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Position paper of the ESICM Working Group on Nutrition and Metabolism

Metabolic basis of nutrition in intensive care unit patients: ten critical questions

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Abstract The metabolic changes associated with critical illness involve several pathways acting at different steps of the utilization of nutritive substrates. The understanding of the role of these pathways and of their complex regulation has led to the development of new strategies for the metabolic and nutritional management of critically ill patients, including the development of new products for nutritional support. The rationale for changing the profile of nutritional support solutions by adding novel substrates is also discussed. This review focuses on the metabolic specificities of critically ill patients and also includes an analysis of the adequacy of tools to monitor the metabolic status and the adequacy of the nutritional support.

Keywords Critical illness · Stress · Nutritional support · Nutritional assessment · Metabolism

Introduction

Critically ill patients are characterized by a number of alterations in carbohydrate (Fig. 1), lipid (Fig. 2), amino acid and protein (Fig. 3) metabolism. These changes lead to increased energy requirement and protein catabolism and contribute to alterations of the immune system and the gastrointestinal tract. The acute phase response to stress is probably designed to provide energy and substrates for protein synthesis and cell replication in visceral tissues (i.e., liver, gut, immune cells, wound tissue, etc.). However, during prolonged intense stress, a severe depletion of body stores may adversely affect the morbidity and mortality of patients and delay the recovery from illness. Therefore, a number of therapeutic approaches have been developed in an attempt to improve the efficacy of conventional nutritional support [1, 2]. The present paper raises ten clinically relevant questions focused on the metabolic therapy of the critically ill patient, but is not intended to be a systematic review of the literature.

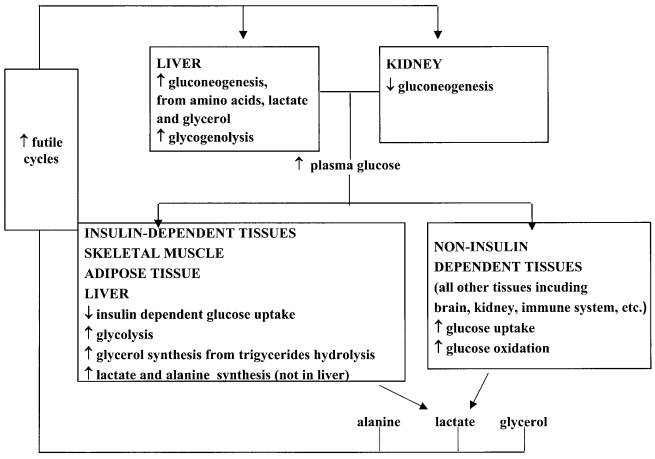

Fig. 1 Changes of glucose metabolism during critical illness. An increased hepatic glucose production and a decreased insulin-mediated glucose utilization in skeletal muscle and adipose tissue are the main causes of hyperglycaemia. The rate of glycolysis is increased in the immune system, wound tissue, lung and skeletal muscle, resulting in an accelerated production of pyruvate. The excess of pyruvate is reduced to lactate (by the lactate dehydrogenase) or aminated to alanine (by the alanine aminotranferase). Lactate, alanine and glycerol deriving from an accelerated lipolysis are used by the liver as gluconeogenetic substrates. Lactate production is further accelerated during hypoxia or tissue hypoperfusion

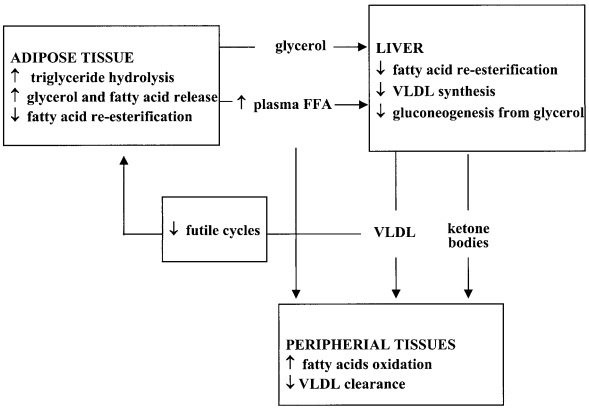

Fig. 2 Changes of lipid metabolism during critical illness. Endogenous lipids represent the main source of energy in critical illness when nutritional support is insufficient. In the adipose tissue, triglycerides (TGs) are hydrolysed at a high rate to release free fatty acids (FFAs) and glycerol into the bloodstream. Mobilization of FFAs is markedly increased with a resulting depletion of intracellular TG stores that cannot be efficiently inhibited by infusions of carbohydrates. In peripheral tissues the oxidation of FFAs is increased to produce energy. In the liver FFAs are converted to ketone bodies or re-esterified to TGs and released into the bloodstream as very low density lipoprotein (VLDL), whose clearance is impaired. Plasma FFA levels are increased proportionally to the severity of the injury, as FFA production exceeds FFA utilization

