Impairment of albumin and whole body postprandial protein synthesis in compensated liver cirrhosis

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LIVER CIRRHOSIS is a protein-catabolic disease, which at advanced stages is usually associated with loss of lean body mass (represented mainly by proteins and water), decreased albumin concentration, and an increased ratio of aromatic (AAA) to branched-chain amino acid (BCAA) concentrations (18, 23, 24, 39). These metabolic alterations reflect the impaired liver functional capacity and can heavily complicate the clinical course of the disease (21).

The maintenance of protein homeostasis is achieved physiologically through meal ingestion and assimilation, which counteract the interprandial catabolic phases (8, 20, 37). One key component of the anabolic response to a meal is the stimulation of protein synthesis. Indeed, in healthy humans, intake of a mixed meal of adequate amino acid and caloric content results in the acute increase of whole body, albumin, and muscle protein synthesis (8, 20, 37). However, whether these effects are preserved in cirrhosis has not been thoroughly investigated. In a previous study (3), albumin synthesis was found to be grossly unaltered in postabsorptive cirrhotic patients, but it correlated inversely with the patients’ clinical status. However, the response to a mixed meal was not tested. In another study (22), no stimulation by an enteral diet of whole body protein synthesis was found in cirrhosis, although the caloric and amino acid content might have been insufficient to elicit a response (37). As a matter of fact, no study has yet investigated whether a balanced mixed meal of adequate caloric intake is capable of stimulating both whole body and albumin protein synthesis in liver cirrhosis.

The changes in body protein content as well as in plasma protein and amino acid concentrations that occur in advanced cirrhosis likely represent the endpoint of long-lasting alterations. Thus it is of interest to investigate whether the mechanism(s) controlling protein synthesis postprandially in cirrhosis are already altered at an early disease stage. To this aim, we have measured the response of both whole body protein and plasma albumin synthesis to mixed meal ingestion in nondiabetic, stable cirrhotic patients and in normal subjects by use of leucine tracer precursor-product relationships and whole body kinetics.

METHODS

Subjects. Six male patients with established liver cirrhosis (CP) and seven male normal control subjects (N) were recruited. All subjects were informed about the aims of the study and signed their consent to it. The study was approved by the Ethics Committee of the Medical Faculty at the University of Padova, Italy, and it was performed according to

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diagnosed. In the sixth, nonbiopsied patient, cirrhosis was established through medical history, clinical examination, ultrasound criteria, biochemical data, and laparoscopy in all patients. In addition, in five patients a liver biopsy was performed, and a chronic hepatitis C virus (HCV) infection was diagnosed. In the sixth, nonbiopsied patient, cirrhosis was defined as cryptogenic. Only one patient had (minimal) endoscopic signs of esophageal varices (P:W, i.e., white and straight varices) (4). According to Child-Pugh classification (5, 30), three patients were in Class A and three in Class B (Table 1). Albumin concentrations were nearly normal in most of the patients (Table 1); therefore, their inclusion in either Child-Pugh class was due to the other biochemical and clinical abnormalities considered by this classification (30). In all patients, ascites was excluded through both clinical and ultrasonographic criteria. No patient had any sign of hepatic encephalopathy or was taking any pharmacological therapy at the time of study. The patients were slightly but insignificantly older than the controls (Table 1). However, age was found not to affect albumin fractional synthesis rate (FSR) in humans (11). Lean body mass (LBM, in kg) was estimated in all subjects by Hume’s formula (14). In addition, in four cirrhotic patients, LBM was directly measured also by means of dual-energy X-ray absorptiometry (DEXA) (17, 29). In these patients, DEXA-determined LBM (56 ± 2 (SE) kg) was not different from that calculated by Hume’s formula (58 ± 2 kg). Therefore, we used for all subjects the LBM values determined by Hume’s formula. In the patients, body mass index (BMI, expressed as weight in kg divided by squared height in meters) and LBM were slightly greater (+13 and +9%, respectively, P < 0.05) than those measures in control subjects (Table 1), whereas the fraction of body weight accounted for by LBM was lower (−7%, P < 0.05) (Table 1).

