Presepsin as a Biomarker for Sepsis Evolutions in Diabetis

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The paper presents the correlations between seric presepsin value and evolutive aspects (especially mortality) in diabetic patients with sepsis. The study included a total of 60 patients with a mean age of 64.65 ± 12.99 years, (Male = 51.6 %, Female = 48.4%), consecutively hospitalized in the Clinic of Diabetes, Nutrition and Metabolic Diseases in 1 year (2013), with diagnosis of sepsis. We selected the patients who fulfilled at least 2 criterions for sepsis: suspected or proved infection, together with system inflammatory response. The presepsin determination was performed by using a chemiluminescent enzyme immunoassay of EDTA (Ethylenediaminetetraacetic acid) plasma. The clinical evolution was expected by calculating SAPS II score (Simplified Acute Physiology Score) in first 24 hours of internship.The median age was 64.65 ± 12.99 years, Male = 51.6%. Diabetic keto-acidosis was associated to sepsis in 32.3% of patients. Mortality rate was 32.3%. There were semnificative correlations between mortality rate and SAPS II score (p = 0.001), presepsine (p = 0.001), and fibrinogen value (p = 0.048). There were no semnificative correlations between age, sex, keto-acidosis, another inflammatory markers, glycemia, HbA1c and mortality rate in these patients. Presepsin level in blood semnificative correlated with seric fibrinogen, mortality rate, SAPS II score, blood urea and creatinine and may be considered an important serum biomarker for early detection of sepsis.

Keywords: presepsine, glycemia, keto-acidosis, biomarker, blood urea

The sepsis represents a systemic inflammatory response syndrome caused by severe infection. Sepsis causes millions of deaths globally each year.The criteria according to the systemic inflammatory response syndrome (SIRS) represents a clinical expression of the host response to inflammation and beeing described 24 years ago. This approach was codified by the consensus statement of the American College of Chest Physicians and Society of Critical Care Medicine in 1993 and has been the predominant approach to classifying sepsis. As a costly disease, sepsis not only lowers patient's living quality, but also increases the mortality[1-4]. Early diagnosis in sepsis is imperative to save patient life. Sensitive biomarkers are required for early diagnosis and as indexes of prognosis sepsis.

Presepsin is a circulating soluble form of CD14 subtype (sCD14-ST) representing a new emerging early marker for sepsis. The mean cutoff levels of presepsin are important to discriminate between systemic bacterial and nonbacterial infectious diseases [5]. Presepsin is an early predictor of host response and mortality in septic patients [6]. Many Studies emphasized the capability of this biomarker for diagnosing sepsis, assessing the severity of the disease and providing a prognostic evaluation of patient outcome [5-8].

Usually, in older age, sepsis is associated with increased mortality. The severity of illness have to be predicted earlier in these fragile pacients, by using some factors which include the admitting diagnosis, comorbidities, and the functional status of the patient [8]. The most used prognostic scoring models include the Simplified Acute Physiologic Score II (SAPS II), Acute Physiology and Chronic Health Evaluation II (APACHE II), and the newly developed SAPS III [8].

Experimental part

The aim of the study was to establish the correlations between seric presepsin value and evolutive aspects (especially mortality) in diabetic patients with sepsis.

Material and methods

The study group included a total of 60 patients with a mean age of 64.65 ± 12.99 years, (Male = 51.6 %, Female = 48.4%), consecutively hospitalized in the Clinic of Diabetes, Nutrition and Metabolic Diseases in 1 year, with diagnosis of sepsis.

Was selected the patients who fulfilled at least 2 criterion for sepsis: the suspected or proved infection, together with systemic inflammatory response (at least – fever/ hypothermia, tachycardia, tachypnea, leucocytosis/ leucopenia). There were considered as main biochemical analysis: glycemia, blood urea, level of seric bicarbonates, seric creatinine, ketonuria (level of ketone bodies in urine), presepsine, HbA1c, inflamatory markers (leucocites, neutrophiles, hemoglobine, C - reactive protein, Eritrocite Sedimentation Rate = ESR). The quick method for presepsin determination uses a chemiluminescent enzyme immunoassay of EDTA plasma. The evolution was determined by calculating SAPS II score (Simplified Acute Physiology Score) in first 24 hours of hospitalization.

