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Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study[1–3]

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ABSTRACT

Background: Data describing the nutritional status of patients with liver cirrhosis of diverse origin, as assessed by direct body-composition methods, are limited.

Objective: We sought to provide a comprehensive assessment of nutritional status and metabolic activity in patients with liver cirrhosis by using the most accurate direct methods available.

Design: Two hundred sixty-eight patients (179 M, 89 F; $\bar{x} \pm$ SEM age: 50.1 $\pm$ 0.6 y) with liver cirrhosis underwent measurements of total body protein by neutron activation analysis, of total body fat and bone mineral by dual-energy X-ray absorptiometry, of resting energy expenditure by indirect calorimetry, of grip strength by dynamometry, and of respiratory muscle strength by using a pressure transducer. Dietary intakes of energy and protein were assessed and indexed to resting energy expenditure and energy intake, respectively.

Results: Significant protein depletion, seen in 51% of patients, was significantly ($P < 0.0001$) more prevalent in men (63%) than in women (28%). This sex difference occurred irrespective of disease severity or origin. The prevalence of protein depletion increased significantly ($P < 0.0001$) with disease severity. Protein depletion was associated with decreased muscle function but not with lower energy and protein intake. Energy intake was significantly ($P = 0.002$) higher in men than in women, whereas protein intakes did not differ significantly ($P = 0.12$). Hypermetabolism, seen in 15% of patients, was not associated with sex, origin or severity of disease, protein depletion, ascites, or presence of tumor.

Conclusions: Poor nutritional status with protein depletion and reduced muscle function was a common finding, particularly in men, and was not related to the presence of hypermetabolism or reduced energy and protein intakes. The greater conservation of protein stores in women than in men warrants further investigation. *Am J Clin Nutr* 2007;85:1257–66.

KEY WORDS Liver disease, nutritional status, protein depletion, energy expenditure, body composition, neutron activation, dual-energy X-ray absorptiometry, muscle function, dietary intake

INTRODUCTION

Protein-energy malnutrition (PEM) is common in chronic liver disease because of a variety of factors including poor dietary intake, malabsorption, increased intestinal protein losses, decreased hepatic protein synthesis, abnormal substrate utilization, and hypermetabolism (1). In these patients, PEM is associated with an increased risk of complications, including variceal bleeding, ascites, encephalopathy, and hepatorenal syndrome (2, 3), and it independently predicts patient survival (4–6).

Despite its importance, PEM is often underdiagnosed in cirrhosis patients, particularly in the early stages of disease (7). The cachexia of liver disease often develops insidiously and can be masked by edema. In addition, the conventional parameters used to assess nutritional status are frequently altered in these patients by factors other than the nutritional factors related to the underlying cirrhosis (8–11). For instance, impaired hepatic synthetic function invalidates the use of visceral proteins (12). Although widely used, upper-arm anthropometric measures such as mid-arm muscle circumference (MAMC) may be affected by edema (13), and the reliability of such measures in individual subjects is questionable. Several studies have shown that 20–30% of healthy controls would be considered undernourished according to the standards in common use for MAMC (14, 15). Similarly, tissue edema and ascites can affect the accuracy of body-composition measurement by bioimpedance analysis (16–18).

A primary component of the assessment of nutritional status is the measurement of muscle or protein depletion. Protein represents a key structural and functional component of the body, and loss of body protein is associated with loss of function (19, 20). The technique of in vivo neutron activation analysis (IVNAA) is the gold standard for measurement of protein depletion. To date, the only published studies using this approach in cirrhosis patients are those by Prijatmoko et al (21) in alcoholic males and by Plank et al (22) in patients before elective liver transplantation.

We present in this report comprehensive data on body composition, metabolic activity, functional status, and dietary intake in a large, heterogeneous group of patients with liver cirrhosis. We used the most accurate direct measurement methods available, including IVNAA and dual-energy X-ray absorptiometry (DXA), and correlated the findings with severity of liver disease, sex, disease origin, and malnutrition.

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SUBJECTS AND METHODS

Subjects

Patients (aged >16 y) who had established liver cirrhosis were included in this cross-sectional study conducted between February 1998 and October 2003. The diagnosis of cirrhosis was based on clinical, laboratory, and radiologic evidence or liver histologic tests. Patients underwent assessments as part of ongoing nutritional studies in the Department of Surgery, University of Auckland. Severity of liver disease was assessed according to the Child-Pugh score (23). Patients underwent body composition, energy expenditure and physiologic function measurements in a dedicated unit within the Department of Surgery.

All patients gave written informed consent. These studies were approved by the Auckland Regional Ethics Committee.

Body composition

Anthropometry

Body weight was recorded to the nearest 0.1 kg by using a beam balance, and adjustment was made for the estimated weight of clothing. Height was measured by using a stadiometer and was used to calculate body mass index (BMI; in kg/m^2).

Total body nitrogen

Total body nitrogen was measured by prompt gamma IVNAA (24) with a precision of 2.7% (25) and an accuracy of within 4% (26) (based on anthropomorphic phantoms). Total body protein (TBP) was calculated as 6.25 times total body nitrogen. For each patient, a preillness TBP was estimated on the basis of height, sex, age and preillness body weight by using equations developed in our laboratory from measurements of 386 healthy volunteers (163 M, 223 F; age range: 17–82 y) (22). Preillness weight was that recalled by the patient (confirmed if possible by a family member or clinical records), which provides a more accurate estimate of the patient's weight when the patient was well than does the weight predicted from published tables (27). For the healthy control subjects, protein index (PI) was 1.00 ± 0.09 in both sexes. Significant protein depletion was defined as PI < 0.82 or 2 SDs below the mean PI for the controls.

Total body fat and bone mineral

Total body fat (TBF), bone mineral content (BMC) and bone mineral density (BMD) were measured by DXA (model DPX+, software version 3.6y, extended research analysis mode; Lunar Radiation Corp, Madison, WI). Using anthropomorphic phantoms of known fat content and with different levels of overhydration, the precision of the technique for TBF was 1.3% and the accuracy was within 5% (26). The precision for BMC and BMD based on repeated measurements of healthy subjects has been reported as 1% and 0.6%, respectively, by using the current software version (28). BMD is an areal density calculated by dividing BMC by the projected area of the skeleton measured from the same DXA scan. BMD was divided by height to provide a measure of volumetric density that is independent of frame size (29).

Total body water

Total body water (TBW) was derived from the IVNAA and DXA results by using a difference method that assumes a 6-compartment model for the body and that is described in detail elsewhere (30). Briefly, TBW equals the difference between body weight and the sum of TBP, TBF, BMC, nonbone minerals, and glycogen. The small nonbone mineral and glycogen compartments are estimated from TBP and total minerals, respectively, on the basis of the sizes of these compartments in the Reference Man (31). Error propagation calculations suggest that precision close to 1% may be achieved for TBW derived by this method with accuracy better than 3%. For each patient, as a measure of hydration status, a hydration index was derived as the ratio of TBW to fat-free mass (FFM), in which the latter is calculated as body weight minus TBF. Significant overhydration was defined as hydration index > 0.76, which represents 2 SDs above the mean (0.73) for the distribution of this variable in the 229 healthy volunteers undergoing the measurements described above.

