Influence of the metabolic sequelae of liver cirrhosis on nutritional intake[1–3]

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ABSTRACT

Background: The liver plays a central role in ingestive behavior; alterations in metabolic signaling to the brain stem as a result of chronic liver disease could influence intake.

Objective: We examined the influence of metabolic sequelae of liver disease on nutrient intake and nutritional status.

Design: Nutritional status and spontaneous dietary intake were examined in 65 cirrhotic patients and 14 control subjects. The response to feeding was investigated in 14 control subjects and a subgroup of 31 cirrhotic patients. Comparisons were made between patients with primary biliary cirrhosis (PBC) and hepatocellular cirrhosis (HC).

Results: Patients were nutritionally depleted. The fasting rate of lipid oxidation in the HC group was greater than in the control group ($P < 0.01$). In the fasting state, only HC patients were hyperinsulinemic [121.2 ± 78.5 compared with 41.3 ± 18.6 pmol/L in control subjects ($P < 0.001$) and 64.7 ± 15.8 pmol/L in PBC patients ($P < 0.05$)] and this persisted during the response to feeding. In the fed state, the magnitude of change in carbohydrate oxidation was greatest in the HC group (HC: 34.6%; control: 23.1%; PBC: 25.2%). Carbohydrate and energy intakes of the HC group were lower than in control subjects (carbohydrate: 193 ± 38.3 compared with 262 ± 48.1 g/d, $P < 0.05$; energy: 6.29 ± 1.40 compared with 9.0 ± 2.12 MJ/d, $P < 0.05$).

Conclusions: Reductions in carbohydrate intake could be mediated by hyperinsulinemia and compounded by preferential uptake of carbohydrate. This may enhance gastrointestinal satiety signaling and contribute to hypophagia. *Am J Clin Nutr* 1999;69:331–7.

KEY WORDS Liver cirrhosis, primary biliary cirrhosis, hepatocellular cirrhosis, substrate oxidation, metabolic regulation, ingestive behavior, carbohydrate intake, humans

INTRODUCTION

The nutritional and metabolic consequences of cirrhosis have attracted considerable interest over the past decade (1–5); given the central role of the liver in metabolism, it is not surprising that undernutrition is common in chronic liver disease (6–8). In recent years, the focus of research in this area has been on the identification of clinical or biochemical markers associated with nutritional risk (9, 10). These studies have predominantly considered the relation between factors such as pathology, disease staging, energy status, body-composition status, and substrate oxidation (11, 12); most studies were performed in subjects admitted to the hospital for disease management.

There is emerging interest in the liver as an organ involved in the metabolic control of eating (13–15). Normally, after the delivery of nutrient-rich blood from the portal vein to the hepatocytes, the quantity and quality of substrate oxidation activates hepatic metabolic signaling (via the hepatic afferent nerves) to the brain stem, which influences eating behavior (16). However, with progressive damage, pathophysiologic changes produce alterations in hepatic substrate oxidation, which may cause aberrant metabolic signaling. This phenomenon influences the quantity and quality of nutrients ingested, which consequently affects nutritional status.

In cholestatic cirrhosis [primary biliary cirrhosis (PBC)] or hepatocellular cirrhosis (HC; alcoholic liver disease, hepatitis C, or cryptogenic cirrhosis) the histologic picture is different. PBC is characterized by inflammation of the biliary canaliculi and HC involves primary hepatocellular damage. It was shown previously that the metabolic profile of cirrhosis is influenced by etiology (17, 18). Given that cirrhotic patients represent a heterogeneous population, both the selection and characterization of patients is important in clinical and metabolic studies. In these cases in which nutrient handling and substrate metabolism may influence dietary intake, which in turn would affect nutritional status, there are limited data on the metabolic response to feeding in homogeneous groups of cirrhotic patients.

To examine the possible mechanisms responsible for the undernutrition reported in this patient population, we investigated the influence of liver disease on nutrient intake. We considered nutritional status, metabolic response to a test meal, and spontaneous nutritional intake in stable cirrhotic patients referred for assessment of orthotopic liver transplantation and

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made comparisons between PBC and HC patients and with a matched group of healthy control subjects.

SUBJECTS AND METHODS

Patients admitted to the Scottish Liver Transplant Unit between October 1996 and August 1997 for consideration of orthotopic liver transplantation were eligible for the study. Patients with alcohol-related disease were required to be abstinent for ≥6 mo. Patients with diabetes, significantly impaired renal or respiratory function, thyroid dysfunction, active inflammatory bowel disease, sepsis, severe ascites, or grade 3–4 encephalopathy were excluded from the study. A group of 14 healthy volunteers was also recruited. The study protocol was reviewed and approved by the local ethical committee. All procedures relating to the study were explained to subjects, who were required to give their written consent.

