Two-component models are of limited value for the assessment of body composition in patients with cirrhosis1–3

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ABSTRACT
Background: Most techniques for measuring body composition are based on 2-component models (2-CMs) and depend on assumptions relating to the constancy of the density (D_{FFM}) and hydration fraction (H_{FFM}) of fat-free mass (FFM).

Objectives: The objectives were to determine whether these assumptions are systematically violated in patients with cirrhosis and to assess the validity of the estimates of body composition obtained in these patients by using 2-CM techniques.

Design: Body composition was assessed by using a 4-component model (4-CM), which was based on data obtained from densitometry, deuterium dilution, and dual-energy X-ray absorptiometry, in 20 patients with cirrhosis who had no evidence of fluid retention and in 20 pair-matched healthy control subjects. The results were compared with those obtained by using “reference” and “bedside” 2-CM techniques.

Results: The mean (±SD) D_{FFM} was significantly lower in the patients with cirrhosis (1.091 ± 0.008 compared with 1.100 ± 0.006 kg/L; P < 0.001); no significant difference in H_{FFM} was observed between the patients and control subjects (74.5 ± 2.6 compared with 73.5 ± 2.1), although there was greater variability in the patients. Significant differences were observed in the body-composition variables obtained by using the “reference” 2-CM techniques compared with the 4-CM—the 95% limits of agreement in the patients with cirrhosis exceeded 5% body fat and 3 kg FFM; the corresponding values for the “bedside” 2-CM techniques were 11% body fat and 7.5 kg FFM.

Conclusions: Assumptions relating to the constancy of the D_{FFM} and H_{FFM} are violated in patients with cirrhosis. Thus, standard 2-CM techniques provide inaccurate body composition estimates in this patient population. Am J Clin Nutr 2006;84:1151–62.

KEY WORDS Anthropometric measures, bioelectrical impedance analysis, body composition, cirrhosis, 4-component model, densitometry, density of fat-free mass, deuterium dilution, dual-energy X-ray absorptiometry, fat-free mass, healthy control subjects, hydration of fat-free mass, near-infrared interactance, percentage fat mass, urinary creatinine

INTRODUCTION

Patients with cirrhosis are frequently malnourished (1, 2), and this has a detrimental effect on outcome (3–5). The changes in body composition that occur in this patient population are, however, poorly researched and inadequately documented (6–8).

The most frequently used “reference” techniques for assessing body composition are densitometry, deuterium dilution, and dual-energy X-ray absorptiometry (DXA) (9–11). All 3 methods are based, conceptually, on 2-component models (2-CMs), which distinguish the chemically distinct fat mass from the fat-free mass (FFM; essentially water, protein, and mineral). These, and the so-called “bedside” assessment techniques—eg, skin-fold thickness anthropometry and bioelectrical impedance analysis (BIA), which are also based on 2-CMs—are critically dependent on the constancy of the relations among the gross components of the FFM and on assumptions relating to its density (D_{FFM}) and hydration fraction (H_{FFM}). Over- or underestimates of body composition variables will be obtained if these assumptions are invalid.

In recent years, multicomponent techniques have been developed in an attempt to measure FFM constituents more directly and with greater certainty. The 3-CM, which defines the chemically distinct water, fat, and protein plus mineral (fat-free dry matter) compartments, is based on measurements obtained from densitometry and water dilution (12). The 4-CM, which defines the chemically distinct water, fat, protein, and mineral, is based, similar to the 3-CM, on measurements of body density (BD) and total body water (TBW) but also incorporates a direct measure of bone mineral content (BMC) obtained with the use of DXA (13, 14). Although the 4-CM depends on an assumed constant ratio of BMC to nonosseous mineral (13, 15), it is fairly robust to major changes in this ratio (14). Use of multicomponent models will obviate the need for some of the assumptions inherent in the use of single techniques, thereby increasing the accuracy of the assessment, without loss of precision (7, 14).

Many of the assumptions made in the assessment of body composition variables in healthy persons are violated in patients with cirrhosis because of the abnormalities in fluid homeostasis and compartmentalization (16), protein metabolism (17), and bone modeling and remineralization (18) that characterize this

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Received February 20, 2006. Accepted for publication June 27, 2006.
condition. Nevertheless, few attempts have been made to obtain accurate body composition data in this patient population by using multicomponent models (19–22), even though these data are needed for a number of reasons: first, to allow definition of the pattern of tissue loss; this may provide insights into the disease process and information on outcome and prognosis; it may also affect approaches to nutritional therapy, its monitoring and evaluation; second, to obtain accurate definition of the metabolically active tissue compartments so that variables such as energy expenditure and protein synthesis can be correctly referenced (6); and third, to validate the techniques currently used to assess nutritional status so that their use can be optimized in the clinical setting.

The aim of the present study was to assess body composition in patients with cirrhosis by using a 4-CM in order to test the following hypotheses: 1) the assumptions made with regard to the constancy of $D_{BPM}$ and $HF_{BPM}$ are systematically and significantly violated in patients with cirrhosis, even in the absence of overt fluid retention; 2) standard 2-CM techniques for assessing body composition provide inaccurate estimates in patients with cirrhosis; and 3) the extent of variation in the estimates of body composition variables obtained with the use of standard “reference” and “bedside” 2-CM techniques may preclude the development of meaningful population-specific correction factors or prediction equations.

SUBJECTS AND METHODS

Subjects

Twenty patients [10 men and 10 women; \(\bar{x}\) (range) age: 49 y (28–66 y)] with biopsy-proven, alcohol-related cirrhosis were recruited for the study. Patients were excluded if they had documented evidence of alcohol misuse, fluid retention, or variceal bleeding within the previous 3 mo; a history of major gastrointestinal surgery; overt hepatic encephalopathy; any gross anatomical defect, for example limb amputation; poor mobility; or lack of the necessary robustness to undergo the investigative procedures. The functional severity of their liver disease was determined by using the Pugh’s modification of the Child’s grading system (23).

The reference population comprised 20 healthy control subjects [10 men and 10 women; \(\bar{x}\) (range) age: 49 y (28–65 y)] who were individually matched to the patients by sex, age (within 3 y), and body weight (within 2 kg). None gave a history, nor had clinical or laboratory evidence of alcohol misuse or chronic liver disease; none drank >20 g alcohol/d.

Approval for the present study was granted by the Ethical Practice Subcommittee of the Royal Free Hampstead NHS Trust, London, and the Ethics Committee of the MRC Dunn Clinical Nutrition Centre, Cambridge. All subjects provided written, informed consent.