Resting energy expenditure

Resting energy expenditure (REE) was measured by using open-circuit indirect calorimetry (Deltatrac Metabolic Monitor; Datex Instruments, Helsinki, Finland) ≥4 h after a meal and after a rest period of ≥30 min. For each patient, a predicted REE (REE_{pred}) was calculated by using the following equation, developed from measurements of 80 healthy volunteers in our department (22):

$$REE_{pred}\ (kcal/d) = 16.85 \times FFM_{corr} + 725 \quad (SEE = 174\ kcal/d;\ r^2 = 0.52) \quad (1)$$

where FFM_{corr} is the fat-free mass (in kg) of the patient corrected for abnormal hydration, as derived below, and SEE is the SE of the estimate. Hypermetabolism was defined as a ratio of REE to REE_{pred} ($REE:REE_{pred}$) >1.22, which represents 2 SDs above unity for the distribution of this ratio in the 80 volunteers. Hypermetabolic patients were also identified according to a ratio of REE to REE_{HB} ($REE:REE_{HB}$) >1.20, in which REE_{HB} was derived from the equations of Harris and Benedict (32).

Derivation of hydration-corrected fat-free mass

The measured FFM is made up of the FFM_{corr} that contains water (TBWc) at normal hydration plus a component that represents the deviation of measured TBW from the water that accompanies FFM_{corr} (ie, TBW − TBWc). This could be calculated as in the following equation:

$$FFM = FFM_{corr} + TBW - TBWc \quad (2)$$

This equation can be rearranged as follows:

$$FFM_{corr} = FFM\ (1 - TBW/FFM)/(1 - TBWc/FFM_{corr}) \quad (3)$$

where $TBWc:FFM_{corr}$ is the ratio of TBW to FFM in healthy subjects (ie, 0.73).

Dietary intake

Dietary energy and macronutrient intakes based on a comprehensive dietary recall (33) were assessed in each patient by a dietitian. Nutrient analysis was performed by using

TABLE 1
Demographic and clinical characteristics of 268 patients with cirrhosis grouped by Child-Pugh grade[1]

	All (n = 268)	Group A (n = 92)	Group B (n = 95)	Group C (n = 81)	P[2]
M/F	179/89	67/25	54/41	58/23	0.037
Age (y)	50.1 ± 0.6[3]	49.8 ± 1.0	49.7 ± 1.1	50.7 ± 1.1	0.77
Weight (kg)	76.9 ± 1.0	77.7 ± 1.6	74.8 ± 1.7	78.4 ± 1.6	0.28
BMI (kg/m^2)	26.9 ± 0.3	26.7 ± 0.5	26.8 ± 0.6	27.4 ± 0.5	0.67
Etiology					0.001
Viral[4]	150 (56)[5]	66[6]	47	37	—
ALD	43 (16)	8	13	22	—
Cholestatic	28 (10)	6	15	7	—
Other[7]	47 (18)	12	20	15	—
HCC	48 (18)	24	14	10	0.043
Ascites	93 (35)	1	26	66	<0.0001

[1] ALD, alcoholic liver disease; HCC, hepatocellular carcinoma.
[2] Comparison of groups A, B, and C by Fisher's exact test or one-factor ANOVA.
[3] $\bar{x}$ ± SEM (all such values).
[4] n = 77, 71, and 2 for hepatitis B, hepatitis C, and hepatitis B and C, respectively.
[5] n; % in parentheses (all such values).
[6] n (all such values).
[7] Comprises nonalcoholic steatohepatitis, cryptogenic cirrhosis, autoimmune cirrhosis, sarcoidosis, cirrhosis secondary to cystic fibrosis, Wilson disease, biliary atresia, methotrexate-induced cirrhosis, hemochromatosis, and Budd-Chiari syndrome.

FOODWORKS software (version 3.02; Xyris Software, Highgate Hill, Australia), which is based on the New Zealand food composition database.

Physiologic function

Grip strength

Voluntary handgrip strength was measured in the dominant hand by using a dynamometer (model 78010; Lafayette Instrument Co, Lafayette, IN). Patients with arthritis or other secondary diseases that could affect grip strength were excluded. The best of 3 consistent attempts was recorded, allowing a recovery of ≥1 min between attempts. Sex, age, and height are the major determinants of grip strength (34, 35), and adjustment for these variables allowed comparative assessment between groups of patients.

Respiratory muscle strength

Respiratory muscle strength (RMS) was calculated as the average of 2 values: the maximal inspiratory pressure measured at functional residual lung capacity after maximal expiration and the maximal expiratory pressure at total lung capacity after maximal inspiration. Pressures were measured as the best of 3 consistent readings with a bidifferential pressure transducer (Validyne Engineering Corp, Northridge, CA). Pressures had to be maintained for ≥1 s, and a small leak was introduced in the circuit to prevent falsely high readings due to the contraction of cheek muscles. Patients with active lung disease—eg, exacerbation of obstructive airways disease—or who had clear difficulty with technique were excluded. For comparison between patient groups, RMS was adjusted for sex, age, and height (36, 37).

Statistical analysis

Two-factor analysis of variance (ANOVA) was used to test for significant pairwise interaction effects between sex, disease origin, and Child-Pugh grade. Tukey's multiple-comparison procedure was used to test for significant differences between individual means if significant interaction effects were found, or, if no significant interaction effects were found, to test for significant differences between levels of each factor. For simple comparison between 2 groups, Student's t test was used. Covariance analysis was used to adjust the mean differences between measured and preillness TBP for comparison by sex and to adjust the means for TBP and REE for comparison between Child-Pugh groups. Bivariate associations were examined by using Pearson or Spearman rank correlation coefficients, as appropriate, and, for categorical data, Fisher's exact test. In all cases, the 5% level was chosen for statistical significance. Statistical analysis was carried out with SAS software (version 8.02; SAS Institute, Cary, NC). Results are expressed as mean ± SEM unless otherwise stated.

RESULTS

Subjects

A total of 268 patients (179 M, 89 F) were studied; the cohort comprised 167 Europeans, 51 Asians, 42 Maori and Pacific Islanders, and 8 of other ethnicity. Patient characteristics are summarized in **Table 1**. Mean age for men was 50.0 ± 0.7 (range: 20–71) y and that for women was 50.3 ± 1.2 (23–73) y. Hepatocellular carcinoma (HCC) was present in 48 patients (18%), 41 of whom had viral cirrhosis. Clinical or radiologic evidence of ascites was present in 93 patients (35%). All patients were clinically stable at the time of assessment. The median Child-Pugh score was 8 (range: 5–14), and the number and proportion of patients within each Child-Pugh grade was 92 (34%), 95 (36%), and 81 (30%) in grade A, B, and C, respectively. The distribution of patients among groups according to disease origin varied with Child-Pugh grade (P = 0.001, Table 1) and sex (P < 0.0001). In grade A, the origin of disease in 72% of the patients was viral and that in 9% was alcoholic, whereas, in grade C, the origin of disease in 46% was viral and that in 27% was alcoholic. Disease origin was predominantly viral (64%) in men, in whom 7% of disease was cholestatic, 18% was alcoholic, and 11% was other,

whereas the respective proportions in women were 39%, 18%, 13%, and 30%.

Body-composition measurements

The mean ± SEM data for preillness and measured body weight and TBP, TBW, TBF, BMC, and BMD of both men and women are shown in **Table 2**.