Assessment of disease severity and nutritional status

Disease severity

Disease severity was scored by using Pugh et al's (19) modification of Child's classification. All patients underwent ultrasound scanning as part of the assessment; this confirmed the clinical assessment of the amount of ascites.

Anthropometry

Subjects' heights were measured without shoes by using a stadiometer (Docherty Medical, London). Subjects were weighed in light clothing to an accuracy of 100 g on mobile sitting scales (Weymed Ltd, London). Body mass index was calculated and patients were asked to recall any weight loss during the preceding year; recent weight loss (RWL) was expressed as a percentage of actual body weight. Triceps skinfold thickness (TSF) and arm muscle circumference (AMC) were measured on 3 occasions by the same trained observer (RAR) to reduce error. Results were averaged and expressed as a percentage of standard values to permit comparisons between men and women (20).

Multifrequency bioelectrical impedance analysis

This was performed on the day of investigation by using a Xitron 4000B analyzer (Xitron Technologies, San Diego) operated at 200 μA at previously defined optimal frequencies of 5 and 200 kHz (21). The alternating current was passed between a set of pregelled current injection electrodes placed on the right hand and foot, proximal to the third metacarpal and metatarsal bones, respectively. Similar detection electrodes were placed on the right wrist between the radius and ulna and on the right ankle between the malleoli. Measurements were taken on the morning of study with the subject in a supine position with his or her legs and leads apart. Total body and extracellular water were calculated from predictive equations derived previously from isotopic studies of surgical patients performed in our unit (22) and body cell mass (BCM) was derived from the equations of Shizgal (23). Bioelectrical impedance analysis in patients with mild and moderate ascites has been validated as a method of assessing the metabolically active component of body composition, the BCM, in a cirrhotic patient population (4).

Indirect calorimetry

Measurements of oxygen consumption (pragmatic oxygen sensor) and carbon dioxide production (infrared carbon dioxide sensor) were performed by using a Datex Deltatrac Metabolic Monitor (Engstrom Ltd, Helsinki). Subjects were placed under a ventilated plastic hood and room air was delivered at a constant flow rate (41 L/min). Monthly calibrations to check the flow rate and respiratory quotient were carried out by using an alcohol burning kit (variation between calibrations was <2.0%). Throughout the study, all subjects remained in bed in a quiet area of the ward. After subjects had fasted overnight (10 h), measurements were made over 40 min (10 min of acclimatization and 30 min of calorimetry); in the fed state, metabolic measurements were taken at 4 time points over a period of 2 h and 15 min (3 min of acclimatization and 10 min of calorimetry). Minute-by-minute readings were taken and averaged over each measurement period. Two timed urine collections were made, one over the study period to determine protein oxidation and a 24-h collection to allow calculation of the nonprotein respiratory quotient (NPRQ) from urinary nitrogen analysis (LECO analyzer, Chicago). Measured energy expenditure (MEE) and substrate oxidation were derived from the equations of de Weir (24) and Acheson et al (25), respectively.

Test meal

After fasting calorimetry was performed, subjects ingested the meal within a 5-min period. Those subjects being studied in the fed state (31 patients, 14 control subjects) were given a palatable and easily prepared dietary challenge (Fortisip and Polycal; Nutricia Ltd, Trowbridge, United Kingdom: 60% carbohydrate, 30% fat, and 10% protein) that provided 15 kJ/kg body wt. This intake ensured that the maximum metabolic effect of the meal would be observed within the study time frame.

Dietary intake

To assess subjects' usual dietary intake, food diaries (recording intake for 2 weekdays and 1 weekend day) were completed after discharge. Diaries were analyzed with a computerized dietary analysis program (COMP-EAT; Nutrition Systems, London). To minimize error, subjects were fully instructed on how to record intake by the research dietitian (RAR). To ensure that subjects understood how to complete the diet diaries, they were questioned at the end of their interviews. If the diaries were not returned within 1 wk of discharge, subjects were reminded twice to do so by telephone. Diet diaries were analyzed and results averaged to give an estimate of daily macronutrient and energy intakes.

