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Kinetics of circulating fetuin-A may predict mortality independently from adiponectin, high molecular weight adiponectin and prognostic factors in critically ill patients with sepsis: A prospective study

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ABSTRACT

Purpose: Fetuin-A and adiponectin, major hepatokine and adipokine respectively, have been implicated in systematic inflammation. Our aim was to jointly investigate whether kinetics of circulating fetuin-A, adiponectin and its isoform HMWA predict 28-day mortality in sepsis.
Materials and methods: In a prospective study, serum fetuin-A, adiponectin and HMWA were determined in 102 ICU patients fulfilling the diagnostic criteria of SEPSIS-3, at enrollment and one week after, and in 102 healthy controls matched on age and gender.
Results: Serum fetuin-A was significantly lower in septic patients than controls ($p < 0.001$). Among septic patients, those with septic shock and nonsurvivors presented lower fetuin-A, but higher adiponectin and HMWA compared to patients with sepsis and survivors respectively, both at baseline and day 7 ($p < 0.001$). Fetuin-A exhibited negative correlations with APACHE II, CRP, procalcitonin, adiponectin and IL-6 but a positive one with albumin. Reduced fetuin-A as well as lower serum kinetics of fetuin-A (HR: 0.55, 95% C.I. 0.34–0.91, $p = 0.02$), adiponectin but not HMWA were independently associated with 28-day mortality adjusting for age, gender, BMI, APACHE II, septic shock and laboratory biomarkers.
Conclusions: Circulating fetuin-A kinetics may be a prognostic biomarker in septic patients. More research is essential to elucidate fetuin-A's ontological role in sepsis pathophysiology.

1. Introduction

Sepsis, a life-threatening systemic inflammatory response caused by a dysregulated host response to infection, constitutes an important worldwide public health issue associated with increasing incidence and mortality among hospitalized and critically ill patients [1-3]. Although the cellular and biochemical mechanisms in sepsis are complex and have been partially elucidated during the last decades, the pathobiology of sepsis remains poorly understood [1,4]. As many established biomolecules including C-reactive protein (CRP) and procalcitonin have not gained wide clinical acceptance, the study of emerging biomarkers and their kinetics for the prompt diagnosis, monitoring and prognosis of sepsis represents an important objective and challenge in the field of critical care [5,6].

In response to inflammation, the liver and the visceral adipose tissue orchestrate the production and systemic discharge of acute phase proteins (APP) with decreasing or increasing plasma concentrations, and adipokines with proinflammatory or anti-inflammatory properties [7-9]. The adipose-tissue synthesized hormones, referred to as adipokines, are implicated in the regulation of various metabolic, immune and inflammatory processes [8]. Adiponectin, the most abundant adipose-tissue hormone with pleiotropic actions in a plethora of tissues

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; APP, acute phase protein; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CV, coefficient of variation; ELISA, enzyme linked immunosorbent assay; HMGB-1, high mobility group box-1; HMWA, high molecular weight adiponectin; HR, hazard ratio; ICU, intensive care unit; IFN, interferon; IL, interleukin; PCT, procalcitonin; PPAR, peroxisome proliferator-activated receptor; ROC, Receiver Operating Characteristic; SOFA, sequential organ failure assessment score; suPAR, soluble urokinase-type Plasminogen Activator Receptor; TNF-α, tumor necrosis factor-alpha.

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and organs, exhibits insulin-sensitizing and anti-inflammatory properties in immune regulation pathways [8,10,11]. Clinical data on adiponectin, particularly its main isoform High Molecular Weight Adiponectin (HMWA), and their kinetics during sepsis are few and conflicting [9,12-14].

Analogously to the adipokines, hepatokines are functional proteins released from the liver participating in metabolic, immune and inflammatory processes [7,15,16]. Apart from the canonical hepatic response to acute stimuli, the multifunctional hepatokine fetuin-A, also known as α2-HS-glycoprotein, with major pathogenetic role in metabolism, atherogenesis and calcium homeostasis [15,17,18], exerts a Janus effect as a negative APP mainly in chronic inflammatory diseases [19-21] and a positive APP in ischemic injury [7,22]. Fetuin-A may present a protective role in lethal systemic inflammation as shown in an animal model [23], and in few mechanistic [7,23,24], proteomic [5,6] and amino-acid analysis [25] studies. However, there are only scant clinical observational data with very small sample sizes (N = 19 to 23 patients) regarding its role in human sepsis [26,27].

To date, the contribution of fetuin-A, adiponectin and its main isoform HMWA in sepsis, have not been thoroughly explored. Moreover, the interconnection of the major hepatokine fetuin-A and the predominant adipokine adiponectin in sepsis pathophysiology has not been investigated yet. Hence, in a prospective study, we aimed at studying jointly the kinetics of fetuin-A and adiponectin in sepsis, their association with the severity and outcome of sepsis as well as with other well-known laboratory prognostic markers. A secondary aim was to compare serum baseline fetuin-A and adiponectin levels in septic patients and healthy controls.

