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RECOMMENDATIONS FOR SPECIALIZED NUTRITIONAL-METABOLIC TREATMENT OF THE CRITICAL PATIENT

Recommendations for specialized nutritional-metabolic treatment of the critical patient: Metabolic response to stress. Metabolism and Nutrition Working Group of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC)☆

Recomendaciones para el tratamiento nutrometabólico especializado del paciente crítico: respuesta metabólica al estrés. Grupo de Trabajo de Metabolismo y Nutrición de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias (SEMICYUC)

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Introduction

Critical patients experience endocrinological and metabolic changes, seeking to survive a potentially fatal situation. Thanks to the availability of improved diagnostic and therapeutic tools, survival has improved, resulting in manifest catabolic, inflammatory and immune depression changes in these patients.

Questions

1. What are the metabolic and hormonal changes in the critically ill? Do these changes vary according to the evolutive phase of the patient?

The stress generated by critical illness generates a series of metabolic and hormonal changes mediated by two main components.[1,2]

The neuroendocrine component is activated in the paraventricular nucleus or *locus coeruleus*, and the response reaches the sympathetic nervous system (SNS) and hypothalamus-pituitary axis. The SNS is in charge of rapid internal organ control through adrenergic recep-

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tor activation by the adrenal gland catecholamines and the postganglionic neurons of the SNS. Activation of the hypothalamus-pituitary axis produces an increase in ACTH, TSH, GH, FSH and LH, but the concentrations of peripheral hormones are reduced as a consequence of their inactivation in the peripheral tissues. In the chronic phase, the concentrations of both the pituitary factors and of the peripheral hormones decrease. During both phases (acute and chronic), resistance to GH, insulin, thyroid hormone and cortisol is maintained.[3]

The inflammatory component in turn is partially regulated by the central nervous system, adipokines and hormones of the gastrointestinal tract. The humoral component, which includes antibodies and cytokines, is the most relevant element. The most important cytokines are tumor necrosis factor, interleukin (IL)-1 and IL-6. These cytokines induce the clinical signs of sepsis, weight loss, collaborate in proteolysis and lipolysis, and appear to trigger anorexia at hypothalamic level.[4]

The metabolic consequences of all these changes are: 1) uncontrolled catabolism; and 2) insulin resistance. Their objective is to prioritize the use of energy substrates in vital organs over the insulin-dependent organs (fat and muscle).

2. What are the clinical consequences of the neuroendocrine changes in the critically ill?

Energy expenditure (EE): during the initial hypodynamic and catabolic (ebb) phase, EE is lower than before injury. This situation is followed by an increase in the flow phase and another decrease in the chronic phase in a differential manner conditioned to the type of injury (persistently elevated EE in burn patients, for example). These evolutive dynamics advise the use of indirect calorimetry.

Use of energy substrates: the oxidation of macronutrients is increased in critical disease. Overall, carbohydrate oxidation is proportionately greater than lipid and protein oxidation, except in the context of non-septic trauma:

- Carbohydrates: glucose is the preferential substrate during critical illness. The metabolic changes include the use of stored glycogen and neoglycogenesis from lactate, glycerol and alanine. Stress hyperglycemia and peripheral resistance to insulin action is also observed, correlated to the severity of the disease and to mortality, and may prove severe and persist over time in the critical patient.[5]
- Lipids: their oxidation requires important oxygen consumption and correct mitochondrial function. In the ebb phase, metabolism is fundamentally characterized by liver ketogenesis, and peripheral beta-oxidation only predominates once tissue oxygenation has been restored.
- Proteins: their degradation through different mechanisms is the norm, and is partially balanced by the protein synthesis predominantly of inflammatory mediators – though the net balance between synthesis and degradation is negative (anabolic resistance and reverse regulation).[6] The amino acids obtained are reused or oxidized.

Changes in body composition: these include sarcopenia and the loss of fat deposits. The number of small adipocytes increases, as well as macrophage infiltration, with a gain in weight in the recovery phase that exceeds the increase in muscle mass. A loss of bone mass is also observed, directly related to the low triiodothyronine (T3) levels.

Psychosocial and behavioral changes: over the long term, catabolism is perpetuated (related to the metabolic response to stress) and anorexia appears, associated to the development of changes in the gastrointestinal hormones.[7]

3. What is and what are the consequences of inflammation-immune depression syndrome and persistent catabolism in the critically ill?