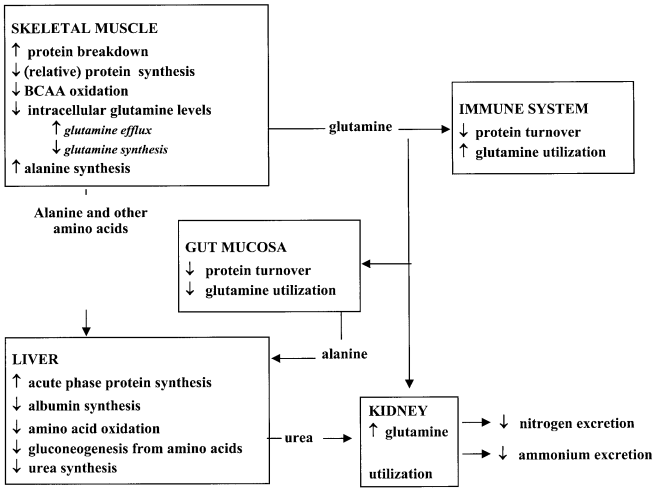

Fig. 3 Changes of protein and amino acid metabolism during critical illness. The loss of muscle mass results mainly from a sustained increase of the rate of protein breakdown. Skeletal muscle is the main tissue involved in glutamine production and serves as a reservoir of the free amino acids. Patients are characterized by a severe depletion of the intramuscular glutamine pool and an increased glutamine requirement in the gut, liver, kidney, immune system and wound tissue. In these tissues glutamine is utilized as a major fuel for rapidly dividing cells and as a precursor for gluconeogenesis, nucleotide synthesis, ammonia excretion and glutathione formation. Mechanisms of intramuscular glutamine depletion involve an increased glutamine efflux and a decreased rate of glutamine de novo synthesis. The massive protein breakdown, mainly from skeletal muscle, is partially compensated by an increase in the rate of protein synthesis in visceral tissues (i.e., liver, gut, immune cells, wound tissue, etc.). The excess of amino acids is oxidized in the liver and in muscle (the branched chain amino acids) and the nitrogen excreted by the kidneys

1. What are the key effectors of metabolism in the critically ill?

In physiological conditions, metabolic pathways are largely regulated by circulating hormones, inflammatory mediators, neurotransmitters, changes in organ blood flow and body composition and by the loss of physical activity. The quantitative roles of these different pathways in the clinical setting are still largely unknown.

The hormonal regulation of metabolic substrates in physiological conditions is briefly described in Table 1. During critical illness, typical alterations of hormone secretion and action include increased secretion of cortisol, glucagon and the catecholamines, decreased secretion of testosterone and insulin-like growth factor-1 (IGF-1) and resistance to the combined effects of insulin and growth hormone [3] and growth hormone alone [4]. Nonetheless, these hormonal changes may explain only in part the metabolic alterations of the patients. The endocrine system interacts with other factors to induce the metabolic response. Inflammatory mediators, such as cytokines and eicosanoids, affect metabolic pathways either

Table 1 Main hormones involved in the endocrine regulation of protein, carbohydrates and lipid metabolism

	Anabolic	Catabolic
Protein	Insulin Growth hormone Insulin-like growth factor-1 Testosterone Catecholamines	Cortisol Glucagon Catecholamines
Carbohydrate	Insulin	Cortisol Glucagon Growth hormone Catecholamines
Fat	Insulin	Catecholamines

directly, at the cellular level, or indirectly by altering regional blood flow. In the liver, interleukin-6 regulates the synthesis of the acute phase proteins. Tumour necrosis factor-alpha (TNFα) and interleukin-1 can potentially mediate most of the metabolic alterations seen in critical illness such as accelerated gluconeogenesis, protein degradation, the increase of energy expenditure and the decreases of muscle protein synthesis, lipoprotein lipase activity and the clearance of very low density lipoproteins (VLDL).

In addition to these humoral mediators, a low level of physical activity and an inappropriate nutritional support may also contribute to the metabolic alterations of the patients. An example of the synergy of action between different catabolic factors is shown in a recent study demonstrating that physical inactivity amplifies the catabolic effects of cortisol on muscle protein degradation [5]. In critical illness, tissue perfusion can be either decreased or increased. The release of free fatty acids (FFA) from adipose tissue is markedly decreased when blood flow is limited [6], whereas an increased tissue blood flow may promote glucose and amino acid utilization [7]. Furthermore, a decrease in cellular hydration may lead to tissue protein catabolism [8]. Cell shrinkage appears to be a catabolic signal, whereas cell swelling is an anabolic phenomenon. Cellular hydration is regulated by the intracellular concentrations of ions and metabolites like glutamine. It has been hypothesized that modification of cellular hydration could be the link between the depletion of intracellular glutamine and muscle protein catabolism in diseased states.

2. Is protein metabolism something a clinician has to care about?

Proteins are the basic compounds that represent biological life. In this sense protein metabolism is, of course, of the utmost importance for any clinician. The efficiency of protein metabolism needs sufficient protein and energy intake. Many factors influence constantly occurring protein breakdown and synthesis (Fig. 3). In the healthy adult there is presumably a steady state in which synthesis and degradation are similar, at least over a period of 24 h with normal intake and activity. Small changes in either synthesis or degradation or both may result in considerable changes in body composition over time [2].

Nitrogen balance is an investigational tool used in clinical studies to evaluate the efficacy of nutritional treatment. Nitrogen balance closely reflects net protein metabolism, and a negative nitrogen balance indicates a net loss of proteins. The shortcoming with such a measure is that it looks upon the human body as a black box. There are differences between organs and tissues that are not reflected on a whole body basis. Nitrogen balance measurements should be measured only once the patient is fully adapted to the intake of energy and nitrogen. Today protein metabolism is often studied with the help of isotopic labels and with the help of molecular biology. Both represent valuable tools in the research of protein metabolism. However, interpretation of data in a clinical perspective is sometimes controversial, and some level of expertise may be needed [9]. It is conceivable that in the near future simple methodologies will be available to clinicians to measure protein kinetics accurately in patients with stable isotopes.