Blood analysis

Blood samples were taken from an indwelling cannula (Venflon; Ohmeda, Helsinborg, Sweden) in the brachial vein that was kept patent with a minimal infusion of normal saline. Blood samples were taken to measure glucose at baseline and every 20 min for 2 h. Insulin was measured at baseline, 60 min, and 120 min. Plasma glucose was measured by the timed endpoint method (Cobas MIRA Plus; Roche Diagnostics Ltd, Lewes, United Kingdom) and plasma insulin was measured by a 2-site immunoenzymometric assay (AIA-pack IRI assay, AIA-600 enzyme immunoassay analyzer; Tosoh Corporation, Tokyo).

Statistics

Data were analyzed by using STATVIEW (version 4.02; Abacus Concepts, Berkeley, CA). Results are expressed as means ± SDs. Differences between groups were determined by

TABLE 1
Clinical and anthropometric assessment of cirrhotic patients and control subjects[1]

	Patients			
	All (n = 25 M, 40 F)	PBC (n = 3 M, 31 F)	HC (n = 22 M, 9 F)	Control subjects (n = 5 M, 9 F)
Number with ascites	20	9	11	0
Age (y)	54.6 ± 8.5[2]	57.7 ± 6.9	51.2 ± 8.9	49.5 ± 11.0
BMI (kg/m^2)	24.1 ± 4.7	23.5 ± 5.8	24.7 ± 3.5	26.0 ± 3.7
RWL (%)	−7.0 ± 9.7	−7.7 ± 8.4	−6.3 ± 11.3	0
TSF (%)	81 ± 34.1[3]	82 ± 37.2[4]	79 ± 31.0[3]	113 ± 39.0
AMC (%)	94 ± 12.9[5]	94 ± 15.0[5]	93 ± 10.5[5]	105 ± 9.7
BCM (kg)	23.1 ± 5.7	20.1 ± 4.9[6]	26.1 ± 4.7	24.8 ± 5.2
Child's score	8.5 ± 2.6	7.6 ± 2.8	9.2 ± 2.3	—

[1] PBC, primary biliary cirrhosis; HC, hepatocellular cirrhosis; RWL, recent weight loss, expressed as percentage of actual body weight; TSF, triceps skinfold thickness, expressed as percentage of standard values (20); AMC, arm muscle circumference, expressed as percentage of standard values; BCM, body cell mass; Child's score as modified by Pugh et al (19).
[2] $\bar{x}$ ± SD.
[3–5] Significantly different from control subjects: [3] $P < 0.005$, [4] $P < 0.01$, [5] $P < 0.05$.
[6] Significantly different from HC patients, $P < 0.005$.

using Student's t test for 2 groups and analysis of variance (ANOVA) for 3 groups. The effects of the test meal were analyzed by two-factor repeated-measures ANOVA. Scheffe's test was used to compare means. The linear relation between MEE and BCM was determined by using regression analysis and the method of least squares was used to derive correlation coefficients (r). The limit for significance was at the 5% level.

RESULTS

Sixty-five clinically stable patients with histologic confirmation of the diagnosis of cirrhosis were included in the study of clinical and nutritional status. Clinical and nutritional data are shown in **Table 1**. There were more women in the PBC group and more men in the HC group. The severity of liver disease was similar in both patient groups. In the patient groups, pharmacologic regimens during the assessment period included diuretic therapy (41 patients), vitamin supplements (13 patients), and lactulose (12 patients).

Energy expenditure was measured by indirect calorimetry and, given that BCM is the oxygen-consuming component of body composition, the relation between MEE and BCM was examined in both patients and control subjects. There was a strong, positive correlation between MEE and BCM in both patients and control subjects. In addition, this relation held in patients with mild and moderate ascites and there were no significant differences in the slopes of the regression lines between any groups (**Figure 1**). This finding confirms that multifrequency bioelectrical impedance analysis is of value for estimating body composition in populations of cirrhotic patients with mild and moderate ascites.

Endogenous fat reserves and muscle mass, determined by measuring TSF and AMC, respectively, were significantly lower in cirrhotic patients than in control subjects (for all patients combined: $P < 0.005$ for TSF and $P < 0.05$ for AMC; for the PBC group: $P < 0.01$ for TSF and $P < 0.05$ for AMC; and for the HC group, $P < 0.005$ for TSF and $P < 0.05$ for AMC). There was no significant difference in BCM between control subjects and the PBC and HC groups. BCM was significantly lower, however, in the PBC group than in the HC group ($P < 0.005$) and accounted for 31% of body weight, which is within the normal range for women of this age (26). The mean RWL did not exceed 10% of body weight in any group.

