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Original/*Intensivos*

Imbalances in protein metabolism in critical care patient with systemic inflammatory response syndrome at admission in intensive care unit

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Abstract

Background: **trauma and severe infections cause remarkable metabolic changes in patient with SIRS from an adaptive response aimed to control the underlying disease, repairing damaged tissue, and to synthesize substrates. If the attack is intense and sustained and the patient has a compromised nutritional status, can evolve into multiple organ failure and death.**

Objective: **assessment of nutritional proteic status and the involvement of proteins and inflammatory factors in critically ill patients.**

Method: **multicenter observational analytical study in critical ill patients at the admission in ICU.**

Results and discussion: **patients showed disturbances in clinical nutritional parameters which confirm their hypercatabolic situation, showing malnutrition state at admission, where 42.9% had plasma levels below the reference prealbumin. Amino acid profile was situated below the reference values and 99% of patients had low plasma transferrin. Significant differences were observed in total protein, ferritin and transferrin parameters adjusted by CRP levels, being higher when patients presented high inflammation in the case of ferritin and the opposite for the rest of parameters. Adjusting APACHE and SOFA scores according to low, medium and high severity, results showed significant differences in creatinine, urea, and transferrin, being lower at high severity grade for the last one.**

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ALTERACIÓN DEL METABOLISMO PROTEICO EN PACIENTE CRÍTICO CON SÍNDROME DE RESPUESTA INFLAMATORIA SISTÉMICA AL INGRESO EN LA UNIDAD DE CUIDADOS INTENSIVOS

Resumen

Antecedentes: **el trauma y las infecciones severas causan cambios metabólicos notables en los pacientes con SRIS como una respuesta adaptativa dirigida a controlar la enfermedad subyacente, la reparación del tejido dañado y para sintetizar sustratos. Si el ataque es intenso y sostenido y el paciente tiene un estado nutricional comprometido puede evolucionar a insuficiencia orgánica múltiple y muerte.**

Objetivo: **evaluación del estado nutricional proteico y la participación de las proteínas y los factores inflamatorios en pacientes críticamente enfermos.**

Método: **estudio analítico observacional multicéntrico en pacientes enfermos críticos en la admisión en la UCI.**

Resultados y discusión: **los pacientes mostraron alteraciones en los parámetros nutricionales clínicos que confirman su situación hipercatabólica, mostrando malnutrición a la admisión en UCI, donde el 42,9% tenían niveles plasmáticos de prealbúmina por debajo de la referencia. Los aminoácidos se encuentran por debajo de los valores de referencia y el 99% de los pacientes presentaron bajos niveles plasmáticos de transferrina. Se observaron diferencias significativas en los niveles de proteína total, ferritina y transferrina ajustados por los niveles de PCR, siendo mayor cuando los pacientes presentaron altos valores de inflamación, en el caso de la ferritina, y lo opuesto para el resto de parámetros. Al estratificar por las puntuaciones APACHE y SOFA de acuerdo a la gravedad baja, media y alta, los resultados mostraron diferencias significativas en creatinina, urea y transferrina, siendo menor cuanto mayor era el grado de severidad para la transferrina.**

Conclusion: **critical illness is characterized by a high degree of stress and accelerated degradation of proteins that cause malnutrition, systemic inflammation and organ dysfunction, with a significant association between albumin, ferritin and transferrin.**

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Key words: *Critical patient. Hypercatabolism. Protein status. Amino acids. SIRS.*

Conclusión: **la enfermedad crítica se caracteriza por un alto grado de estrés y la degradación acelerada de proteínas que causan malnutrición, inflamación sistémica y la disfunción de órganos, con una asociación significativa entre albúmina, ferritina y transferrina.**

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Palabras clave: *Paciente crítico. Hipercatabolismo. Estatus proteico. Aminoácidos. SRIS.*

Abbreviations

SIRS: Systemic Inflammatory Response Syndrome.
ICU: Intensive Care Unit.
APACHE: Acute Physiology and Chronic Health Evaluation.
SOFA: Sequential Organ Failure Assessment.
MODS: Multiple Organ Dysfunction Syndrome.
CRP: C Reactive Protein.
ROS: Reactive Oxygen Species.
AGA: American Gastroenterology Association.
GLY: Glycine.
SER: Serine.
ARG: Arginine.
GLN: Glutamine.
HIS: Histidine.