The minimum requirement of individual amino acids has been established in healthy individuals [10]. The applicability of these results to patients is not fully confirmed in clinical studies. Some amino acids, although non-essential, may become critical in diseased states, such as tyrosine for uraemic patients, glutamine and cysteine for catabolic patients, and taurine for neonates. However, these amino acids are not essential in a strict sense. As a nutrient, proteins and amino acids have a high thermogenic coefficient. This means that they cannot be stored, but have to be metabolically handled, which requires energy and results in heat production. Therefore a very high nitrogen intake may be associated with an increase in body temperature, something that happens in health as well as in disease [11]. In patients this may be a metabolic burden which is undesirable. Therefore the protein intake should be balanced and tailored to the individual patient according to his/her needs. A protein intake between 1.2 and 1.5 g/kg per day is usually recommended [12].

3. Is muscle depletion dangerous for the critically ill patient and can it be prevented?

Although substantial mortality can be related to protracted fasting and extreme muscle depletion, the critical level of muscular wasting has not yet been defined in critically ill patients. However, muscle protein depletion in critical illness is faster and more extensive than can be expected from inactivity alone [13]. Proteins are degrad-

ed into constituting amino acids but glutamine and alanine, synthesized by transamination, are released in large excess regarding their relative abundance [14]. In the splanchnic area glutamine is mainly used as oxidative substrate or as a precursor for nucleotide and glutathione synthesis while alanine is used for gluconeogenesis (Fig. 1), ammonia being converted to urea. This export of glutamine is necessary for the immunocompetent cells and the enterocytes. Low glutamine availability [15] may lead to a relative immune insufficiency and to altered permeability of the intestinal wall. The release of amino acids from muscle is eventually impaired as depletion develops. Therefore, in these situations glutamine has been termed "conditionally essential", to describe the situation in which insufficient amounts of glutamine are produced. On the other hand, muscle mass depletion resulting from glutamine release might be associated with increased morbidity and mortality [16]. In elderly patients, the full restoration of the lost muscle protein mass is unlikely.

Muscle protein depletion cannot be totally prevented, but adequate nutritional support, mobilization and good metabolic care are especially desirable as they can slow down the process [17]. Sufficient energy and nitrogen intakes are therefore important. Mobilization and physiotherapy are also important to save muscle mass as well as muscle force, while electrical stimulation has been tried with some success [18]. It has been reported that growth hormone, anabolic steroids, testosterone and insulin have beneficial effects on muscle metabolism but were not associated with an unequivocal improvement in outcome, except for insulin (see question 8). In the case of growth hormone, while beneficial effects were reported in many smaller studies (see 19 for review), an increase in mortality was reported in a large study of supplementation [20]. Therefore, the use of growth hormone, anabolic steroids and testosterone cannot be recommended at present.

4. Which metabolic conditions require a specially designed amino acid solution?

Amino acid metabolism is profoundly altered in critically ill patients. Most papers report a decrease of total amount of plasma amino acids, with an increase in phenylalanine and tryptophane and a decrease in leucine, isoleucine and valine [21]. The concentrations of nearly all amino acids are decreased in the liver. In contrast, the intracellular muscle content of free glutamine is depleted in the critically ill, and branched chain amino acids are increased [13, 22]. Finally, plasma glutamine seems to be a marker related to the prognosis of critically ill patients, while the levels of branched chain amino acids in plasma are not reflected in skeletal muscle concentrations [23]. Such changes in amino acid metabolism in critical illness raised the question of the clinical relevance of plasma levels. New amino acid solutions were developed. A high amount of branched chain amino acids was correlated with an anti-catabolic effect. Recently, a prospective, randomized, controlled trial showed that a high level of branched chain amino acid supply reduced the ICU mortality rate [24].

It could be noted that the amount of branched chain amino acids and of glutamine administered exceeded the demand for these amino acids as nutritional substrates by far. Therefore, in these circumstances such high amounts of specific amino acids seemed to have a pharmacological effect [24]. A milestone in this development was the discovery of the role of arginine as the unique precursor of nitric oxide, a mediator of a variety of physiological effects. The administration of arginine may then theoretically influence vascular relaxation, inhibit platelet aggregation, activate macrophages and influence the oxygen radical metabolism. Infusion of arginine in an experimental model improved cardiac output and liver blood flow and reduced pulmonary vascular resistance [25]. In clinical studies performed in critically ill patients with enteral nutrition containing arginine (in combination with omega-3 fatty acids and nucleotides), reductions in infection rate, ventilatory days and hospital length of stay were reported [26]. However, this issue is a matter of debate, especially since the publication of a large meta-analysis [27], discussed in question 10.

What about the future? Interestingly, the number of publications showing that amino acids affect the immune system is rising. An immunoregulatory property was described for glutamine, arginine, cysteine, taurine and glycine. Three of them, namely glutamine (via glutamate), glycine and cysteine are precursors of glutathione, which is involved in the oxidant/antioxidant metabolism of the cell. Critical illness can lead to depletion of glutathione stores in tissue and plasma, which subsequently may impair T-cell and macrophage immune function [28]. Therefore, some of the immunomodulating amino acids may act via stimulation of glutathione synthesis. However, a clear delineation of the metabolic conditions that could benefit from an especially designed amino acid solution is still lacking at present.

