

EDITORIAL

# Malnutrition and hypermetabolism in patients with liver cirrhosis<sup>1, 2</sup>

Manfred J Müller

<sup>1</sup> From the Institut für Humanernährung und Lebensmittelkunde (Institute for Human Nutrition and Food Science), Christian Albrechts University of Kiel, Kiel, Germany

<sup>2</sup> Address reprint requests to MJ Müller, Institut für Humanernährung und Lebensmittelkunde, Christian Albrechts Universität zu Kiel, Düsternbrooker Weg 17-19, D-24105 Kiel, Germany. E-mail: mmueller{at}nutrfoodsc.uni-kiel.de.

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Clinical signs of protein-energy malnutrition (PEM) are frequently seen in cirrhotic patients and may be obvious at all clinical stages of liver disease and even in clinically stable situations (1). Malnutrition in cirrhotic patients is readily understood as a consequence of metabolic disturbances in combination with low spontaneous dietary intake (1). Because PEM is associated with clinical complications of cirrhosis, such as ascites, and because it increases mortality with and without liver transplantation (2, 3), its early identification and characterization are mandatory. However, PEM is frequently underdiagnosed in clinical practice. This is explained in part by the fact that water retention increases body weight and thus masks losses of body mass. There are also methodologic limitations: for example, standard 2-component models used for assessment of body composition cannot be used with confidence in cirrhotic patients because of great variability in the density and hydration of fat-free mass [FFM (4)].

In this issue of the Journal, Peng et al (5) addressed body composition as well as the metabolic and functional consequences of malnutrition in cirrhotic patients. This cross-sectional study is exceptional, because the authors have taken into account essential procedural issues relevant to establishing nutritional status and metabolism. The strengths of the study include a large population of 268 well-characterized, clinically stable patients and detailed measurements of body composition, muscle function, and resting energy expenditure (REE) obtained by using state-of-the-art technologies, including neutron activation and a 6-compartment model of body composition. Functional and metabolic data can thus be adjusted for tissue hydration to allow comparisons between individual subjects. Whereas the prevalence of overhydration varied between 40% and 84%, Peng et al found significant protein depletion in 51% of the patient group. Protein depletion was more likely in men than in women, for an unexplained effect of sex. The severity of PEM increased with progression of liver disease and was associated with reduced muscle strength. In addition, hypermetabolism that was independent of clinical data as well as of PEM was found in ≈15% of the patients. The limits of cross-sectional data became evident, because energy and protein intake also showed no association with PEM. Thus, further longitudinal studies are needed.

The finding of significant protein depletion is in line with previous data (4, 6) suggesting that neutron activation and multicomponent models have high accuracy without loss of precision in their assessment of PEM in the cirrhotic patient. Because these methods are cumbersome and not available in clinical practice, simpler nutritional assessment schemes are required for clinical use. A global assessment scheme combining body mass index and midupper arm circumference with dietary intake data provided a reproducible and valid method for assessing nutritional status in patients with cirrhosis (7). However, only detailed body composition analysis, as was performed by Peng et al, identifies early and specific deficits that can provide a suitable basis for targeted interventions.

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The finding of a high prevalence of hypermetabolism extends our present knowledge on the variance of REE in cirrhosis. The prevalence of hypermetabolism was lower in the study of Peng et al than in 2 other comprehensive studies in this area (8, 9). These differences are explained in part by the use of different definitions of hypermetabolism. Peng et al (5) used predicted REE on the basis of FFM corrected for hydration, whereas others used standard body weight–based formulae such as Harris-Benedict or uncorrected FFM values, or both. Approximately 50% of the variance in REE in clinically stable cirrhosis patients was explained by FFM, irrespective of the method used to assess FFM and of a suitable correction for hydration (5, 8, 9). The data suggest that FFM is the major determinant of REE in cirrhosis.

Although hypermetabolism is a frequent feature of cirrhosis, its cause is still unclear. Peng et al (5) found no association of hypermetabolism with sex, etiology, severity of disease, protein depletion, or the presence of ascites or tumor. There is indirect evidence that increased sympathetic nervous system activity, possibly due to disturbances in liver circulation resulting in a hyperdynamic status, explains ≈25% of hypermetabolism in liver cirrhosis (8). More detailed body-composition analyses may provide further clues. One may speculate that the composition of FFM—ie, the relation between muscle and organ mass—varies in cirrhosis. The greater loss of muscle mass than of nonmuscle FFM results in a relative increase in the mass of "high-metabolic-rate" organs such as heart, brain, and kidneys, which increases the REE per kg FFM (10). This idea is supported by the finding that hypermetabolic patients tended to weigh less (5) and to suffer more frequently from malnutrition (8) than did normometabolic patients. The fact that functional liver mass is also reduced in cirrhosis adds to interindividual variances in metabolic data.

Although the variables of clinical staging, such as the Child-Pugh score, did not add much to the variance of REE in prior studies (5, 8, 9), deviations in REE should still be considered as part of liver disease. I consider hypermetabolism as an expression of the allostatic load (AL), which is the cumulative burden exacted on the body through attempts to adapt to the demands of stress associated with disease. In cirrhosis, the body varies certain characteristics of its internal milieu as a matter of adaptation (11). A new steady state may be reached that is at the end of or even outside of the normal range. The presence of hypermetabolism indicates that this adaptation is outside of the normal operating range, and "wear and tear" on this regulatory system are obvious (11). In the face of this idea, it is not surprising that hypermetabolic patients fail more frequently and have a higher mortality than do normometabolic patients (3). Because both hypermetabolism and a high Child-Pugh score are associated with poor prognosis, their observed nonassociation in cross-sectional studies suggests that they reflect 2 different features of the disease—ie, the overall burden of disease or specific liver damage and failure. To obtain an idea of the prognosis, the load of disease as well as the liver damage and function have to be characterized. The burden of disease can be assessed on the basis of an operationalization of AL including the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, cardiovascular system, insulin resistance, and other metabolic sequelae of cirrhosis (11).

Although Peng et al (5) used state-of-the-art methods for the assessment of body composition, their data also point to the limits of the current approach. Metabolism is usually referred to as static measures of body composition that reflect more-or-less unknown functional body masses. Thus, the present body composition approach should be extended to the assessment of functional body composition. Such an approach would help to integrate body composition into a broader view of regulatory systems and would lead to a new chapter of functional body composition research in studies on liver cirrhosis.

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