ISSN: 03875547
Volume 44, Issue 04, August, 2021

Screening of mannose receptor (CD206) level in rheumatoid arthritis patients

Hayam A. Mohammed[1], Ayman A. Othman Alrawi[2], Zahra'a A. Ahmed[1*]

Department of Biology, College of Science for Women, University of Baghdad, Baghdad, Iraq[1]
Ministry of Health, Baghdad Health Directorate, Abu Ghraib Hospital, Baghdad, Iraq[2]

Corresponding Author: 1*

Keywords:
mannose receptor (MR), CD206, rheumatoid arthritis (RA), autoimmune diseases, COVID-19

ABSTRACT

The mannose receptor (MR-CD206), is one of type I transmembrane proteins that possess structurally and functionally related domains as a pattern recognition receptor. It is expressed primarily on the membrane of M2 macrophages and dendritic cells, which have an important role in nonspecific and specific immunity. In this study, the serum levels of MR were examined in rheumatoid arthritis (RA). MR concentrations were measured in the sera of 50 patients and 38 healthy individuals (control) groups. COVID-19 infection in RA patients has also been investigated. The MR value of RA patients was significantly higher than that of the control group ($p < 0.005$). There is no significant difference in gender, however males have higher MR levels than females, whereas COVID-19 infected RA patients did not show any change or significant difference in the concentrations of MR serum level. We found that untreated RA patients have elevated serum MR levels, making MR a potential marker of the pathogenesis and progression of RA.

1. INTRODUCTION

The term Rheumatoid arthritis (RA) was first used in 1859 by Alfred Baring Garrod to distinguish inflammatory polyarthritis and polyarticular osteoarthritis from forms of arthritis already known as rheumatic fever or gout. In 1922 it was intended solely for inflammatory polyarthritis, and in 1941 it was accepted by the American Association of Rheumatology [1]. RA is one of the most chronic joint diseases in Iraq, characterized by synovitis and bone destruction, and may lead to real disability. The pathogenesis of RA is associated with the activation of inflammatory cells that play a significant role in the development and progression of RA. T cells are strongly implicated in the progression of RA, T helper-1 plays important role in the pathogenesis of RA via the pro-inflammatory cytokines it produced. While T helper-2 immune responses and T-regulatory cells have protective effects in RA [2]. Macrophages and neutrophils are effector cells with abundant synovitis. Macrophage's activation is the major driver of disease during inflammation and tissue damage and is associated with stimulation of inflammatory factor secretion, antigen presentation, and phagocytosis [3]. Macrophages can differentiate into Ml and M2, The M2 (or alternatively activated macrophages) play a potential role in resolving inflammation by releasing anti-inflammatory cytokines, damage repair, and inducing immunotolerance. M2 macrophage and dendritic cells

(DCs) expressed mannose receptors (MR or CD206) on their surfaces. MR acts as a pattern recognition receptor to identify pathogens and is involved in antigen processing and presenting [4], [5]. Moreover, several functions to MR have been reported such as removal of endogenous molecules, T cell differentiation, and cellular activation [6], thus, peripheral serum MR levels gradually increase with acute and chronic diseases [5]. Previous studies demonstrated increased uptake of soluble IgG-mediated by mannose receptor on macrophages and dendritic cells [7]. Therefore, we aim to evaluate the value of the MR level in RA patients and compare it to RA patients with and without COVID-19 and in healthy controls.

2. Methods

A total of 50 patients suffering from RA were enrolled in the study. They were referred to the Rheumatology Consultation Clinic /Baghdad Teaching Hospital in Baghdad for diagnosis and treatment during the period December 2020 to April 2021. In addition, 38 healthy controls volunteered during this time period. Written informed consent was obtained from the Ministry of Health and all participants prior to the study. The diagnosis of RA was based on institute medical staff and laboratory tests. Demographic, clinical data, and laboratory tests (including ESR, CRP, Anti-ccp, and RF) were evaluated. In addition, at the time of diagnosis of RA, COVID-19 infection were assessed for all participants, they were evaluated by rapid test diagnosis for IgM and IgG. The serum level of MR was measured using a commercial enzyme-linked immunosorbent assay kit (Bioassay Technology Laboratory; China). The data were statistically analyzed using program SPSS version 14.0. Data were expressed as the mean ± standard error and then correlation analysis was used to evaluate the associations between the MR and other laboratory analyses. p-value < 0.05 was considered to indicate a statistically significant difference.

