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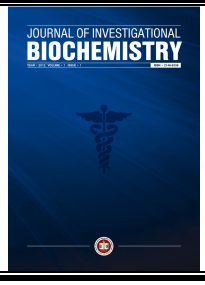

Mini Review

A new marker for the diagnosis of sepsis: Presepsin

Mehmet Agilli, Irfan Sener, Fatih Yesildal, Tevfik Honca, Ibrahim Aydin, Emin Ozgur Akgul, Halil Yaman

Department of Medical Biochemistry, Gulhane Military Medical Academy, Ankara, Turkey

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Corresponding Author:
Mehmet Agilli,
Gulhane School of Medicine, Department of Biochemistry, Ankara, Turkey
mehmetagilli@yahoo.com

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Abstract

Sepsis is a clinical syndrome that complicates severe infection. It is characterized by the cardinal signs of inflammation (vasodilatation, leukocyte accumulation, increased microvascular permeability) occurring in tissues which are remote from the infection. The clinical definitions of sepsis are basically nonspecific, often resulting in the delay of the diagnosis. During the last decade, a variety of different molecules have been suggested as clinical biomarkers in sepsis, most of which are still in experimental stage. However, some have came into use in clinical practice and have evolved as valuable tools for diagnosis, therapy monitoring, and outcome prediction.

Presepsin, which is approximately 13 kDa, has been identified as a protein whose levels increase specifically in the blood of sepsis patients. Presepsin is thought to be a more specific and sensitive marker for the diagnosis of sepsis compared with interleukin-6 and procalcitonin (PCT). Presepsin concentrations in blood were increased faster than PCT and CRP in sepsis patients. Although there are a lot of biomarkers to diagnose sepsis, presepsin could be a new candidate for this purpose. In this mini review, we discussed a new biomarker, presepsin, and its clinical relevance

INTRODUCTION

Sepsis is a clinical state, which is complicated with severe infection and characterized with systemic inflammation and disseminated tissue damage [1]. It would be better to explain SIRS primarily, so that sepsis could be understood according to this definition.

SIRS : SIRS is the clinical syndrome that results from a dysregulated inflammatory response to a noninfectious insult, such as an autoimmune disorder, pancreatitis, vasculitis, thromboembolism, burns, or surgery. It requires that two or more of the following abnormalities be present [2].

1. Body temperature > 38,5 or < 36 °C
2. Heart rate > 90/minute
3. Respiratory rate > 20/minute or $PaCO_2$ < 32 mmHg
4. Leukocyte count > 12000/mm^3 or < 4000/mm^3

Sepsis: Sepsis is the clinical syndrome that results from a dysregulated inflammatory response to an infection. It exists if two or more of the above abnormalities are present, along with either a culture-proven or visually identified infection.

Biomarkers can have an important role in the presence, absence or severity of sepsis, and can differentiate bacterial from viral and fungal infection, and systemic sepsis from local infection [3, 4]. Other potential uses of biomarkers include roles in prognosis, antibiotic therapy, evaluating the response to therapy and recovery from sepsis, differentiating gram-positive from gram-negative microorganisms as the cause of sepsis, predicting sepsis complications and the development of organ dysfunction (heart, kidneys, liver or multiple organ dysfunction). However, the exact role of biomarkers in the management of septic patients remains undefined [5]. C-reactive protein (CRP) has been used for many years but its specificity has been challenged [6]. Procalcitonin (PCT) has been proposed as a more specific [7] and better prognostic marker than CRP, although its value has also been challenged [8]. It remains difficult to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome, and studies are being continued to define a reliable biomarker [8].

In a rewiev, more than 170 different biomarkers have been assessed for potential use in sepsis, more for prognosis than for diagnosis [9]. These biomarkers could be divided 9 subheadings according to their structure. These are;

Cytokine/chemokine biomarkers (IL-6, IL-8, IL10, e.g.), Cell marker biomarkers (CD11b, CD14, CD64, e.g.), Receptor biomarkers (Toll-like receptor (TLR) 2 and 4, triggering receptor expressed on myeloid cells (TREM-1), receptor for advanced glycation end-products (RAGE), e.g.), Coagulation biomarkers (Antithrombin, Protein C and S, D-dimer, e.g.), Biomarkers related to vascular endothelial damage (Neopterin, Laminin, P-Selectin, e.g.), Biomarkers related to vasodilatation (Elastin, Copeptin, Anandamide, e.g.), Biomarkers of organ dysfunction (Atrial natriuretic peptide (ANP), Brain natriuretic peptide (BNP), Protein S-100b, e.g.), Acute phase protein biomarkers (CRP, Serum amyloid A, Pentraxin 3, e.g.) and Other biomarkers (Neurotensin, Leptin, Resistin, e.g.). 34 biomarkers of them were identified that have been assessed for use specifically in the diagnosis of sepsis; of these just five reported sensitivity and specificity values greater than 90%. These were: CD11b, CD64, IL-12, interferon induced protein-10 (IP-10) and phospholipase A2 – II (PLA2-II) soluble. Importance of these five biomarkers were; CD11b: higher values in neonates with sepsis than in those with possible infection, CD64: higher expressions may indicate early diagnosis of sepsis, IL-12: higher values may indicate diagnosis of sepsis in pediatric patients, IP-10: higher values may indicate early diagnosis of sepsis in newborns, PLA2-II: higher values may distinguish between bacteremic and non-bacteremic infections. But these biomarkers were studied in a very narrow study group. For example IP-10 was higher in neonates with sepsis and necrotizing enterocolitis than in neonates who had only necrotizing enterocolitis [10]. Or, CD 64 had high sensitivity and specificity for the early diagnosis of sepsis in adults, but could not reliably distinguish viral from bacterial infections, or local infection from systemic sepsis [11]. Actually, there are some findings about diagnostic biomarkers but none has sufficient capability to diagnose all etiological kinds of sepsis or specificity - sensitivity to be routinely employed in clinical practice. Currently, PCT and CRP have been most widely used in clinical practice, despite their limited abilities to specify sepsis or to predict outcome [9].

