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Cytokine production and hospital mortality in patients with sepsis-induced stress hyperglycemia

Leonidia Leonidou [a], Athanassia Mouzaki [b], Marina Michalaki [c], Anna Lisa DeLastic [b], Venezana Kyriazopoulou [c], Harry P. Bassaris [a], Charalambos A. Gogos [a,*]

[a] *Department of Internal Medicine, Section of Infectious Diseases, Patras University Hospital, Rion-Patras 26500, Greece*
[b] *Department of Hematology, Patras University Medical School, Rion-Patras 26500, Greece*
[c] *Department of Diabetes and Endocrinology, Patras University Hospital, Rion-Patras 26500, Greece*

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Summary *Objectives:* To investigate whether stress hyperglycemia affects the production of the main pro- and anti-inflammatory cytokines and the 28-day hospital mortality in patients with severe sepsis.
Methods: The study included 62 patients with severe sepsis, divided in three groups according to their glycemic profile within 24 h after admission: patients with stress hyperglycemia (group SH, $n = 16$), diabetes mellitus type II (group DM, $n = 27$), and normal glucose levels (group NG, $n = 19$). The serum levels of the cytokines TNF-alpha, IL-6, IL-10 and TGFbeta-1 were measured within 24 h after admission.
Results: A higher percentage of septic patients with stress hyperglycemia died compared to diabetic patients (43.7 vs. 14.8%) and group NG (43.7 vs. 5.2%). Group SH had higher SOFA score and levels of IL-6 and IL-10 than group DM and group NG. It also had higher levels of TNF-alpha than group DM but not group NG. There was no difference in the levels of TGFbeta-1 among the three groups. Non-survivors had higher levels of IL-10, no difference was detected for IL-6, TNF-alpha, IL-10/TNF-alpha ratio and TGFbeta-1. Interleukin-10 values, mean fasting glucose values and age were found as prognostic factors associated with outcome.
Conclusions: Stress hyperglycemia is associated with increased cytokine production and an adverse clinical outcome in patients with severe sepsis.

Introduction

Stress hyperglycemia is a medical term referring to elevation of blood glucose levels in the absence of diabetes due to various kinds of stress, like trauma, burn injury, surgery, myocardial infarction and sepsis. It is a common occurrence

* Corresponding author. Department of Medicine, Patras University Medical School, Rion-Patras 26500, Greece. Tel.: +302610999737.
E-mail address: cgogos@med.upatras.gr (C.A. Gogos).

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in critically ill patients and it has been identified as an independent risk factor for in-hospital morbidity and mortality in adult patients with or without a history of diabetes mellitus.[1–6] On the other hand, tight glycemic control through intensive insulin therapy has been shown to improve outcome.[7–10] The metabolic milieu in which stress induced hyperglycemia develops in the critically ill, in the absence of pre-existing diabetes mellitus, is complex. A combination of several factors, including the presence of excessive counter regulatory hormones, the exogenous administration of catecholamines, dextrose and nutritional support together with relative insulin deficiency, seem to play an important role.[11,12] Overall, increased gluconeogenesis combined with hepatic insulin resistance seems to be the major factor leading to hyperglycemia.[12,13]

The production and/or release of cytokines such as IL-6, TNF-alpha and IL-10 have been shown to play a significant role in the development of hyperglycemia. *In vivo* studies in animals have shown that hyperglycemia induced by glucose infusion for only 3 h can significantly diminish immune function[14] and induce a state of hepatic oxidative stress associated with cytokine activation.[15] Interleukin-6 is a pleiotropic cytokine with a broad range of effects relating to inflammation, host defence and tissue injury,[16] while it has been shown to be associated with the severity of critical illness[17] and the presence of sepsis in patients with diabetic ketoacidosis.[18] Interestingly, increased IL-6 serum concentrations are related to insulin resistance[19] and IL-6 contributes to hyperglycemia through glucose release from hepatic glycogen stores.[20] On the other hand, hyperglycemia itself increases the serum concentrations of IL-6, possibly through augmented production in monocytes.[21]

Tumour necrosis factor alpha is the main pro-inflammatory cytokine implicated in the pathogenesis of sepsis syndrome and has been related to the severity of sepsis.[22,23] It has been demonstrated to induce insulin resistance in animals by itself[24] or through inducing an increase in circulating levels of free fatty acids.[25,26] In glucose-loaded fasting animals, tumour necrosis factor (TNF)-alpha release is dramatically amplified after lipopolysaccharide administration compared to controls.[27]

