營養與身體組成間的相互影響

The interplay between nutrition and body composition

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Stress and malnutrition are associated with altered body composition. Extracellular fluid increases, with wt gain, but in response to stress BCM may gradually shrink with wt loss. In catabolic illness there is extracellular fluid expansion and erosion of AT and BCM. In stress, net loss of body fat was associated with interstitial accumulation of lipids preferentially in muscle, although BIA did not indicate increased fat and decreased water. Severe trauma and sepsis exerted prolonged effects on tissue electrolyte and water metabolism. Treatment of the critically-ill is of the primary illness. Nutritional therapy is an effective adjunct except in chronic sepsis or critical patients with MOF with great wt and protein loss. Glutamine dipeptides may help with cellular hydration and address catabolic changes.

Introduction

Injury, sepsis, malnutrition as well as dietary intake all have important effects on body composition and therefore, on the therapeutic approaches to be adopted. Indirectly these factors may also influence the goals of nutritional therapy.

Rapid weight loss, due to 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 ketoacidosis, 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. Severe complications are however to be expected during prolonged illness in nutritionally-depleted patients. In the long-term, these complications prolong convalescence and impede recovery[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, and on their accompanying physiological and biochemical effects, is required[5]. Recent technological advances, like nuclear medicine, radiology and medical physics have opened up new possibilities for measurement of body composition. However, there are considerable limitations in applying such measurements to clinical situations. Indeed, such methods are as yet confined to research centres and hospitals and their progression further into the community seems at present unlikely[6]. The need for simple and valid techniques is thus a growing concern of practitioners in clinical nutrition.

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

This paper will review the major common alterations in body composition during critical illness and identify stress-induced changes in the various body compartments and electrolytes. A further critical question is whether therapeutic and/or nutritional efforts influence beneficially the variety of alterations in critically-ill patients.

Body composition changes associated with trauma, sepsis and malnutrition

A meaningful discussion about disease-induced alterations of body composition needs a understanding of normal compartmentalization. In healthy volunteers the body is composed of two distinct non-osseous compartments: fat mass and fat-free body mass, the latter being composed of water, protein, minerals and glycogen[5,7]. Normal values of these components for a typical healthy adult are given in Figure 1. In normal individuals, adipose tissue composes 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 further subdivide both body water (plasma-intravessel, interstitial and intracellular water) and body protein (muscle protein, visceral protein and structural protein).

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

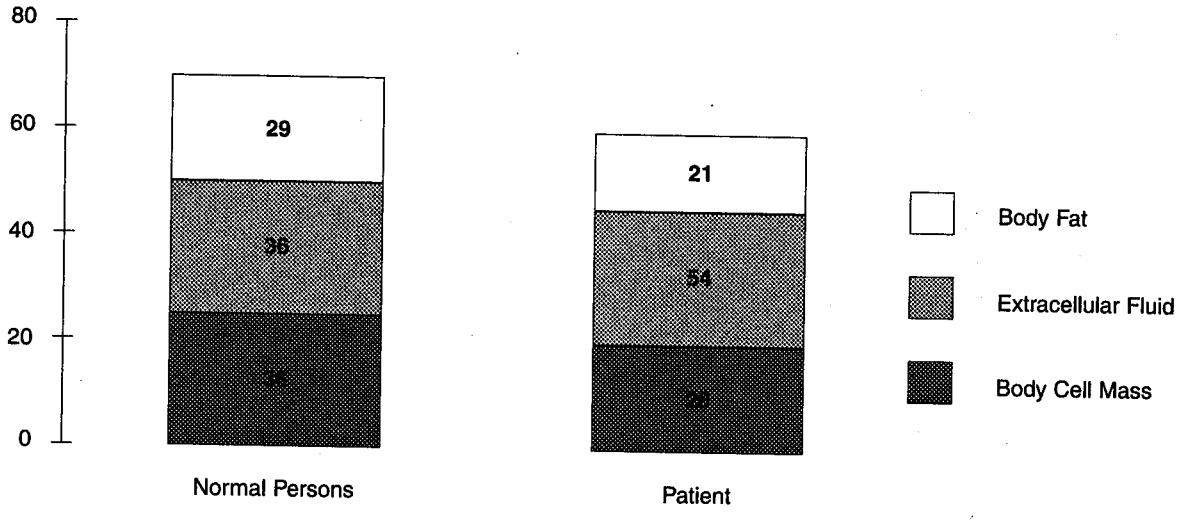

Figure 1. Normal body composition (%) and the components of weight changes in patients suffering from critical illness. Figures denote percent of body weight. Adopted from Shizgal, 1983[7] with permission.

