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Clinical studies

Changes in zinc status and zinc transporters expression in whole blood of patients with Systemic Inflammatory Response Syndrome (SIRS)

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ABSTRACT

Introduction: Critically ill patients develop severe stress, inflammation and a clinical state that may raise the utilization and metabolic replacement of many nutrients and especially zinc, depleting their body reserves. This study was designed to assess the zinc status in critical care patients with systemic inflammatory response syndrome (SIRS), comparing them with a group of healthy people, and studying the association with expression of zinc transporters.

Material and methods: This investigation was a prospective, multicentre, comparative, observational and analytic study. Twelve critically ill patients from different hospitals and 12 healthy subjects from Granada, Spain, all with informed consent were recruited. Data on daily nutritional assessment, ICU severity scores, inflammation, clinical and nutritional parameters, plasma and blood cell zinc concentrations, and levels of transcripts for zinc transporters in whole blood were taken at admission and at the seventh day of the ICU stay.

Results: Zinc levels on critical ill patient are diminish comparing with the healthy control (HS: 0.94 ± 0.19; CIPF: 0.67 ± 0.16 mg/dL). The 58% of critical ill patients showed zinc plasma deficiency at beginning of study while 50.0% of critical ill after 7 days of ICU stay. ZnT7, ZIP4 and ZIP9 were the zinc transporters with highest expression in whole blood. In general, all zinc transporters were significantly down-regulated ($P < 0.05$) in the critical ill population at admission in comparison with healthy subjects. Severity scores and inflammation were significantly associated ($P < 0.05$) with zinc plasma levels, and zinc transporters ZIP3, ZIP4, ZIP8, ZnT6, ZnT7. Expression of 11 out of 24 zinc transporters was analysed, and ZnT1, ZnT4, ZnT5 and ZIP4, which were downregulated by more than 3-fold in whole blood of patients.

Conclusion: In summary, in our study an alteration of zinc status was related with the severity-of-illness scores and inflammation in critical ill patients since admission in ICU stay. SIRS caused a general shut-down of expression of zinc transporters in whole blood. That behavior was associated with severity and inflammation of patients at ICU admission regardless zinc status. We conclude that zinc transporters in blood might be useful indicators of severity of systemic inflammation and outcome for critically ill patients.

Abbreviations: ICU, Intensive Care Unit; SIRS, Systemic Inflammatory Response Syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ZnT/SCL30A (1-10), Solute Carrier Family 30; ZIP/SCL39A (1-14), Solute Carrier Family 39; HS, healthy subject; CIP, critically ill patients; CIPB, critically ill patient baseline; CIP7, critically ill patient 7 days; EN, enteral nutrition; PN, parenteral nutrition; CHO, carbohydrates; CRP, C-reactive protein

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1. Introduction

Zinc is an essential component in all levels of metabolism, and is a key component in structure of genetic material [1]. Zinc homeostasis depends on the balance between absorption of zinc from diet and endogenous secretions by the daily intake of the element [2]. These basic conditions may be complicated by diseases or dysfunctions as multiple organ failure that in critically ill patients require a correct and timely provision of energy and nutrients as zinc that can save life, so adequate nutrition should be included in their clinical treatment [3,4]. In critically ill patients, low zinc concentrations have been reported linked to oxidative stress, systemic inflammatory response syndrome (SIRS) and immune disorders [4,5], particularly in patients with sepsis [6–9]. Then, zinc deficiency could be considered as an important factor in the pathogenesis of different diseases [5]. Nevertheless, increased zinc demands are justified by hypercatabolic situation and a high degree of stress as surgical, traumatic and septic shock, which could develop malnutrition status [10].

Zinc is an element very difficult to be determined by non-invasive techniques in human body tissues, therefore its represents a challenge in the determination of a suitable biomarker of zinc status for critical condition. Although studies concluded that plasma, urinary and hair zinc are reliable biomarkers of zinc status [11], there is no consensus. Recently, Lowe et al. [12], concluded that zinc is mostly determined in plasma or serum samples. Nevertheless, peripheral blood tissue is an accessible tissue to use for the exploration of biomarkers for human zinc homeostasis [13] but cellular blood zinc needs further investigation [12]. Over the time has been studied to find other biomarkers for zinc status in human body [11] on these days many of research is concentrated on zinc transporters. Some authors suggest that zinc transporters could express independently of dietary or plasma zinc in healthy individuals [14]. On the other hand, the dysregulation of expression and activity of ZIP and ZnT transporters involved in the pathogenesis and progression in chronic diseases have been described [15]. However, their molecular relationship with the etiology of acute diseases is far from complete. Clarifying these issues would lead to therapeutic innovation in critical illness, and therefore, great attention should be paid to ZIP and ZnT transporters.