3. Results

Study samples were collected during the period from December 2020 to April 2021, which was within the period of the spread of the COVID -19 pandemic around the world. The demographic results showed a higher incidence of RA in the middle age, with a mean age of 49.580 ± 1.863 years, and a greater percentage of up to 88% for age groups above 40 years. By gender, RA occurs more in women 84%than in men16%, and according to blood groups, a recurrence of disease with blood type O+ 50% was observed in patients compared to other blood types. The results of laboratory analysis showed a significant increase in the ESR rate in patients 44.465 ± 3.690 mm/hr compared to the healthy control 21,593 ± 1.707mm/hr, in addition, the RF and Anti-ccp test had positive results in the patients. During the study, 20% of enrolled RA patients were diagnosed with infection by COVID-19. When measuring the MR concentration, a high concentration of MR was observed in patients 6.897 ± 0.251 ng/ml compared to the control 4.232 ± 0.250 ng/ml, as shown in Figure 1. Despite the smaller number of RA males, the concentration of MR was slightly increased without statistically significant differences in males compared to females, Figure 2. While MR concentration did not increase significantly or differences were observed between RA patients infected with COVID-19 and non-infected RA patients, as well as those with a positive CRP test. Elevated levels of MR increased with first diagnosis and untreated RA patients compared to treated RA patients, but this increased level was not statistically significantly different.

ISSN: 03875547
Volume 44, Issue 04, August, 2021

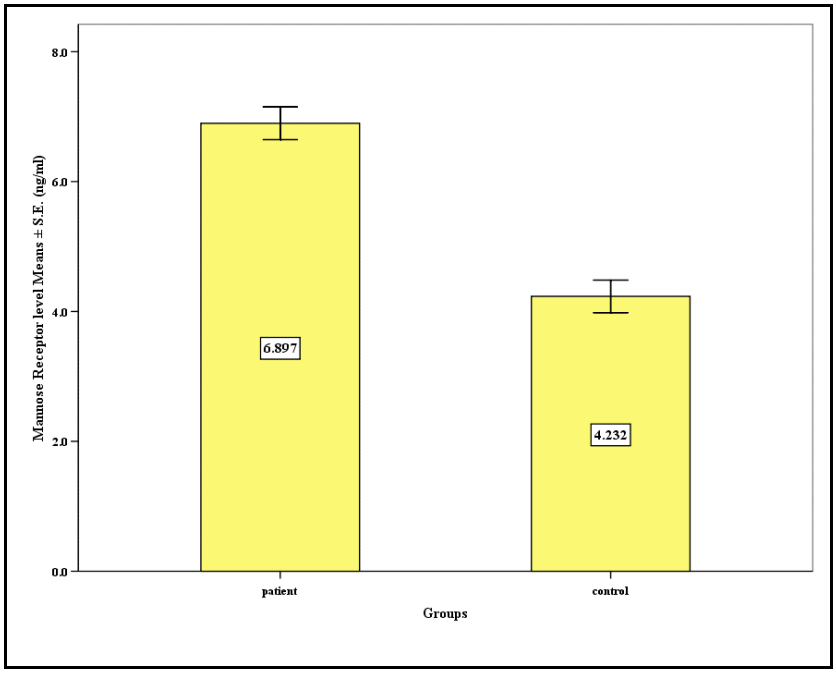

Figure 1. Serum level of MR in RA patients and controls.