5. Do all critically ill patients need glutamine supplementation?

In critically ill patients, glutamine can become an essential amino acid, as their body stores and the rate of synthesis of this amino acid are rapidly decreased, despite an increased rate of synthesis through transamination in skeletal muscle concentrations [23]. Physiological functions requiring glutamine include gluconeogenesis, the provision of substrate for the Krebs' cycle (except for immune cells and enterocytes), the synthesis of proteins,

glutathione and nucleotides. Hence, supplemental glutamine might be beneficial in a severe catabolic state, when facing a major oxidative stress, or in patients in whom the maintenance of a high cell replication rate is critical, i.e. during severe infection or in the case of gut mucosal atrophy. Most patients suffering from a prolonged critical illness will probably undergo at least one of these disorders. However, the categories of critically ill patients who should benefit from glutamine-enriched nutritional support have not yet been defined.

The available large-scale clinical trials performed in intensive care units studied the effects of glutamine in enteral solutions following multiple trauma [29] or in parenteral solutions in medical or surgical patients unable to tolerate enteral feeding [30, 31]. Significant decreases in infectious morbidity and 6-month mortality, respectively, were reported, paving the way for the recommendation of the routine use of glutamine-enriched nutritional formulas in every long-term critically ill patient. Importantly, a decrease in septic morbidity following enteral glutamine supplementation was reported in one study [29], but not in another [32]. Additional trials are mandatory to delineate clearly which patients are susceptible to benefit from glutamine supplementation and to define the optimal modality of administration. At present the preliminary evidence available supports the use of glutamine in the artificial nutrition administered to the patients undergoing the heaviest metabolic stress, i.e. trauma (including burns), sepsis and post-surgical patients.

6. Why do we need new fat emulsions?

The utilization of lipids is profoundly altered during critical illness. Stress is associated with substantial changes in fat metabolism brought about by hormones or cytokines [33]. Peroxidation of lipids (FFA) results in the formation of toxic and unstable lipid peroxides.

The clearance of lipid emulsions can be reduced to various extents depending on clinical conditions (e.g., sepsis, hepatic and renal failure, disorders of lipid metabolism, etc.) and on chemical composition. Therefore, the triglycerides (TGs) incorporated in lipid emulsion have been changed, in order to minimize the risk of toxicity associated with the traditional soybean-derived long-chain TG (LCT, >18 carbon atoms) solutions. Metabolic differences related to the nature of exogenous TG can involve each step of the pathway. Lipoprotein lipase (LPL) activity depends on various factors including fatty acid chain length. Metabolism of LCT solutions and fish oil TGs rich in n-3 fatty acids is slower than medium-chain TGs (MCT), either as a physical mixture with LCT or as structured TGs. The inhibitory effect of non-esterified FFA on LPL is stronger in the case of LCT, as compared to MCT [34]. Remaining TGs escaping from LPL hydrolysis are transferred to high- or low-density lipoproteins, and the remnants are taken up by the liver and extra-hepatic tissues and subsequently undergo intracellular lipolysis in lysosomes.

Remnants from mixed MCT/LCT and from n-3 fatty acid emulsions are smaller and more rapidly cleared from the circulation than those from LCT solutions [35]. LCT and, to a lesser extent, the MCT emulsion are susceptible to peroxidation, due to high concentrations of polyunsaturated fatty acids and low alpha-tocopherol content. In contrast, the olive oil containing emulsions have a high content of monounsaturated fatty acid, together with a high content of antioxidant, that might reduce the risk of peroxidation. The MCT emulsions provide more essential fatty acids than the others for incorporation into membrane phospholipids [36]. The n-3 fatty acids incorporated into cell membranes can be converted into less inflammatory and non-thrombogenic eicosanoids than those derived from arachidonic acid. Although very attractive, these biochemical advantages need to be assessed and possibly translated into clinical benefit in large-scale trials.

7. Which proportion of omega-3 versus omega-6 fatty acids is desirable for the modulation of immune system?

The n-6 and n-3 polyunsaturated fatty acids (PUFA) are enzymatically converted into a series of oxygenated metabolites called eicosanoids. The n-6 PUFAs are found in vegetable oils, such as soybean and safflower, whereas the n-3 are contained in fish oils. They are essential nutrients because of the inability of humans to desaturate long-chain organic acids at the n-3 and n-6 positions. The n-6 and n-3 PUFAs are metabolized by the same enzymes, making them competitive. Nonetheless, the n-3 PUFA are the precursors of less inflammatory eicosanoids than n-6. While eicosanoids derived from n-6 PUFAs are generally proinflammatory, prothrombotic and chemoreactant, the n-3 PUFAs are able to decrease the production of proinflammatory cytokines and reactive oxygen species and the reactivity of lymphocytes. Furthermore, n-3 PUFAs also modulate several nuclear transcription factors (e.g., the peroxisome proliferation activator receptor, the nuclear factor kappa B, etc.) and influence gene expression. On this basis, selective dietary supplementations with n-6 and n-3 PUFAs in different proportions have been clinically used to influence the course of immunological and inflammatory processes [37]. In selected chronic inflammatory states, such as ulcerative colitis, Crohn's disease, rheumatoid arthritis, psoriasis and transplant recipients, dietary supplementation with n-3 PUFAs has been associated with some clinical benefits.

The immunomodulating properties of the n-3 PUFAs have led to applications also in critically ill patients [36].