Introduction

Malnutrition and underfeeding are major challenges in caring for critically ill patients. In critical illness, has been shown to be significantly associated with increased complications, costs, and mortality[1]. Therefore, nutritional adequacy as regular and systematic provision of a set of chemicals known by the generic name nutriments[2] is needed to supply and maintain metabolism in critical situation.

The critical ill patient is characterised by a hypercatabolic situation, high surgical stress, traumatic and shock septic, resulting in malnutrition that could be complicated by other diseases or dysfunctions. This situation may lead to a generalized inflammatory response known as systemic inflammatory response syndrome (SIRS). An exaggerated inflammatory response occurs following the release of endogenous as stress hormones and cytokines that result in significant metabolic changes[3]. Pro-inflammatory cytokines induces the hepatic synthesis of acute phase reactant proteins. The increase in these proteins is accompanied by a rapid decrease in lean body mass and increased urine urea nitrogen, resulting to a negative nitrogen balance[4]. Moreover, increased oxidative stress[5] and intense generation of oxygen free radicals could promote damage on amino acids and alterations in protein conformation and its functions[6]. The maintained metabolic reaction in critically ill patients, could lead to consume organic protein reserve determining dysfunction and multiple organ failure (MODS)[7] which would be the result of high mortality. Early detection mechanisms to detect patients with an unfavourable initial state or risk of death are essential to prevent MODS progression[8].

The study of biochemical parameters is a very interesting target, both for assessing the state of the disease and the analysis of intake that can provide useful information about the presence of nutritional deficiencies or excesses[9]. Parameters such as C-reactive protein (CRP) which is involved in different immune functions[10], is a marker of inflammatory response, and high plasma concentration was related to the presence and evolution of some infections[11]. Its values, higher in SIRS, remain elevated in patients with multisystem dysfunction and could be normalized in patients with a good therapeutic response[12]. Guidelines recommended the use of this biomarker for an early bacterial detection and sepsis in patients during the first day of admission to intensive care unit (ICU)[13]. Albumin, prealbumin, ferritin and transferrin, among others, provide information to evaluate the overall nutritional status and protein status of critically ill patients. One of the most interesting amino acid is glutamine. This parameter is decreased in critically ill patients, increasing the risk of infections, insulin resistance and MODS[14].

The diminished protein parameters in critically ill patients caused by intense protein destruction and hypercatabolism become necessary the control of protein support, being absolutely necessary to be increased even in situations of increased protein loss, as in critical situation. As a result, the application of a treatment is required by nutritional support to cover the energy and essential nutrients due to their adjusted needs with the aim of preserving life and morbid-mortality[15].

The aim of the study was to assess the disturbances in protein metabolism of critically ill patients admitted to intensive care unit (ICU) from Granada, evaluating the nutritional state at the admission.

Subjects and methodology

Study design

The study design is based on an observational and analytical study, monitoring the critically ill patient at

the admission of ICU stay, from different hospitals of Southern Spain (Virgen de las Nieves, San Cecilio, General of Baza and Santa Ana of Motril, Granada). This study was approved by the Ethics Committee of the University of Granada. Written informed consent was obtained from legal relatives taking into account the approval of the Ethics Committee and the Research Committee of the Centre. The present study was conducted according to the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonization/Good Clinical Practice Standards and all procedures involving human subjects was approved by the University of Granada.

Inclusion criteria were to be critically ill patients older than 18 years, admitted in the ICU; with SIRS and Acute Physiology and Chronic Health Evaluation (APACHE) II score≥15; to have artificial nutritional support (enteral and mixed enteral and parenteral nutrition); to present non neurological, muscular, skeletal, or situations that affected the mouth or upper digestive tract or contraindicate the passage of nutrients to the other portions of the digestive system. Finally, a total of 115 subjects were included in the study.

Nutritional assessment

During ICU stay in hospitals included in our study, all patients usually receive nutritional standard supply via enteral, parenteral or combined administration based on standard formulas by the Dietary Recommended Allowances (DRAs) of Food and Nutrition Board of National Research Council (FNB-NRC)[16] and the specific requirements for critically ill patients with or without sepsis by ASPEN[17]. Non adjusted proteic administration is performed to balance proteic metabolism. Table I shows the recommendations for protein intake according to some clinical situations (AGA, American Gastroenterology Association)[18].