2. Material and methods

2.1. Study population and protocol

This observational prospective study was conducted in the ICU of Attikon General University Hospital, a multivalent adult medical/surgical unit. We prospectively enrolled 167 consecutive patients admitted to the ICU between August 2013 and July 2015. All patients fulfilled the criteria of sepsis or septic shock as recently defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS-3) [1,28]. The inclusion criteria were: diagnosis of sepsis within the last 48 h and age above 18 years. The exclusion criteria were: pregnancy, history of diabetes, history of malignancy (solid organ or haematopoietic system), HIV infection, neutropenia defined as an absolute neutrophil count below 1000/mm^3 attributed to causes other than sepsis, immunosuppressive therapy or radiation and history of chronic steroid use, defined as daily intake of >0.4 mg/kg of equivalent prednisone for >15 days.

We followed patients for 28 days and we analyzed only samples collected from patients who were still in the ICU after at least a week from inclusion to the study. Of the initial 167 patients, 23 patients died and 13 patients were discharged before completing a week of hospitalization in the ICU after the diagnosis of sepsis, while 29 patients were excluded due to diabetes, malignancy, immunosuppression and HIV infection (Fig. 1). A hundred and two patients were studied and treated according to the Surviving Sepsis Campaign clinical guidelines [2]. The following demographic, clinical and laboratory data were recorded: age, gender, weight, height, body mass index (BMI), admission diagnosis, site of infection, causative pathogen, 28-day mortality (main outcome), complete blood count and biochemical parameters including glucose, albumin and lactate. The Acute Physiology and Chronic Health Evaluation (APACHE) II and the Sequential Organ Failure Assessment (SOFA) scores were also determined.

The control group for main study laboratory variables consisted of 102 apparently healthy overnight-fasted controls (57 men, 45 women; mean age: 66.4 ± 10.3 years; mean BMI: 28.1 ± 5.01 kg/m^2), without any type of malignancy, infection and diabetes, who came for an annual check-up examination in the Outpatient Clinic of the Laboratory Department of the same hospital. For every eligible case, an attempt was made to randomly identify a control as closely as possible in time to the admission of the corresponding case (±1 month) and matched to cases on age (±5 years) and gender.

The study was approved by the Scientific and Ethical Committee of the hospital. Informed consent was given by all study participants or their next of kin.

2.2. Laboratory analysis

Patients' blood samples for determination of fetuin-A, adiponectin, HMW adiponectin, tumor necrosis factor-alpha (TNF-α) and interleukins (ILs) were collected upon enrollment to the study and one week after enrollment. All specimens were centrifuged and sera were frozen at −80 °C. Serum fetuin-A was measured using an enzyme linked immunosorbent assay-ELISA (DIAsourceImmunoAssays S.A., Nivelles, Belgium) with a sensitivity of 5 ng/mL, an intra-assay coefficient of

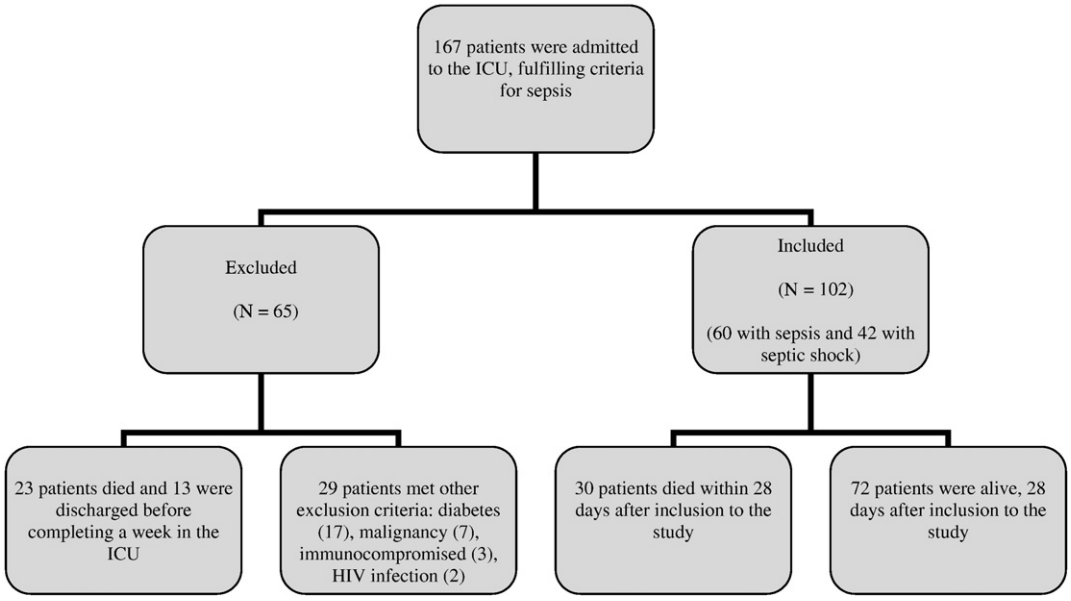

Fig. 1. Flowchart of the study population.