In these patients the optimal effect can probably be achieved through the parenteral administration of n-3 PUFA containing lipid emulsions. The effects of the n-3 PUFA enriched solutions are dependent not only on their absolute content in n-3 PUFAs but also on the n-6/n-3 ratio. Soybean- and olive/soybean-containing lipid emulsions have a n-6/n-3 ratio of about 7:1 and 9:1, respectively. In the usual diet of Western Europe and North America, the n-6/n-3 PUFA ratio averages 10:1 (range 7.5:1–20:1), while most authorities agree that it should be less than 5:1. On this basis, a ratio of n-6/n-3 PUFAs of 4:1 to 2:1 has been recommended for critically ill patients [38]. In the septic patients, an early hyperinflammatory period and the late phase with features of paralysis of the immune system can often be observed. Therefore, in theory, parenteral administration of lipid emulsions with low n-6:n-3 PUFA may lead to a rapid and marked anti-inflammatory effect, whilst the use of the same mixture in the late phase of sepsis may potentially result in a patient's decreased ability to counteract the infection.

8. What is the optimal blood glucose level in critically ill patients?

In acute illness plasma glucose levels are often increased (Fig. 1) and generally parallel the severity of stress. Common adverse effects of hyperglycaemia are listed in Table 2. Hyperglycaemia may be particularly severe in the ageing and in patients with diabetes mellitus, obesity, liver cirrhosis or chronic uraemia. In these conditions, the achievement of "good" control of glycaemia may require high doses of insulin and frequent blood glucose determinations to prevent both hyperglycaemia and hypoglycaemia. Besides its effects on glycaemia, insulin itself may exert beneficial effects on the myocardium.

In the clinical setting, the management of glycaemia (usually maintained at <13 mmol/l) includes appropriate amounts of insulin and carbohydrates. Recently, a prospective, randomized, controlled trial [39] included 1548 patients admitted to the ICU (post-cardiac surgery for 67%) and receiving either intensive insulin therapy, titrated to maintain glycaemia between 4.4 and 6.1 mmol/l, or conventional insulin therapy. Intensive insulin therapy was associated with a 40% reduction in mortality rate. This unique finding strongly suggests that tight glycaemia control may improve the outcome of ICU patients and should be confirmed before routine implementation. Studies in surgical patients indicate that early perioperative hyperglycaemia is an important predictor of subsequent nosocomial infections in the postoperative period [40, 41, 42]. In severely burned children poor control of glycaemia was associated with a greater incidence of infection, impaired wound healing and increased mortality [43]. In the critically ill patients, therefore, hyperglycaemia should be considered both a sign of underlying infections and a risk factor for future infection [44]. Evidence indicates that an intensive insulin treatment aimed at maintaining control of glycaemia lower than 6 mmol/l may be an effective means to prevent infectious complications.

Table 2 Adverse effects of hyperglycaemia

Electrolytes and fluid imbalance
Dehydration
Increased susceptibility to infections
Increased coagulability • platelet aggregation • coagulation factors • fibrinogen, plasminogen activator inhibitor (PAI)-1, von Willebrand factor
Impaired wound healing
Decreased antibacterial function of polymorphonuclear leucocytes • adhesion capacity • chemotaxis • phagocytosis, superoxide radical production

9. How to assess the adequacy of nutritional support?

As critical illness is associated with several electrolytic and metabolic disturbances, no single marker has been validated as specific for the nutritional status of critically ill patients. Studies of body composition could fulfil this role, but their are presently not useable for routine monitoring in ICU patients. In fact, nutritional markers should serve the dual purpose of ensuring that sufficient amounts of substrates are administered to meet the patients' needs while alerting the clinician to any untoward effects on various key organ functions [45]. They should also be both easily and rapidly available in all hospitals, and be cost-effective. Abnormal plasma levels of any of these markers are often influenced by factors other than nutritional support, such as over/dehydration, acute phase response, sepsis or organ dysfunction.

Besides the increase in blood glucose levels related to increased glycogenolysis and gluconeogenesis (Fig. 1), utilization of glucose by insulin-sensitive tissues is decreased in acute inflammatory conditions [46]. Hence, hyperglycaemia is more often documented than hypoglycaemia in critical illness, and its presence does not necessarily imply excess substrate administration. Hypoglycaemia can nonetheless occur in acute liver failure, exogenous insulin treatment, interruption of glucose or feeding solution administration.

Serum TG levels provide valuable information, mostly pertaining to excessive infusion of lipids and carbohydrates. In the clinical setting, excessive glucose loads stimulate lipid production, which in extreme cases can

lead to acute hepatic steatosis, especially if a large amount of insulin is given concomitantly [47]. Serum TG elevations can also occur as a consequence and maybe as a cause of acute pancreatitis, prompting their close monitoring in this condition [48] or in cases of pre-existing hyperlipidaemia.

The metabolism of usual markers of body protein status (albumin, transferrin, pre-albumin) is markedly influenced by the acute phase response. Therefore, plasma concentrations of these markers are deeply altered by the patient's hydration state and exsudation at the capillary level while providing little qualitative information, since total protein levels can be maintained at the expense of muscle protein stores. This concept is supported by the observation that the correction of hypoalbuminaemia by the intravenous administration of albumin does not improve clinical outcome [49].

