P < 0.05$.

treated male patients than in control subjects. In both male and female celiac disease patients, the GFD treatment resulted in an increase in both FM and %FM.

Energy expenditure and substrate oxidation rates

The metabolic variables measured in the different groups are reported in **Table 3**. No significant differences were found in RMR values among the 3 groups of subjects. Multiple linear regression analysis indicated that FM ($P < 0.05$), FFM ($P < 0.0001$), sex ($P < 0.01$), and disease ($P < 0.01$), but not treatment, were all significant determinants of RMR, with celiac disease patients having higher RMR values than control subjects ($r = 0.75$, SEE = 114). The only significant predictor of npRQ was the GFD treatment ($r = 0.48$, SEE = 0.03, $P < 0.0001$).

Untreated patients had a significantly higher npRQ value than did treated celiac disease patients and control subjects after adjustment for %FM, %FFM, RMR, and age. As a consequence, untreated celiac disease patients oxidized a higher amount of carbohydrate than did treated celiac disease patients and healthy volunteers. Treated patients had a higher lipid oxidation rate than did both untreated patients and control subjects. No significant differences were found in nitrogen excretion among groups [untreated patients: 457 mmol/L (range: 378–525 mmol/L); treated patients: 435 mmol/L (range: 393–507 mmol/L); control subjects: 400 mmol/L (range: 357–478 mmol/L)]. The mean duration of symptoms did not correlate with any of the variables examined.

Dietary assessment

Although total daily energy intake did not differ significantly among groups, untreated patients had a significantly higher intake of carbohydrates than did treated patients and control subjects (Table 3). Lipid intake was significantly higher in treated patients than in both untreated patients and control subjects, whereas protein intake did not differ significantly among groups.

Fecal losses

As expected, fecal lipid loss was significantly greater in untreated patients (428 ± 126 kJ/d) than in treated patients (106 ± 21 kJ/d) and control subjects (85 ± 12 kJ/d). Untreated patients (62 ± 21 kJ/d) lost more carbohydrate in the stool than did both treated patients (23 ± 9 kJ/d) and control subjects (14 ± 6 kJ/d). Fecal lipid loss correlated positively with the carbohydrate oxidation rate in treated celiac disease patients (**Figure 1**), whereas no correlation existed between control subjects and untreated celiac disease patients. A forward stepwise multiple regression analysis identified %FM as the best predictor of the change in FM (ΔFM) before and after GFD treatment. %FM negatively influenced ΔFM (kg) as follows ($r = 0.72$, SEE = 1.52; $P < 0.01$):

$$(\Delta FM = 6.42 \pm 1.02) - (0.045 \pm 0.019\ \%FM) \qquad (1)$$

DISCUSSION

Untreated patients with the classic form of celiac disease may be malnourished and have impaired dietary substrate utilization (15, 28). This longitudinal study was the first to evaluate changes in energy expenditure and substrate oxidation induced by treatment with a GFD. Because differences in disease severity can play a crucial role in energy requirements and body-composition status (11), only adult subjects with the classic form of celiac disease were

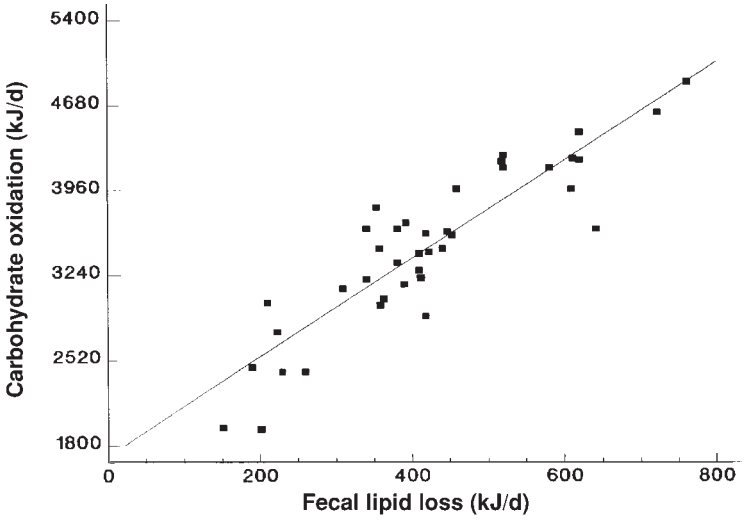

FIGURE 1. Regression analysis between fecal lipid loss and carbohydrate oxidation in untreated celiac disease patients ($r = 0.80$, SEE = 0.014, $P < 0.0001$).

