The interplay between nutrition and body composition

P. Fürst, H. Leweling

Injury, sepsis, malnutrition and, indeed, dietary intake all have important effects on body composition and therefore on therapeutic modalities and efforts. Indirectly, these factors may also influence the goals of nutritional therapy. Rapid weight loss due to the loss of body fat and skeletal muscle mass frequently accompanies short-term, self-limiting disease processes like injury and infection.[1,2] Similar catabolic events are associated with other disorders, like diabetic keto-acidosis, multiple organ failure, chemotherapy or radiation treatment for cancer.[3,4] The loss of body tissue may be minimal and of little consequence in a patient with normal nutritional status and a brief, uncomplicated illness. However, severe complications are to be expected during prolonged illness in nutritionally depleted patients. In the long term, these complications limit the ability of patients, prolong convalescence and impede patients' return to health.[2]

For a proper understanding of the alterations brought about by nutritional and metabolic imbalances during illness and recovery, detailed information on the morphological changes induced, together with their accompanying physiological and biochemical effects, is required.[5] Recent technological advances, like nuclear medicine, radiology, and medical physics, have opened up new ways of measuring body composition. However, there are considerable limitations in the application of such measurements to clinical situations. Indeed, such methods are as yet confined to research centres and hospitals and their extension into the community seems unlikely at present.[6] The need for simple and valid techniques is therefore a growing concern of practitioners in clinical nutrition.

Irrespective of the considerable limitations of these methods, studies of body composition have contributed much valuable information and have gained new impetus with the growing awareness of the importance of nutrition in patient care.[5]

This paper reviews the major common alterations in body composition during critical illness and identifies stress-induced changes in the various body compartments and electrolytes. Another critical issue is whether therapeutic and/or nutritional efforts beneficially influence the variety of alterations in critically ill patients.

Department of Biological Chemistry and Nutrition, University of Hohenheim, Stuttgart, Germany

P. Fürst, M.D., PH.D., F.A.I.N., F.A.C.N., F.A.S.

I Medical Clinic Mannheim, Department of Pathophysiology, University of Heidelberg, Germany

H. Leweling, PH.D.

Body composition changes associated with trauma, sepsis and malnutrition

A meaningful discussion about disease-induced alterations of body composition requires a description of the normal compartmentalisation. In healthy volunteers the body is composed of two distinct non-osseous compartments: fat mass and fat-free body mass, the latter composed of water, protein, minerals and glycogen.[5,7] Normal values of these components in a typical healthy adult are given in Fig. 1. In normal people, adipose tissue comprises 25 - 35% of body weight, extracellular fluid 30 - 40%, and body cell mass (BCM) (the actively functioning protein-rich tissue and its intracellular fluid) 25 - 40%. It is helpful to subdivide both the body water (plasma-intravasal, interstitial and intracellular water) and body protein (muscle protein, visceral protein and structural protein).
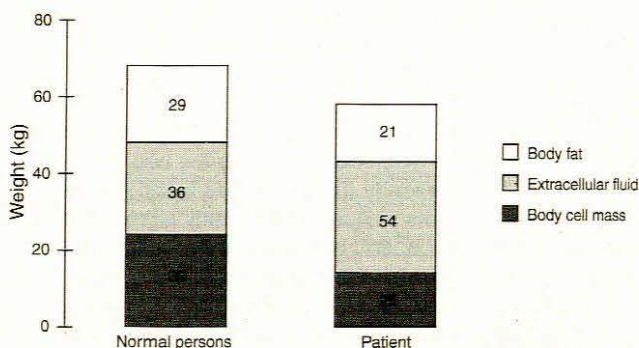

Fig. 1. Normal body composition and the components of weight changes in patients suffering from critical illness. Figures denote percentage of body weight. (Adopted from Shizgal (1983)[7] — with permission.)