Potassium, phosphorus, calcium and magnesium levels are useful markers of adequate supplementation with these key electrolytes and should be monitored on a frequent and regular basis (once a day for potassium, 2–4 times a week for the others) [45] according to expected risks for abnormalities (i.e. renal failure with/without replacement therapy, hyperparathyroidia, bone malignancy, etc.).

Finally, liver function tests (transaminase and bilirubin) should be monitored every other day, especially during total parenteral nutrition (TPN), due to its higher associated incidence of hepatic dysfunction [45] or in cases of acute hepatitis.

10. What are the main "novel substrates" and how likely are they to influence the metabolic response?

Recently, attention has focused on the relationship between the severity of the inflammatory response and mortality. Patients who did not survive sepsis [50] or cerebral malaria [51] elicited a much higher TNFα response than did survivors. These findings have provided the framework for therapeutic strategies based on either anti-cytokine antibodies or nutritional modulation by "novel substrates" [52]. Novel substrates can act at different points of the inflammatory response by (1) downregulating excessive cytokine production (Type 1) or (2) upregulating the immune response to infection (Type 2) or (3) by reducing the secondary effects of TNFα, IL-1 and IL-6 which may lead to multiple system organ failure (Type 3), or (4) by preserving organ function in the face of this high catabolic drive (Type 4). Molecules under development will not be reviewed. The novel substrates which have been investigated include lipids (see questions 6 and 7) and nucleotides (Types 1 and 3), glutamine and ornithine α-ketoglutarate (Types 2 and 4) arginine (Types 1 and 4) and sulphur amino acid derivatives (Type 4).

Glutamine supplementation (see question 5) has been associated with enhancement of immune responsiveness, decrease in number of infections and improved survival in critically ill patients [30, 53]. Ornithine a-ketoglutarate may have similar properties to glutamine and, in addition, is a potentiator of growth hormone secretion and collagen synthesis. A recent trial in severely burned patients demonstrated better wound healing and hepatic protein synthesis whilst weight loss was reduced [54].

Nucleotides are not only the building blocks of RNA and DNA but are also the common currency of energy metabolism in the form of ATP [55]. They can be either synthesized de novo from amino acids and ribose (an expensive process in terms of use of energy) or salvaged from dietary sources or from RNA/DNA breakdown [56]. Supplementation of infant milk formulas has been shown to stimulate growth in children born underweight whilst reducing the incidence of infectious diarrhoea. Their use in the treatment of critically ill patients has been limited to inclusion with arginine and fish-oil in so-called immune enhancing diets (see below). Dietary addition of nucleotides results in significant immunomodulation, as suggested by animal studies which have shown reduced mortality following fungal infection [44] and a shift in Th1/Th2 balance toward Th1-dominant immunity in mice [57]. Intravenous nucleotide supplementation has been shown to yield better preservation of gut mucosal barrier function, more rapid liver re-growth following hepatectomy and better metabolic tissue recovery from cardiac ischaemia/reperfusion [58, 59].

Arginine as a urea cycle intermediate, has been used to correct hyperammonaemia arising from hepatic insufficiency. It is also a potent stimulator of growth hormone secretion and has marked stimulatory effects on T-cell function. As a precursor of nitric oxide it is also important in reducing ischaemia/reperfusion injury [59].

In most clinical studies the "novel substrates" have been administered in various combinations in an attempt to maximize their influence on the immune and inflammatory response of the patients. Thus, it is difficult now critically to evaluate the clinical efficacy of each individual factor. A recent meta-analysis [27] examined the relationship between enteral nutrition supplemented with any combination of arginine, glutamine, nucleotides and n-3 fatty acids and infectious complications and mortality rates in critically ill patients. The analysis indicated that immunonutrition may decrease infectious complication rates but the effect on the overall mortality was dependent on the intervention (a high arginine content was associated with a trend toward a lower mortality rate) and the patient population (a trend towards higher mortality in the critically ill patients).

Conclusion

Successful nutritional and pharmacological interventions require the understanding of the basic mechanisms and their interactions, at both cellular and organ levels. Numerous promising approaches are under extensive investigation. So far, in some instances glutamine, insulin, arginine, nucleotides and modified lipids have improved the nutritional management and clinical outcome of ICU patients. Nevertheless, the possibility exists that the metabolic interventions designed to reduce hypermetabolism and protein loss in patients by modulating hormones of inflammatory mediators could be accompanied by unpredicted side effects.