Substrate oxidation rates during fasting and feeding are shown in **Table 2**. In the PBC group, the NPRQ and macronutrient metabolism were not significantly different from that in control

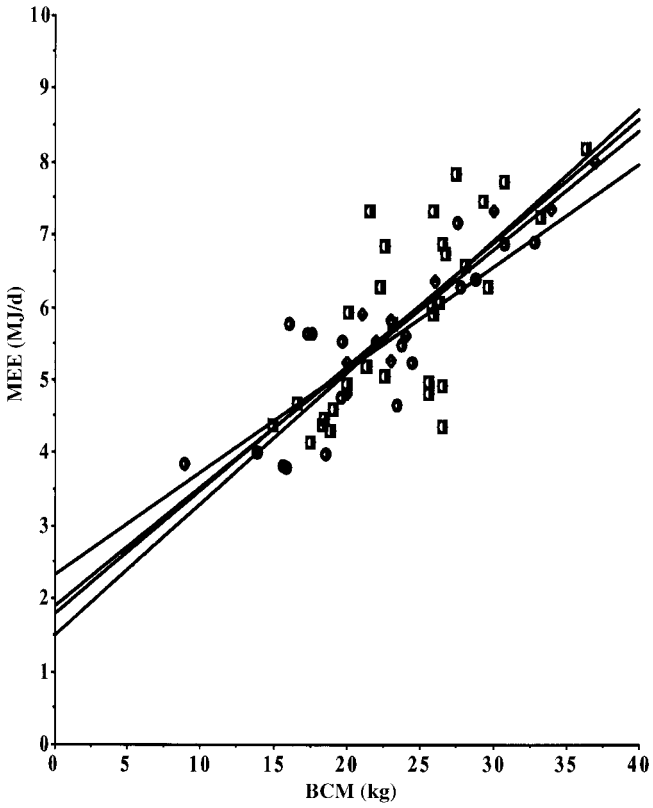

FIGURE 1. Relation between measured energy expenditure (MEE) and body cell mass (BCM) in cirrhotic patients and control subjects. There was a linear relation in all groups and the best-fitting line was determined by linear regression (○, all patients, $r = 0.765$, $P < 0.0001$; Δ, patients with no ascites, $r = 0.732$, $P < 0.0001$; □, patients with ascites, $r = 0.809$, $P < 0.0001$; ◇, control subjects, $r = 0.952$, $P < 0.0001$).

TABLE 2
Substrate oxidation during fasting and feeding in cirrhotic patients and control subjects[1]

	PBC patients (n = 18)		HC patients (n = 13)		Control subjects (n = 14)	
	Fasting	Feeding	Fasting	Feeding	Fasting	Feeding
NPRQ	0.82 ± 0.04	0.89 ± 0.06	0.78 ± 0.03[2]	0.89 ± 0.08	0.84 ± 0.04	0.93 ± 0.06
Carbohydrate						
(mg/min)	88.6 ± 32.5	156.2 ± 72.6	80.5 ± 34.6	188.0 ± 71.6	119.0 ± 47.1	186.0 ± 59.5
(%)	37.0 ± 12.2	62.2 ± 15.1	29.7 ± 11.1[2]	64.3 ± 25.6	46.2 ± 13.8	69.3 ± 13.6
Fat						
(mg/min)	46.3 ± 19.5	28.3 ± 17.1	66.7 ± 13.0[2,3]	34.0 ± 27.2	42.1 ± 8.21	18.4 ± 18.6
(%)	47.5 ± 13.7	27.3 ± 16.0	59.1 ± 12.3[2]	27.5 ± 22.9	39.3 ± 11.8	14.7 ± 15.5
Protein						
(mg/min)	30.8 ± 14.0	29.0 ± 17.9	29.2 ± 16.4	25.2 ± 19.6	36.9 ± 12.5	45.5 ± 23.0
(%)	14.2 ± 6.5	12.0 ± 7.6	11.3 ± 6.4	9.0 ± 9.3	14.6 ± 3.4	16.4 ± 6.7

[1] $\bar{x}$ ± SD. PBC, primary biliary cirrhosis; HC, hepatocellular cirrhosis; NPRQ, nonprotein respiratory quotient.
[2] Significantly different from control subjects, $P < 0.01$.
[3] Significantly different from PBC patients, $P < 0.01$.

subjects, whereas in the HC group, the fasting NPRQ was significantly lower than in control subjects. The fasting lipid oxidation rate of the HC group was significantly higher than in both control subjects and PBC patients. Additionally, when fasting macronutrient oxidation was calculated as a percentage of energy expenditure, the contribution from fat-derived energy was higher and that from carbohydrate-derived energy was lower in the HC group than in control subjects. Two hours after ingestion of the test meal, there was a switch to carbohydrate oxidation and at this time no significant differences in NPRQ or substrate utilization were observed. From the fasted to fed state, the magnitude of change in carbohydrate oxidation was 23.1% in the control group, 25.2% in the PBC group, and 34.6% in the HC group.