Because glucose intolerance and/or diabetes is frequent in cirrhosis, and it may determine alterations in both whole body and albumin protein turnover, an oral glucose tolerance test was performed in all patients to exclude any abnormality in glucose homeostasis, according to established criteria (31). In the normal subjects, there was no clinical or familial history of either diabetes or impaired glucose tolerance, and their glucose tolerance was normal.

### Table 1. Clinical characteristics of the cirrhotic and normal subjects studied

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>BMI, kg/m²</th>
<th>LBM, kg</th>
<th>%body wt</th>
<th>Histology</th>
<th>Class</th>
<th>Albumin, g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhotic patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>27.8</td>
<td>67</td>
<td>75</td>
<td>HCV-cirrhosis</td>
<td>B</td>
<td>36</td>
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<tr>
<td>56</td>
<td>28.9</td>
<td>56</td>
<td>74</td>
<td>HCV-cirrhosis</td>
<td>B</td>
<td>44.2</td>
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<tr>
<td>53</td>
<td>26.3</td>
<td>58</td>
<td>77</td>
<td>HCV-cirrhosis</td>
<td>A</td>
<td>43.5</td>
</tr>
<tr>
<td>45</td>
<td>27.8</td>
<td>67</td>
<td>75</td>
<td>Cryptogenic cirrhosis</td>
<td>A</td>
<td>42</td>
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<tr>
<td>38</td>
<td>27.1</td>
<td>63</td>
<td>76</td>
<td>HCV-cirrhosis</td>
<td>B</td>
<td>48</td>
</tr>
<tr>
<td>54</td>
<td>30.1</td>
<td>65</td>
<td>66</td>
<td>HCV-cirrhosis</td>
<td>A</td>
<td>42.2</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>49 ± 3</td>
<td>26.9 ± 0.7*</td>
<td>61.1 ± 2.4*</td>
<td>76.4 ± 1.1*</td>
<td>42.7 ± 1.6</td>
<td></td>
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<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
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<tr>
<td>35 ± 7</td>
<td>23.9 ± 1.3</td>
<td>56.2 ± 0.9</td>
<td>82.0 ± 1.6</td>
<td>42.3 ± 0.9</td>
<td></td>
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</tbody>
</table>

BMI, body mass index; LBM, lean body mass; Class, discrimination on basis of Child-Pugh classification (5); HCV, hepatitis C virus. *P ≤ 0.05 vs. control subjects.

Experimental design. All subjects were admitted to the Clinical Study Unit at 7:00 AM after an overnight fast. A polyethylene catheter was placed percutaneously in retrograde fashion into a superficial vein of one arm, which was kept at 60°C in a heated box for arterialized venous blood sampling. Another catheter was placed into an antecubital vein of the opposite arm for isotope infusions. At ~240 min, a primed continuous infusion of [14C]Leu was started by means of a calibrated pump. The rate of isotope constant infusion was 5,200–5,500 dpm·kg⁻¹·min⁻¹, and the priming dose was 60 times the constant infusion rate per minute. The bicarbonate pool was primed with 3 μCi of [14C]bicarbonate. Samples were frequently taken over 3 h (data not shown) to allow the achievement of steady state in plasma leucine and α-ketosiccroprate (KIC) isotope and substrate concentrations. Steady state was defined as absence of a slope significantly different from 0, as well as of changes in concentrations, specific activities, and enrichments <5%, and it was usually achieved after ~2.5 h (Fig. 1). Between ~80 and 0 min, five baseline 10-ml blood samples were collected at 20-min intervals into EDTA tubes and rapidly centrifuged at +4°C. The plasma was then stored at −20°C before assay. Samples of expired air for 14CO2 measurements were collected at the same time points.