Study outline

Data measurements in each patient were completed within 24 h. The patients attended the Royal Free Hospital, London, between 0700 and 0900 after fasting and refraining from smoking for \(\geq 8\) h. On arrival, the patients voided the last sample of a 24-h collection period. Total 24-h urine volumes were measured, and aliquots were stored at \(-20\) °C until assayed. Urinary creatinine concentration was assessed calorimetrically on an automated Hitachi 911 instrument (Hitachi Europe Ltd., London, United Kingdom) by using its reaction with alkaline picrate (26); excretion rates were determined by extrapolation from the 24-h urinary volume. Recovery of PABA was measured calorimetrically by using its reaction with naphthylene oxide and determined by using the 24-h urinary volume. Recoveries of PABA (85% of the administered dose) were considered complete (27). Creatinine clearance was calculated from the serum and urinary creatinine concentrations and the 24-h urinary volume.

Deuterium dilution

A baseline salivary sample was collected with small balls of cotton wool, which were chewed and then expectorated into solution containing deuterium was administered orally for the estimation of TBW. A snack providing a total of 200 kcal and 3 g protein was given to the patients before transfer to the MRC Dunn Clinical Nutrition Centre in Cambridge. Densitometry and DXA measurements were undertaken shortly after arrival; a small sandwich lunch was then provided. Bla and near-infrared interactant (NIRI) were undertaken \(\approx 1\) h later. Food and fluid intake were monitored until the collection of the 6-h postdose salivary sample for the deuterium dilution studies, after which intake was unrestricted.

The healthy subjects were recruited from the Cambridge area and attended the MRC Dunn Clinical Nutrition Centre directly from home. All reference measurements were undertaken by using the same protocol employed in the patient group; urinary creatinine data were not collected in these persons.

Assessment methods

Anthropometric measures

Height was measured to the nearest 0.5 cm, in bare feet, by using a freestanding stadiometer (Seca, Hamburg, Germany). Body weight (BWt) was measured to the nearest 0.1 kg with subjects in swimwear by using an electronic digital scale (Sauter Type E1210; Todd Scales, Newmarket, Suffolk, United Kingdom). Body mass index was calculated as BWt (in kg)/height\(^2\) (in m).

Skinfold anthropometric measures were undertaken by using the same steel tape measure and Holtain/Tanner-Whitehouse skinfold calipers (Holtain Ltd, Crymych, Dyfed, United Kingdom) in all subjects. Standardized techniques were used to measure the triceps, biceps, subscapular, and suprailiac skinfolds and midupper arm circumferences at set anatomical landmarks on the nondominant side of the body (24). Each measurement was made to the nearest 0.1 mm, and a mean result calculated from 3 or 4 readings. Bone-free, midupper arm muscle cross-sectional area was calculated (25).

Urinary creatinine excretion

Twenty-four-h urine samples were collected in plastic bottles containing boric acid preservative following a standard procedure. The completeness of the collection was assessed in 16 of the patients using para-amino benzoic acid (PABA); Laboratories for Applied Biology Ltd, London, United Kingdom; one 80-ml PABA tablet was taken at each of 3 regular meals during the 24-h collection period. Total 24-h urine volumes were measured, and aliquots were stored at \(-20\) °C until assayed.

Urinary creatinine concentration was assessed calorimetrically on an automated Hitachi 911 instrument (Hitachi Europe Ltd., London, United Kingdom) by using its reaction with alkaline picrate (26); excretion rates were determined by extrapolation from the 24-h urinary volume. Recovery of PABA was measured calorimetrically by using its reaction with naphthylene oxide and determined by using the 24-h urinary volume. Recoveries of PABA (85% of the administered dose) were considered complete (27). Creatinine clearance was calculated from the serum and urinary creatinine concentrations and the 24-h urinary volume.
small sealable specimen jars. Care was taken to prevent fractionation with exogenous water. An accurately weighed amount of oral dosing solution was given to provide a nominal dose equivalent to 0.40 g deuterium oxide/kg BWt (99.9 atom percent excess; Sigma Chemical Company, Poole, Dorset, United Kingdom). The mouth was rinsed with an additional 150 mL tap water to minimize deuterium losses. A further salivary sample was collected 6 h after dosing.

The extracted saliva, which varied in volume from 4–8 mL, was centrifuged at 1207 × g for 10 min at 4°C, and the supernatant was transferred into sealed plastic tubes for storage at −20°C until analyzed. Deuterium enrichment in salivary samples was measured, in duplicate, with Fourier transformed infrared spectroscopy (ATI Mattson Genesis Series FTIR; ATI, Cambridge, United Kingdom) as described previously (28). The difference in enrichment between the baseline and the 6-h postdose salivary sample was used to calculate deuterium dilution space. TBW was determined by using a correction factor of 1.04 for nonaqueous exchange (29, 30):

\[
\text{TBW} = C_1 W_i / (C_2 \times 1.04) \quad (1)
\]

where \( C_1 \) is the deuterium concentration in the dosing solution, \( W_i \) is the weight of the dose given, and \( C_2 \) is the deuterium concentration of the sample difference.

**Densitometry**

Assessment of body volume (BV), and hence body density (BD), was undertaken with the use of the underwater weighing procedure described by Akers and Buskirk (9), modified to include measurement of lung volumes by helium dilution (14).

BV was calculated from the adjusted underwater weight employing corrections for the respiratory gas volume at body temperature and pressure, the gastrointestinal gas volume estimated employing corrections for the respiratory gas volume at body temperature and pressure, the gastrointestinal gas volume estimated at 100 mL (9), and the temperature and density of the displaced water. BD was calculated from the volume and weight measurements (BD = BWt/BV).

**Dual-energy X-ray absorptiometry**

Whole-body DXA scanning was undertaken with the use of a Hologic QDR-1000/W scanner (Hologic Inc, Waltham, MA). The typical scanning time was 15 min; the associated radiation exposure was < 0.6 μSv (11), which is lower than the daily background radiation level in the Cambridge area. The Enhanced Whole Body V5.61 analysis program (Hologic Inc) was used to provide estimates of BMC, fat, and fat-free soft tissue (FFST = FFM – BMC).

**Bioelectrical impedance analysis**

Whole-body measurements were performed by using a multifrequency BIA instrument (SFB2; SEAC, Brisbane, Australia) according to standard recommendations (31). The subjects lay on a flat surface with their limbs abducted 30–45° from the torso. Data were imported into a computer program, and the impedance (Z), resistance (R), and reactance (Xc) at 50 kHz were abstracted for subsequent analysis with the use of established equations.