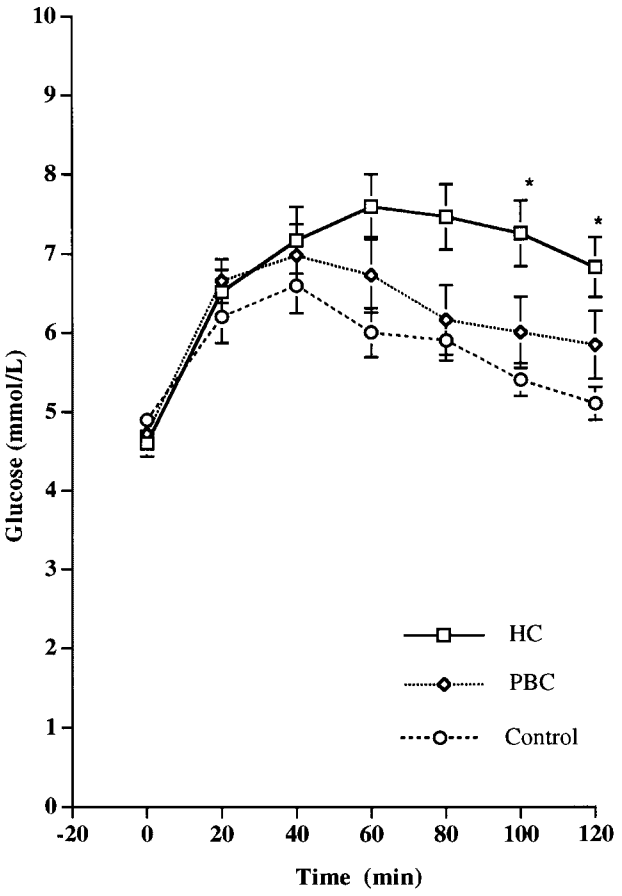

FIGURE 2. Mean (±SD) glucose response to the test meal in cirrhotic patients and control subjects. HC, hepatocellular cirrhosis; PBC, primary biliary cirrhosis. *Significantly different from control subjects, $P < 0.05$.

Glucose and insulin responses to the test meal are illustrated in **Figures 2** and **3**, respectively. The peak glucose response in the control group occurred 40 min after ingestion of the test meal. There was no significant difference in the glucose response curve between the PBC group and the control group. There was, however, a significantly higher response in the HC group than in the control group at 100 (7.2 ± 1.6 compared with 5.6 ± 1.1 mmol/L) and 120 min (6.8 ± 1.5 compared with 5.2 ± 0.95 mmol/L). Fasting plasma insulin concentrations were significantly higher in the HC group (121.2 ± 78.5 pmol/L) than in the control group (41.3 ± 18.6 pmol/L) and the PBC group (64.0 ± 15.8 pmol/L). Plasma insulin concentrations rose sharply in the HC group 60 min after ingestion of the meal and were significantly different from concentrations in control subjects (635.0 ± 641.2 compared with 203.9 ± 86.8 pmol/L). The peak insulin response to the meal in the control group was at 60 min. Insulin concentrations in the HC group remained higher and plateaued over 60–120 min when compared with the average concentration over this time period in control subjects (at 120 min: 629.5 ± 636.8 compared with 95.0 ± 57.2 pmol/L). At 120 min after the test meal, there were also significant differences in insulin response between the HC and PBC groups (629.5 ± 636.8 compared with 140.5 ± 97.8 pmol/L, respectively).

As shown in **Figure 4**, protein intake was significantly lower in the PBC group than in control subjects (58.7 ± 23.1 compared with 80.2 ± 22.3 g/d), whereas both protein and carbohydrate intakes were significantly lower in the HC group than in control subjects (protein: 50.4 ± 11.6 compared with 80.2 ± 22.3 g/d; carbohydrate: 193 ± 38.3 compared with 262 ± 48.1 g/d). Consequently, total daily energy intake was lower in the HC group than in control subjects (6.3 ± 1.39 compared with 9.0 ± 2.12 MJ/d; **Figure 5**).