Protein

The distribution of PI for the 268 patients is compared with that for the 386 healthy volunteers in **Figure 1**. TBP for the patients averaged 82.5 ± 0.7% of predicted normal body protein. Significant protein depletion (PI < 0.82) was seen in 138 (51%) patients; 113 (63%) of this group were men, and 25 (28%) were women ($P < 0.0001$). Mean PI was significantly lower in group C patients than group B ($P = 0.0002$) and group A ($P < 0.0001$) patients. In group C, 72% of patients were protein depleted, compared with 43% in group B and 42% in group A ($P < 0.0001$). The increase in protein depletion with rising Child-Pugh grade, as evident by the PI, was also apparent when TBP was compared across the Child-Pugh grades after adjustment for FFM_{corr}: the adjusted TBP was significantly lower in group C patients than in group B ($P = 0.0015$) or group A ($P < 0.0001$) patients.

When compared with values in the healthy vounteers, the distributions of TBP in both male and female cirrhosis patients were shifted toward lower values (**Figure 2**). Male group C patients had lower TBP than did male group A patients, whereas, in women, TBP did not differ between the 3 Child-Pugh groups. Men had higher TBP than women, but their PI was significantly lower ($P < 0.0001$). The mean difference between preillness and measured TBP was 2.52 ± 0.10 kg for men (20% reduction in TBP) and 0.98 ± 0.10 kg for women (11% reduction; $P < 0.0001$). After adjustment of these means for the higher preillness TBP in men, a significant difference remained (2.23 ± 0.11 compared with 1.55 ± 0.18 kg; $P = 0.005$). The inclusion of TBF as an additional covariate eliminated the difference in the adjusted means (2.09 ± 0.12 compared with 1.84 ± 0.21 kg; $P = 0.39$). As shown in **Figure 3**, PI was consistently lower in men than in women across Child-Pugh grades and disease-origin groups. Patients with alcoholic liver disease (ALD) were significantly ($P < 0.0001$) more protein depleted than were patients with viral cirrhosis, cholestatic disease, or other diseases.

Fat

Women with cirrhosis had significantly higher percentage body fat (%BF) than did men, and this difference was consistent within Child-Pugh grades and disease-origin groups. The %BF was significantly ($P < 0.05$) lower in group C than in group A. There were no significant differences between disease-origin groups. The %BF did not differ significantly between patients with and without significant protein depletion (**Table 3**).

Bone mineral

No significant differences were found in total body BMD or in the ratio of BMD to height (BMD:height) between Child-Pugh groups or between disease-origin groups. Men had a significantly higher total body BMD than did women ($P < 0.0001$), but BMD:height did not differ significantly between the sexes ($P = 0.87$). BMD:height (with or without age adjustment) tended to be lower in patients with significant protein depletion than in those without ($P = 0.05$). BMD:height (adjusted for age) was significantly lower for both male ($P = 0.0006$) and female ($P = 0.020$) subjects than for the healthy volunteers. The data for BMD:height were not shown.

Water

Of the 268 patients, 174 (65%) were overhydrated. Hydration index was positively correlated with Child-Pugh score ($r = 0.41$, $P < 0.0001$) and negatively correlated with PI ($r = -0.54$, $P < 0.0001$). The mean hydration index for group A patients (0.757 ± 0.002) was significantly ($P < 0.0001$) lower than that for group B (0.773 ± 0.002) or group C (0.781 ± 0.002) patients. Hydration indexes for patients with and without ascites were 0.783 ± 0.003 and 0.763 ± 0.001, respectively, and those for patients with and without significant protein depletion were 0.779 ± 0.002 and 0.760 ± 0.002, respectively ($P < 0.0001$ for both). In the protein-depleted group, 47% had ascites; in the group without protein depletion, 22% had ascites ($P < 0.0001$).

Resting energy expenditure

Measured REE did not differ between Child-Pugh grades (Table 2). After adjustment for FFM_{corr}, REE was significantly higher in group B than in group A, and group C had an intermediate value. Forty-one patients (27 M, 14 F; 15%) were hypermetabolic. Hypermetabolism was not associated with sex ($P = 0.86$), severity of disease ($P = 0.17$), disease origin ($P = 0.27$), protein depletion ($P = 0.61$), or the presence of tumor ($P = 0.99$) or ascites ($P = 0.59$). With the use of the Harris-Benedict prediction equations, 22 (8%) patients were identified as hypermetabolic; 20 of this group were hypermetabolic according to the FFM prediction equation.

Dietary intake

Energy and protein intakes were obtained for 239 patients (Table 2). As a proportion of REE, energy intake was significantly higher in men than in women, and it decreased with increasing severity of disease. No significant differences ($P = 0.49$) were found in daily energy intake (as a proportion of REE) between disease-origin groups. Dietary protein intake expressed as a proportion of energy intake did not differ significantly between men and women, or between Child-Pugh grades or disease-origin groups. Neither energy (as a proportion of REE) nor protein intake (as a proportion of energy intake) differed significantly between patients with significant protein depletion and those without (Table 3). Conversely, patients with energy intake < 1.2 REE were not more protein depleted than were those with energy intakes ≥1.2 REE ($P = 0.99$; data not shown).

Muscle function

Grip strength measurements were obtained in 256 patients (Table 2). Grip strength was lower for male group B and C patients than for male group A patients, whereas no difference in grip strength was seen in women across the severity groupings. After adjustment for age and height, the same patterns were observed ($P = 0.008$ for men and 0.99 for women). Adjusted grip strength differed significantly between patients with viral cirrhosis (33.9 ± 0.8 kg) and those with ALD (28.1 ± 1.4 kg; $P = 0.0004$), cholestatic liver disease (28.6 ± 1.5 kg; $P = 0.002$) and other (28.7 ± 1.3 kg; $P = 0.0004$). In both men and women,

TABLE 2
Results of body-composition, energy expenditure, dietary intake, and muscle function measurements in men and women with liver cirrhosis grouped by Child-Pugh grade