Results and discussions

Sepsis was defined as a suspected infection accompanied by systemic inflammatory response syndrome (at least 2 criteria: fever/hypothermia,

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Table 1
DESCRIPTIVE CHARACTERISTICS OF BIOLOGICAL PARAMETERS AND PROGNOSTIC SCORES

Variable	Descriptive statistics			
	Mean	Minimum	Maximum	Std. deviation
Co-morbidities score	6.13	1.00	12.00	2.849
SAPSii	1.68	6.00	78.00	18.003
Death	1.68	1.00	3.00	0.475
Diabetes duration	12.68	0.00	34.00	8.761
Heart rate	109.84	68.00	150.00	22.971
Lactate	45.20	16.00	181.50	40.366
CRP	18.21	0.73	38.05	9.768
Predicted mortality	33.48	0.50	91.20	24.982
White blood cells	17458.06	2940	4264	7948.59
Neutrophils	81.68	55.00	94.50	11.003
Hemoglobine	11.85	8.50	17.90	2.216
Presepsin	1588.42	100.00	7263.00	1872.844
Eritrocyte Sedimentation Rate	89.45	5.00	121.00	26.789
Fibrinogen	529.19	186.00	900.00	147.205
HbA1c	9.09	5.700	13.30	2.108
Glycemia	335.26	27.00	560.00	280.95

tachycardia, tachypnea, leukocytosis/leukopenia). Table 1 presents the *statistical analysis*.Fever was present in 54.3 % of patients. 25.8 % of patients with sepsis had multisystem organ syndrome (MSOF). The evaluation of patient outcomes was assessed by calculating the SAPS II score (Simplified Acute Physiology Score) in the first 24 hours of hospitalization. The mean duration of diabetes was 12.68 ± 8.76 years. Diabetic keto-acidosis was associated to sepsis in 32,3% of patients. Regarding chronic complications they were present in the following proportions: sensor motor neuropathy - 26%, autonomic neuropathy - 16.12 %, diabetic retinopathy - 45.16 % and diabetic nephropathy - 32.25 %.

In our study, mortality rate was 32.3%. There were semnificative correlations between mortality rate and SAPS II score (p = 0.001), presepsine (p = 0.001), and fibrinogen value (p = 0.048). There were no semnificative correlations between age, sex, keto-acidosis, another inflammatory markers: leucocites, neutrophiles, hemoglobine, C-reactive Protein (CRP),Eritocyte Sedimentation Rate), glycemia, HbA1c and mortality rate in these patients. There were significant correlations between SAPS score, PMN value (r = 0.6112, p = 0.015) and presepsine value (r = 0.65, p = 0.009) (table 2).

The diabetics are predisposed to infections. Some studies have detected a deficiency of the immunity, in diabetics, in C4 component of complement system, which is probably associated with leucocite dysfunction and reduced cytokine response [9, 10]. Glycation of immunoglobulin occurs in patients with diabetes in proportion with the increase in HbA1c, and this may harm the biological function of the antibodies [11, 12]. Infections may precipitate metabolic derangements, the most severe beeing diabetic ketoacidosis (DKA), which is life threatening [13].

Diabetic ketoacidosis (DKA) is a complex disordered metabolic state characterized by hyperglycemia, ketoacidosis, and ketonuria. Hepatic gluconeogenesis, glycogenolysis secondary to insulin deficiency, and counter-regulatory hormone increase glucose level in blood excess result in severe hyperglycemia. Lipolysis of triglycerides from fatty tissue increases serum free fatty acids. Triglycerides are lipid fractions, formed by combining

Variables	SAPSii score
White blood cells	0.6112 **p = 0.015**
Neutrophils	0.3182 p = 2.48
Hemoglobin	-0.2669 p = 0.346
Fibrinogen	-0.0061 p = 0.161
HbA1c	0.3810 p = 0.161
Glycemia	0.2439 p = 0.381
Diabetes duration	0.0095 p = 0.973
Heart rate	0.3057 p = 0.268
Lactate	0.1153 p = 0.0682
Predicted mortality	0.9883 **p = 0.000**
CRP	0.1884 p = 0.501
Co-morbidities score	0.4250 p = 0.114
Presepsin	0.6509 **p = 0.009**

Table 2
CORRELATIONS BETWEEN SAPSii SCORE AND MAIN BIOLOGICAL PARAMETERS

glycerol with three fatty acid molecules. Organic acids have a carboxyl (-COOH) group. Each fatty acid has a carboxyl group

$$(\text{-COOH}).\text{R''COOH} \rightarrow \text{RCO}_2\text{CH}_2\text{CH(OOCR')CH}_2\text{COOR''} + 3\text{H}_2\text{O}.$$