Appendix

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References

1. Nitenberg G (2000) Nutritional support in sepsis: still sceptical? Curr Opin Crit Care Med 6:253–266
2. Chiolero R, Kinney JM (2001) Metabolic and nutritional support in critically ill patients: feeding the whole body or individual organs? Curr Opin Clin Nutr Metab Care 4:127–130
3. Shangraw RE, Jahoor F, Miyoshi H, Neff WA, Stuart CA, Herndon DN, Wolfe RR (1989) Differentiation between septic and postburn insulin resistance. Metabolism 38:983–989
4. Jenkins RC, Ross RJ (1998) Acquired growth hormone resistance in adults. Baillieres Clin Endocrinol Metab 12:315–329
5. Ferrando AA (2000). Effects of inactivity and hormonal mediators on skeletal muscle during recovery from trauma. Curr Opin Clin Nutr Metab Care 3:171–175
6. Samra JS, Simpson EJ, Clark ML, Forster CD, Humphreys SM, Macdonald IA, Frayn KN (1996) Effects of epinephrine infusion on adipose tissue: interactions between blood flow and lipid metabolism. Am J Physiol 271:E834–E839
7. Biolo G, Tipton KD, Klein S, Wolfe RR (1997) An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Physiol 273:E122–E129
8. Haussinger D, Roth E, Lang F, Gerok W (1993) Cellular hydration state: an important determinant of protein catabolism in health and disease. Lancet 341:1330–1332
9. Matthews DE (1999) The methods to measure stable isotope tracers and their applications to clinical nutrition problems keep getting better. Curr Opin Clin Nutr Metab Care 2:439–440
10. Young VR, Borgonha S (2000) Nitrogen and amino acid requirements: the Massachusetts Institute of Technology amino acid requirement pattern. J Nutr 130:1841–1849
11. Giovannini I, Chiarla C, Boldrini G, Castiglioni GC, Castagneto M (1988) Calorimetric response to amino acid infusion in sepsis and critical illness. Crit Care Med 16:667–670
12. Jolliet P, Pichard C, Biolo G, Chiolero R, Grimble G, Leverve X Nitenberg G, Novak I, Planas M, Preiser JC, Roth E, Schols AM, Wernerman J (1998) Enteral nutrition in intensive care patients: a practical approach. Working Group on Nutrition and Metabolism, ESICM. European Society of Intensive Care Medicine. Intensive Care Med 24:848–859
13. Gamrin L, Andersson K, Hultman E, Nilsson E, Essen P, Wernerman J (1997) Longitudinal changes of biochemical parameters in muscle during critical illness. Metabolism 47:756–762
14. Argiles JM, Busquets S, Lopez-Soriano FJ (2001) Metabolic interrelationships between liver and skeletal muscle in pathological states. Life Sci 69:1345–1361
15. Kotler DP (2000) Cachexia. Ann Intern Med 133:622–634
16. Biolo G, Fleming RY, Maggi SP, Nguyen TT, Herndon DN, Wolfe RR (2000) Inhibition of muscle glutamine formation in hypercatabolic patients. Clin Sci 99:189–194
17. Leverve X, Guignier M, Carpentier F, Serre JC, Caravel JP (1984) Effect of parenteral nutrition on muscle amino acid output and 3-methylhistidine excretion in septic patients. Metabolism 33:471–477
18. Vinge O, Edvardsen L, Jensen F, Jensen FG, Wernerman J, Kehlet H (1996) Effect of transcutaneous electrical muscle stimulation on postoperative muscle mass and protein synthesis. Br J Surg 83:360–363
19. Raguso CA, Genton L, Kyle U, Pichard C (2001) Management of catabolism in metabolically stressed patients: a literature survey about growth hormone application. Curr Opin Clin Nutr Metab Care 4:313–320
20. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, Hinds CJ (1999) Increased mortality associated with growth hormone treatment in critically ill adults. New Engl J Med 341:785–792
21. Vente JP, Von Meyenfeldt MF, Van Eijk HM, Van Berlo CL, Gouma DJ, Van der Linden CJ, Soeters PB (1989) Plasma-amino acid profiles in sepsis and stress. Ann Surg 209:57–62
22. Jackson NC, Carroll PV, Russell-Jones DL, Sonksen PH, Treacher DF, Umpleby AM (1999) The metabolic consequences of critical illness: acute effects on glutamine and protein metabolism. Am J Physiol 276:E163–E170
23. Gamrin L, Essen P, Forsberg AM, Hultman E, Wernerman J (1996) A descriptive study of skeletal muscle metabolism in critically ill patients: free amino acids, energy-rich phosphates, protein, nucleic acids, fat, water and electrolytes. Crit Care Med 24:575–583