						P^1		
	Sex (*n*)	All	Group A	Group B	Group C	Sex	Grade	Sex × grade
Body weight								
Body weight before illness (kg)	M (179)	82.5 ± 1.1[2]	82.6 ± 1.9	80.7 ± 2.1	84.2 ± 1.9	0.0003	0.012	0.17
	W (89)	73.7 ± 1.9	70.9 ± 3.6	70.7 ± 2.5[3]	82.1 ± 4.2			
Body weight (kg)	M (179)	79.7 ± 1.1	81.0 ± 1.7	78.6 ± 2.4	79.3 ± 1.9	<0.0001	0.40	0.26
	W (89)	71.1 ± 1.6	68.9 ± 3.2	69.9 ± 2.3	75.7 ± 3.1			
Body composition								
Body protein before illness (kg)	M (179)	12.27 ± 0.11	12.41 ± 0.19	12.11 ± 0.21	12.29 ± 0.20	<0.0001	0.084	0.12
	W (89)	8.37 ± 0.14	8.12 ± 0.27	8.15 ± 0.17	9.05 ± 0.29			
Total body protein (kg)	M (179)	9.76 ± 0.13	10.29 ± 0.20	9.65 ± 0.27	9.26 ± 0.22[3]	<0.0001	0.39	0.056
	W (89)	7.39 ± 0.15	7.29 ± 0.27	7.34 ± 0.18	7.61 ± 0.39			
Prevalence of protein depletion (%)	M (179)	63	51	59	81	0.003	0.008	—
	W (89)	28	20	22	48			
Fat-free mass (kg)	M (179)	60.3 ± 0.7	59.1 ± 1.0	60.9 ± 1.4	61.1 ± 1.2	<0.0001	0.015	0.25
	W (89)	44.9 ± 0.8	42.0 ± 1.5	44.6 ± 1.0	48.6 ± 1.8			
Corrected fat-free mass (kg)	M (179)	50.6 ± 0.6	52.8 ± 1.0	50.2 ± 1.1	48.9 ± 1.0	<0.0001	0.61	0.084
	W (89)	38.8 ± 0.9	38.1 ± 1.6	38.2 ± 1.2	40.2 ± 1.6			
Total body water (L)	M (179)	46.6 ± 0.6	44.8 ± 0.8	47.3 ± 1.1	47.9 ± 1.0	<0.0001	0.0005	0.28
	W (89)	34.4 ± 0.7	31.7 ± 1.1	34.2 ± 0.8	37.7 ± 1.5			
Prevalence of overhydration (%)	M (179)	69	46	81	84	0.086	0.047	—
	W (89)	57	40	61	70			
Total body fat (kg)	M (179)	19.4 ± 0.7	21.9 ± 1.1	17.7 ± 1.3	18.2 ± 1.1	<0.0001	0.17	0.47
	W (89)	26.2 ± 1.2	26.9 ± 2.1	25.3 ± 1.7	27.2 ± 2.6			
Total body fat (% of body wt)	M (179)	23.5 ± 0.6	26.3 ± 0.9	21.3 ± 1.1	22.4 ± 1.0	<0.0001	0.005	0.76
	W (89)	35.7 ± 1.0	37.9 ± 1.6	34.8 ± 1.4	34.8 ± 2.4			
Bone mineral content (kg)	M (179)	2.87 ± 0.03	2.86 ± 0.05	2.85 ± 0.07	2.91 ± 0.06	<0.0001	0.12	0.53
	W (89)	2.23 ± 0.04	2.19 ± 0.07	2.17 ± 0.06	2.39 ± 0.09			
Bone mineral density (g/cm^2)	M (179)	1.18 ± 0.01	1.16 ± 0.01	1.17 ± 0.02	1.20 ± 0.01	<0.0001	0.27	0.98
	W (89)	1.10 ± 0.01	1.09 ± 0.02	1.09 ± 0.02	1.11 ± 0.02			
Energy expenditure								
Predicted resting energy expenditure (kcal/d)	M (179)	1578 ± 10	1614 ± 17	1571 ± 19	1549 ± 18	<0.0001	0.50	0.23
	W (89)	1372 ± 15	1367 ± 28	1367 ± 22	1381 ± 29			
Resting energy expenditure (kcal/d)	M (179)	1662 ± 23	1660 ± 37	1715 ± 47	1614 ± 38	<0.0001	0.13	0.24
	W (89)	1414 ± 27	1323 ± 51	1453 ± 37	1447 ± 54			
Adjusted resting energy expenditure (kcal/d)[4]	M (179)	1568 ± 18	1517 ± 29	1632 ± 31	1561 ± 29	0.38	0.003	0.72
	W (89)	1606 ± 28	1524 ± 47	1653 ± 38	1627 ± 48			
Prevalence of hypermetabolism (%)	M (179)	15	12	19	16	0.18	0.72	—
	W (89)	16	4	20	22			
Nutrition								
Energy intake (kcal/d)	M (157)	2070 ± 52	2198 ± 80	2138 ± 108	1853 ± 78	<0.0001	0.020	0.74
	W (82)	1516 ± 47	1599 ± 77	1535 ± 76	1389 ± 90			
Energy intake/resting energy expenditure	M (157)	1.26 ± 0.03	1.33 ± 0.05	1.27 ± 0.06	1.16 ± 0.05	0.0015	0.005	0.67
	W (82)	1.09 ± 0.03	1.23 ± 0.05	1.07 ± 0.05	0.99 ± 0.07			
Protein intake (g)	M (157)	86.1 ± 2.5	89.7 ± 3.9	93.3 ± 4.9	75.0 ± 4.1	<0.0001	0.051	0.30
	W (82)	66.3 ± 2.2	66.1 ± 3.7	68.0 ± 3.3	63.6 ± 4.8			
Protein intake (% of energy intake)	M (157)	16.9 ± 0.4	16.6 ± 0.6	17.9 ± 0.8	16.2 ± 0.6	0.12	0.11	0.34
	W (82)	18.0 ± 0.5	16.7 ± 0.7	18.5 ± 0.9	18.6 ± 1.0			
Muscle strength								
Grip strength (kg)	M (171)	37.7 ± 0.8	41.2 ± 1.1	36.2 ± 1.3[3]	35.1 ± 1.4[3]	<0.0001	0.21	0.045
	W (85)	23.4 ± 0.8	22.8 ± 1.8	23.4 ± 1.0	24.1 ± 1.5			
Respiratory muscle strength (cm H_2O)	M (159)	94.0 ± 2.5	98.8 ± 4.0	96.8 ± 4.8	84.3 ± 3.9	<0.0001	0.027	0.84
	W (71)	59.2 ± 2.8	59.9 ± 4.8	63.6 ± 4.6	50.1 ± 3.9			

[1] Two-factor ANOVA (arcsin square root transformation was applied for prevalence data).
[2] $\bar{x}$ ± SEM (all such values).
[3] Significantly different from group A men, $P < 0.05$ (Tukey's test).
[4] Adjusted for fat-free mass corrected to normal hydration.

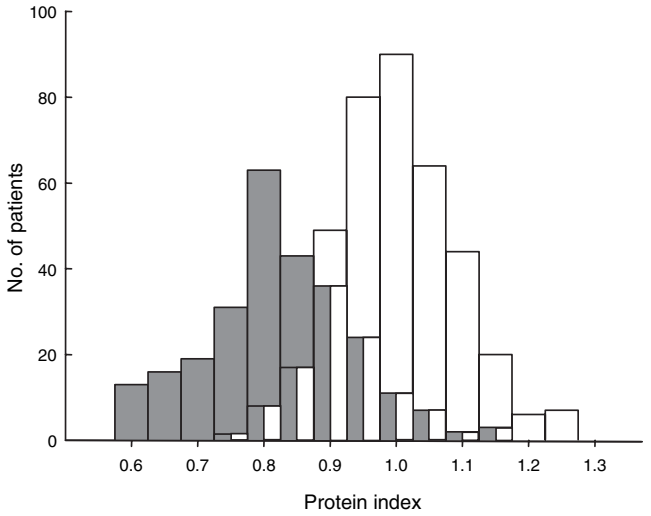

FIGURE 1. Distribution of protein index (ratio of measured to estimated preillness total body protein) in 268 patients with liver cirrhosis (■) compared with that in 386 healthy volunteers (□).

measured and adjusted grip strengths were significantly lower in patients with protein depletion than in those without (Table 3).