Trauma-, injury-, sepsis or malnutrition-induced weight loss is due to the accelerated breakdown of body protein and fat. Using in vivo neutron activation analysis, tissue composition of the weight loss was measured two weeks after 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]. 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 share of protein corresponds to about 31 g/day. Body composition changes in patients suffering from critical illness as compared with normal values are illustrated in Figure 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 has been measured by using bio-electrical impedance analysis (BIA) in surviving and non-surviving septic and multiple trauma patients (Table 1). BIA measurements were performed daily at a single frequency (50 kHz, 800 μA; Danninger Medical Inc, Columbus/Ohio USA). Resistance and reactance were measured in triplicate and the mean was used for computerized calculation BCM, lean body mass (LBM) and extra cellular mass (ECM). The formulae of McDougall and Shizgall[9a] were used for these calculations. In these formulae, ECM is derived from the difference between LBM and BCM and ECM includes bone minerals. Compared with healthy subjects, 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 LBM. At discharge a tendency for normalization of ECM was observed in surviving patients, while with sepsis BCM remained low. 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) were detected. The results thus indicate that a considerable portion of BCM had been lost. Since the observed water shifts apparently did not directly affect the size of BCM, it may be assumed that the diminished mass seen was due to loss of fat and preferentially to substantial amounts of intracellular protein. The poor correlation between body water changes and the size 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 the requirement being covered via catecholamine-induced ↑cAMP mediated lipolysis[11]. It is notable that the net loss of body fat is associated with a simultaneous interstitial accumulation of lipids preferentially in muscle tissue. Interstitial fat has been measured in muscle biopsy specimens in patients suffering from various catabolic diseases as shown in Table 2. The data suggest that interstitial fat may increase multifold per unit of muscle fat-free dry mass[12–14]. The increment in injury or sepsis corresponds to not less than 28 g, and in severe burns 36 g, of interstitial lipid per kg muscle or about 700–1000 g in the whole body, assuming muscle mass is 40% of the body weight and a uniform

Table 1. Body composition in surviving and non-surviving septic and multiple trauma patients (n) receiving TPN over 8 – 20 days. Energy was given according to the actual requirements as measured by indirect calorimetry in form of equal amounts of glucose and fat. Amino acids 2.0 g per kg body weight were provided daily. All patients were mechanically ventilated. Non-surviving patients developed one or more multi-organ failure (MOF). Values are given as Mean ± SEM (Fürst P & Leweling H, unpublished).

Mass	Normal (8)	Septic				Multiple trauma			
		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.
*Differs significantly from normal ($P<0.05$).

Table 2. Muscle water and electrolytes in critically ill-patients[13] and in patients with liver cirrosis[14]. All values are calculated with 100 g fat-free solids (FFS) as the basis of reference (Mean ± SEM). Significance with normal values $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.

	Normal (85)	Multiple injury and burns (25) 8 day	30 day	Sepsis on admission (17)	Subsequent sepsis day 10 (6)	Convalescence day 20 (6)	Liver cirrosis (7)
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*	