**Near-infrared interactance**

A beam of infrared radiation was directed at a single site on the anterior aspect of the belly of the left biceps, halfway between the antecubital fossa and acromion, when the arm was slightly flexed.

Two readings of the absorption of the reflected radiation, one at 940 nm (OD1) and one at 950 nm (OD2), were made with the use of a Futrex 5000 instrument (Futrex Inc, Gaithersburg, MD). These data were abstracted for subsequent analysis with the use of the manufacturer’s equations.

**Calculations**

Wherever necessary, appropriate interconversion of units of measurement was implemented by using the following equations:

\[
\text{FFM (kg)} = [\text{TBW (L)} \times D_{\text{water (kg/L)}}] / \text{FFM} \quad (2)
\]

\[
\text{Fat (\% \text{BWt})} = (\text{BWt} - \text{FFM}) \times 100 / \text{BWt} \quad (3)
\]

where \( D_{\text{water}} \) is the density of water.

**Two-component models**

**Anthropometric measures**

Estimates of body fat were calculated from measurements of skinfold thicknesses, assuming that BD is proportional to the logarithmic sum of the 4 skinfold-thickness measurements and that the density of fat and FFM are constant at 0.9 and 1.1 kg/L, respectively. BD was measured as follows (24):

\[
\text{BD} = c - (m \times \log \text{skinfold sum}) \quad (4)
\]

where \( c \) and \( m \) are age- and sex-dependent variables, respectively.

Body fat was then calculated from the Siri equation (12)

\[
\text{Fat (\%)} = ([4.95 / \text{BD}] - 4.5) \times 100 \quad (5)
\]

**Urinary creatinine excretion**

FFM was calculated assuming constant relations between urinary creatinine excretion and skeletal muscle mass, between skeletal muscle mass and lean body mass, and a constant \( HF_{\text{FFM}} \) of 0.732 (32). FFM was measured as follows (33):

\[
\text{FFM (kg)} = 0.02908 \times \text{creatinine (mg/24 h)} + 7.32 \quad (6)
\]

**Deuterium dilution**

FFM was estimated from TBW, assuming a constant \( HF_{\text{FFM}} \) of 0.732 (32):

\[
\text{FFM} = \text{TBW} / 0.732 \quad (7)
\]

Fat mass was derived by extrapolation:

\[
\text{Fat (\%)} = (\text{BWt} - [\text{TBW}/0.732]) \times 100 / \text{BWt} \quad (8)
\]

**Densitometry**

Estimates of body fat, as a percentage of BWt, were calculated from BD by using equation 5, assuming constant densities for fat and FFM of 0.9 and 1.1 kg/L, respectively.

**Dual-energy X-ray absorptiometry**

The data obtained were analyzed by using the Enhanced Whole Body V5.61 program (Hologic Inc), which is based on the assumptions that the ratio of low- to high-energy attenuation by fat and FFM is constant and not influenced by changes in \( HF_{\text{FFM}} \) (34).
DXA estimates of fat, BMC, and FFST were recorded and FFM was calculated as follows:

\[
FFM = BMC + FFST
\]  

(9)

Bioelectrical impedance

The whole-body resistance and reactance data obtained at 50 kHz were incorporated into equations that were previously used in patients with cirrhosis for the derivation of FFM (35) and TBW (36–38). FFM was calculated as follows (35):

\[
FFM (kg) = (0.756 \times \text{height}^2/R_{50}) + (0.11 \times BWt) + (0.107 \times X_{50}) - 5.463
\]  

(10)

TBW was calculated with the following equation in men (36):

\[
TBW (L) = 0.396 \times \text{height}^2/R_{50} + 0.143 \times BWt + 8.399
\]  

(11)

TBW was calculated with the following equation in women (36):

\[
TBW (L) = 0.382 \times \text{height}^2/R_{50} + 0.105 \times BWt + 8.315
\]  

(12)

TBW was also calculated in both sexes with the following 2 equations (37, 38):

\[
TBW (L) = 3.751 + 0.595 \times \text{height}^2/R_{50}
\]  

(13)

\[
TBW (L) = 6.59 + 0.5596 \times \text{height}^2/Z_{50}
\]  

(14)

Fat mass and FFM were derived by extrapolation.

Near-infrared interactance

Body fat was estimated by using the manufacturer’s equations (39).

For the men, the following equation was used:

\[
\text{Fat} (\%) = 54.172 + 0.1232 (BWt) - 0.11693 \text{ (height)} - 139.4 \text{ (A)} - 14.9 \times (OD_1) - 4.2 \times (OD_2)
\]  

(15)

For the women, the following equation was used:

\[
\text{Fat} (\%) = 60.228 + 0.1232 (BWt) - 0.11693 \text{ (height)} - 139.4 \text{ (A)} - 14.9 \times (OD_1) - 4.2 \times (OD_2)
\]  

(16)

where A is a graded physical activity score (39).

The 3-component model

The 3-CM divides the body into fat, water, and the remaining fat-free dry mass, which is assumed to have a constant protein-to-mineral ratio. It avoids the assumption that the water content of FFM is constant. This model uses data on BWt, BV, and TBW obtained from the densitometry and deuterium dilution studies. Fat mass was calculated from the basic measurements as follows (14):

\[
\text{Fat} (kg) = 2.22 (BV) - 0.764 (TBW) - 1.465 (BWt)
\]  

(17)

where BV and TBW are in L and BWt is in kg, and the factor for TBW contains corrections for the Dwater and body temperature. This model can provide estimates of the density and hydration of FFM.

**TABLE 1**

Precision estimates of the basic measurements and the derived body composition variables*  

<table>
<thead>
<tr>
<th>Method</th>
<th>Measurement (%) CV</th>
<th>Body fat/FFM (kg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>0.01</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>Body height</td>
<td>0.4</td>
<td>—</td>
<td>40</td>
</tr>
<tr>
<td>Skinfold thickness</td>
<td>9.0</td>
<td>0.65</td>
<td>40</td>
</tr>
<tr>
<td>Creatinine excretion</td>
<td>&lt; 2</td>
<td>1.2</td>
<td>33</td>
</tr>
<tr>
<td>Deuterium dilution</td>
<td>0.45</td>
<td>0.62</td>
<td>14</td>
</tr>
<tr>
<td>Densitometry</td>
<td>0.0025</td>
<td>0.78</td>
<td>12</td>
</tr>
<tr>
<td>DXA (TBM)</td>
<td>0.9</td>
<td>0.45</td>
<td>41</td>
</tr>
<tr>
<td>BIA resistance</td>
<td>1.2</td>
<td>0.35</td>
<td>40</td>
</tr>
<tr>
<td>NIRI</td>
<td>5.9</td>
<td>0.60</td>
<td>40</td>
</tr>
<tr>
<td>3-CM</td>
<td>—</td>
<td>0.49</td>
<td>14</td>
</tr>
<tr>
<td>4-CM</td>
<td>—</td>
<td>0.54</td>
<td>14</td>
</tr>
</tbody>
</table>

*FFM, fat-free mass; DXA, dual-energy X-ray absorptiometry; TBM, total body mineral; BIA, bioelectrical impedance analysis; NIRI, near-infrared interactance; CM, component model.