RMS was measured in 230 patients (Table 2). It was significantly ($P < 0.05$) lower in group C patients than in group A patients. After adjustment for age and height, changes in RMS did not differ significantly ($P = 0.14$) between Child-Pugh grades. Adjusted RMS varied with disease origin; it was significantly higher in patients with viral cirrhosis (84 ± 3 cm H_2O) than in those with ALD (69 ± 6 cm H_2O; $P = 0.021$) or other diseases (67 ± 4 cm H_2O; $P = 0.001$), and the values for cholestatic liver disease were intermediate (75 ± 6 cm H_2O). RMS (measured or adjusted) was significantly lower in patients with protein depletion than in those without (Table 3).

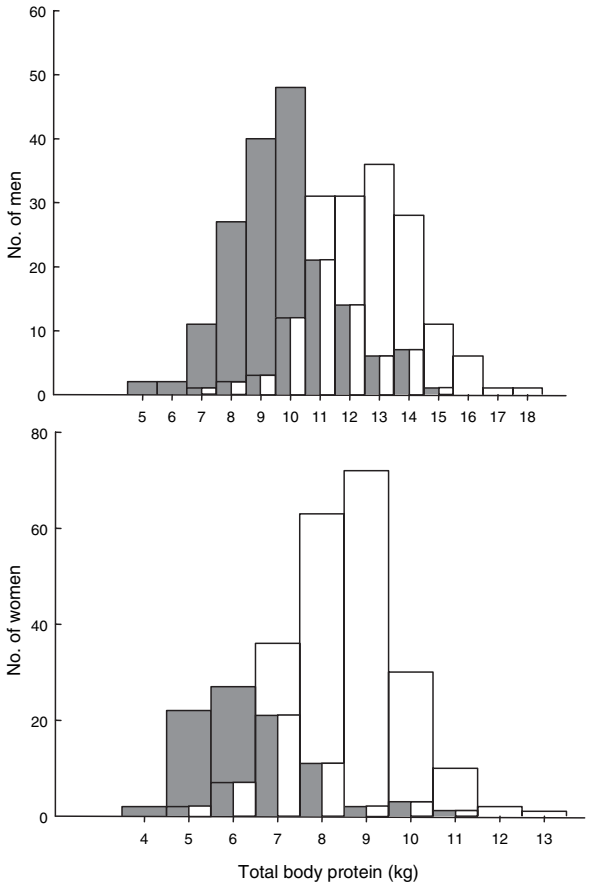

FIGURE 2. Distribution of total body protein in 179 male and 89 female liver cirrhosis patients (■) compared with that in 163 male and 223 female healthy volunteers (□).

DISCUSSION

We report the largest single-center study to comprehensively assess body composition by using state-of-the-art techniques and to evaluate energy metabolism and muscle function in patients with liver cirrhosis according to disease severity, disease origin, and sex.

Sex differences

A key finding of our study was the relative conservation of protein stores in women; 28% of the women had significant protein depletion, compared with 63% of the men. On average, men had lost 20% and women had lost 11% of their body protein stores. This marked sex difference occurred irrespective of disease severity or origin. Other groups have reported, on the basis of measurements of muscle and fat by anthropometry, that the characteristics of tissue loss differ in men and women with cirrhosis, with men having more muscle depletion and women having more fat depletion (4, 5, 9, 10, 38). This sex difference in muscle depletion is shown for the first time through direct measurement of TBP. Our results indicate that the much higher preillness muscle stores found in men than in women do not adequately account for the men's greater loss of muscle. However, adjustment for the greater fat stores in women, even in advanced stages of liver disease, accounts for the differential loss of muscle mass, which supports the assertion that preservation of muscle mass in women is related to their greater fat stores (38). Adjustment for measured fat mass alone does not account for the difference in protein depletion.

Other factors may contribute to the sex difference in patterns of tissue loss. Sex hormone alterations in advanced liver disease that result in feminization, hypogonadism, and gynecomastia in men with cirrhosis may play a role (4, 39). Few data comparing endocrinologic variables between men and women with chronic liver disease are available. It is not clear whether the hyperinsulinemia and resistance to the actions of growth hormone and insulin, all characteristic of advanced cirrhosis (40), are sex dependent. Nikolic et al (41) did not find any sex differences in plasma concentrations of insulin-like growth factor I and II in cirrhosis patients. Serum leptin concentrations were reported to be higher in women than in men with alcoholic cirrhosis (42). However, for nonalcoholic liver disease, current data are conflicting (43).

A better dietary intake by women than by their male counterparts could contribute to the more favorable TBP status of women. Our data suggest, however, that this is not the case: the men achieved higher energy intakes than did the women, whereas the protein intakes did not differ significantly between the sexes. We did not, however. measure physical activity levels or total energy expenditure, so that overall energy balance cannot be compared. Hypermetabolism, which may contribute to negative energy balance, was not more prevalent in men than in women.