DISCUSSION

Undernutrition in cirrhotic patients and its relation with morbidity and mortality is well documented (7–9). Studies that iden-

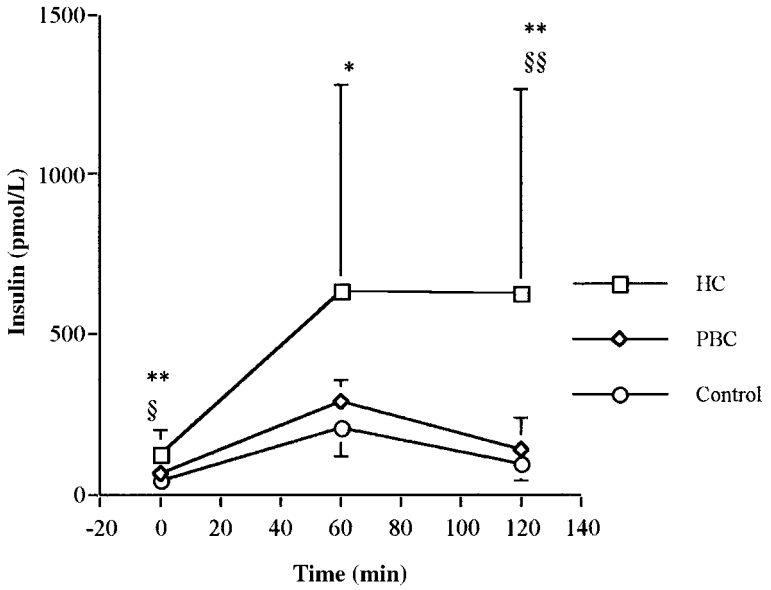

FIGURE 3. Mean (±SD) insulin response to the test meal in cirrhotic patients and control subjects. HC, hepatocellular cirrhosis; PBC, primary biliary cirrhosis. *,**Significantly different from control subjects: *$P < 0.05$, **$P < 0.001$. §,§§Significantly different from PBC patients: §$P < 0.05$, §§$P < 0.01$.

tify the prevalence and degree of undernutrition in chronic liver disease are important in that they permit the targeting of nutritional support to undernourished patients. However, as a result of the metabolic sequelae of cirrhosis, traditional high-energy, high-carbohydrate regimens may not be tolerated by some patients.

The present study examined the effect of histologically proven cirrhosis on nutritional intake in stable, chronic cirrhosis patients being assessed for liver transplantation. Interpretation of data relating to BMI and RWL can be influenced by the presence of ascites, but in this study there were no significant differences in TSF, AMC, or BCM between patients with and without ascites. The arm was used to estimate fat and muscle reserves because measurements at this site are less affected by fluid shifts (9). In the present study, no patient's ascites was severe enough to warrant drainage, which supports our finding that no patient was grossly ascitic. This study focused predominantly on the metabolic sequelae of cirrhosis and their influences on intake; given that there were no significant differences in those nutritional indexes unaffected by ascites (ie, arm anthropometry) or in the relation between MEE and BCM, patients were stratified by primary diagnosis.

The underlying cause of cirrhosis may influence metabolism. Alcoholic cirrhosis, cryptogenic cirrhosis, and hepatitis C are characterized by hepatocellular damage, whereas PBC is a disease that predominantly affects women in their middle years and is cholestatic in nature. All patients in the study were shown to be depleted in fat and muscle when compared with the normally nourished control group. BCM was lower in patients with PBC than in those with HC but was not significantly different from that in control subjects. This finding may be accounted for by the predominance of women in the PBC group, who normally have a higher ratio of fat to lean tissue than do men. It has been suggested that cirrhotic patients with a BCM <30% of body weight are undernourished (27), which is within the normal range for women in their 50s (26). In our study population, BCM as a percentage of body weight accounted for 31% of PBC, reflecting the sex bias.

The lower fasting NPRQ and higher lipid oxidation rate in the HC group suggests early depletion of hepatic glycogen stores with a concomitant switch to lipolysis and indicates an extended period of fasting. Interestingly, in this study, the HC group had the smallest endogenous fat reserves but the highest rate of fasting lipid oxidation. Conversely, the fasting substrate profile in the PBC group was similar to that in control subjects, suggesting that hepatic glycogen reserves are better preserved in PBC. This increased reliance on endogenous lipids to meet energy requirements in the HC group may be an adaptive process, and one that serves to preserve lean body mass during periods of nutrient deprivation.