The possible outcomes of a patient with acute and severe injury are:

1 Rapid recovery of patient stability following control of the effects of injury.
2 Early death as a consequence of injury or early multiorgan failure.
3 Late death following stabilization of initial injury due to repeat multiorgan failure resulting from second noxae.
4 Persistence of the dysfunction of one or more organs that may be stabilized through supportive treatment and which leaves the patient in a stationary phase. In some of these patients (up to 50% in the largest series published to date[8]), the substrate of maintained organ dysfunction can be explained from the perspective of persistent inflammation, immunosuppression and catabolism syndrome (PICS).[9] This type of response is determined from the start and depends on both the magnitude and the duration of the simultaneous over-regulation of genes implicated in inflammation and innate immunity, and the under-regulation of those genes implicated in adaptive immunity.[10]

The components of PICS are:

- Inflammation: the inflammatory response is partially regulated by cytokines. In the population of patients employed to typify inflammation in PICS, no differential profiles were identified – only increased amplification and duration of the inflammatory response. Such low intensity but persistent inflammation could be explained by the increased release of damage-related molecules and endogenous alarmins from the damaged tissues and organs, but also from the initially affected organs that maintain an inflammatory state during the recovery phase, such as the kidneys or lungs subjected to mechanical ventilation.[11]
- Recurrent nosocomial infection: the immune anergy state resulting from the impairment of adaptive immunity explains patient susceptibility to infectious complications. The myeloid derived suppressor cells appear to play a crucial role in the alteration of adaptive immunity, since they are amplified in patients with PICS and have immunosuppressor and proinflammatory properties, and moreover are poor antigen-presenting cells.[12]
- Sarcopenia: progressive loss of muscle mass and function is observed due to the sustained protein catabolic state, with a net negative protein balance. Muscle mass losses of up to 70% have been reported.

Table 1 Effect of different agents upon anabolism, catabolism, inflammation and glycemia.

Agent	Anabolism	Anti-catabolism	Inflammation	Glycemia
Glutamine	↑	↑	–	–
Arginine	↑	–	–	–
HMB	↑	↑	–	–
Insulin	↑	↑	–	↓
IGF-1	↑	↑	–	↓
IGF-1 + IGFBP-3	↑	↑	↓	–
Testosterone	↑	↑	–	–
Oxandrolone	↑	↑	–	–
hGH	↑	↑	–	↑

HBM: β-hydroxy-β-methylbutyrate; hGH: growth hormone; IGF-1: insulin-like growth factor; IGFBP-3: insulin-like growth factor binding protein.

4. To what extent do the critical condition of the patient and the loss of muscle mass condition the metabolic-nutritional requirements?

The loss of muscle mass concomitant to chronicity of the patient condition can condition nutritional therapy.

Amount of energy: the diminished muscle mass undoubtedly conditions less total EE than expected in comparison with patients exhibiting favorable recovery. In any case, the effects of modifying the caloric target according to depletion of the proteic compartment have not been described.

Amount of proteins: protein catabolism persists despite the supply of substrates (it cannot be suppressed through caloric or protein overload, or with the administration of specific substrates). In fact, substrate overload in the initial phases could adversely affect the mechanism of autophagia in the muscle tissues, with increased destruction, dysfunction and lesser regeneration.[13]

The loss of muscle mass can reach 5% a day (70% of the skeletal muscle) and persists in both the initial and the late phases of recovery or chronification.

Hyperglycemia of cachexia: muscle and glycemia are related in a special way in the critical patient. Increasing glycemia is associated to lesser muscle mass, while diminished muscle mass is associated to increased glycemia.

5. Can we treat or modulate the metabolic response in the critically ill?

Up until the stabilization phase, a low supply of non-protein calories is recommended, maintaining a correct provision of proteins. Care should focus on adequate vitamin and electrolyte supply from the start, correcting disorders of the different minerals. In some situations (burn patients), good results are being obtained with drugs such as propranolol (which reduces supraphysiological thermogenesis and peripheral lipolysis)[14] and oxandrolone. Further research with other anabolic, anticatabolic or inflammation-regulating agents is pending (Table 1).[15]

Key ideas

- The metabolic response to injury is adaptive, but its persistence in late phases is associated to a poorer prognosis.
- The body compartment most affected by injury is the muscle tissue, and its impairment is linked to a poorer survival and functional outcomes.
- The metabolic response is sequential as regards central hormonal regulation and immunity, but is simultaneous as regards inflammation.
- Beyond the hyperacute, subacute and late metabolic response, chronification is a reality that can manifest in the form of PICS.
- An abundant supply of energy substrates has not been shown to reduce the metabolic response to injury.

Conflicts of interest

Note to supplement

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