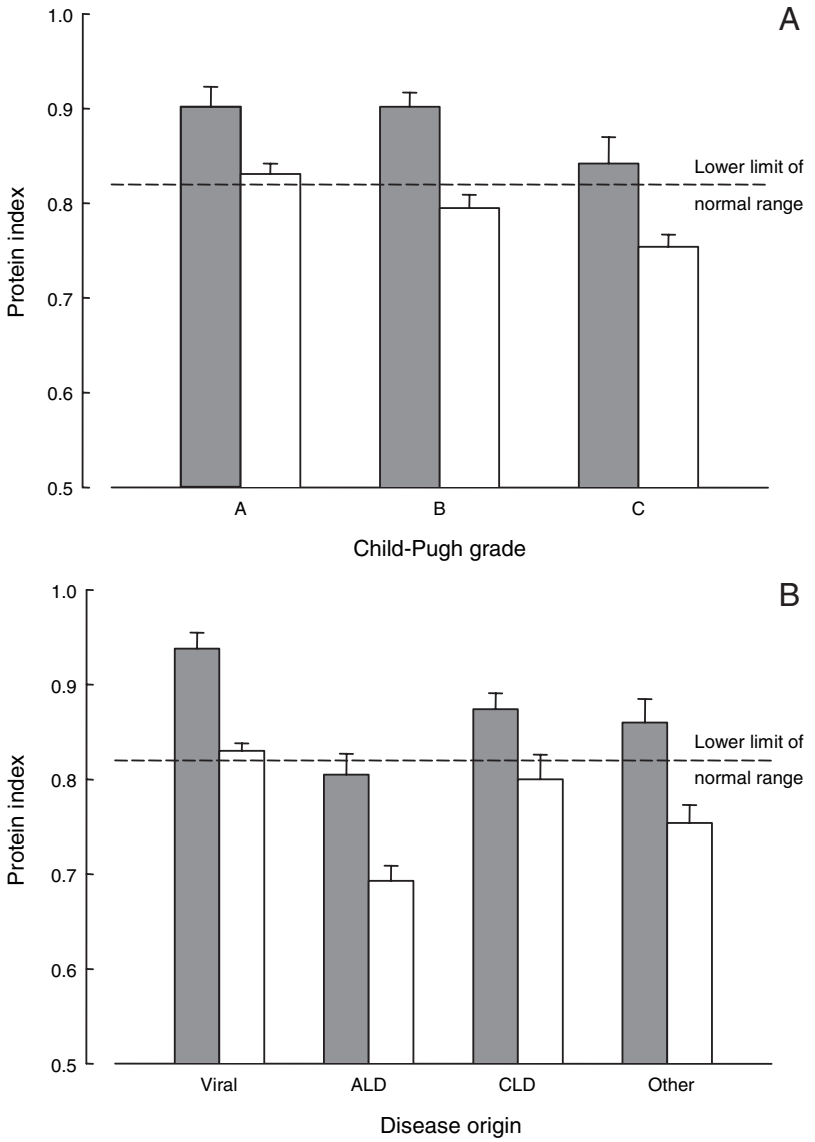

FIGURE 3. Mean (±SEM) protein index (ratio of measured to estimated preillness total body protein) in 179 men (□) and 89 women (■) with liver cirrhosis. - - -, the lower 2-SD limit of protein index for healthy controls. A: patients grouped according to severity of liver disease as assessed by Child-Pugh grade. $P = 0.49$ for grade × sex interaction, $P = 0.003$ for grade effect, and $P < 0.0001$ for sex effect (2-factor ANOVA for all). B: patients grouped according to disease origin [alcoholic liver disease (ALD), cholestatic liver disease (CLD)]. $P = 0.87$ for disease origin × sex interaction, $P < 0.0001$ for disease origin effect, and $P < 0.0001$ for sex effect (2-factor ANOVA for all).

Hypermetabolism

In the patient group in the current study, the prevalence of hypermetabolism was 15%. We predicted REE by using FFM_{corr}. Others have observed that subgroups of cirrhosis patients were hypermetabolic (44–48), but the reported prevalence has varied widely. Direct comparison of these studies is difficult because of the wide range of approaches used to identify hypermetabolic patients. In the largest study to date, Müller et al (44) found that 34% of patients were hypermetabolic and had an REE >120% of that predicted by the Harris-Benedict equations. We found that only 8% of our patients were hypermetabolic according to this approach; 90% of these patients were hypermetabolic according to the FFM prediction. Hypermetabolic patients in that group tended to weigh less than the normometabolic patients (5 kg difference, $P = 0.11$), and the hydration of the FFM did not differ significantly ($P = 0.13$) from that in the normometabolic patients. Müller al (44) also found the hypermetabolic group to weigh less than the normometabolic group. In contrast, the hypermetabolic group identified by less deranged body-composition markers had higher measured body weight (9-kg difference; $P = 0.0007$) and hydration of the FFM ($P < 0.0001$) than did the normometabolic patients. Not surprisingly, the Harris-Benedict equations appear to have identified a group of hypermetabolic patients for whom the confounding effects of overhydration were small, so that their body weight provided a more accurate prediction of REE. The use of β-blockade in a significant proportion of our patients also may have contributed to the marked difference in prevalence between the 2 approaches. β-blockade is undoubtedly a confounding factor in interpreting published studies. We found no association between hypermetabolism and protein depletion, but a longitudinal body-composition study is

TABLE 3
Body composition, energy expenditure, dietary intake, and muscle function in men and women with liver cirrhosis with and without significant protein depletion

				P^1		
	Sex (*n*)	Not depleted	Depleted	Sex	Group	Sex × group
Body weight						
Body weight before illness (kg)	M (179)	82.5 ± 2.0[2]	82.5 ± 1.5	0.003	0.079	0.080
	W (89)	71.4 ± 2.0	79.5 ± 3.3			
Body weight (kg)	M (179)	85.0 ± 1.8	76.6 ± 1.4	<0.0001	0.044	0.055
	W (89)	71.2 ± 1.9	71.0 ± 3.0			
Body composition						
Body protein before illness (kg)	M (179)	12.42 ± 0.19	12.20 ± 0.14	<0.0001	0.87	0.38
	W (89)	8.33 ± 0.19	8.48 ± 0.31			
Total body protein (kg)	M (179)	11.15 ± 0.17	8.95 ± 0.13[3]	<0.0001	<0.0001	0.034
	W (89)	7.77 ± 0.18	6.43 ± 0.28[3]			
Total body water (L)	M (179)	48.8 ± 0.9	45.2 ± 0.7	<0.0001	0.086	0.061
	W (89)	34.5 ± 0.9	34.6 ± 1.4			
Fat-free mass (kg)	M (179)	64.2 ± 1.0	58.0 ± 0.8	<0.0001	0.0009	0.057
	W (89)	45.4 ± 1.0	43.7 ± 1.7			
Total body fat (kg)	M (179)	20.8 ± 1.2	18.6 ± 0.9	<0.0001	0.81	0.19
	W (89)	25.8 ± 1.2	27.3 ± 2.0			
Total body fat (% of body wt)	M (179)	23.7 ± 1.0	23.4 ± 0.8	<0.0001	0.41	0.29
	W (89)	35.0 ± 1.1	37.3 ± 1.7			
Energy expenditure						
Resting energy expenditure (kcal/d)	M (179)	1795 ± 35	1584 ± 27	<0.0001	0.0004	0.10
	W (89)	1435 ± 35	1358 ± 58			
Adjusted resting energy expenditure (kcal/d)[4]	M (179)	1546 ± 34	1572 ± 21	0.068	0.083	0.25
	W (89)	1590 ± 31	1690 ± 53			
Nutrition						
Energy intake (kcal/d)	M (157)	2297 ± 91	1944 ± 60	<0.0001	0.010	0.15
	W (82)	1541 ± 54	1441 ± 101			
Energy intake/resting energy expenditure	M (157)	1.30 ± 0.05	1.23 ± 0.04	0.002	0.62	0.47
	W (82)	1.09 ± 0.04	1.10 ± 0.07			
Protein intake (g)	M (157)	98.0 ± 4.3	79.5 ± 2.9	<0.0001	0.002	0.16
	W (82)	68.1 ± 2.3	61.2 ± 5.3			
Protein intake (% of energy intake)	M (157)	17.4 ± 0.6	16.6 ± 0.5	0.23	0.27	0.97
	W (82)	18.2 ± 0.6	17.4 ± 1.3			
Muscle strength						
Grip strength (kg)	M (171)	43.8 ± 1.3	34.0 ± 0.8[3]	<0.0001	<0.0001	0.045
	W (85)	24.8 ± 0.9	19.8 ± 1.2[3]			
Adjusted grip strength (kg)[5]	M (171)	42.2 ± 1.0	33.5 ± 0.8[3]	<0.0001	<0.0001	0.028
	W (85)	26.3 ± 1.1	22.6 ± 1.7[3]			
Respiratory muscle strength (cm H_2O)	M (159)	107.8 ± 3.8	85.3 ± 3.0	<0.0001	0.0003	0.17
	W (71)	61.0 ± 3.1	53.1 ± 6.3			
Adjusted respiratory muscle strength (cm H_2O)[5]	M (159)	104.8 ± 3.7	84.7 ± 2.9	<0.0001	0.003	0.14
	W (71)	64.3 ± 4.3	57.3 ± 7.1			

[1] Two-factor ANOVA.
[2] $\bar{x}$ ± SEM (all such values).
[3] $P < 0.05$ for within-sex comparison with nondepleted group (Tukey test).
[4] Adjusted for fat-free mass corrected to normal hydration.
[5] Adjusted for age and height.

needed to confirm whether hypermetabolism contributes to malnutrition.