included in the present study. As a consequence of the greater loss of intestinal absorptive surface area in patients with the classic form of celiac disease, a longer period of GFD treatment is required than in patients with subclinical celiac disease to obtain an improvement in nutritional status (29–32). Strict adherence to a GFD was reported to greatly improve nutritional status, essentially because of an increase in fat and bone compartments (33).

In agreement with previous reports (11, 13, 15, 28), we found lower body weights and lower FM and FFM contents in both untreated and treated celiac disease patients than in control subjects. Untreated patients of both sexes and treated male patients had FFM values that were significantly higher than those of control subjects. There was a significant increase in body weight and FM after the GFD treatment, whereas the FFM content improved slightly, but not significantly so, probably because of the small sample size. As a consequence of the larger decrease in FM than in FFM in male celiac disease patients after the GFD treatment, these patients had very high %FFM values. The most effective outcome of the dietary treatment on the biochemical indexes was the increase in blood iron and folic acid concentrations.

After adjustment for age, sex, FM, and FFM, higher RMR values were found in both celiac disease groups than in control subjects. Because RMR represents 60–80% of total energy expenditure in healthy control subjects (34), it can be considered a reliable indicator of daily energy requirements. The increased rate of intestinal mucosa protein synthesis and of renewal and migration of epithelial cells reported in untreated celiac disease (35, 36) could be considered partially responsible for the increased RMRs in these patients in addition to the inflammatory nature of the disease. However, whether a persistently high intestinal epithelial cell proliferation rate and a crypt hyperplastic response are responsible for the metabolic abnormalities found in treated celiac disease patients remains to be shown.

The higher npRQ value in untreated patients than in control subjects and treated patients indicates that the untreated patients oxidized more carbohydrates under resting metabolic conditions. As hypothesized previously (37, 15), clinical conditions characterized by considerable, chronic lipid malabsorption might be associated with increased carbohydrate utilization to provide energy to the organism. The lower carbohydrate oxidation rate shown after the GFD treatment, which resulted in the restoration of the absorptive capacity, along with the good correlation between fecal lipid loss and carbohydrate oxidation in celiac disease patients seems consistent with this hypothesis. Because the presence of small-bowel bacterial overgrowth was an exclusion criterion, the metabolic features of patients with celiac disease described in the present study do not necessarily apply to patients with bacterial overgrowth and further studies are warranted to evaluate the influence of this condition on substrate utilization in celiac disease patients.

Total daily energy intake did not differ significantly among groups, whereas carbohydrate consumption was greater in celiac disease patients than in control subjects both before and after the GFD treatment, confirming previous reports (12, 15). Moreover, lipid consumption was greater in treated patients than in both untreated patients and control subjects. The untreated patients may have had a lower lipid intake because of their attempts to reduce abdominal discomfort and diarrhea. However, to correctly interpret these findings it was necessary to take into account the high carbohydrate content relative to the fat content in the Italian diet, which could partly explain the differences between our results and those of others collected in populations living in different countries. The high carbohydrate intake in the untreated celiac disease patients might also account for this groups' high npRQ values (38). Therefore, early detection of celiac disease and follow-up to prevent malnutrition-related complications such as damage to gut barrier function, which can lead to increased risk of infection and sepsis, are important (39).

In conclusion, this longitudinal study confirms our previous observations. Patients with the classic form of celiac disease had lower body weights, FMs, and FFMs than did control subjects. In addition, untreated patients had higher carbohydrate oxidation rates than did treated patients, probably because untreated patients had greater lipid malabsorption and higher carbohydrate intakes, although lipid utilization increased with the restoration of the intestinal mucosa. Finally, because the metabolic variables were measured under basal conditions in the present study, future studies are needed to determine 24-h energy balances in celiac disease patients.

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