†Precision values equate to 1 SD and were obtained by repeat measurements or, in the case of the creatinine excretion and deuterium dilution, by repeat assays on the same biological samples. The precision for the estimate for FFM is equal to that for fat mass.

‡Underwater weighing.

The 4-component model

The 4-CM divides the body into fat, water, protein, and mineral, thereby avoiding the assumption that the protein-to-mineral ratio in FFM is constant. Constancy of the ratio between BMC and total body mineral (TBM) is, however, still assumed. This model uses data on BWt, V, TBW, and total BMC from the densitometry, deuterium dilution, and DXA studies. Fat mass was calculated from the basic measurements as follows (14):

\[
\text{Fat} (kg) = 2.747 (BV) - 0.71 (TBW) + 1.46 (BMC) - 2.05 (BWt)
\]  

(18)

FFM (kg), DFFM (kg/L), HF_FFM, TBM, and total body protein (TBP) were also calculated from this model together with the mineral and protein content of FFM and the protein-to-mineral ratio in FFM (14).

Hydration and density of FFM

FFM was calculated in each model as the difference between BWt and fat mass. The HF_FFM was calculated as TBW/FFM. The DFFM was calculated as:

\[
\text{(Mass of water + protein + mineral)} / (\text{volume of water + protein + mineral})
\]  

(19)

Precisions of individual method and body composition variables

The errors in the basic measurements and, consequently, the estimates of body composition they provided were determined by repeat measures or, in the case of the creatinine excretion and deuterium dilution, by repeat assays on the same biological samples with propagation of errors for the multicomponent models (Table 1). Most precision estimates were obtained from in-house published data (12, 14, 40, 41).
Statistical analysis

Throughout, data are presented for total populations and for men and women separately because 1) the prevalence of anthropometric abnormalities in patients with cirrhosis varies between men and women (2, 3, 5), which reflects, at least in part, intrinsic sex differences in body composition; and 2) malnutrition, which is commonly observed in this patient population, is characterized by preferential loss of fat mass in women and muscle mass in men (2, 3, 5). Data were analyzed by using the STATA statistical package version 9.1 (StataCorp, College Station, TX). Descriptive statistics for body composition indexes were calculated and expressed as a mean (±SD). Student’s paired t tests were used to distinguish differences in characteristics between the patients with cirrhosis and the pair-matched healthy controls. Student’s unpaired t tests were used to ascertain the significance of any unmatched comparisons. Bias and 95% limits of agreement (bias ± 2SDs) were determined between the 4-CM and alternative techniques for assessments of body fat and FFM (42). Analysis of variance was used to compare the extent of variation in measured indexes. Variability attributable to biological factors ($V_b$) was calculated from total variability ($V_t$) and methodologic variation ($V_m$) as follows (43):

$$V_t^2 = V_b^2 + V_m^2$$

where $V_t$ is the observable SD of a given measurement, and $V_m$ is the SD of the propagated methodologic error in the same units using appropriate values previously calculated (14), which are assumed to be uncorrelated with the biological variation.

RESULTS

All 20 patients had stable, alcohol-related cirrhosis and had been abstinent from alcohol for a mean (range) 24.4 mo (3–76 mo). None had evidence of overt fluid retention either on clinical examination or on abdominal ultrasonography. Thirteen patients were classified as Child’s grade A (7 men and 6 women) and 7 as grade B (3 men and 4 women). The median plasma creatinine concentration was 83 (57–100) μmol/L, and the median creatinine clearance was 84.1 (22.9–142.8) mL/min; 9 patients (3 men and 6 women) had creatinine clearances of <80 mL/min.

All subjects completed the study as per protocol. Urine collections were considered complete in 8 of the 16 patients; with a mean PABA recovery of 96% (85–106%). PABA excretion ranged from 24% to 82% in the remaining 8 patients.

Overall, there were few significant differences in anthropometric variables between the healthy controls and the patients with cirrhosis, although there was some evidence, in the male patients, of a reduction in muscle mass (Table 2).

No significant differences in mean body fat or in mean body FFM, derived from the 4-CM, were observed between the healthy controls and the patients with cirrhosis, either in the patient group as a whole (fat: 21.5 ± 8.7 compared with 22.7 ± 8.2 kg; FFM: 52.4 ± 11.7 compared with 50.1 ± 10.4 kg), or when separated by sex (Table 3).

The mean BMC in the patients with cirrhosis was significantly lower than in the healthy controls, in the group as a whole (2.14 ± 0.44 compared with 2.66 ± 0.49 kg; $P < 0.001$) and in both men ($P < 0.001$) and women ($P < 0.001$) when considered separately (Table 3). In consequence, significant intergroup differences in the derived values for TBG and the contribution of TBG to FFM were observed, because the same correction factor was used for both groups (Table 3). The mean $D_{FFM}$ in the healthy controls, derived from the 4-CM, was comparable to the established reference mean of 1.1 kg/L (12) and to the values previously obtained in healthy men (1.1024 ± 0.0078 kg/L) and women (1.1003 ± 0.0066 kg/L) by using the same 4-CM (14) (Table 3). The mean $D_{FFM}$ in the patients with cirrhosis was significantly lower than that in the healthy controls, both in the group as a whole (1.091 ± 0.008 compared with 1.100 ± 0.006 kg/L; $P < 0.001$) and when separated by sex (Table 2).

The mean HF$_{FFM}$ in the healthy controls, derived from the 4-CM, was comparable to the reference value of 73.2% (32) and was not significantly different from the values previously obtained in healthy men (73.3 ± 2.2%) and women (74.5 ± 1.9%) by using the same 4-CM (14) (Table 3). Overall, the values for HF$_{FFM}$ were higher in the patients with cirrhosis than in the healthy controls, but the mean HF$_{FFM}$ did not differ significantly from control values either in the group as a whole or when separated by sex (Table 3).