At 0 min, the administration of a mixed liquid meal of defined composition (Nutrodrip Protein, Sandoz Nutrition, Wander Italia SPA, Milano, Italy; 49% of calories as carbohydrates, 22% as proteins, and 29% as lipids) was started. The entire meal (~62 kcal/kg of body wt) was given as isocaloric aliquots of 0.94 ml/kg of body wt every 20 min over 4 h. Meal composition (g/100 ml) was carbohydrates, 14.8; protein hydrolysate, 6.6; lipids, 4. It also contained minerals and vitamins. The proteins were derived from soy and casein hydrolysate. The lipids were constituted by 40% linoleic acid, 6.5% MCT oil, and the remainder by mono- and diglycerides.

Expired air and blood samples were again collected at 170, 190, 210, 230, and 250 min, i.e., every 10 min after administration of each meal aliquot after the achievement of the new steady state (Fig. 1). Although this pattern of meal administration (i.e., continuous) might be considered slightly unphysiological, it allowed us to perform all kinetic measurements at near steady state, thus avoiding uncertainties due to time-dependent changes in amino acid pool sizes and specific activities after a bolus meal. Notably, the prandial steady-state amino acid concentrations were in the range of physiological, it allowed us to perform all kinetic measurements at near steady state, thus avoiding uncertainties due to time-dependent changes in amino acid pool sizes and specific activities after a bolus meal. Notably, the prandial steady-state amino acid concentrations were in the range of
those attained after a mixed meal ingested as a bolus, at least at its peak value (26). In addition, a continuous oral feeding was shown to stimulate whole body, albumin, and muscle protein synthesis (8, 37).

Analytic measurements. Plasma leucine and KIC concentrations and SA were determined by HPLC (13, 33). Plasma total amino acid concentrations were determined by ion exchange chromatography with a Beckman amino acid analyzer. The $^{14}$CO$_2$ in the expired air was determined as described previously (33, 37). Insulin and glucagon concentrations were measured by radioimmunoassay (37). Plasma glucose was determined using a Beckman Glucose Analyzer 2.

Albumin was isolated from plasma as described previously (13), with an additional acid precipitation to avoid contamination from free amino acids. Hydrolysis was accomplished by adding 4 ml of 4 N HCl to the isolated protein and by incubating the samples in air-tight vials at 110°C for 72 h. The albumin-derived free amino acids were

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Fig. 1. A: plasma leucine and $\alpha$-ketoisocaproate (KIC) concentrations (in $\mu$mol/l) in the cirrhotic patients (filled symbols) and normal subjects (open symbols). B: plasma leucine and $^{14}$C-labeled $\alpha$-ketoisocaproate ($^{14}$C[KIC]) specific activities (SAs, in dpm/nmol) in cirrhotic patients (filled symbols) and normal subjects (open symbols). C: expired $^{14}$CO$_2$ (in dpm·kg$^{-1}$·min$^{-1}$) in cirrhotic patients (*) and normal subjects (open symbols).
then further purified through cation-exchange Ag 50 × 8 columns. Leucine SA in the hydrolysate was determined by HPLC (13).

Calculations. The steady-state values of plasma leucine and KIC SA in the last 80 min of the basal, postabsorptive state and in the last 80 min of meal administration (i.e., between 170 and 250 min) were averaged. All calculations were performed using these mean values.

Whole body leucine rate of appearance (Ra) was calculated using plasma [14C]KIC SA as precursor pool (32). Leucine oxidation was calculated by dividing the rate of 14CO2 expiration (in dpm/kg·min−1), corrected for 20% fixation in body bicarbonate pool, over plasma [14C]KIC SA. The rate of nonoxidative leucine disposal (NOLD), indicating leucine disposal into whole body protein synthesis, was calculated by subtracting oxidation from total leucine Ra, (equal to the rate of disappearance at steady state).