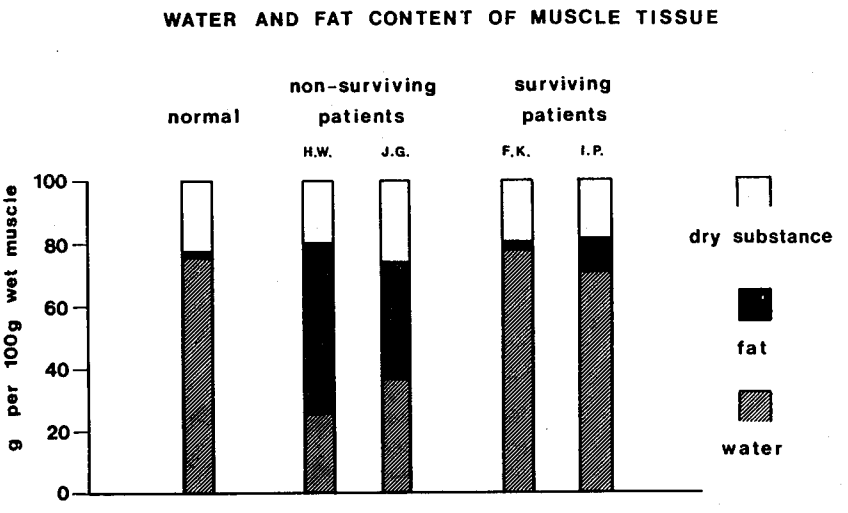

Figure 2. Water and fat content in muscle tissue in two surviving and two non-surviving patients as compared with the normal distributions. In the exceptionally degenerated muscle tissue from the non-surviving patients a considerable accumulation of the interstitial (extracellular) fat and marked decreased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

allotment of the lipids. Roth and co-workers observed exceptional degeneration of muscle tissue in two non-surviving burned patients (Fig 2). The lipid portion in muscle was 53% and 37% of the wet-weight, associated with a markedly decreased share of muscle water[14].

Thus it appears that, in critically-ill patients, increased lipolysis and augmented free-fatty acid flux coexist with decreased peripheral utilization of available fatty acids. This biochemical event is presumably due to diminished intracellular oxidative capacity caused by energy deficit of the sick cell[13,15–17]. In the light of these results it is remarkable that increased fat and decreased water contents are not shown by BIA in terminal patients. One may speculate that in these patients their substantial interstitial fat was not detected and thus that the redistribution of lipids to the extracellular compartment was simply accounted for by ECM. The redistribution of body fat compartments in critical and terminal illness, though of essential metabolic and quantitative importance, has not yet been acknowledged in the evaluations of body composition changes during injury and infection.

About two-thirds of total body water and 96% of body potassium are intracellular. The intracellular content of magnesium is also high in comparison with the content 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 generalized 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 kations, potassium and magnesium contents are decreased[13,18] (Table 2). An evaluation of the decreased protein and increased extracellular water contents, and the changes in electrolyte concentrations, suggest 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 1).

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 occurred 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 2 suggest that extracellular

water in muscle tissue increases to two to three 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 of fluid, if uniformly distributed in the skeletal musculature. As shown in Table 1, patients may exhibit considerable higher excess of ECM when sepsis and multiple injury is 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 Na^+ retention in muscle persists for as long as 30 days after injury or sepsis (Table 2), and that high ECM is measured at discharge following sepsis and multiple trauma (Table 1), at a time when most patients would be expected to be beyond a period of diuresis[26]. In further support of a prolonged abnormality of muscle electrolyte metabolism are the observations that the contents of muscle K^+ were low in late convalescence and that, in many patients, muscle magnesium was low on the day 30, in relation to fat-free solids or to muscle potassium (Table 2). It is indeed difficult to assess whether the decreased content of potassium and magnesium is a sign of true intracellular depletion of these ions or simply an effect of a 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 due to 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 may seriously influence metabolism, substrate utilization 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 thus inactivity certainly contribute to muscle protein loss and consequently 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 four days did not reveal most of the alterations in muscle, which were observed three to four days after operation or injury[18,28]. Except for the slight net loss of potassium, there were no significant changes in water and electrolytes. This suggest that the changes occurring following injury cannot be explained in the basis of inactivity associated with semi-starvation and are probably related to trauma.