The major proportion of the total variance observed in $D_{FFM}$ and HF$_{FFM}$ in the healthy controls (89%) and in the patients with cirrhosis (94%) was accounted for by biological variance. The major factor responsible for the reduction in the mean $D_{FFM}$ in the patients with cirrhosis was the reduction in BMC, although the reductions observed in TBG and TBW in the male patients may also have contributed, even though the intergroup mean differences for these variables were not statistically significant.

Significant differences in the estimates of body fat and FFM obtained from the 4-CM and other established body composition techniques were observed in both the healthy controls and in the patients with cirrhosis, although the discrepancies in the patient population were greater (Table 4 and Table 5; Figure 1 and Figure 2).

The urinary creatinine excretion provided the least accurate estimates of body fat and FFM in the patients with cirrhosis. Some improvements in the estimates were observed when data from patients in whom PABA excretion indicated an incomplete collection or in whom the creatinine clearance was <80 mL/min were excluded. Nevertheless, even with these exclusions, the technique still provided overall discrepancies exceeding 12% body fat and 10 kg FFM.

In men with cirrhosis, deuterium dilution provided estimates of body fat that were closest to those obtained with the 4-CM, whereas DXA provided the closest estimates of FFM; nevertheless, the 95% limits of agreement between the results exceeded 5% body fat and 3 kg FFM. The least accurate estimates of body fat and FFM were provided by creatinine excretion, the use of which resulted in discrepancies exceeding 14% body fat and 11 kg FFM (Tables 4 and 5; Figures 1 and 2).

In women with cirrhosis, BIA measured by using the Schloerb equation (38) provided estimates of body fat and FFM that were closest to those obtained with the 4-CM; nevertheless, the 95% limits of agreement between the results exceeded 5% body fat and 5 kg FFM. In these patients, the least accurate estimates of body fat and FFM were provided by creatinine excretion, the use of which resulted in discrepancies exceeding 25% body fat and 16 kg FFM.

The mean value for $D_{FFM}$ in the patients with cirrhosis (1.0907 kg/L) and the established mean for the density of fat (0.9007 kg/L) were applied, according to Archimedes principle (15), and simplified according to the format of the Siri equation (12), to
### TABLE 2

Anthropometric variables in the patients with cirrhosis and in the pair-matched healthy control subjects

| Anthropometric variable | Healthy controls | | | Patients with cirrhosis | | | p² |
|-------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                         | Total (n = 20)   | Men (n = 10)     | Women (n = 10)   | Total (n = 20)   | Men (n = 10)     | Women (n = 10)   |                  |
| Weight (kg)             | 73.9 ± 14.3      | 79.9 ± 11.1      | 67.9 ± 15.2      | 72.8 ± 13.6      | 77.9 ± 11.4      | 67.7 ± 14.2      | NS               |
| Height (m)              | 1.71 ± 0.08      | 1.77 ± 0.07      | 1.66 ± 0.06      | 1.67 ± 0.12      | 1.75 ± 0.07      | 1.59 ± 0.09      | NS               |
| BMI (kg/m²)             | 25.0 ± 3.8       | 25.5 ± 2.9       | 24.6 ± 4.9       | 26.1 ± 4.5       | 25.5 ± 4.8       | 26.6 ± 4.4       | NS               |
| MUAC (cm)               | 30.6 ± 3.5       | 31.9 ± 3.0       | 29.3 ± 3.6       | 29.6 ± 4.3       | 29.4 ± 3.9       | 29.8 ± 5.0       | < 0.01           |
| MUAMA (cm²)             | 46.5 ± 14.8      | 55.8 ± 11.6      | 37.3 ± 11.7      | 34.4 ± 9.7       | 34.2 ± 8.0       | 34.6 ± 11.7      | < 0.01           |
| Triceps SFT (mm)        | 14.8 ± 5.7       | 10.3 ± 3.2       | 19.3 ± 3.7       | 21.0 ± 7.8       | 18.9 ± 7.7       | 23.0 ± 7.8       | < 0.01           |
| Biceps SFT (mm)         | 8.5 ± 3.3        | 6.7 ± 1.9        | 10.2 ± 3.7       | 13.0 ± 8.2       | 10.2 ± 6.0       | 15.8 ± 9.6       | < 0.05           |
| Subscapular SFT (mm)    | 16.1 ± 6.1       | 15.4 ± 4.7       | 16.9 ± 7.5       | 17.1 ± 7.7       | 16.6 ± 9.2       | 17.7 ± 6.4       | NS               |
| Suprailiac SFT (mm)     | 14.1 ± 6.3       | 13.0 ± 5.9       | 15.1 ± 7.0       | 16.9 ± 7.3       | 16.6 ± 8.3       | 17.3 ± 7.5       | NS               |
| Sum of 4 SFT (mm)       | 53.5 ± 17.8      | 45.5 ± 12.0      | 61.4 ± 19.8      | 68.1 ± 27.7      | 62.3 ± 28.6      | 73.8 ± 27.4      | NS               |

¹ MUAC, midupper arm circumference; MUAMA, midupper arm muscle area; SFT, skinfold thickness.
² Paired t test for differences between healthy controls and patients with cirrhosis.
³ ± 1 SD; 95% CI in parentheses (all such values).

### TABLE 3

Body composition measured by using the 4-component model in the patients with cirrhosis and in the pair-matched healthy control subjects