Albumin FSR was calculated from the samples taken at −80, −60, −40, −20, and 0 min in the basal state, and at 170, 190, 210, 230, and 250 min after the start of meal administration, by use of a standard precursor-product linear relationship (8, 11, 13)

\[
\text{FSR} = \frac{\text{SA}_{t(2)} - \text{SA}_{t(1)}}{t(2) - t(1)} \times \frac{1}{\text{[14C]} \text{KIC SA}} \times 1,440 \times 100
\]

where \( \text{SA}_{t(2)} \) and \( \text{SA}_{t(1)} \) are albumin-bound leucine specific activities (in dpm/nmol) at time points \( t(2) \) and \( t(1) \), respectively; \([14C] \text{KIC SA} \) is the steady-state plasma \([14C] \text{KIC} \) specific activity (in dpm/nmol); the factor “1,440” is used to convert the data from minutes to 1 day; and “100” is used to convert FSR to a percentage. The term at the numerator of Eq. 1 actually corresponds to the slope of the change in leucine-specific activity vs. time, calculated by use of five time points. The coefficients of linear regression of the slopes were >0.9 in both the basal and the meal periods in each subject of both groups. Thus, as precursor pool for both whole body protein and albumin synthesis, we used plasma KIC SA, which represents a standard approach recently validated also as a surrogate of leucyl-tRNA in liver (1, 32).

Statistical analysis. All data are expressed as means ± SE. The changes vs. basal within each group were analyzed with the two-tailed Student \( t \)-test for paired data. Comparison of single sets of data between the two groups (such as the relative differences vs. baseline, expressed as either percentages or deltas) was analyzed using the two-tailed Student \( t \)-test for unpaired data. The two-way ANOVA for repeated measures was also employed to compare the meal effects in the two groups simultaneously. A \( P \) value <0.05 was considered to be statistically significant.

RESULTS

Albumin FSR and leucine kinetics. In the fasting state, albumin FSR in the cirrhotic patients (CP; 8.5 ± 1.5 %/day) was slightly but insignificantly lower than that of the normal subjects (N; 10.9 ± 1.5 %/day, \( P = \) nonsignificant (NS)). After the meal, albumin FSR did not change in the CP (to 8.8 ± 1.7%/day, \( P = \) NS vs. baseline), whereas it increased in the N by an average of ≈45% (to 15.9 ± 1.9%/day, \( P < 0.002 \) vs. baseline; \( P < 0.025 \) by ANOVA between groups). The albumin FSR value in the CP during meal absorption was significantly lower (\( P = 0.022 \)) than in the N (Fig. 2).

Fasting leucine Ra, expressed over kilogram of body weight, was not different between the two groups (2.20 ± 0.24 μmol·kg−1·min−1 in CP; 2.36 ± 0.16 μmol·kg−1·min−1 in N). Similarly, leucine oxidation (0.51 ± 0.08 vs. 0.56 ± 0.07) and NOLD (1.68 ± 0.22 vs. 1.80 ± 0.14, respectively) were not different between CP and N (Fig. 3). Also, no differences were observed when the data were expressed over the estimated LBM (CP: leucine Ra, 2.89 ± 0.32 μmol·kg−1·min−1; oxidation, 0.68 ± 0.11; NOLD, 2.21 ± 0.3; N: leucine Ra, 2.88 ± 0.18; oxidation, 0.68 ± 0.08; NOLD, 2.20 ± 0.17). After the meal, total leucine Ra increased (\( P < 0.01 \) or less vs. basal) in both groups (to 2.78 ± 0.27 μmol·kg−1·min−1 in CP; and to 3.29 ± 0.26 μmol·kg−1·min−1 in N; Fig. 3). Although postprandial leucine Ra tended to be lower in the patients, this difference was not significant. Leucine oxidation increased (\( P < 0.0001 \)) to similar values (\( P = \) NS between groups) in both patients (to 1.24 ± 0.14 μmol·kg−1·min−1) and normal subjects (to 1.18 ± 0.11). In contrast, NOLD increased only in N (to 2.10 ± 0.19 μmol·kg−1·min−1, \( P = 0.032 \) vs. basal), whereas it did not change in CP (to 1.54 ± 0.26 μmol·kg−1·min−1, \( P > 0.1 \) vs. basal; \( P < 0.01 \) by ANOVA for interaction between groups). The relative change vs. basal (expressed as μmol·kg−1·min−1) in NOLD was significantly greater (\( P < 0.01 \)) in N (0.31 ± 0.11 μmol·kg−1·min−1) than in CP (−0.15 ± 0.07 μmol·kg−1·min−1). The same pattern was observed when the data were expressed over LBM (CP: leucine Ra, 3.66 ± 0.38 μmol·kg−1·LBM−1·min−1; oxidation, 1.64 ± 0.19; NOLD, 2.02 ± 0.34; N: leucine Ra, 3.99 ± 0.27; oxidation, 1.43 ± 0.11; NOLD, 2.56 ± 0.22).