Biochemical parameters

Fasting blood samples were drawn from ICU patients by venepuncture after the hemodynamic stabilization phase of admission. Total protein, albumin, creatinine, uric acid, urea and CRP will be performed by the hospital laboratory using different standard techniques. Albumin, prealbumin, ferritin, transferrin profile were determined by colorimetric immunoassay techniques using a Hitachi® (Roche Diagnostics, Germany). Amino acid profile was determined by high performance liquid chromatography (HPLC) in the central services of the University of Granada (Waters Alliance 269020®, Germany). Quality control and established procedures were performed.

Table I
Recommendations for protein intake in parenteral nutrition according to the clinical state (AGA)

Clinical state	*Daily protein requirement**
Normal	0.8
Metabolic stress	1.0-1.5
Acute renal failure without dialysis	0,8-1.0
Haemodialysis	1.2-1.4

* = g/kg/day

Data analysis

Data was analysed using the SPSS statistical software (version 20.0, SPSS Inc., Chicago, USA). For continuous variables, the assumption of normality was tested using the Shapiro-Wilk curve-fitting test. Biochemical parameters were stratified according reference levels and showed as percentage of subjects. Comparative one way ANOVA test was performed to evaluate significant differences between according the grade of severity in critical ill patients which were classified in low = APACHE < 19 and SOFA < 8; Moderate = APACHE < 19 and SOFA > 8; High: APACHE > 19 and SOFA > 8. Comparative t-student test was analysed to evaluate the influence of high and low status of clinical nutritional and inflammation parameters according reference levels. Bivariate Pearson correlation test (r) was performed to evaluate the associations between biochemical parameters and critically ill severity scores.

Results and discussion

In critically ill patients, the demand for nutrients differs radically compared to healthy individuals as a result of profound changes in metabolism. In the United States, recent research focuses on the so-called "nutraceuticals" specific nutrients that alter the metabolic behaviour in pathological states or become "conditionally" essential in particular situations, such as liver or kidney failure[19]. Some amino acids have important effects as immune stimulators or specific from tissues, which may alter the course of disease with positive results. Nutritional therapy in critically ill patients could preserve lean body mass and enhance metabolic functions, although the loss of lean body mass is inevitable for the increased rate of proteolysis, amino acid mobilization from peripheral tissues to the liver to enter the gluconeogenesis pathway and produce proteins of acute phase. The physiological mission of the latter is to stimulate the immune defence, promoting wound healing and helping to recover renal function in the acid-base balance. Prolonged immobilization and, in some cases the critical condition associated starvation, also contribute to the decrease in lean mass[19].

Turnover, synthesis and oxidation protein rates increase when sepsis, large wounds and the critical condition occur. The grade of this response depends on the severity of disease and the intensity of metabolic response. A protein intake of 1.1 g/kg/day in septic patients decreased protein catabolic rate, and if the contribution increases to 1.6 g/kg/day catabolism decreases further, however, above this supply protein catabolism increases again[20]. The balance is not positive in patients with critical contributions above 1.5 g/kg/day[21].

Tables II and III show general characteristics and biochemical profile in critical ill patients at admission in ICU stay. Taking into account biochemical parameters, critical care patients showed in general disturbances in clinical nutritional parameters that confirm their hypercatabolic situation. Regarding these nutritional variables like albumin, prealbumin and transferrin, a high percentage of patients presented levels below references from the beginning of the ICU stay. Bivariate analysis showed logical significant association between clinical parameters including total protein with albumin ($r=0.42$; $p<0.001$), prealbumin ($r=0.26$; $p<0.001$) and with transferrin ($r=0.52$; $p<0.001$). On the other hand, transferrin was associated with albumin ($r=0.27$, $p<0.001$) and prealbumin ($r=0.40$, $p<0.001$). Herrero *et al*.[22] attributed these changes to their property as acute phase reactant under stress, in addition to the long half-life (around 20 days). Together with albumin, prealbumin and transferrin play an important role in the assessment of nutritional status in critically ill patients, so they are widely used. In this study, the results show a malnutrition state in admission to the ICU, where almost half of the subjects (42.9%) had plasma levels below the prealbumin reference value. Sandoval *et al*.[23] obtained similar results being directly linked to low levels of prealbumin with the highest risk of severe malnutrition in the patient. In order to focus nutritional influence, table IV shows comparative analysis of clinical nutritional and inflammation parameters according to reference levels. Taking into account nutritional parameters, patients with low status of albumin and prealbumin presented higher significant mean values for CRP, lower significant mean values for total protein and transferrin. Regarding inflammation, measured by CRP, significant differences were observed in total protein, ferritin and transferrin parameters being higher when patients presented high CRP levels in the case of ferritin and the opposite for the rest of parameters.