| Measurement variable | Healthy controls | | | Patients with cirrhosis | | | p² |
|----------------------|------------------|------------------|------------------|------------------|------------------|------------------|                  |
| TBW (kg)             | 38.4 ± 8.1       | 44.5 ± 5.4       | 32.3 ± 5.1       | 37.2 ± 7.3       | 41.0 ± 5.9       | 33.4 ± 6.7       | NS               |
| BD (kg/L)            | 1.03 ± 0.02      | 1.05 ± 0.02      | 1.02 ± 0.02      | 1.02 ± 0.12      | 1.00 ± 0.02      | 1.00 ± 0.02      | NS               |
| BMC (kg)             | 2.66 ± 0.49      | 2.94 ± 0.41      | 2.38 ± 0.40      | 2.14 ± 0.44      | 2.37 ± 0.38      | 1.90 ± 0.41      | < 0.001          |
| Body fat (kg)        | 21.5 ± 8.7       | 18.5 ± 6.7       | 24.5 ± 9.6       | 22.7 ± 8.2       | 22.0 ± 8.8       | 23.2 ± 7.9       | < 0.001          |
| Fat mass (kg)        | 1300.0 ± 28.8    | 22.7 ± 7.1       | 35.0 ± 7.0       | 30.8 ± 9.1       | 27.8 ± 10.1      | 33.9 ± 7.3       | < 0.001          |
| FFM (kg/m²)          | 74.2 ± 3.0       | 5.9 ± 21.4       | 8.8 ± 3.2        | 8.3 ± 3.3        | 7.3 ± 3.4        | 9.2 ± 3.0        | NS               |
| FFM (%)              | 52.4 ± 11.7      | 61.4 ± 79.6      | 43.4 ± 6.9       | 50.1 ± 10.4      | 55.8 ± 8.8       | 44.4 ± 8.8       | NS               |
| FFM (kg/m²⁺)         | 177.2 ± 2.8      | 196.1 ± 176.7    | 157 ± 22.4       | 178 ± 26.1       | 182 ± 29.1       | 17 , ± 23.2      | NS               |
| TBP (kg)             | 106.3 ± 3.4      | 131.2 ± 27.1     | 8.1 ± 19.7       | 10.2 ± 3.0       | 11.8 ± 3.0       | 8.6 ± 2.1        | NS               |
| TB (kg)              | 3.39 ± 6.2       | 3.75 ± 03.5      | 3.03 ± 0.51      | 2.72 ± 0.56      | 3.01 ± 0.45      | 2.43 ± 0.53      | < 0.001          |
| DFFM (kg)            | 1.100 ± 0.006    | 1.100 ± 0.007    | 1.099 ± 0.006    | 1.091 ± 0.008    | 1.093 ± 0.007    | 1.088 ± 0.009    | < 0.001          |
| HFFM (%)             | 73.5 ± 2.1       | 72.6 ± 19.7      | 74.3 ± 19        | 74.5 ± 2.6       | 73.7 ± 2.5       | 75.3 ± 2.6       | NS               |
| Protein (% of FFM)   | 19.9 ± 2.7       | 21.2 ± 23.9      | 18.6 ± 25.5      | 20.1 ± 2.8       | 20.9 ± 2.7       | 19.2 ± 2.7       | NS               |
| Mineral (g of FFM)   | 66.6 ± 1.1       | 6.2 ± 10.5       | 7.0 ± 10.6       | 5.5 ± 0.6        | 5.4 ± 0.5        | 5.5 ± 0.5        | < 0.005          |
| Protein:Mineral      | 3.6 ± 0.9        | 3.6 ± 0.9        | 2.7 ± 0.7        | 3.7 ± 0.8        | 3.9 ± 0.7        | 3.6 ± 0.3        | < 0.01           |

¹ TBW, total body water; BD, body density; BMC, bone mineral content; FMI, fat mass index; FFM, fat-free mass; FFM, fat-free mass index; TBP, total body protein; TB, total body mineral; DFFM, density of FFM; HFFM, hydration fraction of FFM.
² Paired t test for differences between healthy controls and patients with cirrhosis.
³ ± 1 SD; 95% CI in parentheses (all such values).
TABLE 4
Comparison of values for percentage body fat obtained by using various established techniques with the values obtained by using the 4-component model (4-CM) in the patients with cirrhosis and in the pair-matched healthy control subjects

<table>
<thead>
<tr>
<th>Measurement technique</th>
<th>Total (n = 20)</th>
<th>Men (n = 10)</th>
<th>Women (n = 10)</th>
<th>Total (n = 20)</th>
<th>Men (n = 10)</th>
<th>Women (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
<td>%</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>4-CM</td>
<td>28.9 (24.8, 33.0)</td>
<td>22.7 (18.3, 27.1)</td>
<td>35.0 (30.7, 39.4)</td>
<td>30.8 (26.8, 34.8)</td>
<td>27.8 (21.6, 34.1)</td>
<td>33.9 (29.3, 38.4)</td>
</tr>
<tr>
<td>3-CM</td>
<td>0.68 ± 1.56αβχ</td>
<td>0.36 ± 1.76αβχ</td>
<td>1.00 ± 1.32αβχ</td>
<td>0.10 ± 1.14αβχ</td>
<td>-0.02 ± 1.13αβχ</td>
<td>0.23 ± 1.14αβχ</td>
</tr>
<tr>
<td>Underwater weighing</td>
<td>-0.08 ± 3.63αβχ</td>
<td>0.04 ± 4.23αβχ</td>
<td>-0.20 ± 3.14αβχ</td>
<td>-2.66 ± 4.73αβχ</td>
<td>-2.10 ± 4.21αβχ</td>
<td>-3.23 ± 5.15αβχ</td>
</tr>
<tr>
<td>Deuterium dilution</td>
<td>1.79 ± 3.77αβχ</td>
<td>1.13 ± 3.81αβχ</td>
<td>2.46 ± 3.41αβχ</td>
<td>1.22 ± 5.03αβχ</td>
<td>0.48 ± 5.06αβχ</td>
<td>1.97 ± 4.80αβχ</td>
</tr>
<tr>
<td>DXA</td>
<td>2.34 ± 3.62αβχ</td>
<td>3.59 ± 2.45αβχ</td>
<td>1.09 ± 2.79αβχ</td>
<td>3.19 ± 6.14αβχ</td>
<td>4.05 ± 8.82αβχ</td>
<td>2.33 ± 7.05αβχ</td>
</tr>
<tr>
<td>Skinfold thicknesses</td>
<td>0.91 ± 7.66αβχ</td>
<td>1.00 ± 8.46αβχ</td>
<td>0.81 ± 7.22αβχ</td>
<td>4.64 ± 12.68αβχ</td>
<td>7.72 ± 11.14αβχ</td>
<td>1.56 ± 11.45αβχ</td>
</tr>
<tr>
<td>BIA (35)</td>
<td>-0.46 ± 10.12αβχ</td>
<td>-2.47 ± 9.78αβχ</td>
<td>1.55 ± 9.20αβχ</td>
<td>-0.41 ± 11.15αβχ</td>
<td>0.99 ± 13.90αβχ</td>
<td>-1.80 ± 7.22αβχ</td>
</tr>
<tr>
<td>BIA (36)</td>
<td>1.77 ± 9.48αβχ</td>
<td>0.85 ± 10.15αβχ</td>
<td>2.69 ± 8.89αβχ</td>
<td>3.19 ± 11.09αβχ</td>
<td>5.46 ± 11.08αβχ</td>
<td>0.92 ± 9.54αβχ</td>
</tr>
<tr>
<td>BIA (37)</td>
<td>-2.60 ± 10.91αβχ</td>
<td>-4.35 ± 11.02αβχ</td>
<td>-0.86 ± 10.51αβχ</td>
<td>-1.80 ± 11.78αβχ</td>
<td>-0.39 ± 14.02αβχ</td>
<td>-3.20 ± 8.88αβχ</td>
</tr>
<tr>
<td>BIA (38)</td>
<td>-0.66 ± 11.46αβχ</td>
<td>-3.22 ± 10.64αβχ</td>
<td>1.90 ± 10.29αβχ</td>
<td>0.33 ± 11.53αβχ</td>
<td>0.96 ± 14.05αβχ</td>
<td>-0.30 ± 8.92αβχ</td>
</tr>
<tr>
<td>NRI</td>
<td>3.95 ± 8.06αβχ</td>
<td>2.98 ± 7.40αβχ</td>
<td>4.92 ± 8.61αβχ</td>
<td>5.39 ± 11.95αβχ</td>
<td>6.94 ± 12.08αβχ</td>
<td>3.84 ± 11.58αβχ</td>
</tr>
<tr>
<td>Creatinine excretion</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Mean values for body fat derived by using this population-specific equation did not differ significantly from those derived by using the 4-CM either for the population as a whole (30.99 ± 9.54% compared with 30.84 ± 9.12%) or when separated by sex.