In the postingestive period carbohydrate oxidation predominated at rates that were not significantly different between patients and control subjects. Nonetheless, the magnitude of change was greatest in the HC group, suggesting that in this group carbohydrate was preferentially oxidized after ingestion of a mixed meal. This finding supports the work of Levine et al (28), who, when supplying a test meal 3 times as large as the one used in the current study (59 kJ/kg), observed avid oxidation of carbohydrate by patients with alcohol cirrhosis 2 h after ingestion of the meal.

In the fasted state, only the HC group had elevated plasma insulin concentrations. After consumption of the test meal, the PBC group exhibited a normal insulin response that contrasted markedly with the hyperinsulinemia seen in the HC group. The pathogenesis of insulin resistance in cirrhosis is still unknown; several researchers have failed to attribute cirrhotic hyperinsulinemia to portal systemic shunting but rather attributed it to deficits in binding and postbinding insulin target organ cells (17, 29, 30). Earlier work linked hyperinsulinemia with deficient hepatic insulin extraction or the shunting of portal venous blood to the systemic circulation (31). There is, however, no consensus as to the exact mechanisms involved in the hyperinsulinemia of cirrhosis but portosystemic shunting seems unlikely because hyperinsulinemia is not found in patients with portal vein thrombosis and normal liver function (32). In the current study, there

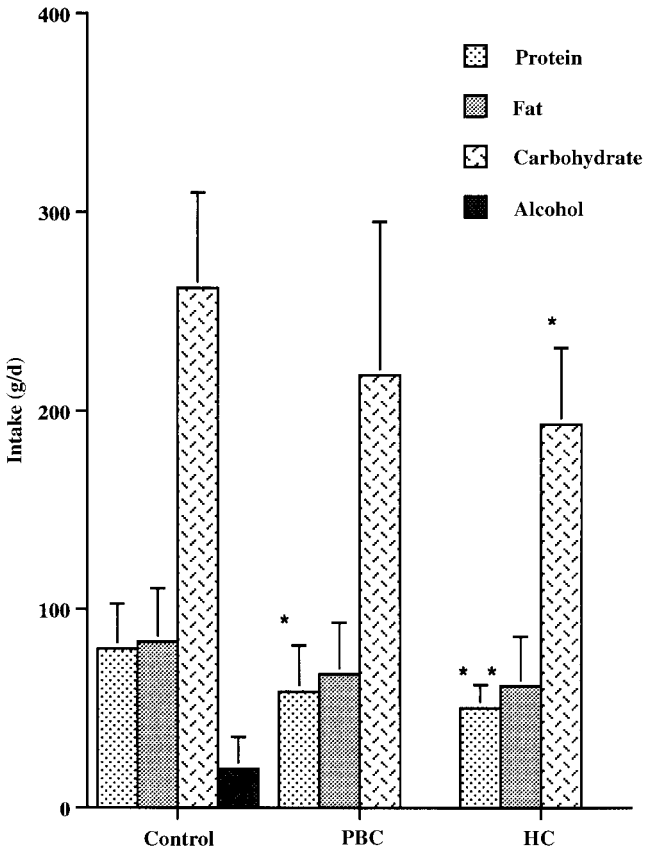

FIGURE 4. Mean (±SD) daily macronutrient intake in cirrhotic patients and control subjects. PBC, primary biliary cirrhosis; HC, hepatocellular cirrhosis. *,**Significantly different from control subjects: *$P < 0.05$, **$P < 0.01$.