In this article, a new biomarker, which is a candidate biomarker for early diagnosis of sepsis, namely presepsin (sCD14-ST) is going to be mentioned.

A Newly Used Biomarker: Presepsin (sCD14-ST)

In these days, a new biomarker, presepsin or sCD14-ST, is proposed in the field of sepsis. It was firstly defined in 2005 [12] and has been a new important marker for diagnosis and prognosis of sepsis in recent years.

CD14 is a glycoprotein expressed on the surface membrane of monocytes/macrophages (mCD14) and serves as a receptor for complexes of lipopolysaccharides (LPS) and LPS binding protein (LPBP). mCD14 co-localizes with toll-like receptor 4 (TLR4). Upon binding of the LPBP complex CD14 activates the TLR4-specific proinflammatory signaling cascade thereby starting the inflammatory reaction of the host against infectious agents. The complex of LPS-LPBP-CD14 is released into circulation by shedding of CD14 from the cell membrane yielding soluble CD14 (sCD14). However, plasma protease activity generates also another sCD14 molecule called sCD14 subtype (sCD14-ST) or presepsin [13]. Although many aspects of its production in vivo are unknown, based on the results of animal experiments, etc., it is thought that phagocytosis in response to bacterial infection may play a major role, and the possibility that the lysosomal enzymes, e.g., aspartic proteases (cathepsin, etc.), are involved in the mechanism of production is suspected based on the results of enzyme inhibition experiments [14].

DISCUSSION

Sepsis is a leading cause of death in critically ill patients despite the use of modern antibiotics and resuscitation treatments [15]. The septic response is an intensely complex chain of events involving inflammatory and anti-inflammatory processes, humoral and cellular reactions and circulatory abnormalities [16]. The diagnosis of sepsis and evaluation of its severity is complicated by the highly variable and non-specific nature of the signs and symptoms [17]. However, the early diagnosis and stratification of the severity of sepsis is vital, in timing and specific treatment [18].

Presepsin is thought to be a new candidate biomarker for diagnosis of sepsis. Presepsin levels of patients with sepsis were found significantly elevated in comparison with patients having SIRS and healthy people, in a clinical study [13] [12]. The rise in presepsin levels was found to be earlier with respect to the rise in IL-6 and D-Dimer levels as a result of a study by creating an animal model of bacteriemia [19]. It is indicated that presepsin levels may be an important marker for diagnosis of sepsis.

Shozushima et al. [20] studied presepsin and PCT levels for diagnosis of sepsis and found presepsin more useful in diagnosis of sepsis compared to PCT. As the cut-off value of presepsin is determined 415 pg/ml; it was found that clinical sensitivity was %80.1, specificity was %81. ROC analyse was made and Area Under the Curve (AUC) of presepsin was found higher than PCT and presepsin was thought to be more precious in diagnosis compared to PCT. In this study, it was found that PCT levels elevated in patients with SIRS also, but presepsin levels elevated only in patients with sepsis.

In another clinical study, presepsin was compared with CRP, IL-6 and PCT again. In this prospective cohort study; healthy, local infection, SIRS, sepsis and severe sepsis groups were compared for diagnostic performance for sepsis in 41 patients with SIRS. When they divided the patients into an infection group and a non-infection group and plotted the ROC curves of each of the markers to compare presepsin with other markers, the results showed that presepsin was the best, followed by CRP, IL-6, and PCT. Although PCT is thought to be one of the best markers for diagnosis of sepsis, there were 12 patients with trauma and burn in that study and so PCT levels thought to be increased as a reflection of the severity of the body's reaction to the traumatic stimuli in the early stage of trauma in the absence of signs of infection [20]. Yaegashi et al. also found same findings for diagnostic performance of presepsin compared other biomarkers as IL-6 and PCT [12]. These studies thought that PCT was not capable enough to distinguish sepsis and SIRS but presepsin was. Same finding for PCT was reported in a rewiev and they thought PCT could not reliably differentiate sepsis from other non-infectious causes of SIRS in critically ill adult patients. Moreover they do not lend support to the widespread use of the PCT test in

critical care settings [8].

According to several studies, presepsin could be seen a valuable biomarker for early diagnosis for sepsis and distinguish it from non-infectious diseases. But there is no data about presepsin levels on prognosis of sepsis or therapy modification. Whereas widely used biomarkers routinely as CRP, lactate or PCT levels could be used for this purpose and could change the treatment. However presepsin is claimed to be an ideal biomarker for diagnosis sepsis and distinguish it from non-infectious diseases, PCT, CRP or lactate are each more capable to achieve prognosis, response to therapy. Combination of presepsin and several sepsis biomarkers may be more effective. For example, presepsin can be used for diagnosis and specify sepsis, and PCT or other biomarkers can be used prognosis and therapy modification, but this requires further evaluation.

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