It is possible that cellular energy metabolism may be related to the findings since decreased contents of energy-rich phosphates and reduced 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 K^+ content cannot be maintained. A low muscle magnesium level is consistent with this hypothesis. Up to 80–85% magnesium is known to be bound to adenine nucleotides in the cell[32]. Thus one would expect a low tissue magnesium content when ATP, ADP and total adenine nucleotides are low. Consequently, a significant correlation between 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, finally, the possibility that nutrition was inadequate with regard to one or more specific, nutrients, contributing 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: (1) malnourished, remote from injury or sepsis; (2) previously well-nourished, acutely injured or septic; (3) malnourished, injured or septic who respond to nutritional efforts, and (4) malnourished, injured or septic patients who cannot respond appropriately to nutrition[37,38].

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 due to chronic starvation, eg in anorexia nervosa, is equally divided between BCM and fat. With fasting or acute starvation the composition of weight loss is about 70% of BCM and 30% fat[38,39]. Undoubtedly, aggressive enteral or parenteral nutrition, with high intakes of energy and protein, may lead to gain in both protein and fat in depleted critically-ill patients during short-term therapy[40].

Nutritional treatment of acutely-ill, injured, septic or burned patients, with or without malnutrition, is associated with severe problems. The obvious goal for these patients is to minimize losses of BCM in order 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 stress. Weight gain may be observed in

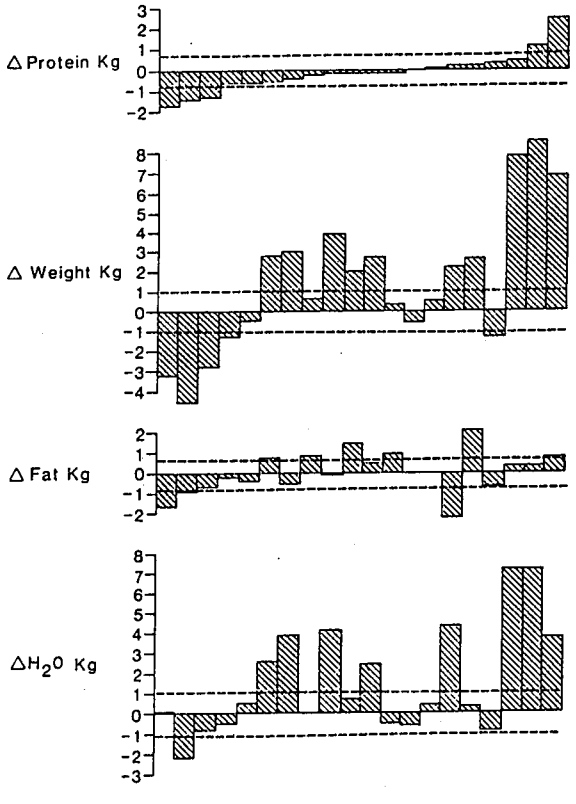

Figure 3. Changes in body composition that occurred in 20 patients with gastrointestinal dysfunction receiving TPN over a 2-week period. The broken lines indicate the maximum difference between the measurements, which can with 95% probability to be attributed to measurement error alone. Most of the weight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

patients treated with iv nutrition but 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 2700 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 gastrointestinal dysfunction receiving TPN over a two-week period are illustrated in Figure 3. It is obvious that most of the weight gain can be accounted for in terms of water and, to a lesser extent, to fat. All patients but two revealed loss of protein, on average 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 RME and 1.5 g amino acids per kg ideal body weight (Table 3). 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 & Leweling, unpublished). In other patients with a wide variety of gastrointestinal diseases body weight was similarly reduced by 20% and total body protein by 21%[5] (Beddoe et al., unpublished),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 were demonstrated[47]. Nutritional therapy with enteral or parenteral nutrition was directed toward maintenance of BCM and a restoration 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 conforms with the finding that the repletion value of BCM was correlated with the degree of malnutrition, the Na_e/K_e ratio and with the amounts of nutrient infused[48].

As described, the alterations seen in muscle composition following post-operative 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 were related to the severity of injury. It appears that the different nutritional regimens used were without influence on the concentration changes observed in response to trauma. Neither different amino acid composition nor hypocaloric nor 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, and whether lipid was included in the intake[31]. The changes in muscle water and electrolytes were essentially similar whether amino acids were given or not during the first eight days after the trauma[13].