24. Garcia-de-Lorenzo A, Ortiz-Leyba C, Planas M, Montejo JC, Nunez R, Ordonez FJ, Aragon C, Jimenez FJ (1997) Parenteral administration of different amounts of branch-chain amino acids in septic patients: Clinical and metabolic aspects. Crit Care Med 25:418–424
25. Langle F, Steininger R, Waldmann E, Grunberger T, Benditte H, Mittlbock M, Soliman T, Schindl M, Windberger U, Muhlbacher F, Roth E (1997) Improvement of cardiac output and liver blood flow and reduction of pulmonary vascular resistance by intravenous infusion of L-arginine during the early reperfusion period in pig liver transplantation. Transplantation 63:1225–1233
26. Beale RJ, Bryg DJ, Bihari DJ (1999) Immunonutrition in the critically ill: a systematic review of clinical outcome. Crit Care Med 27:2799–8005
27. Heyland DK, Novak F, Drover JW, Jain M, Su X, Suchner U (2001) Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA 286:944–953
28. Robinson MK, Rodrick ML, Jacobs DO, Rounds JD, Collins KH, Saporoschetz IB, Mannick JA, Wilmore DW (1993) Glutathione depletion in rats impairs T-cell and macrophage immune function. Arch Surg 128:29–34
29. Houdijk AP, Rijnsburger ER, Jansen J, Wesdorp RI, Weiss JK, McCamish MA, Teerlink T, Meuwissen SG, Haarman HJ, Thijs LG, Van Leeuwen PA (1998) Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. Lancet 352:772–776
30. Griffiths RD, Jones C, Palmer TEA (1997) Six-month outcome of critically ill patients given glutamine-supplemented parenteral nutrition. Nutrition 13:295–302
31. Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L, Kahana M (2001) Glutamine administration reduces gram-negative bacteremia in severely burned patients: A prospective, randomized, double blind trial versus isonitrogenous control. Crit Care Med 29:2075–2080
32. Jones C, Palmer TE, Griffiths RD (1999) Randomized clinical outcome study of critically ill patients given glutamine-supplemented enteral nutrition. Nutrition 15:108–115
33. Robin AP, Nordenström J, Askanazi J, Carpentier YA, Elwyn DA, Kinney JM (1984) Influence of parenteral carbohydrate on fat oxidation in surgical patients. Surgery 95:608–617
34. Lutz O, Lave T, Frey A, Meraihi Z, Bach AC (1989) Activities of lipoprotein lipase and hepatic lipase on long- and medium-chain triglyceride emulsions used in parenteral nutrition. Metabolism 38:507–513
35. Richelle M, Deckelbaum RJ, Vanweyenberg V, Carpentier YA (1997) Lipoprotein metabolism during and after a 6-h infusion of MCT/LTC vs LTC emulsion in man. Clin Nutr 16:119–123
36. Carpentier YA, Simoens C, Siderova V, El Nakadi I, Vanweyenberg V, Eggerickx D, Deckelbaum RJ (1997) Recent developments in lipid emulsions: relevance to intensive care. Nutrition 13:73–78
37. James MJ, Gibson RA, Cleland LG (2000) Dietary polyunsaturated fatty acids and inflammatory mediator production. Am J Clin Nutr 71:343–348
38. Furst P, Kuhn KS (2000) Fish oil emulsions: what benefits can they bring? Clin Nutr 19:7–14
39. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R (2001) Intensive insulin therapy in critically ill patients. New Engl J Med 345:1359–1367
40. Zarr K, Furnary A, Grunkemeier G, Bookin S, Kanhere V, Starr A (1997) Glucose control lowers the risk of wound infection in diabetics after open heart operation. Ann Thorac Surg 63:356–361
41. Rady M, Ryan T, Starr N (1998) Perioperative determinants of morbidity and mortality in elderly patients undergoing cardiac surgery. Crit Care Med 6:225–235
42. Preiser JC, Devos P, Van Den Berghe G (2002) Tight control of glycaemia in critically ill patients. Curr Opin Clin Nutr Metab Care 5:533–537
43. Gore DC, Chinkes D, Heggers J, Herndon DN, Wolf SE, Desai M (2001) Association of hyperglycemia with increased mortality after severe burn injury. J Trauma 51:540–544
44. Bistrian BR (2001) Hyperglycemia and infection: which is the chicken and which is the egg? JPEN J Parent Enteral Nutr 25:180–181
45. Pichard C, Fitting JW, Chevrolet JC (1997) Nutritional monitoring. In: Tobin MJ (ed) Principles and practice of intensive care monitoring. McGraw-Hill, New York, pp 1099–1124
46. Brandi LS, Santoro D, Natali A, Altomonte F, Baldi SF, Frascerra S, Ferrannini E (1993) Insulin resistance of stress: sites and mechanisms. Clin Sci 85:525–535
47. Jolliet P, Leverve X, Pichard C (2001) Acute hepatic steatosis complicating massive insulin overdose and excessive glucose administration. Intensive Care Med 27:313–316
48. McClave SA, Ritchie CS (2000) Artificial nutrition in pancreatic disease: what lessons have we learned from the literature. Clin Nutr 19:1–6
49. Wilkes MM, Navickis RJ (2001) Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med 7:135–164
50. Stuber F, Petersen M, Bokelmann F, Schade U (1996) A genomic polymorphism within the tumor necrosis factor locus influences plasma tumor necrosis factor-alpha concentrations and outcome of patients with severe sepsis. Crit Care Med 24:381–384
51. Kwiatkowski D, Hill AV, Sambou I, Twumasi P, Castracane J, Manogue KR, Cerami A, Brewster DR, Greenwood BM (1990) TNF concentration in fatal cerebral, non-fatal cerebral and uncomplicated Plasmodium falciparum malaria. Lancet 336:1201–1204
52. Grimble RF (1998) Nutritional modulation of cytokine biology. Nutrition 14:634–640
53. Donati L, Ziegler F, Pongelli G, Signorini MS (1999) Nutritional and clinical efficacy of ornithine alpha-ketoglutarate in severe burn patients. Clin Nutr 18:307–311
54. Griffiths RD (2001) Glutamine: a life-threatening deficiency in the critically ill? Intensive Care Med 27:12–15
55. Grimble GK, Malik SB, Boza JJ (2000) Methods for measuring tissue RNA turnover. Curr Opin Clin Nutr Metab Care 3:399–408
56. Grimble GK, Westwood OMR (2000) Nucleotides and immunity. In: Gershwin ME, German B, Keen CL (eds) Nutrition and Immunity. Humana Press, Totwa N.J. pp 375–387
57. Sudo N, Aiba Y, Takaki A, Tanaka K, Yu XN, Oyama N, Koga Y, Kubo C (2000) Dietary nucleic acids promote a shift in Th1/Th2 balance toward Th1-dominant immunity. Clin Exp Allergy 30:979–987
58. Roth E, Karner J, Ollenschlager G, Karner J, Simmel A, Furst P, Funovics J (1988) Alanyl-glutamine reduces muscle loss of alanine and glutamine in post-operative anaesthetized dogs. Clin Sci 75:641–648
59. Roth E (1998) The impact of L-arginine-nitric oxide metabolism on ischemia/reperfusion injury. Curr Opin Clin Nutr Metab Care 1:97–99