There are few studies that comprehensively addressed the zinc transporters levels in the whole blood in humans. Our aim was to investigate the zinc concentrations and its association with the expression level of all zinc transporters in blood from healthy and critically ill individuals and determine their differences in expression. We also want to explore the relationship among zinc expression transporter levels in blood and the severity situation in critical ill condition. It is indispensable to find a biomarker for zinc status in order to ameliorate the evolution of critical ill patient and to optimize their clinical intervention during their ICU stay.

2. Material and methods

2.1. Study design

The study design is based on a prospective, multicentre, observational and analytic study, monitoring the critically ill patient, from admission until the seventh day of ICU stay, from different hospitals of Southern Spain (Virgen de las Nieves, San Cecilio, General of Baza and Santa Ana of Motril, Granada). The study was carried out according to the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and the International Conference on Harmonization/Good Clinical Practice Standards. Informed consent was obtained from patients or family who had agreed to participate in the study, considering the approval of the Ethics Committee and the Research Committee of the Centre involved.

2.2. Participants

A total of 12 and 12 subjects were included in healthy control (HS) and critically ill groups, respectively (CIPB, critical ill patients on admission; CIPF critical ill patient follow-up), aged and gender matched. Inclusion criteria for the healthy population were: not to present any alteration that could have influence on their nutritional status and to have agreed to form part of the study. In critical ill population, the study was carried out with consecutive patients admitted to ICU. The criteria to be included in the study were: critically ill patients older than 18 years, admitted in the ICU; with SIRS and APACHE II score > 15; to have artificial nutritional support (enteral and mixed enteral and parenteral nutrition); to present no 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; and to continue in the Unit for at least 7 days. Exclusion criteria were: refusal by the patient or their legal representatives to participate in the study; pregnancy; highly contagious disease; allergies; cancer; HIV; food orally intake before obtaining the analytical sample at baseline; intolerance or contraindication for using enteral route. Clinical characteristics as age, sex and diagnosis were recorded at study enrolment (ICU admission). SIRS, the Acute Physiology and Chronic Health Evaluation (APACHE II) and the Sequential Organ Failure Assessment (SOFA) scores and mortality was included at admission and seven days in ICU stay.

2.3. Nutritional profile

Nutritional intake profile in healthy population was made through personal interview by trained staff in the use of nutritional techniques, employing questionnaires with the following sections: personal data and consumption habits, the nutritional intake by 72 h recall and food frequency consumption (FFQ) questionnaires. Nutrient intake and adequacy were calculated with the Nutriber® software, comparing with the Recommended Dietary Allowances (RDAs) for healthy population [16]. Nutritional support protocol in critical ill patients was assessed according to the Clinical Nutrition Units of hospitals, based on American Society for Parenteral and Enteral Nutrition and the European Society of Parenteral and Enteral Nutrition Guidelines [17]. All patients received nutritional standard support via enteral, parenteral or combined, administrating nutritional formulas elaborated in the pharmacies of the hospitals or from commercial products. A daily nutritional log was kept for each patient (type, volume and composition of intake, tolerance, among other factors) from admission to seven days in ICU. Zinc support was daily calculated and registered by the nutritionists and represented as the average of a seven-day period of stay the ICU.

2.4. Biochemical parameters

Fasting blood samples (10 mL) were drawn from ICU patients (between the hours of 08:30 am and 10:00 am during fasting) by venepuncture after the hemodynamic stabilization phase of admission and after 7 days of stay. The same methodology was applied for healthy subjects for biochemical testing. Vacutainer tubes (Venoject®, BD, UK) containing a solution of heparin of lithium as anticoagulant were used. Samples were centrifuged at 3000 RPM for 15 min at 4 °C. Blood drawn was centrifuged to separate plasma and cells and stored at −80 °C. Biochemical variables such as glucose, albumin, prealbumin, urea, uric acid, alkaline phosphatase, CPK, C-reactive protein (CRP), rheumatoid factor, total protein, transferrin, homocysteine, leucocytes, cooper and iron concentrations were determined by the hospital laboratory using standard techniques and following the quality control and established procedures.