Plasma and albumin-bound SAs. Albumin concentration was similar in CP and N groups (Table 1). Postabsorptive plasma [14C]KIC SA was 2.38 ± 0.16 E307

Fig. 2. Individual and mean values of albumin fractional secretion/synthesis rate (FSR) measured at steady-state conditions in both the basal, postabsorptive state and after mixed meal administration in normal control subjects (left) and in cirrhotic patients (right).
and 2.45 ± 0.19 dpm/nmol in CP and in N, respectively (Fig. 1). Leucine [14C]SA was 3.09 ± 0.23 and 2.96 ± 0.25 dpm/nmol in CP and N, respectively. No significant differences between groups were found in the KIC-to-leucine SA ratios (CP: 0.83 ± 0.03; N: 0.78 ± 0.04). After the meal, the [14C]KIC SA decreased (P < 0.01 or less vs. baseline) to 1.91 ± 0.12 and to 1.75 ± 0.17 dpm/nmol in CP and N, respectively, and that of [14C]leucine to 2.18 ± 0.18 and to 2.24 ± 0.26 dpm/nmol, respectively. The ratio of [14C]KIC to [14C]leucine SA tended to increase (although insignificantly) in the CP (to 0.88 ± 0.03, P > 0.1), whereas it did not change at all in the N (to 0.79 ± 0.05). The slope of changes of albumin-bound leucine 14C SA vs. time tended to decrease (although insignificantly) in the CP (from 0.138 ± 0.016 to 0.119 ± 0.025 dpm·μmol⁻¹·min⁻¹; P = NS), whereas it did not change in the N (from 0.182 ± 0.029 to 0.191 ± 0.029 dpm·μmol⁻¹·min⁻¹).

**Substrate and hormone concentrations.** Plasma concentrations of the AA phenylalanine and tyrosine were ~40% greater (P < 0.01) in CP than in N in both the basal and the postprandial states (Table 2). Methionine concentration in the CP was also increased (P < 0.001; fasting state: 25 ± 2 vs. 15 ± 1; postprandial state: 42 ± 4 vs. 31 ± 1). Leucine and KIC concentrations were not different between the two groups (Fig. 1, Table 2), although the sum of the BCAA concentrations was slightly greater (by ~15%, P < 0.05) in CP. The BCAA-to-AAA (BCAA/AAA) ratio in the CP was ~20% lower (P < 0.05) than in N both in the fasted (CP: 3.25 ± 0.26; CS: 3.92 ± 0.2) and the fed states (3.23 ± 0.25 and 3.79 ± 0.18, respectively). The sum of total amino acids was not different between the groups (Table 2).

Plasma glucose and insulin concentrations in the CP were greater than in N (P < 0.01 by ANOVA) both in the fasted and the fed states, whereas glucagon concentration was not different (Table 2). In the CP, plasma insulin concentration increased to an ~100% greater value (P < 0.01) than that in N postprandially (Table 2). Glucagon concentration did not significantly change from basal in either group (Table 2).