Protein parameters by severity in critically ill patients are shown in table V. In spite of no significant association between APACHE and SOFA scores with different biochemical protein parameters, when comparing these variables according to low, medium and high severity, results showed significant differences in creatinine, urea, and transferrin, being lower at high severity grade for the last one. During SIRS, increa-

Table II
General characteristics of patients

	N	*Critical ill Patient*
Age Mean (y)	111	63.5 (12.1)
Gender		
Men	115	68.0
Women	115	32.0
Diagnostic (%)		
Respiratory	27	23.5
Cardiovascular	40	35.0
Abdominal	40	35.0
Other	08	6.50
APACHE II	97	19.5 (6.00)
SOFA	110	8.58 (3.03)

N = Sample; Mean (Sd) = Mean (standard deviation).

Table III
Biochemical parameters in critical ill patients at admission in ICU stay

	N	*Mean (Sd)*	*Reference*	*< Reference value (%)*	*> Reference value (%)*
Urea (mg/dL)	111	87.5 (53.3)	70-110	45.9	27.8
Creatinine (mg/dL)	114	2.07 (1.69)	0.8-1.2	23.7	64.0
Uric Acid (mg/dL)	107	5.35 (2.73)	3-7	22.4	26.2
PCR (mg/dL)	92	18.7 (13.7)	0.1-1	0	95.7
Total proteins (g/100 mL)	112	5.15 (0.96)	6-8	83.0	0
Albumin (g/dL)	110	2.70 (0.61)	3-5	73.6	0
Prealbumin (mg/dL)	105	13.7 (8.69)	10-40	42.9	1.00
Ferritin (ng/mL)	115	534.0 (712.0)	12-119	0	90.4
Transferrin (mg/dL)	103	142.4 (57.7)	245-370	99.0	0

N = Sample; Mean (Sd) = Mean (standard deviation).

Table IV
Comparative analysis of clinical nutritional and inflammation parameters according to reference levels

	Albumin		*Prealbumin*		*CRP*	
	Low	*High*	*Low*	*High*	*Low*	*High*
	Mean (Sd)	*Mean (Sd)*	*Mean (Sd)*	*Mean (Sd)*	*Mean (Sd)*	*Mean (Sd)*
APACHE	19.5 (5.5)	18.6 (6.87)	19.8 (5.26)	18.8 (6.44)	21.3 (4.04)	19.0 (5.83)
SOFA	8.61 (2.91)	8.17 (3.20)	8.40 (3.20)	8.70 (2.91)	10.0 (2.16)	8.46 (2.94)
Urea (mg/dL)	90.6 (55.3)	77.8 (48.2)	85.4 (55.5)	86.9 (53.8)	75.2 (33.8)	82.8 (47.0)
Creatinine (mg/dL)	2.17 (1.72)	1.61 (1.17)	1.79 (1.54)	2.18 (1.68)	1.57 (1.22)	2.02 (1.66)
Uric acid (mg/dL)	5.19 (2.81)	5.72 (2.60)	4.92 (5.42)	5.42 (2.67)	4.56 (2.49)	5.13 (2.50)
CRP (mg/dL)	21.0 (13.3)	13.7 (13.2)*	24.5 (15.7)	15.8 (11.1)**	-	-
Total protein (g/dL)	4.90 (0.81)	5.89 (0.87)**	5.04 (0.93)	5.22 (0.93)	6.07 (0.49)	5.11 (0.92)*
Albumin (g/dL)	-	-	0.20 (0.40)	0.28 (0.45)	4.13 (0.15)	2.67 (0.58)
Prealbumin (mg/dL)	13.0 (7.72)	15.4 (11.1)	-	-	18.1 (15.2)	13.4 (7.44)
Ferritin (ng/mL)	570.8 (768.1)	363.9 (463.5)	519.9 (675.6)	537.1 (754.0)	195.5 (162.5)	482.8 (640.8)*
Transferrin (mg/dL)	132.5 (51.2)	171.4 (66.6)**	121.5 (48.2)	157.9 (59.6)**	212.6 (25.4)	138.7 (58.7)*