TABLE 5
Comparison of values for fat-free mass obtained by using various established techniques with the values obtained by using the 4-component model (4-CM) in patients with cirrhosis and the pair-matched healthy control subjects

<table>
<thead>
<tr>
<th>Measurement technique</th>
<th>Total (n = 20)</th>
<th>Men (n = 10)</th>
<th>Women (n = 10)</th>
<th>Total (n = 20)</th>
<th>Men (n = 10)</th>
<th>Women (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg</td>
<td>kg</td>
<td></td>
<td>kg</td>
<td>kg</td>
<td></td>
</tr>
<tr>
<td>4-CM</td>
<td>52.4 (47.3, 57.5)</td>
<td>61.4 (56.5, 66.3)</td>
<td>43.4 (39.2, 47.7)</td>
<td>50.1 (45.6, 54.7)</td>
<td>55.8 (50.3, 61.3)</td>
<td>44.4 (38.9, 49.8)</td>
</tr>
<tr>
<td>3-CM</td>
<td>-0.45 ± 1.17αβχ</td>
<td>-0.23 ± 1.23αβχ</td>
<td>-0.66 ± 0.98αβχ</td>
<td>-0.04 ± 0.81αβχ</td>
<td>0.05 ± 0.89αβχ</td>
<td>-0.13 ± 0.73αβχ</td>
</tr>
<tr>
<td>Underwater weighing</td>
<td>0.10 ± 2.56αβχ</td>
<td>0.02 ± 3.14αβχ</td>
<td>0.17 ± 2.00αβχ</td>
<td>1.81 ± 3.16αβχ</td>
<td>1.53 ± 3.11αβχ</td>
<td>2.09 ± 3.27αβχ</td>
</tr>
<tr>
<td>Deuterium dilution</td>
<td>-1.26 ± 2.77αβχ</td>
<td>-0.85 ± 3.04αβχ</td>
<td>-1.67 ± 2.33αβχ</td>
<td>-0.73 ± 3.47αβχ</td>
<td>-0.25 ± 3.95αβχ</td>
<td>-1.22 ± 2.78αβχ</td>
</tr>
<tr>
<td>DXA</td>
<td>-1.80 ± 2.94αβχ</td>
<td>-2.91 ± 2.30αβχ</td>
<td>-0.70 ± 1.68αβχ</td>
<td>0.33 ± 3.70αβχ</td>
<td>-0.07 ± 3.34αβχ</td>
<td>0.73 ± 4.04αβχ</td>
</tr>
<tr>
<td>Skinfold thicknesses</td>
<td>-0.76 ± 6.18αβχ</td>
<td>-0.72 ± 6.91αβχ</td>
<td>-0.81 ± 5.73αβχ</td>
<td>-3.34 ± 9.10αβχ</td>
<td>-5.88 ± 8.26αβχ</td>
<td>-0.79 ± 6.99αβχ</td>
</tr>
<tr>
<td>BIA (35)</td>
<td>0.42 ± 8.22αβχ</td>
<td>1.87 ± 7.98αβχ</td>
<td>-1.03 ± 3.88αβχ</td>
<td>0.27 ± 7.48αβχ</td>
<td>-0.37 ± 9.66αβχ</td>
<td>-0.91 ± 4.57αβχ</td>
</tr>
<tr>
<td>BIA (36)</td>
<td>-1.19 ± 7.73αβχ</td>
<td>-0.70 ± 8.47αβχ</td>
<td>-1.68 ± 7.22αβχ</td>
<td>-2.16 ± 7.51αβχ</td>
<td>-3.90 ± 8.05αβχ</td>
<td>-0.43 ± 5.27αβχ</td>
</tr>
<tr>
<td>BIA (37)</td>
<td>2.04 ± 9.14αβχ</td>
<td>3.39 ± 9.15αβχ</td>
<td>0.69 ± 8.74αβχ</td>
<td>1.41 ± 8.09αβχ</td>
<td>0.78 ± 10.05αβχ</td>
<td>2.04 ± 8.50αβχ</td>
</tr>
<tr>
<td>BIA (38)</td>
<td>0.75 ± 9.35αβχ</td>
<td>2.55 ± 9.01αβχ</td>
<td>-1.05 ± 8.62αβχ</td>
<td>0.02 ± 7.88αβχ</td>
<td>-0.23 ± 10.02αβχ</td>
<td>0.27 ± 5.47αβχ</td>
</tr>
<tr>
<td>NRI</td>
<td>-3.06 ± 6.44αβχ</td>
<td>-2.51 ± 6.34αβχ</td>
<td>-3.61 ± 6.68αβχ</td>
<td>-4.04 ± 8.72αβχ</td>
<td>-5.34 ± 9.27αβχ</td>
<td>-2.75 ± 7.73αβχ</td>
</tr>
<tr>
<td>Creatinine excretion</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Mean values for body fat derived by using this population-specific equation did not differ significantly from those derived by using the 4-CM either for the population as a whole (30.99 ± 9.54% compared with 30.84 ± 9.12%) or when separated by sex.
men: 27.24 ± 10.42% compared with 27.82 ± 10.10%; women: 34.74 ± 7.24% compared with 33.86 ± 7.29%). The bias and 95% limits of agreement between estimates of percentage body fat derived with the new prediction equation and the 4-CM were 0.15 and 4.90 for the whole population, 0.58 and 4.35 for men, and 0.88 and 5.21 for women; these data are not significantly different from those derived by using the original Siri formula (12) and the 4-CM.