Protein depletion

Significant protein depletion was present in 51% of our patients. The prevalence of protein depletion increased with disease severity, as defined by Child-Pugh grade. Even in patients with relatively mild liver dysfunction (Child-Pugh grade A), malnutrition was observed in >40%. The disease-origin group with the greatest protein depletion was the patients with ALD, irrespective of Child-Pugh grade. We examined the associations of protein malnutrition with body composition, bone density, function, and dietary intake. Hydration of the FFM was higher in protein-depleted patients than in those without protein depletion. Protein depletion significantly affected bone density, grip strength, and RMS. Energy intake (relative to REE) and protein intake as a percentage of energy intake did not differ between normally nourished and malnourished patients.

The prevalence of PEM in liver disease has varied widely in reports of studies, which have relied mostly on indirect methods of assessment with relatively small samples and a focus on patients with disease of alcoholic origin. Direct assessment of functional tissue loss using neutron activation and whole-body counting for total body potassium has been carried out in men with

alcoholic cirrhosis (21) and in subjects with nonalcoholic cirrhosis (49), respectively. These studies reported increasing tissue loss with worsening liver disease. The more severe liver disease and greater prevalence of malnutrition that we observed in patients with alcoholic cirrhosis than in those without alcoholic cirrhosis have also been reported in other studies (9, 50).

Assessment of muscle wasting in cross-sectional studies of cirrhosis patients is problematic. Appropriate comparison with their healthy counterparts is necessary for both direct and indirect methods. In the current study, we showed the presence of protein depletion in our patients by direct comparison of TBP stores with those in a large group of healthy volunteers and by comparison of measured body protein with that predicted when the patient is well, according to appropriate matching with the healthy volunteers. Increasing protein depletion with worsening disease was evident by comparison of measured and predicted preillness body protein across Child-Pugh grade and by reduction in TBP as a proportion of FFM_{corr}. Without adjustment for "dry" (ie, normally hydrated) weight or FFM, changes in measured body protein may be misleading.

Hydration status

Fluid retention is a well-recognized accompaniment to severe liver disease, and we found that a large proportion of these patients in the current study (64%) were overhydrated; this proportion was almost twice that of the patients with ascites (35%). Greater hydration was associated with more severe liver disease and accounts for the greater hydration seen in ALD patients than in those in other disease-origin groups. The high prevalence of overhydration highlights the importance of predicting energy expenditure in these patients by using equations that do not rely on measurements, such as body weight, that are confounded by fluid accumulation. Measurements of hydration status in this study rely on TBW assessed by using a multicompartment technique. We found good agreement between this approach and an accepted gold standard approach (tritium dilution) for patients with generalized overhydration (30). For patients with ascites, we expect similarly good agreement, given that fat and bone mass measurements by DXA are not seriously perturbed by the presence of ascites (51). The 4-compartment body-composition model based on measurement of total body density, TBW, and bone mineral (52), a widely used reference approach, does not include direct measurement of body protein, which is the principal focus of the current study.

Bone metabolism

Osteopenia is associated with chronic liver disease of both cholestatic (53) and noncholestatic (54, 55) origin. Our results confirm that, across a broad spectrum of liver disease origins, whole-body bone density is lower than that in a healthy population.

Summary

In a large group of patients with liver cirrhosis, who are broadly representative of the population of cirrhosis patients in New Zealand, we found that 50% had significant protein depletion. Men were significantly more protein depleted than were women, regardless of disease severity or origin. Loss of body protein was more prevalent in alcoholic cirrhosis; it increased with greater disease severity and was associated with loss of skeletal muscle function. Protein depletion was not associated with reduced dietary energy and protein intake. Hypermetabolism, which is predictive of survival in patients with viral cirrhosis (45) and in liver posttransplant patients (47), was found in a subgroup of patients. An understanding of the role of sex in the pathogenesis of malnutrition in cirrhosis requires further investigation in a longitudinal setting and more detailed analyses of nutrient intakes and energy requirements than were possible in the present study. Elucidation of the mechanisms underlying the hypermetabolic state may lead to therapeutic interventions with significant clinical benefit.

The authors' contributions were as follows—SP: patient recruitment, collection of data, data analysis, and manuscript preparation; LDP: study design, patient recruitment, data collection, data analysis, and manuscript preparation; JLM: study design, data interpretation, and manuscript preparation; LKG: data collection and manuscript preparation; KM: data collection and manuscript preparation; and EJG: study design, patient recruitment, and manuscript preparation. None of the authors had a personal or financial conflict of interest.

REFERENCES

1. Cabre E, Gassull MA. Nutritional aspects of chronic liver disease. Clin Nutr 1993;12:S52–63.
2. Moller S, Bendtsen F, Christensen E, Henriksen JH. Prognostic variables in patients with cirrhosis and oesophageal varices without prior bleeding. J Hepatol 1994;21:940–6.
3. Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res 1995;19:635–41.
4. Alberino F, Gatta A, Amodio P, et al. Nutrition and survival in patients with liver cirrhosis. Nutrition 2001;17:445–50.
5. Caregaro L, Alberino F, Amodio P, et al. Malnutrition in alcoholic and virus-related cirrhosis. Am J Clin Nutr 1996;63:602–9.
6. Kalman DR, Saltzman JR. Nutrition status predicts survival in cirrhosis. Nutr Rev 1992;54:217–9.
7. Cabre E, Gassull MA. Nutrition in chronic liver disease and liver transplantation. Curr Opin Clin Nutr Metab Care 1998;1:423–30.
8. Hehir DJ, Jenkins RL, Bistrian BR, Blackburn GL. Nutrition in patients undergoing orthotopic liver transplant. JPEN J Parenter Enteral Nutr 1985;9:695–700.
9. Nutritional status in cirrhosis. Italian Multicentre Cooperative Project on Nutrition in Liver Cirrhosis. J Hepatol 1994;21:317–25.
10. Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of nutritional practice in hospitalized cirrhotic patients: results of a prospective study. Nutrition 2003;19:515–21.
11. Lautz HU, Selberg O, Korber J, Burger M, Müller MJ. Protein-calorie malnutrition in liver cirrhosis. Clin Investig 1992;70:478–86.
12. Merli M, Romiti A, Riggio O, Capocaccia L. Optimal nutritional indexes in chronic liver disease. JPEN J Parenter Enteral Nutr 1987;11:130S–4S.
13. Heymsfield SB, Casper K. Anthropometric assessment of the adult hospitalized patient. JPEN J Parenter Enteral Nutr 1987;11:36S–41S.
14. Harries AD, Jones LA, Heatley RV, Rhodes J. Malnutrition in inflammatory bowel disease: an anthropometric study. Hum Nutr Clin Nutr 1982;36:307–13.
15. Thuluvath PJ, Triger DR. How valid are our reference standards of nutrition? Nutrition 1995;11:731–3.
16. Bramley P, Oldroyd B, Stewart S, et al. Body composition analysis in liver cirrhosis. The measurement of body fat by dual energy X-ray absorptiometry in comparison to skinfold anthropometry, bioelectrical impedance and total body potassium. In: Ellis KJ, Eastman JD, eds. Human body composition. New York, NY: Plenum, 1993:211–4.
17. Morgan MY, Madden AM. The assessment of body composition in patients with cirrhosis. Eur J Nucl Med 1996;23:213–25.
18. Schloerb PR, Forster J, Delcore R, Kindscher JD. Bioelectrical impedance analysis in the clinical evaluation of liver disease. Am J Clin Nutr 1996;64(suppl):510S–4S.
19. Windsor JA, Hill GL. Grip strength: a measure of the proportion of protein loss in surgical patients. Br J Surg 1988;75:880–2.