**DISCUSSION**

This study shows that ingestion of a mixed meal over 4 h did not acutely stimulate either albumin or whole body protein synthesis in compensated cirrhotic patients, in contrast to normal control subjects.

Several factors may account for these defects. Albumin and body protein synthesis are stimulated physiologically by meal ingestion and/or by hyperaminoacidemia (8, 9, 35, 37), the former also by insulin (8, 9). Both of these stimuli appeared to be ineffective in the cirrhotic patients postprandially. Hyperinsulinemia is

Table 2. Basal and postprandial substrate and hormone concentrations

<table>
<thead>
<tr>
<th></th>
<th>Cirrhotic Patients</th>
<th>Normal Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, mmol/l</td>
<td>5.1 ± 0.1†</td>
<td>4.6 ± 0.4</td>
</tr>
<tr>
<td>Insulin, μU/l</td>
<td>18 ± 5†</td>
<td>136 ± 22‡</td>
</tr>
<tr>
<td>Glucagon, ng/l</td>
<td>120 ± 12</td>
<td>131 ± 16</td>
</tr>
<tr>
<td>Leucine, μmol/l</td>
<td>142 ± 7</td>
<td>213 ± 18‡</td>
</tr>
<tr>
<td>KIC, μmol/l</td>
<td>44 ± 2</td>
<td>32 ± 5</td>
</tr>
<tr>
<td>Sum of BCAA, μmol/l</td>
<td>463 ± 23*‡</td>
<td>761 ± 33‡</td>
</tr>
<tr>
<td>Sum of AAA, μmol/l</td>
<td>146 ± 12†</td>
<td>244 ± 23†</td>
</tr>
<tr>
<td>Total AA, mmol/l</td>
<td>2.4 ± 0.3</td>
<td>3.4 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. KIC, α-ketoisocaproate; BCAA, branched-chain amino acids; AAA, aromatic AA. *P < 0.05; †P < 0.01; ‡P < 0.01 cirrhotic vs. normal subjects; §P ≤ 0.05, meal vs. basal.
a common finding in cirrhosis, and it may be due to hypersecretion and/or decreased hepatic extraction (27). The defective postprandial albumin synthesis despite hyperinsulinemia in cirrhosis is compatible with an insulin-resistant state involving also the hormone proteosynthetic hepatic effect. Such a resistance, in turn, may be secondary to alterations of liver architecture, circulation, and function, which are characteristic of this disease (6), including a shunt of insulin from the portal vein to the posthepatic circulation. A decreased first-pass splanchnic (liver) extraction of some dietary amino acids, such as phenylalanine (34), and the altered plasma profiles [i.e., the increased AAA concentrations and/or the decreased BCAA/AAA ratio (25)] might also have limited albumin synthesis. Among other possible alterations that are observed in cirrhosis (although not measured in this study), toxic effects by cytokines (2, 38), as well as a decreased insulin-like growth factor I (IGF-I) concentration (12), could also be considered. An interesting hypothesis is that albumin synthesis was already maximally stimulated in the postabsorptive state in the patients, thus preventing a further increase after the meal.

Because albumin concentration was normal in the patients despite the defective postprandial stimulation, a decreased albumin catabolism, helping to maintain a nearly normal balance between synthesis and degradation, cannot be excluded. Albumin fractional catabolism could be determined in vivo with the intravenous injection of iodine-labeled albumin (10). In this study, however, we did not perform such a test, mainly because of limitations in subjects’ exposure to radioactive isotopes. Also, iodine kinetics may not correspond accurately to that of native albumin, rather reflecting a different pattern of albumin distribution between intra- and extravascular sites, i.e., its transcapillary escape (10), which may itself be altered in cirrhosis (19). On the other hand, by definition, synthesis must equal catabolism at steady state. Thus the decreased postprandial albumin FSR in the cirrhotic patients may also indicate a decreased fractional catabolic rate. As a matter of fact, the complex relationships between albumin synthesis and catabolism need to be further investigated.

Interestingly, a defective stimulation of whole body protein synthesis in cirrhosis was previously reported by our group, which followed the intravenous infusions of the branched-chain-enriched amino acids, glucose, and insulin (36), and was in agreement with the present findings. The defective albumin synthesis here observed could account at least in part for the impaired postprandial whole body protein synthesis. Indeed, in humans, albumin synthesis accounts for ≈30% of the increase of body protein synthesis after a meal (8), and it may act as a carrier of protein-bound amino acids from visceral to peripheral organs, like muscle, postprandially (8, 10). Thus the impaired postprandial albumin synthesis might contribute to the reduced muscle mass often found in cirrhotic patients.

The defects in protein synthesis observed in the patients cannot be explained by their slightly greater body weight and LBM, because in obesity whole body protein synthesis was found to be normally stimulated by hyperaminoacidemia during insulin infusion (16). Furthermore, we found no correlation between either body weight or estimated LBM and albumin FSR in a large series of observations (unpublished observations). In regard to body composition, we acknowledge that neither Hume’s method (14) nor DEXA (17) may be accurate enough to measure LBM in cirrhosis because of a possible shift of body water from intracellular to extracellular space(s) (10, 19), even in the absence of clinically and instrumentally demonstrable edema and ascites. Nevertheless, this uncertainty may affect only the absolute values of leucine kinetics but not albumin FSR or the relative changes vs. basal of both albumin and whole body protein kinetics.

A key issue is that of the validity of the use of KIC SA as the precursor pool of albumin synthesis also in cirrhosis. Theoretically, a decreased liver protein degradation in cirrhosis could increase the intrahepatic leucine SA locally and lead to an underestimation of albumin FSR, which could be interpreted as decreased synthesis. Only the measurement of intrahepatic leucyl tRNA could address this issue. However, such a measurement is clearly unfeasible in humans, for both ethical and technical reasons. As a matter of fact, limitations of current methods to measure albumin synthesis in vivo both in healthy and diseased states should be kept in mind.

Leucine Rₜ increased postprandially in both groups as a result of meal ingestion. Whether this increase was proportional to the leucine ingested with the meal cannot be established from our data, because no oral amino acid tracer was administered. For the same reason, neither first-pass leucine splanchnic uptake nor leucine Rₜ from endogenous protein breakdown could be accurately determined. However, these issues had been previously investigated by use of combined oral and intravenous isotope administrations (34).

Although either early or late anabolic effects might have been missed in the patients during the 4-h meal administration, these possibilities seem unlikely. Indeed, both whole body protein and albumin kinetics exhibit quite slow patterns (8, 9, 20, 37), i.e., it would be surprising if a brisk stimulation of protein synthesis occurred in cirrhosis early after the start of feeding and before the chosen sampling times. On the other hand, an impaired and/or delayed meal absorption cannot entirely be ruled out in the patients. Nevertheless, the near-elementary composition of the liquid meal, as well as the adequate increase of both amino acid concentrations and leucine oxidation in the patients postprandially, makes this possibility rather unlikely.

The patients’ nearly normal fasting plasma leucine concentration is in agreement with previous (15, 18), although not all, reports (23, 24, 39). These variances might depend on the patients’ weight, body composition, and clinical/nutritional status, as well as on insu-
lin resistance and/or concentration, because BCAA levels are very sensitive to insulin action (9, 28, 35). Thus the patients’ nearly normal BCAA levels may be accounted for by their mild fasting hyperinsulinemia.

In conclusion, a mixed meal ingestion did not acutely stimulate either albumin or whole body protein synthesis in stable cirrhotic patients as opposed to healthy control subjects. The mechanism(s) underlying these abnormalities need to be further investigated.

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