**DISCUSSION**

The considerable difficulties associated with the assessment of body composition in patients with liver disease are well acknowledged (6–8). However, few attempts have been made, to date, to either use the more sophisticated multicomponent approach to provide direct and accurate measures of the FFM constituents (19–22) or to validate existing body composition methods appropriately.

The 4-CM used in the present study was considered to be an appropriate method for assessing body composition in patients with chronic liver disease and for evaluating alternative techniques. This model integrates measurements obtained from BWt, densitometry, deuterium dilution, and DXA to maximize the accuracy of estimates of body fat, water, mineral, and protein, with only slightly worse precision than that encountered when using the measurements individually (13, 14).
The 4-CM does not provide direct estimates of glycogen, urea, free-amino acids, and nucleic acids; these components are included primarily in the estimate of TBP because they have similar densities. However, in healthy persons, these additional components comprise only a small fraction of total body mass, of the order of 1 kg in a 70-kg man, and, in patients with cirrhosis, glycogen stores are depleted (44, 45) and protein synthesis is impaired (17). Thus, inclusion of these additional components should have no major effect on the estimates of TBP in this patient population.

No significant differences were observed in fat mass and FFM between the patients and the pair-matched healthy controls, but intergroup differences were observed in both the HF_{FFM} and the D_{FFM}. These discrepancies have considerable implications, because differences of 0.01 in HF_{FFM} and of 0.01 kg/L in D_{FFM} represent potential errors in the estimation of body fat of 1% and 5%, respectively.

The mean HF_{FFM} value in the patients of 0.745 exceeded the mean in the healthy controls of 0.735; the greater variability observed in HF_{FFM} values in the patients may have masked the

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**FIGURE 2.** Mean (±SD) fat-free mass (FFM) assessed in 20 patients (10 men and 10 women) with cirrhosis (■) and 20 (10 men and 10 women) pair-matched healthy control subjects (□) by using a 3- and a 4-component model (3-CM; 4-CM) of body composition (14) and a variety of other measurement techniques, including underwater weighing (UWW), deuterium dilution (Deuterium), dual-energy X-ray absorptiometry (DXA), skinfold thicknesses (SFT), bioelectrical impedance analysis (BIA; numbers represent references for the used BIA equation), near-infrared interactance (NIRI), and urinary creatinine excretion (Creatinine). ***Bias and 95% limits of agreement were significantly different from the 4-CM (Bland and Altman): * P < 0.05, ** P < 0.01.
reduction in DFFM in the patients with cirrhosis is of clinical absolute and proportional reductions in BMC and TBM. This can be assessed from TBW by using a reference value for HFFFM to the HFFFM, provided estimates of body composition in the individual “reference” techniques, densitometry, deuterium dilution, and DXA. Deuterium dilution, which adopts assumptions with regard to the HFFFM, provided the least inaccurate estimates of body composition in the patients with cirrhosis, but the overall discrepancies still amounted to 5% body fat and 3.5 kg FFM. DXA technology, which also adopts assumptions with regard to the HFFFM, provided estimates of body composition in the patients with cirrhosis with discrepancies up to 6% body fat and 3.7 kg FFM. This technique has been used to provide reference-body-composition data in patients with cirrhosis (19–21, 46), but a more detailed evaluation of the technique, in particular its ability to detect changes in body composition in response to treatment or nutritional intervention, is required before its use as a single technique for body composition analysis can be recommended (48).

The body-composition data obtained in the patients with cirrhosis with the “bedside” techniques of anthropometry, BIA, NII, and creatinine excretion were, as expected, even less accurate than those provided by the individual “reference” techniques. None provided estimates that confidently predicted body fat to within 11% or FFM to within 7.5 kg of the values determined with the use of the 4-CM. These techniques, with the exception of NII, are used routinely in clinical practice to assess and monitor nutritional status in patients with liver disease and in the research setting to provide reference variables for measures such as energy expenditure. None has, however, been validated for these purposes.

The accuracy of the results obtained with BIA is critically dependent on the equation used to process the data. Nevertheless, even the most favorable provided estimates that were discrepant by 11% for body fat and 7.5 kg for FFM, compared with the 4-CM. The accuracy of BIA in the presence of significant fluid retention is likely to be significantly lower (20, 49).

The body-composition data based on urinary creatinine excretion were the least accurate of all the techniques investigated, providing estimates that were discrepant by 21% for body fat and 14 kg for FFM, compared with the 4-CM. Reduced serum creatinine concentrations have been reported in patients with cirrhosis and are generally attributed to low protein intake, impaired hepatic synthesis, a reduction in muscle mass (50), or an increase in renal tubular secretion (51, 52). Pirlich et al (53) recommended that creatinine excretion should not be used to assess body composition in patients with cirrhosis, unless the creatinine clearance exceeded 80 mL/min. In addition, the completeness of the urine collection should always be validated (54). However, even with these impositions, the technique still provided overall discrepancies exceeding 12% body fat and 10 kg FFM in the patients with cirrhosis.

In theory, values for the comparison bias could be used to correct the estimates of body composition derived by using these alternatives techniques (42). However, although group mean values would be valid after such a correction, the 95% limits of agreement would remain substantial, casting doubt on the utility of the corrected data in individual patients.

In conclusion, the assumptions made regarding the constancy of DFFM and HFFFM were systematically and significantly violated in patients with cirrhosis, even in the absence of overt fluid retention. Consequently, the standard methods for assessing body composition not only provide inaccurate estimates in this patient population, but the extent of the variation precludes the development of meaningful population-specific correction factors or prediction equations. It is therefore recommended that, for research purposes or where accurate and precise body-composition data are required, they should be obtained by using a 4-CM or other appropriate multicomponent technique. The underwater weighing procedure is difficult to access, but the less demanding technique of air-displacement plethysmography may be usefully substituted to obtain densitometry data (55). If these facilities are unavailable, then the considerable limitations of the alternative “reference” and “bedside” techniques must be recognized and taken into account when assessing and interpreting the data acquired. Finally, the findings of the present study indicate a compelling need to address the problems of body-composition assessment in patients with cirrhosis, especially in the clinical setting.

We thank the patients for taking part in the study and for their enthusiasm and encouragement and Dr Richard Morris for statistical advice.

MYM and ME originally conceived the study. MYM, ME, AMM, and NJF designed the study. MYM and AMM selected and recruited the patients. AMM and NJF coordinated and undertook the study. GJ undertook the deuterium and PABA assays. NJF, MYM, and AMM undertook the statistical analysis. AMM wrote the first draft of the paper, which was then revised by MYM, NJF, and ME. All authors contributed to the subsequent revision of the

manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES