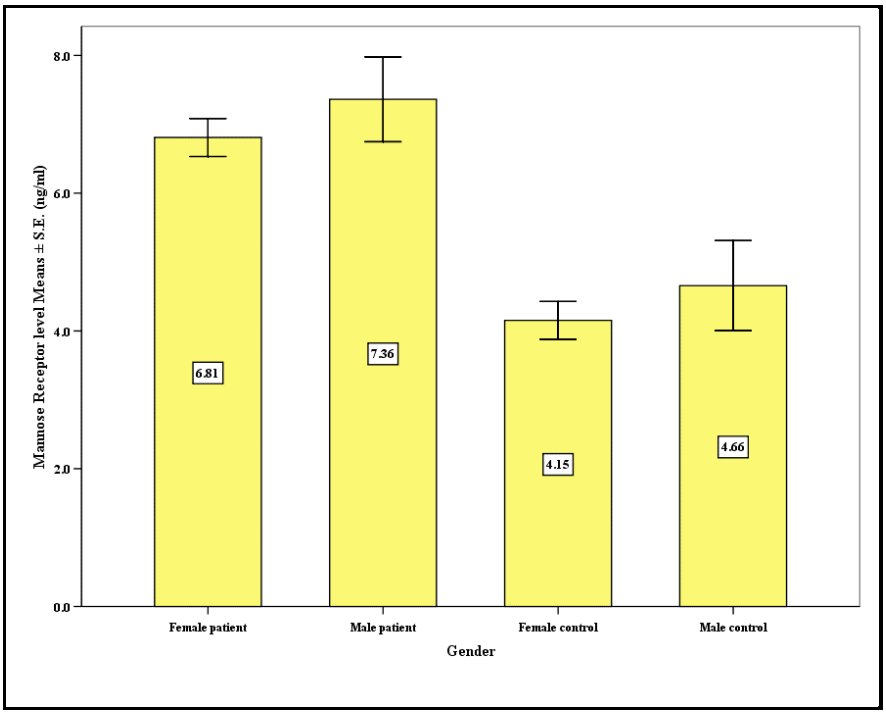

Figure 2. Serum level of MR distributed by gender

4. Discussion

MR (Mannose receptor) also known as CD206 (Cluster of Differentiation 206), is a type of C-type lectin receptor (CLRs) expressed on macrophages, dendritic cells, as well as endothelial cells, and serving as the first line of defense against invading pathogens. MR is also known as a pattern-recognition receptor and contains many extracellular domains, each with its own binding capabilities to different substances [8], [9]. MR can undergo proteolytic processing causing the cell-bound receptor to split into a soluble form, which is dumped into the circulation as soluble MR (sMR). Expression and shedding increase during inflammation,

and thus serum sMR concentration could be a valuable tool for early disease diagnoses [6]. MR is a strong biomarker of inflammation due to its function, such as the participation of MR in antigen presentation, T cell differentiation, modulation of cellular activity, clearance of endogenous molecule, and recognizes a wide range of ligands [10]. In this study, a significantly elevated serum level of MR was observed in the patients than in healthy controls, and in support of such findings, a significantly increased serum MR level has been reported in patients with liver disease and pneumococcal disease [10], [11]. In addition, [2] indicates that the serum level of MR may be an indicator of the prognosis of infections and/or diseases such as hepatitis. The T cells, B cells, and macrophages are the important immune cells in the development of the pathogenesis of RA that mainly affects the joints and causes synovitis [12]. The in vitro and in vivo studies demonstrated the expression of MR on the surface of macrophages in synovial fluid of inflamed paws [13], as well as the expression of MR in the synovial fluid by neutrophils. In macrophages, MR expression is correlated with the M2 phenotype along with anti-inflammatory functions, while the role of MR on neutrophils is still unknown. [14]. Accordingly, MR plays a role in promoting Th2 responses and/or polarization, if the expression of MR is increased in macrophages that undergo alternative M2-like activation, as in the case of macrophages treated with IL-4 and IL-10 [6]. MR has a protective role in inflammatory diseases that depend on the innate immune system, such as RA and psoriasis, the effect has been was associated with a ROS-dependent regulation of M2 macrophages [15]. In many autoimmune diseases including RA, MR can identify galactosyl IgG. Macrophages and DCs can take up large amounts of IgG via MR. This may lead to the processing and presentation of IgG-derived peptides by HLA class II, which can activate T-cell responses [7].

As it is known the autoimmune disease may be caused by microbial infection, some microorganisms conversion the immune profile from T helper Th1/Th17 to Th2/T regulatory (Treg) cells or reversibly, thus affecting innate and adaptive immune responses via cytokine production, which may lead to protection from autoimmune diseases. Some microorganisms also enhance the regulatory phenotype of B cells, DCs, and macrophages. Both tolerogenic DCs and regulatory M2 macrophages can contribute to the shift from a Th1/Th17 response to a Th2/Treg profile [2]. Recent research about COVID-19 has shown that MR can recognize and interact with glycoprotein on the surface of the SARS-CoV-2 virus. Because it represents one of the multiple pathways for SARS-CoV-2 to interact with human cells. Several studies indicate that Inhibiting CLRs that bind the virus to small molecules may reduce the viral spread in COVID-19 patients and potentially limit activation of overactive immune cells [8]. In conclusion, the present study showed elevated serum MR levels in RA patients, and MR may be useful for disease prediction even in naive patients with RA. Therefore, we proposed future studies in order to better understanding the role of MR and macrophage polarization in chronic and infectious diseases.