On the other hand, IL-10 is the main anti-inflammatory cytokine in sepsis and it has been associated with the severity of the disease and the final outcome.[28,29] There are only a few experimental studies on the effect of hyperglycemia and hyperinsulinemia on IL-10 synthesis showing a pronounced cytokine response mainly at organ level.[30] Finally, it is considered that TGFbeta-1 plays a dual role during the course of inflammatory reactions, being pro-inflammatory at first and immunosuppressive later.[31,32] Its role in stress induced hyperglycemia has not still been investigated.

The balance between pro- and anti-inflammatory modulators is considered important in the development of sepsis and the final outcome.[33] In the present study, pro- and anti-inflammatory cytokines in septic patients with stress hyperglycemia were measured and compared to those with diabetes mellitus and normal glucose values, in order to investigate the role of these cytokines in the pathophysiology of sepsis and hyperglycemia. We also investigated the effect of sepsis-induced stress hyperglycemia on the 28-day hospital mortality of patients with severe sepsis.

Patients and methods

A total of 62 patients (30 female, 32 male), who were admitted in Rion Regional University Hospital during a one-year period with severe sepsis, were included in the study. All patients fulfilled the criteria of severe sepsis upon admission. Patients in whom sepsis was developed during hospitalization were excluded. Patients were divided in three groups, according to their glycemic profile within 24 h after admission: patients with baseline stress hyperglycemia (group SH, $n = 16$), patients with diabetes mellitus (group DM, $n = 27$) and patients with normal glucose level and no history of diabetes (group NG, $n = 19$). Stress hyperglycemia was defined as at admission or in-hospital fasting glucose level of $\geq$126 mg/dl or a random blood glucose level of 200 mg/dl or more on $\geq$2 determinations taken within 24 h after admission, in the absence of pre-existing diabetes mellitus. All diabetic patients suffered from type II diabetes mellitus. Seven out of the 27 patients were under insulin treatment before their hospital admission, while five patients were on diet and 15 patients under oral anti-diabetic treatment. In order to have a homogenous population, patients with septic shock or diabetic ketoacidosis were excluded from the study, as critical illness may compromise the immune response. Immuno-compromised patients and patients with severe co-morbidities, like cirrhosis, congestive heart failure, chronic renal failure etc. were also excluded. All patients were admitted to the Intermediate Care Unit of the Department of Internal Medicine. Patients were transferred to the ICU, when necessary. The study was approved by the Rion Regional University Hospital Ethics Committee.

Sepsis was defined according to the criteria of the American College of Chest Physicians — Society of Critical Care Medicine Consensus Conference Committee[34] as the presence of confirmed infection and $\geq$2 of the following criteria: (a) a temperature of $>$38 °C or $<$36 °C, (b) a heart rate of $\geq$90 beats/min, (c) tachypnea, manifested by a respiratory rate of $\geq$20 breaths/min, or hyperventilation, indicated by a $PaCO_2$ of $\leq$32 mmHg, and (d) an altered white blood cell count of $>$12,000 or $<$4000 cells/mm^3 or the presence of $>$10% immature forms. Severe sepsis was defined as the presence of sepsis plus at least one organ dysfunction indicated by the following: (a) hypotension (systolic blood pressure of $\leq$90 mmHg or mean arterial pressure of $\leq$65 mmHg corrected within 1 h by fluid replacement), (b) arterial hypoxemia (PaO_2 of $\leq$75 mmHg without evidence of primary respiratory tract disease), (c) metabolic acidosis (pH $\leq$ 7.3 or a base deficit of $\geq$5 meq/l), (d) oliguria (urine output $\leq$ 30 ml/h), (e) liver dysfunction, (f) acute alteration of mental status, or (g) recent coagulation abnormality (activated partial thromboplastin time $\geq$1.2 times the upper normal limit plus $\geq$500 D-dimers or $\leq$100,000 thrombocytes/μl). Alterations in mental status were evaluated through the Glasgow Coma Score (GCS), while the severity of sepsis was classified by the sepsis-related organ failure assessment score (SOFA).