A series of well-described changes associated with stress and malnutrition are known to alter body composition. The most notable initial change is an increase in the extracellular fluid component, accompanied by sodium retention and probable weight gain.[7] On the other hand, body cell mass might gradually decrease with stress, resulting in loss of weight and body fat. As a general rule these patients have simultaneously increased hydration of their fat-free body mass due to the increase in extracellular water.[8]

Trauma-, injury-, sepsis- or malnutrition-induced weight loss may be due to the accelerated breakdown of body protein and fat. By means of in vivo neutron activation analysis, tissue composition of the weight lost was measured 2 weeks after a major abdominal operation (abdominoperineal excision). The body weight loss was 4.1 kg, composed of 1 kg protein, 1.3 kg fat and 1.8 kg water.[9] Actually, protein- and fat-containing tissues can be lost at rates as rapid as 500 g/day, while the rate of synthesis of lean tissue is approximately only 150 g/day of which the proportion of protein is about 31 g/day. Body composition changes in patients suffering from critical illness as compared with normal values are illustrated in Fig. 1. With catabolic illness, there is expansion of the extracellular fluid compartment and erosion of adipose tissue and BCM.[7]

In an ongoing study, body composition was measured by bio-electrical impedance analysis (BIA) in surviving and non-surviving septic and multiple trauma patients (Table I). Compared with healthy subjects extracellular mass (ECM) was increased at admission, whereas BCM was maintained in trauma and decreased in septic patients. The initial increase of ECM was more accentuated in non-surviving patients and the considerable elevation of ECM was not fully accounted for by a corresponding elevation of lean body mass (LBM). At discharge a tendency toward normalisation of ECM is observed in surviving patients, while BCM remained low in those with sepsis. In non-surviving patients a further marked elevation of the ECM (sepsis 17.8 kg and multiple trauma 19.4 kg) and a decline of BCM (2.0 kg and 4.5 kg, respectively) was detected. The results thus indicate that a considerable portion of BCM was lost. Since the observed water shifts apparently do not directly affect the BCM, it is assumed that the diminished mass is due to loss of fat and especially substantial amounts of intracellular protein. The poor correlation between body water changes and the amount of LBM during stress may explain why it is difficult to relate metabolic and biochemical alterations per unit of LBM.

During stress, injury and infection, fat is the major source of energy,[10] about 50% of requirements being covered via catecholamine-induced cAMP-mediated lipolysis.[11] In this context, it is notable that the net loss of body fat is associated with a simultaneous interstitial accumulation of lipids, predominantly in muscle tissue. The amounts of interstitial fat have been measured in muscle biopsy specimens in patients suffering from various catabolic diseases (Table II). The data suggest that interstitial fat may increase multifold per muscle unit of fat-free dry solid.[12-14]

Actually, the increment in injury or sepsis corresponds to not less than 28 g and in severe burns 36 g interstitial lipids per kg muscle or about 700 - 1 000 g of whole body mass, assuming that muscle mass is 40% of the body weight and that there is a uniform allotment of lipids. Roth and co-workers[14] observed exceptional degeneration of muscle tissue in 2 non-surviving burn patients (Fig. 2.) The lipid portions in these muscles were 53% and 37% of the wet weight, associated with a markedly decreased share of muscle water.[14] It therefore appears that in critically ill patients increased lipolysis and augmented free fatty acid flux coexist with decreased peripheral utilisation of the available fatty acids. This biochemical event is presumably due to diminished intracellular oxidative capacity caused by an energy deficit of the sick cell.[13,15-17]
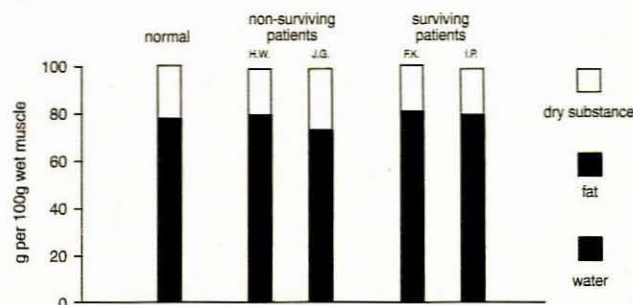

Fig. 2. Water and fat content in muscle tissue in 2 surviving and 2 non-surviving patients as compared with the normal distributions. In the exceptionally degenerated muscle tissue from the non-surviving patients a considerable accumulation of interstitial (extracellular) fat and markedly decreased share of muscle water were found. (From Roth et al. (1991)[14] with permission.)

Table I. Body composition in surviving and non-surviving septic and multiple trauma patients receiving TPN over 8 - 20 days

| | | Septic | | | | Multiple trauma | | | |
| | Normal (8) | Surviving (6) | | Non-surviving (8) | | Surviving (20) | | Non-surviving (7) | |
		Initial	Discharge	Initial	Prior to death	Initial	Discharge	Initial	Prior to death
LBM (kg)	57.6 ± 1.30	59.6 ± 4.9	55.4 ± 8.9	68.7 ± 14.1	78.6 ± 24.2	61.8 ± 10.2	57.0 ± 10.3	67.3 ± 8.8	82.2 ± 12.3
BCM (kg)	26.5 ± 0.75	22.0 ± 3.1*	19.9 ± 2.0	25.6 ± 6.4	23.7 ± 5.8	26.5 ± 5.5	25.1 ± 5.4	28.1 ± 6.9	23.6 ± 4.7
ECM (kg)	31.1 ± 0.70	37.5 ± 3.6*	35.5 ± 7.8	43.1 ± 13.7	54.9 ± 23.8	35.3 ± 7.0	31.9 ± 7.8	39.2 ± 8.3	58.6 ± 14.4

LBM = lean body mass; BCM = body cell mass; ECM = extracellular mass.
Energy was given according to the actual requirements as measured by indirect calorimetry in the form of equal amounts of glucose and fat. 2.0 g amino acids per kg body weight were provided daily. All patients were mechanically ventilated. Non-surviving patients developed failure of one or more organs. Values are given as mean ± SEM. (Fürst P, Leweling H — unpublished data).

Table II. Muscle water and electrolytes in 13 critically ill patients and in 14 patients with liver cirrhosis. All values are calculated with 100 g fat-free solids as the basis of reference (mean ± SEM)

| | Normal (85) | Multiple injury and burns (25) | | Sepsis on admission (17) | Subsequent sepsis day 10 (6) | Convalescence day 20 (6) | Liver cirrhosis (7) |
		8 day	30 day				
Total water (ml)	336 ± 1.50	364 ± 5.8‡	397 ± 7.2‡	359 ± 5.0‡	366 ± 13‡	351 ± 0.3*	413 ± 22.0‡
Extracellular	47 ± 1.40	100 ± 8.0‡	127 ± 11.1‡	79 ± 9.0‡	88 ± 20*	89 ± 17*	158 ± 24.5‡
Intracellular	289 ± 1.50	267 ± 4.6‡	275 ± 6.3*	281 ± 7.0	278 ± 10*	261 ± 15*	256 ± 4.2‡
Fat (g)	4.4 ± 0.22	23.1 ± 1.9‡	13.8 ± 0.91‡	21.6 ± 3.3‡	20.2 ± 4.2†	12.0 ± 2.1‡	22.9 ± 5.1
Sodium (mmol)	9.8 ± 0.21	16.5 ± 5.0‡	19.5 ± 1.4‡	14.0 ± 1.5†	15.5 ± 2.0*	18.2 ± 2.1†	
Chloride (mmol)	6.6 ± 0.15	12.9 ± 0.7‡	16.9 ± 1.4‡	11.0 ± 0.9‡	12.1 ± 2.2	12.3 ± 1.7‡	
Potassium (mmol)	45.9 ± 0.20	40.0 ± 0.5‡	40.0 ± 1.1‡	44.5 ± 0.3‡	43.9 ± 0.6†	44.4 ± 0.6‡	
Magnesium (mmol)	4.3 ± 0.04	3.9 ± 0.004‡	3.7 ± 0.07‡	4.3 ± 0.2	4.0 ± 0.3	4.0 ± 0.2*	

Significance with normal values:
* P < 0.05.
† P < 0.01.
‡ P < 0.001.

In the light of these results it is remarkable that increased fat and decreased water content are not indicated with BIA in terminal patients. One may speculate that in these patients substantial amounts of interstitial fat have been concealed and that the redistribution of lipids to the extracellular compartment can be accounted for by ECM and the BIA technique. The redistribution of body fat compartments in critical and terminal illness, though of essential metabolic and quantitative importance, has not yet been acknowledged in evaluations of body composition changes during injury and infection.

About two-thirds of the total body water and 96% of body potassium are intracellular. The amount of intracellular magnesium is also high in comparison with the amount in the extracellular fluid. Therefore, changes in muscle water distribution and electrolyte composition in regions not adjacent to areas of damage or surgical injury should give valuable quantitative information about the generalised tissue and cell response to stress and infection. The most consistent effects of surgical trauma are increases in muscle water, sodium and chloride, whereas the predominant intracellular electrolytes, potassium and magnesium, are less affected.[12,18-20] The alterations seen in muscle composition following severe injury and sepsis are similar to those observed in postoperative trauma, but apparently more pronounced. Additionally, cell protein and the major intracellular cations, potassium and magnesium contents are decreased (Table II).[13,18] An evaluation of the decreased protein and increased extracellular water contents and the changes in electrolyte concentrations suggests a correlation of these variables with loss of cell content rather than of cell number.[13,20] This assumption is supported by conclusions drawn from BIA suggesting loss of intracellular protein in critically ill patients (Table I).

The findings seen in muscle tissue are consistent with the well-known effect of trauma on retention of water and sodium, determined by metabolic balance studies[21-23] and body composition studies using tracer techniques.[24,25] The finding of an increase in extracellular muscle water is of interest, because it proves that fluid retention occurs in non-injured portions of the body. Since muscle is the largest component of lean tissue, modest changes in muscle can have quantitative significance in explaining changes in the whole body. The results shown in Table II suggest that extracellular water in muscle tissue increases to 2 - 3 times the normal value with uncomplicated course of severe illness, which may represent no less than 150 - 200 ml excess water/kg muscle, or about 5 l fluid if uniformly distributed in the skeletal musculature. As shown in Table I, the patient may exhibit a considerably higher excess of ECM when sepsis and multiple injury are complicated by multiple organ failure.

It is generally assumed that convalescence from acute illness or injury includes diuresis of any fluid retained during the initial days of illness or injury. Therefore, it is surprising that abnormal water and sodium retention in muscle persists for as long as 30 days after injury or sepsis (Table II) and that high ECM is measured at discharge following sepsis and multiple trauma (Table I) when most patients would be expected to be beyond the period of diuresis.[26] In further support of a prolonged abnormality in muscle electrolyte metabolism are the observations that the muscle potassium content was low in late convalescence and that in many patients the muscle magnesium content was low on the 30th day, when considered in relation to fat-free solids or to muscle potassium (Table II). It is difficult to assess whether the decreased potassium and magnesium content is a sign of true intracellular depletion of these ions or simply an effect of decreased cellular mass in relation to total solids. On the other hand, both events may be expected to occur in depletion or in hypercatabolic situations as a result of ion leakage across the cell membrane and as a result of catabolic breakdown of cell protein. Nevertheless, these observations indicate that severe trauma and sepsis exert prolonged effects on tissue electrolyte and water metabolism, a phenomenon which is usually not considered, although it can seriously influence metabolism, substrate utilisation and, indeed, body composition in pathological conditions.

Several factors must be considered as possibly related to the aetiology of the observed composition changes. Prolonged periods of rest and inactivity certainly contribute to muscle protein loss and may influence the water and electrolyte contents. The classic work by Deitrick and co-workers suggests inactivity to be associated with muscle wasting, even if nutrition is adequate,[27] while semi-starved but active muscle is preserved. Clearly, bedrest for 4 days did not bring about most of the alterations in muscle, which were observed 3 - 4 days after operation or injury.[16,28] Except for the slight net loss of potassium, there were no significant changes in water and electrolytes. This suggests that the changes that occur after injury cannot be explained on the basis of inactivity associated with semi-starvation, and are probably trauma-related.

It is possible that cellular energy metabolism could be related to the findings since decreased contents of energy-rich phosphates and energy charge potential are common findings after injury and in critically ill patients.[15-17,29,30] Accordingly, ATP and adenine nucleotides are decreased after critical illness and remained so even at day 30.[31] Hence there is a possibility that the skeletal muscle cells remain metabolically deranged to the extent that a normal intracellular potassium content cannot be maintained. A low muscle magnesium content is consistent with this hypothesis. Magnesium is known to be bound in 80 - 85% of adenine nucleotides in the cell.[32] One would therefore expect a low tissue magnesium content when ATP, ADP and total adenine nucleotide values are low. Consequently, a significant correlation between the ATP/ADP ratio and intracellular magnesium has been demonstrated in the elderly, and in patients with respiratory and liver failure.[16,33-36]

There is also the possibility that nutrition was inadequate in respect of one or more specific nutrients, and that this contributed to the observed results.

The effects of nutritional therapy on body composition

For purposes of nutritional treatment, one may divide critically ill patients into four somewhat arbitrary groups: (i) malnourished, with no injury or sepsis; (ii) previously well nourished, acutely injured or septic; (iii) malnourished, injured or septic and who respond to nutritional efforts; and

(*iv*) malnourished, injured or septic patients, who cannot respond appropriately to nutrition.[37,36]

The long-term goal of nutritional therapy in malnourished critically ill patients without injury or sepsis is to restore BCM. The composition of weight loss caused by chronic starvation like anorexia nervosa is equally divided between BCM and fat. With fasting or acute starvation, the composition of the weight lost is about 70% BCM and 30% fat.[38,39] Undoubtedly, aggressive enteral or parenteral nutrition with high intakes of energy and protein might result in gains of both protein and fat in depleted critically ill patients during short-term therapy.[40]

Nutritional treatment of acutely ill, injured, septic or burned patients, whether complicated not or by malnutrition, is associated with severe problems. The obvious goal for these patients is minimisation of losses of BCM, especially to counteract the accelerated net breakdown of body protein. However, serial measurements of body composition[41] and substrate flux studies[42] indicate that it is extremely difficult to maintain or replenish body protein during situations of stress. Weight gain might be observed in patients treated with intravenous nutrition but that is more likely to be due to water retention and glycogen deposition than true gain in cellular protein;[43] 1 g of glycogen obligating about 3 g of water.[44,45] In critically ill septic patients 10 days of parenteral nutrition with 2 700 kcal and 130 g amino acids per day resulted in a considerable loss of body weight (6.2 kg). The share of protein loss was estimated to yield 1.5 kg, corresponding to 12.5% of the BCM, while body fat increased by 2.2 kg. Changes in body composition that occurred in patients with gastro-intestinal dysfunction receiving total parenteral nutrition (TPN) over a 2-week period are illustrated in Fig. 3. It is obvious that most of the weight gain can be accounted for by water and, to a lesser extent, fat. All but 2 patients revealed an average loss of protein of 1.1 kg.[5]

In a current investigation the effect of TPN on body composition was evaluated in 14 medical and surgical intensive care patients receiving energy corresponding to 1.6 basal metabolic rate and 1.5 g amino acids per kg ideal body weight (Table III). BIA was performed at onset of treatment and after 2 weeks on TPN. In comparison with results obtained in healthy controls a loss of body weight (20%) and BCM (17%) was observed. With the aggressive nutritional therapy employed, BCM remained essentially unchanged at completion (Fürst and Leweling — unpublished data). In other patients with a wide variety of gastro-intestinal diseases body weight was similarly reduced by 20% and total body protein by 21%[5] (Beddoe et al. — unpublished data) compared with the largest body of data on normal humans.[46] In critically ill patients a strong relationship between changes in BCM and energy and protein intakes was demonstrated.[47] Nutritional therapy with enteral or parenteral nutrition was directed toward maintenance of BCM and a reversal of stress- or malnutrition-induced depletion of BCM[47] in agreement with earlier claims.[7] Accordingly, an increase in BCM in response to nutritional efforts is only possible in the presence of a pre-existing malnutrition. This postulate is in keeping with the finding that the value of replenished BCM correlates with the degree of malnutrition, the Na_e/K_e ratio and with the amounts of nutrient infused.[48]
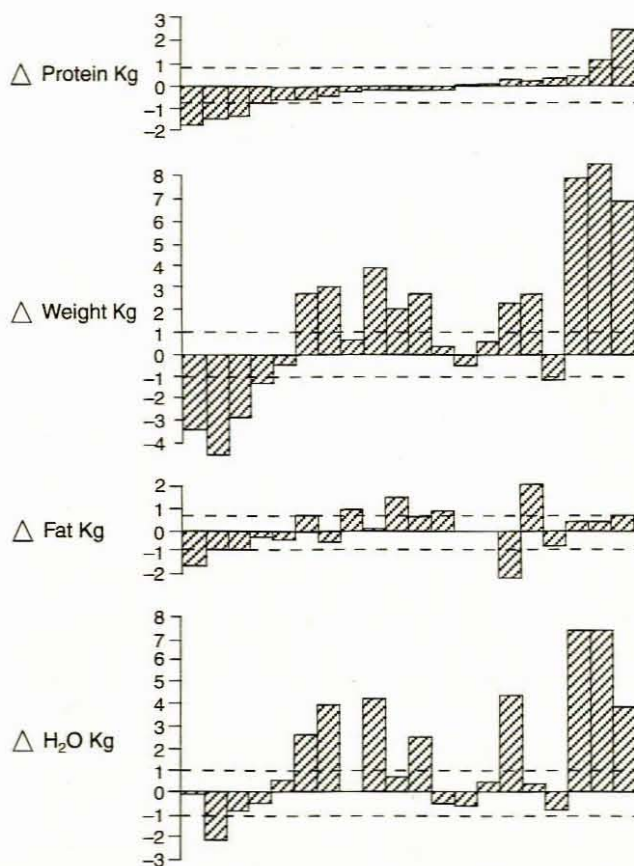

Fig. 3. Changes in body composition that occurred in 20 patients with gastro-intestinal dysfunction receiving TPN over a 2-week period. The broken lines indicate the maximum difference between the measurements, which can with 95% probability be attributed to measurement error alone. Most of the weight gain can be accounted for in terms of water. All patients but 2 revealed loss of protein. (From Hill and Beddoe[5] with permission.)

Table III. The effect of TPN in 14 medical and surgical intensive care patients (5 female and 9 male, age range 21 - 58 yrs, mean body weight 79.3 ± 2.2 kg) at onset and at completion of aggressive nutritional treatment (Energy: 1.6 RME and amino acids 1.5 g/kg ideal body weight). The results are compared with those obtained in 18 apparently healthy controls (age range 22 - 67 yrs, mean body weight 79.3 ± 2.2 kg). (Fürst P and Leweling H — unpublished data)

| | Normal | Critically ill patients | |
		Commencement of TPN	Completion of TPN
LBM (kg)	57.6 ± 1.3	48.7 ± 7.2	48.8 ± 7.4
BCM (kg)	26.5 ± 0.75	21.9 ± 3.6	22.0 ± 4.0
ECM (kg)	31.1 ± 0.7	26.8 ± 4.7	26.7 ± 4.7

LBM = lean body mass; BCM = body cell mass; ECM = extracellular mass.

As described, the alterations seen in muscle composition following postoperative injury[12,20] appear to be similar to those found in critically ill patients[13,18,19] and in patients with multiple trauma;[13,31] the changes are related to the severity of injury. It appears that the different nutritional regimens used did not influence the concentration changes observed in response to trauma. Neither different amino acid composition or hypocaloric or normocaloric supply of

energy revealed differences in post-traumatic muscle composition.[12] In critically ill, septic or burned patients similar findings were obtained, regardless of whether the energy intake was high or low, the glucose intake was high or low, or whether lipid was included in the intake.[31] The changes in muscle water and electrolyte values were essentially similar, whether amino acids were given during the first 8 days after the trauma or not.[13]

Although malnutrition is a severe complication in critically ill patients, it is not the primary cause of their illness and nutrition is considered a necessary adjunct to the primary therapy. With adequate therapy and nutrition the majority of these patients will finally respond with improved nitrogen balance and recovery, despite compromised body composition.[38] However, there is a subgroup of patients with chronic sepsis or multiple organ failure who are unable to respond to nutrition, remain in negative nitrogen balance, reveal pathological alterations in body composition and subsequently die. In malnourished injured and/or septic patients complicated by multi-organ failure, the considerable loss of body weight and body protein are consistent findings, despite maximum intravenous nutritional intakes and positive energy balance.[41] Increased release of catabolic hormones and reduction of the intracellular glutamine pool appear to be the hallmark of the response to injury and infection.[49-52] However, the underlying mechanisms of the alterations seen in body composition and the association of these changes with the metabolic responses to catabolism and subsequent wasting remain unclear.[53]

