Alexandria Journal of Medicine (2016) **52**, 151–157

HOSTED BY

ELSEVIER

Alexandria University Faculty of Medicine

Alexandria Journal of Medicine

http://www.elsevier.com/locate/ajme

ORIGINAL ARTICLE

The plasma level of soluble receptor for advanced glycation end products in systemic lupus erythematosus patients and its relation to disease activity

Anna Nashaat Abou-Raya [a,1], **Maher Abdel Nabi Kamel** [b,2], **Eman Abdel Ghani Sayed** [c,*], **Ahmed Abdel Hamid El-Sharkawy** [d]

[a] *Department of Rheumatology, Faculty of Medicine, University of Alexandria, Egypt*
[b] *Department of Biochemistry, Medical Research Institute, University of Alexandria, Egypt*
[c] *University of Alexandria, Faculty of Medicine, Egypt*
[d] *Karmouz Hospital of Health Insurance, Department of Internal Medicine and Rheumatology, Faculty of Medicine, University of Alexandria, Egypt*

Received 13 January 2015; accepted 23 June 2015
Available online 23 July 2015

KEYWORDS

Advanced glycation end products;
Systemic lupus erythematosus;
High mobility group box-1

Abstract *Introduction:* In recent years, the role of high mobility group box-(HMGB-1) protein and its receptors has received increasing attention. It has been documented that HMGB-1 is associated with disease activity in systemic lupus erythematosus (SLE). HMGB-1 supports the inflammatory clearance of apoptotic cells and remnants. It binds to molecules released from apoptotic cells such as nucleosomes and DNA thereby, increasing the immunogenicity of macrophages through receptors for advanced glycation end products (sRAGE).
Aim of the work: Was to measure the plasma level of sRAGE in SLE patients and to correlate it with the clinical and laboratory parameters of disease activity.
Patients and methods: The study was composed of 35 SLE patients; 31 females and 4 males (Group I) and 20 age and gender matched healthy subjects as a control (Group II). All patients fulfilling the American College of Rheumatology (ACR) classification criteria for the diagnosis of SLE. Active disease was identified using SLE disease activity index (SLE-DAI).
Demographic data, cutaneous manifestations, arthritis, vasculitis, myositis, renal, and hematological disorders were recorded. In addition; complete blood picture, blood urea, serum

* Corresponding author at: University of Alexandria, Faculty of Medicine, 25, Talaat Harb Street, Attarine, Alexandria, Egypt. Tel.: +20 01006893686.
E-mail addresses: annaraya@yahoo.co (A.N. Abou-Raya), maher.kamel@alexu.edu.eg (M.A.N. Kamel), emanmedicine@yahoo.com (E.A.G. Sayed), ahmedelsharkawy@yahoo.com (A.A.H. El-Sharkawy).
[1] Tel.: +20 035924601.
[2] Tel.: +20 01007151191.

Peer review under responsibility of Alexandria University Faculty of Medicine.

http://dx.doi.org/10.1016/j.ajme.2015.06.005

creatinine, 24 h urine proteins, creatinine clearance, protein/creatinine ratio, C3, C4, Anti-nuclear antibody, Anti-double stranded DNA were conducted for all patients and controls.

Results: The mean value of plasma level of (sRAGE) in SLE patients was significantly higher in SLE patients than in the normal healthy controls ($P < 0.001$). There was a statistically significant positive correlation between sRAGE and SLE-DAI ($P < 0.001$).

Conclusion: The plasma level of sRAGE is considered as a potential biomarker for disease activity in SLE, severity and prognosis.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the involvement of multiple organ systems. Its etiology is largely unknown; however, it has been proposed that genetic and environmental factors contribute to breaking tolerance, resulting in the production of a variety of antibodies directed at self-components.[1]

These autoantibodies form immune complexes can be deposited in many tissues, particularly the skin and kidneys.[2,3] Currently, research is being conducted to determine what patho-physiological mechanisms are involved in this entire process.