5. References

[1] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010; 69: 1580-1588. doi: 10.1136/ard.2010.138461.

[2] Yang F, Fan X, Huang H, Dang Q, Lei H, Li Y. A Single Microorganism Epitope Attenuates the Development of Murine Autoimmune Arthritis: Regulation of Dendritic Cells via the Mannose Receptor. Front Immunol 2018; 9:1528. doi: 10.3389/fimmu.2018.01528.

[3] Put S, Westhovens R, Lahoutte T, Matthys P. Molecular imaging of rheumatoid arthritis: emerging markers, tools, and techniques. Arthritis Res Ther 2014; 16(2):208. doi: 10.1186/ar4542.

[4] Tsuchiya K, Suzuki Y, Yoshimura K, Yasui H, Karayama M, Hozumi H, et al. Macrophage Mannose Receptor CD206 Predicts Prognosis in Community-acquired Pneumonia. Sci Rep 2019; 9(1):18750. doi: 10.1038/s41598- 019-55289-2.

[5] Li T, Guan S, Wang Q, Chen L, Yang K, Zhang H. Soluble mannose receptor as a predictor of prognosis of hepatitis B virus-related acute-on-chronic liver failure. World J Gastroenterol 2019; 25(37):5667-5675. doi: 10.3748/wjg.v25.i37.5667.

[6] Martinez-Pomares, L. 2012.The mannose receptor. J Leukoc Biol., 92(6):1177-86. doi: 10.1189/jlb.0512231.

[7] Dong X, Storkus W J, Salter R D. Binding and uptake of agalactosyl IgG by mannose receptor on macrophages and dendritic cells. J Immunol 1999; 163(10):5427-34.

[8] Gao C, Zeng J, Jia N, Stavenhagen K, Matsumoto Y, Zhang H, et al. SARS-CoV-2 Spike Protein Interacts with Multiple Innate Immune Receptors. bioRxiv 2020; 2020 doi: 10.1101/2020.07.29.227462.

[9] De Vlieger G, Vanhorebeek I, Wouters P, Derese I, Casaer M, Debaveye Y, et al. The soluble mannose receptor (sMR/sCD206) in critically ill patients with invasive fungal infections, bacterial infections or non-infectious inflammation: a secondary analysis of the EPaNIC RCT. Crit Care 2019; 23(1):270. doi: 10.1186/s13054-019- 2549-8.

[10] Nielsen M, Gantzel R, Clària J, Trebicka J, Moller H, Gronaek H. Macrophage Activation Markers, CD163 and CD206, in Acute-on-Chronic Liver Failure. Cells 2020; 9(5):1175. doi: 10.3390/cells9051175.

[11] Orntoft N, Blé M, Baiges A, Ferrusquia J, Hernández-Gea V, Turon F, et al. Divergences in Macrophage Activation Markers Soluble CD163 and Mannose Receptor in Patients With Non-cirrhotic and Cirrhotic Portal Hypertension. Front Physiol 2021; 12:649668. doi: 10.3389/fphys.2021.649668.

[12] Ad'hiah A H, Mahmood AS, Al-Kazaz AA, Mayouf KK. Gene Expression and Polymorphism of Interleukin-4 in a Sample of Iraqi Rheumatoid Arthritis Patients. Baghdad Sci. J 2018; 15(2):130-137. doi: http://dx.doi.org/10.21123/bsj.2018.15.2.0130.

[13] Put S, Schoonooghe S, Devoogdt N, Schurgers E, Avau A, Mitera T, et al. SPECT imaging of joint inflammation with Nanobodies targeting the macrophage mannose receptor in a mouse model for rheumatoid arthritis. J Nucl Med 2013; 54(5):807-14. doi: 10.2967/jnumed.112.111781.

[14] Arve-Butler S, Schmidt T, Mossberg A, Berthold E, Gullstrand B, Bengtsson A, et al. Synovial fluid neutrophils in oligoarticular juvenile idiopathic arthritis have an altered phenotype and impaired effector functions. Arthritis Res Ther 2021; 23(1):109. doi: 10.1186/s13075-021-02483-1.

[15] Hagert C, Sareila O, Kelkka T, Jalkanen S, Holmdah R. The Macrophage Mannose Receptor Regulate Mannan- Induced Psoriasis, Psoriatic Arthritis, and Rheumatoid Arthritis-Like Disease Models. Front Immunol 2018; 9:114. doi: 10.3389/fimmu.2018.00114.