Table 3. The effect of TPN in 14 medical and surgical intensive care patients (5 F and 9 M, age range 21 – 58, mean body weight 79.3 ± 2.2) 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, mean body weight 79.3 ± 2.2) (Fürst P & Leweling H, unpublished).

	Normal	Critically ill patients	
		onset 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.

Although malnutrition is a severe complication in critically-ill patients, it is not the primary cause of their illness and nutrition is a necessary adjunct to the primary therapy. The majority of these patients with adequate therapy and nutrition will finally respond with improved N-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 N balance, undergo pathologic alterations in body composition and subsequently die. In malnourished injured and/or septic patients complicated with multi-organ failure, the considerable loss of body weight and body protein are consistent findings, despite maximum iv nutritional intakes and positive energy balance[41]. Increased release of catabolic hormones and reduction of intracellular glutamine pool appear to be the hallmark of the response to injury and infection[59–52]. However, the underlying mechanisms for the alterations seen in body composition, and the association of these changes with the metabolic responses to catabolism and subsequent wasting, remain unclear[53].

A fascinating current hypothesis has been proposed emphasizing the essential importance of the 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 transduction signal set-up, modifying cellular function by changing

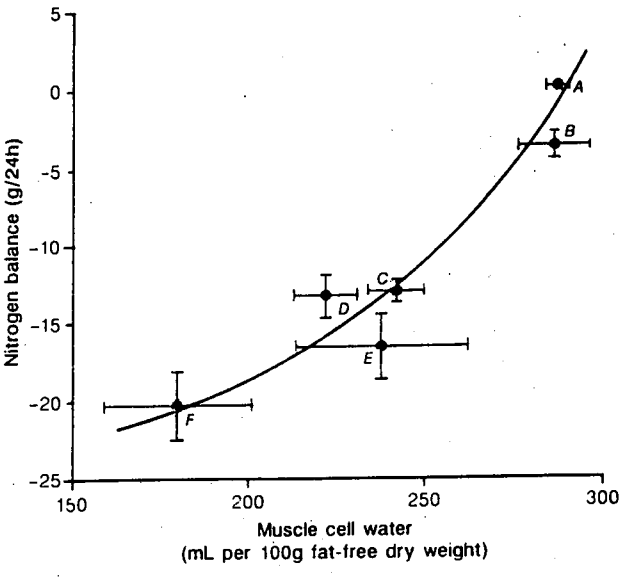

Figure 4. Whole body nitrogen balance and cellular hydration of skeletal muscle. A = healthy subjects (n = 17); other subjects are patients suffering from liver tumours = B (n = 5); polytrauma day 2 = C and day 9 = D after trauma (n - 11); acute necrotizing pancreatitis = E (n = 6); burns = F (n = 4). Skeletal muscle water was assessed in biopsy speciments from m. quadriceps femoris and the extra-/intracellular distribution was calculated by the chloride method, assuming normal membrane potential of -87.2 mV. For references cf Bergström et al., 1981 and 1987[12,13]. From Häussinger et al.[54] with permission.

the hydration state. Low activities of amino acid transporter, Na^+/H^+ antiport or Na-K-2Cell co-transporter, and opening of K^+ 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 contemplates the activity of the ion and substrate transport system and, to a lesser extent, the size of the extracellular space. Indeed, expansion of extracellular water is carefully considered by the physician, whereas changes of intracellular water is largely ignored. Liver or muscle cells swell as much as 10–12% within two minutes under the influence of glutamine and increased cellular hydration is maintained as long as the amino acid is present[59], supporting the notion that glutamine stimulates protein synthesis[61–63]. Thus, changes in cellular hydration state may be the variable linking muscle glutamine content with protein turnover and, because of the large muscle mass, whole body nitrogen balance. Data from previous studies of the relation between intracellular glutamine content and catabolism in patients with various underlying disorders enabled the evaluation of the relation between muscle – cell water content and whole body nitrogen balance, showing an inverse relation (Fig. 4). The concentrative uptake of gluatime 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 therapeutical inter-ventions by improving the cellular hydration state and subsequently modifying or reversing catabolic changes[66,67].

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 however unlikely that, without improved treatment of the primary disease, improved nutrition will be decisive in influencing body composition and recovery.

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