In this context a fascinating current hypothesis has been proposed emphasising the essential importance of cellular hydration state as a determinant of protein catabolism in health and disease.[54] It is postulated that an increase in cellular hydration (swelling) acts as an anabolic proliferative signal, whereas cell shrinkage is catabolic and antiproliferative.[55,56] Undoubtedly, hormone-induced changes in cellular hydration are seen as another 'second messenger' of hormone action.[57,58] Moreover, concentrative amino acid transport systems in the plasma membrane may also act as a signal transduction set-up, modifying cellular function by changing the hydration state. Low activities of amino acid transporter, Na+/H- antiport or Na-K-2Cl co-transport, and opening of potassium channels under the influence of altered nutrition, cytokines and free radicals, can all contribute to cellular shrinkage, which acts as the common end path, triggering net protein breakdown.[58-60] The hypothesis considers the activity of ion and substrate transport systems and, to a lesser extent, the size of the extracellular space. Indeed, expansion of the extracellular water is carefully considered by the physician; whereas changes in the intracellular water are largely ignored. Liver and muscle cells actually swell by as much as 10 - 12% within 2 minutes under the influence of glutamine and the increased cellular hydration is maintained as long as the amino acid is present;[59] this supports the notion that glutamine stimulates protein synthesis.[61-63] Changes in cellular hydration state might therefore be the variable which links muscle glutamine content to protein turnover and, because of the large muscle mass, the whole body nitrogen balance. Data from previous studies on the relationship between intracellular glutamine content and catabolism in patients with various underlying disorders enabled the

evaluation of the relationship between muscle-cell water content and whole-body nitrogen balance; an inverse relationship was demonstrated (Fig. 4.) The concentrated uptake of glutamine into muscle and liver cells would be expected to increase cellular hydration, thereby triggering a protein anabolic signal. Indeed, preparations containing glutamine dipeptides[64,65] may facilitate aggressive therapeutic interventions in order to improve cellular hydration state and subsequently modify or reverse catabolic changes.[66,67]
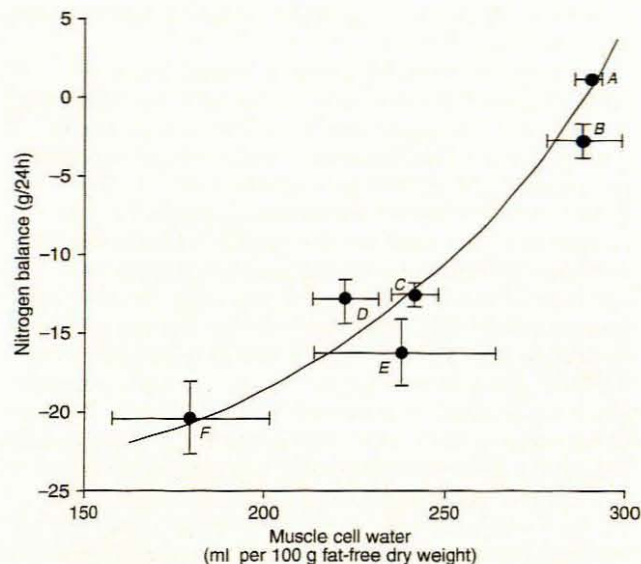

Fig. 4. Whole body nitrogen balance and cellular hydration of skeletal muscle. Healthy subjects (A) (N = 17); other subjects are patients suffering from liver tumours (B) (N = 5); polytrauma day 2 (C) and day 9 (D) after trauma (N = 11); acute necrotising pancreatitis (E) (N = 6); burns (F) (N = 4). Skeletal muscle water was assessed in biopsy specimens from musculus quadriceps femoris and the extra-/intracellular distribution was calculated by the chloride method, assuming normal membrane potential of −87.2 mV. (From Häussinger et al.[54] with permission.)

Although it may be possible to improve the course of critical illness with some more optimal form of nutrition than is presently known, it seems unlikely that, without improved treatment of the primary disease, improved nutrition will be decisive in body composition and recovery.

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