20. Windsor JA, Hill GL. Risk factors for postoperative pneumonia. The importance of protein depletion. Ann Surg 1998;208:209–14.
21. Prijatmoko D, Strauss BJG, Lambert JR, et al. Early detection of protein depletion in alcoholic cirrhosis: role of body composition analysis. Gastroenterology 1993;105:1839–45.
22. Plank LD, Metzger DJ, McCall JL, et al. Sequential changes in the metabolic response to orthotopic liver transplantation during the first year after surgery. Ann Surg 2001;234:245–55.
23. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 73;60:646-9.
24. Beddoe AH, Streat SJ, Hill GL. Evaluation of an in vivo prompt gamma neutron activation facility for body composition studies in critically ill intensive care patients: results on 41 normals. Metabolism 1984;33:270–80.
25. Sutcliffe JF, Mitra S, Hill GL. In vivo measurement of total body carbon using 238Pu/Be neutron sources. Phys Med Biol 1990;35:1089–98.
26. Hill GL, Monk D, Plank LD. Measuring body composition in intensive care patients. In: Wilmore D, Carpentier Y, eds. Metabolic support of the critically ill patient. Berlin, Germany: Springer, 1993:3–18.
27. Morgan DB, Hill GL, Burkinshaw L. The assessment of weight loss from a single measurement of body weight: the problems and limitations. Am J Clin Nutr 1980;33:2101–5.
28. Kiebzak GM, Leamy LJ, Pierson LM, Nord RH, Zhang ZY. Measurement precision of body composition variables using the Lunar DPX-L densitometer. J Clin Densitom 2000;3:35–41.
29. Reid IR, Plank LD, Evans MC. Fat mass is an important determinant of whole body bone density in premenopausal women but not in men. J Clin Endocrinol Metab 1992;75:779–82.
30. Plank LD, Monk DN, Gupta R, Franch-Arcas G, Pang J, Hill GL. Body composition studies in intensive care patients: comparison of methods of measuring total body water. Asia Pac J Clin Nutr 1995;4:125–9.
31. International Committee on Radiological Protection. Report of the Task Force on Reference Man. Oxford, United Kingdom: Pergamon Press, 1975. (Report no. 23.)
32. Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, DC: Carnegie Institute, 1919 (Carnegie Institute of Washington publication no. 279).
33. Tapsell LC, Brenninger V, Barnard J. Applying conversation analysis to foster accurate reporting in the diet history interview. J Am Diet Assoc 2000;100:818–24.
34. Mathiowetz V, Kashman N, Volland G, Weber K, Dowe M, Rogers S. Grip and pinch strength: normative data for adults. Arch Phys Med Rehab 1984;22:69–74.
35. Peolsson A, Hedlund R, Öberg B. Intra- and inter-tester reliability and reference values for hand strength. J Rehab Med 2001;33:36–41.
36. Wilson SH, Cooke NT, Edwards RHT, Spiro SG. Predicted normal values for maximal respiratory pressures in Caucasian adults and children. Thorax 1984;39:535–8.
37. Bruschi C, Cerveri I, Zoia MC, et al. Reference values of maximal respiratory mouth pressures: a population-based study. Am Rev Respir Dis 1992;146:790–3.
38. Riggio O, Angeloni S, Ciuffa L, et al. Malnutrition is not related to alterations in energy balance in patients with stable liver cirrhosis. Clin Nutr 2003;22:553–9.
39. Guechot J, Chazouilleres O, Loris A, et al. Effect of liver transplantation on sex-hormone disorders in male patients with alcohol-induced or post-viral hepatitis advanced liver disease. J Hepatol 1994;20:426–30.
40. Petrides AS, DeFronzo RA. Glucose and insulin metabolism in cirrhosis. J Hepatol 1989;8:107–14.
41. Nikolic JA, Todorovic V, Bozic M, et al. Serum insulin-like growth factor (IGF)-II is more closely associated with liver dysfunction than is IGF-1 in patients with cirrhosis. Clin Chim Acta 2000;294:169–77.
42. McCullough AJ, Bugianesi E, Marchesini G, Kalhan SC. Gender-dependent alterations in serum leptin in alcoholic cirrhosis. Gastroenterology 1998;115:947–53.
43. Comlekci A, Akpinar H, Yesil S, et al. Serum leptin levels in patients with liver cirrhosis and chronic viral hepatitis. Scand J Gastroenterol 2003;38:779–86.
44. Müller MJ, Böttcher, Selberg O, et al. Hypermetabolism in clinically stable patients with liver cirrhosis. Am J Clin Nutr 1999;69:1194–201.
45. Tajika M, Kato M, Mohri H, et al. Prognostic value of energy metabolism in patients with viral liver cirrhosis. Nutrition 2002;18:229–34.
46. Madden AM, Morgan MY. Resting energy expenditure should be measured in patients with cirrhosis, not predicted. Hepatology 1999;30:655–64.
47. Selberg O, Böttcher J, Tusch G, Pichlmayr R, Henkel E, Müller MJ. Identification of high- and low-risk patients before liver transplantation: a prospective cohort study of nutritional and metabolic parameters in 150 patients. Hepatology 1997;25:652–7.
48. Guglielmi FW, Panella C, Buda A, et al. Nutritional state and energy balance in cirrhotic patients with or without hypermetabolism. Multicentre prospective study by the 'Nutritional Problems in Gastroenterology' Section of the Italian Society of Gastroenterology (SIGE). Dig Liv Dis 2005;37:681–8.
49. Crawford DH, Shepherd RW, Halliday JW, et al. Body composition in nonalcoholic cirrhosis: the effect of disease origin and severity on nutritional compartments. Gastroenterology 1994;106:1611–7.
50. Roongpisuthipong C, Sobhonslidsuk A, Nantiruj K, Songchitsomboon S. Nutritional assessment in various stages of liver cirrhosis. Nutrition 2001;17:761–5.
51. Haderslev KV, Svendsen OL, Staun M. Does paracentesis of ascites influence measurements of bone mineral or body composition by dual-energy X-ray absorptiometry? Metabolism 1999;48:373–7.
52. Heymsfield SB, Wang ZM, Withers RT. Multicomponent molecular level models of body composition analysis. In: Roche AF, Heymsfield SB, Lohman TG, eds. Human body composition. Champaign, IL: Human Kinetics, 1996:129–48.
53. Hay JE. Bone disease in cholestatic liver disease. Gastroenterology 1995;108:276–83.
54. Gallego-Rojo FJ, Gonzalez-Calvin JL, Munoz-Torres M, Mundi JL, Fernandez-Perez R, Rodrigo-Moreno D. Bone mineral density, serum insulin-like growth factor I, and bone turnover markers in viral cirrhosis. Hepatology 1998;28:695–9.
55. Carey EJ, Balan V, Kremers WK, Hay JE. Osteopenia and osteoporosis in patients with end-stage liver disease caused by hepatitis C and alcoholic liver disease: not just a cholestatic problem. Liver Transpl 2003;9:1166–73.