Receptor for advanced glycation end products (RAGE) is a multi-ligand member of the immunoglobulin super-family. It is expressed by most types of immune cells, including macrophages, neutrophils, and T cells and interacts with several classes of ligands.[4] Currently, the known RAGE ligands include the high mobility group box-1 (HMGB1) protein, advanced glycation end products (AGEs), and members of the S100/calgranulin family.[5]

One of the proinflammatory mediators is the HMGB1. It was originally recognized as a DNAbinding protein but has recently been identified as a damage-associated molecular pattern (DAMP) molecule.[6,7] This nuclear protein participates in chromatin architecture and transcriptional regulation,[8] but once released, it induces an inflammatory response.[9,10] Extracellular HMGB1 binds to cell surface receptors, including RAGE, toll-like receptors 2 and 4, and others. Studies have shown that interaction between HMGB1 and RAGE results in the production of type -1 interferon, which plays a key role in the pathogenesis of SLE.[11,12] In addition, tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are produced upon HMGB-1 activation of macrophages.[13]

It has also been hypothesized that these cytokines also affect some body organs as well as disease flareups.[14,15] In addition, it has also been postulated that RAGE involvement in all pathophysiological processes is reliant on HMGB1.[16] Some studies have reported a relationship between the high serum level of HMGB1 and flare-ups of lupus disease activity.[17,18] All of these observations support the notion that the HMBG1–RAGE pathway plays a part in the pathogenesis of SLE.

Another class of ligands is the AGEs. They result from a process in which non-enzymatic glycosylation attaches to circulating compounds such as lipids, proteins, or nucleic acids. This process occurs under the effect of oxidative stress (OS) and hyperglycemia.[19] Accumulations of AGEs have been found in certain diseases, including diabetes mellitus (DM) and Alzheimer's. Since RAGE induction is under the effect of AGEs, the RAGE-AGEs pathway is thought to be incriminated in the pathogenesis of these diseases.[20,21]

Receptor for advanced glycation end products is a receptor for a family of about 20 related calcium binding proteins that are only expressed in vertebrates. These include the S100s, which are proteins that alter several intracellular functions.[22]

In addition, many types of body cells release S100s during inflammation; therefore, they can be used as a measure of disease activity.[23,24]

Soluble RAGE (sRAGE), a truncated form of the receptor, has the same structure but lacks the cytosolic and transmembrane domains. Two general mechanisms are usually responsible for the generation of soluble receptors. These are either derived from the alternative splicing of messenger ribonucleic acid (mRNA) or the cleaved products of the membrane-bound form of metalloproteinase.[25,26] Both sRAGE and complete RAGE have the same ligand-binding specificity. Furthermore, sRAGE may act as a trap for pro-inflammatory ligands such as HMGB1 and inhibit their interaction with the RAGE cell surface.[27,28]

2. Aim of the work

Was to measure the plasma level of sRAGE in SLE patients and to correlate it with the clinical and laboratory parameters of disease activity.

3. Patients and methods

The study was composed of 35 patients with SLE 31 females and 4 males (Group I) and 20 age and gender matched healthy subjects (Group II).

All of the patients conformed to the American College of Rheumatology (ACR) classification criteria for the diagnosis of SLE.[29] Active disease was identified using the systemic lupus erythematosus Disease Activity Index (SLE-DAI).[30]

Demographic and clinical data, including cutaneous manifestations, arthritis, vasculitis, myositis, renal disorders were recorded. In addition; complete blood picture,[31] blood urea nitrogen, serum creatinine, 24 h urine proteins, protein/creatinine ratio, creatinine clearance,[32] C_3, C_4,[33] anti-nuclear antibody, (ANA),[34], and anti-double stranded DNA (Anti-ds DNA)[35] were conducted for all patients and controls.

Plasma concentrations of sRAGE levels were measured using enzyme Linked Immunosorbant Assay (ELISA).