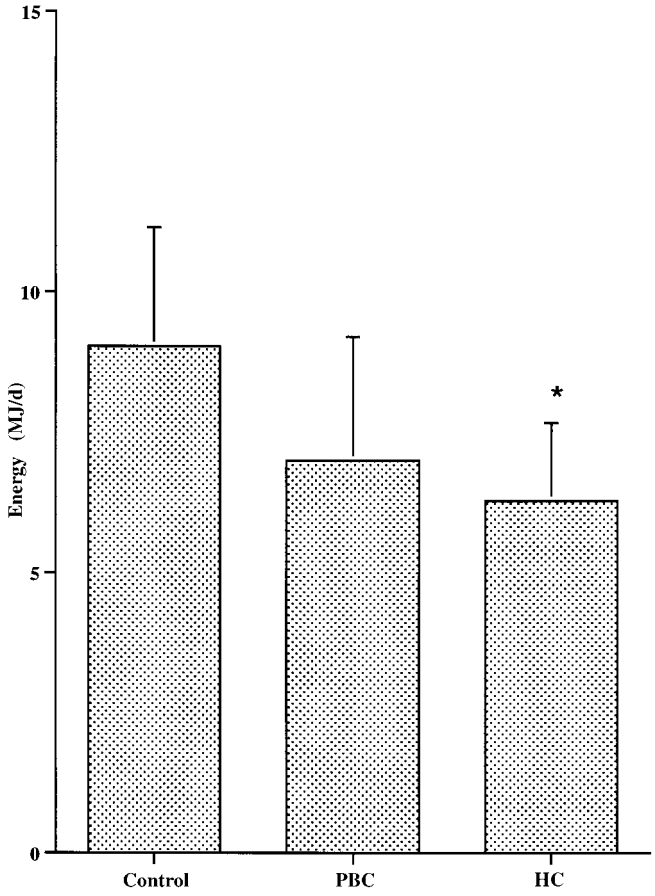

FIGURE 5. Mean (±SD) daily energy intake in cirrhotic patients and control subjects. PBC, primary biliary cirrhosis; HC, hepatocellular cirrhosis. *Significantly different from control subjects, $P < 0.05$.

were no significant differences in insulin concentrations in patients with (n = 10) and without (n = 21) evidence of portosystemic shunting.

Blood glucose concentrations were significantly elevated in the HC group toward the end of the postprandial period, whereas the glucose response curve was normal in the PBC group. The different metabolic response to feeding in HC and PBC is an important finding that has not been widely reported. Taylor et al (17) noted impaired glucose tolerance and insulin resistance in cirrhotic patients but, as in the present study, showed that PBC patients were less insulin resistant than patients with HC. These findings support the notion that hepatocyte function is better preserved in PBC. Insulin is known to inhibit dietary intake by stimulating the satiating effects of cholecystokinin and through its direct action in the brain (33). When we examined the ad libitum dietary intake of our study population, all patients—irrespective of the primary etiology of their disease—had significantly lower protein intakes than did control subjects. The reason for this is unclear but could have been the inappropriate prescribing of low-protein dietary regimens by clinicians (27, 34). Interestingly, a lower carbohydrate intake was noted only in the HC group; it can be hypothesized that the defects in carbohydrate metabolism found in this study could bring about a spontaneous reduction in the consumption of this macronutrient. Furthermore, this reduction in carbohydrate intake could have been caused by the presence of hyperinsulinemia and compounded by the preferential uptake of carbohydrate. This may enhance signaling by the gastrointestinal glucosensors and in turn contribute to hypophagia. Furthermore, the energy intake of the HC group was only about two-thirds that of the control group and this level of intake is consistent with the energy consumption of hospitalized cirrhotic patients (35). If continued over a period of months or years, this reduced intake would contribute significantly to a deterioration in nutritional status. Note that with regard to diet diaries, patients referred to a transplant unit are highly compliant. In addition, through meticulous attention to patient instruction, every effort was made to minimize sources of error (ie, transcription of diaries by RAR).

There is ample evidence from animal studies to support the central role of the liver in controlling ingestive behavior (36). Hepatic metabolic sensors continuously monitor substrate oxidation and relay this information to the brain stem via the hepatic afferent nerves. In this study, we began to study for the first time the effects of the metabolic aberrations of chronic liver disease on eating behavior. The next logical step would be to conduct controlled studies of ingestive behavior to identify clinically acceptable and effective dietary regimens. We conclude that it may be physiologically impossible for patients with HC to follow dietary advice that advocates increasing carbohydrate intake because of the initiation of an amplified satiety cascade mediated by elevated insulin concentrations. Postprandial rises in insulin

are associated with a reduction of hunger and increasing satiety (37). In the HC population, the avid switch to carbohydrate oxidation with feeding, which was maintained in the short-term postprandial period, suggests intracellular uptake of glucose and hence functioning insulin. Early and enhanced postprandial rises in insulin may therefore reduce energy intake through normal satiety mechanisms, which are enhanced in these patients.

Many researchers have considered the relation between nutritional status and liver disease (4, 7, 10). However, as we begin to move into evidence-based nutritional practice, we must develop acceptable and achievable nutritional strategies for cirrhotic patients. Liver transplantation and the hospitalization of cirrhotic patients is expensive clinically, socially, and psychologically. Because research has confirmed that nutritional status is an outcome factor (38), it is of paramount importance to understand the disease-specific nutritional requirements of this patient population. This will only be achieved when the interaction between the metabolic sequelae of primary liver pathology and their influence on ingestive behavior is understood.

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