N = Sample; Mean (Sd) = Mean (standard deviation); Statistically significant differences t-student test * p < 0.05; **p < 0.01. High = Value above references; Low = Value under references.

sed protein catabolism promotes a significant decrease in the rate of protein synthesis called acute phase protein. Among these proteins, CRP increased during critical illness[24] and could explain the high levels of this protein obtained in our study. It is well known that many critically ill patients are severely catabolic and lose mainly muscle protein. The most obvious way to prevent or counteract this loss is by protein feeding. In our study, regarding amino acid profile, Gly (Glycine), Ser (Serine), Arg (Arginine), Glu (Glutamine) e His (Histidine) were situated below the reference values, and 84.5 percent of patients had plasma transferrin (99.0 percent). The amino acids that come from proteolysis following the breakdown of muscle proteins are transported to the liver for use in the synthesis of acute phase proteins and other intended tissue repair. This increases the demand for amino acids in the acute pathophysiological situation[25] and confirms the low levels found in our results.

Certain amino acids exert a pharmacological action in the critical state if given in higher than normal oral intake or nutritional support standard, or what is more important doses viewing requirements of certain amino acids, such as essentials, that change in the critically ill as a result of alterations in metabolic demand. It is hypothesized that if conditionally essential amino acids are proportionately in critical condition, it is easier to meet the metabolic demands and improves clinical evolu-

Table V
Protein parameters by severity in critically ill patients

	Low	*Moderate*	*High*
Creatinine (mg/dL)	1.47 (0.94)[c]	2.27 (1.48)	3.25 (2.43)[c]
Transferrin (mg/dL)	155.0 (57.1)[c]	135.0 (62.0)	117.0 (50.8)[c]
Urea (mg/dL)	66.7 (39.3)[a,c]	102.8 (47.9)[a]	117.9 (70.0)[c]
Albumin (g/dL)	2.73 (0.47)	2.77 (0.68)	2.54 (0.67)
Ferritin (ng/mL)	473.3 (645.1)	620.6 (937.3)	543.8 (618.6)
CRP (mg/dL)	20.1 (12.8)	17.3 (14.7)	20.0 (16.3)
Prealbumin (mg/dL)	13.91 (9.24)	13.97 (8.93)	13.66 (9.28)
Total protein (g/dL)	5.10 (0.97)	5.19 (0.94)	4.90 (0.95)

Severity: Low = APACHE < 19 and SOFA < 8; Moderate = APACHE < 19 and SOFA > 8; High: APACHE > 19 and SOFA > 8; Significant values by severity: a = Low vs Moderate; b = Moderate vs High; c = Low vs High

tion[19]. Therefore, in this situation it is obvious the need for intervention through proper nutrition that includes a balanced intake of protein, although recommendations for critical patients are still unclear[26], varying from 1.2 to 2.5 g/kg/day[17,27].

In these conditions of hypercatabolism, plasma glutamine levels are reduced, which is associated with a poor prognosis. Supplementation with amino acids in general and glutamine in particular, will be crucial. Abilés *et al*.[28] observed that the supply of glutamine in critically ill patients improves the antioxidant defenses and thereby lower morbidity during the ICU stay. In 2015, Liebau *et al*.[29] concluded that an amino acid infusion improves short-term body balance of proteins in patients with critical condition.

Conclusion

Critical illness is characterized by a high degree of stress and accelerated degradation of proteins that cause malnutrition, systemic inflammation and organ dysfunction, with a significant association between plasma proteins such as albumin, transferrin and ferritin as we found in our study.

The present study confirms that it is essential to carry out a monitoring protein profile early in the stay, applying personalized nutritional support to reduce morbidity and mortality, and complications with shorten ICU stay, optimizing the response to treatment.

Conflict of interest

For each author listed on this manuscript, there is no personal or financial support or author involvement with an organization with financial interest in the subject matter and no conflict of interest exists. The authors declare that they have no competing interests.

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