The three fatty acids (RCOOH, R'COOH, R''COOH in the above equation) are usually different, but many kinds of triglycerides are known. The chain lengths of the fatty acids in naturally occurring triglycerides vary, but most contain 16, 18 or 20 carbon atoms. Hepatic metabolism of free fatty acids results in accumulation of acidic intermediate and end metabolites (ketoacids). Ketone bodies have generally included: acetone (C_3H_6O), beta-hydroxybutyrate ($CH_3CH(OH)CH_2CO_2H$), and acetoacetate ($C_4H_5O_3$). When the accumulated ketones exceed the body's capacity to extract them, they overflow into urine (ie, ketonuria). If the situation is not treated promptly, a greater accumulation of organic acids leads to frank clinical metabolic acidosis (ie, ketoacidosis), with a significant drop in *p*H and bicarbonate serum levels [14]. In diabetic patients, infection represents an important stress which induces an increased discharge of cathecolamines and cortisol.

There are some studies that emphasized that during stress or infection, less mature neutrophil forms enter in circulation, including an increased number of bands. Park et al demonstrated that the proportion of immature granulocytes in circulating blood, correlated with disease severity of sepsis in critically ill patients admitted in Intensive Care Unit [18]. There is suggested that incorporating the immature granulocyte assay into the routine algorithms may improve the early detection of severe sepsis or septic shock [18-20]. Another studies demonstrated that neutrophils from septic patients may exert dramatic compromise of endothelial barrier integrity and the effect of septic neutrophils on the endothelium depends upon the initial inflammatory event, correlating with organ dysfunction [20-23]. In our study, no significant differences were observed in SAPS score in patients with chronic complications and patients without chronic complications of diabetes, except in patients with diabetic nephropathy (p = 0.009). SAPS score II differed significantly from those with chronic kidney disease (p = 0.009) or

Effect	Descriptive statistics						
	Level of factor	N	SAPSii Mean	SAPSii Std. Dev.	SAPSii Std. Err	SAPSii -95,00%	SAPSii +95,00%
Total		31	40.35484	18.00287	3.233410	33.75133	46.95834
Nephropathy	yes	10	52.10000	14.48716	4.581242	41.73651	62.46349
Nephropathy	no	21	34.76190	17.02617	3.715415	27.01168	42.51212

Table 3
SAPS SCORE II IN PATIENTS WITH/WITHOUT NEPHROPATHY

Effect	Descriptive statistics						
	Level of factor	N	SAPSii Mean	SAPSii Std. Dev.	SAPSii Std. Err.	SAPSii -95.00%	SAPSii +95.00%
Total		31	40.35484	18.00287	3.233410	33.75133	46.95834
MSOF	Yes	8	58.50000	12.88410	4.555217	47.72862	69.27138
MSOF	No	23	34.04348	15.09208	3.146915	27.51718	40.56978

Table 4
SAPS SCORE II IN PATIENTS WITH / WITHOUT MULTIPLE SYSTEMIC ORGAN FAILURE (MSOF)

acute renal failure (p = 0.009) and patients without renal complications (table 3).

Patients with MSOF had a higher SAPS score (p = 0.001) (table 4).

In some studies [24], presepsin levels were markedly high in patients receiving HD, similar to those seen in patients with severe sepsis or septic shock. In patients who were not receiving hemodialysis, presepsin levels increased and glomerular filtration rate decreased. Some authors [23-26] reported that presepsin levels significantly correlated with serum creatinine levels and the number of days on renal replacement therapy. In a retrospective study, Nakamura et al. [27] found that presepsin levels were markedly high in patients with renal failure and end-stage kidney disease. Masson et al. [6] reported that higher serum creatinine was the strongest determinant of presepsin levels in ICU patients. The evaluation of presepsin levels in patients with chronic kidney disease requires further consideration.

Conclusions

In our study we demonstrated that presepsin level in blood semnificative correlated with seric fibrinogen, mortality rate, SAPS II score and polimorphonuclear neutrophile leucocites, blood urea and creatinine and may be considered an important serum biomarker for early detection of sepsis. The SAPS II score is usefull to estimate the mortality in complicated diabetic patients, with severe sepsis and bad prognosis.

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