INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 11(A); November 2020; Page No.5400-5403
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202011927

Original article

SERUM LEVEL OF CLUSTER OF DIFFERENTIATION 72 IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS AND CORRELATION WITH NEPHRITIS AND DISEASE ACTIVITY (CASE CONTROL STUDY)

Taha Ibrahim Taha Mohamad AlAdrosy[1], Abd Al Maguid Abd Al Aaty Al Ashmawy[2], Dina Sabry Abdu AL Fattah[3], and Abdulaziz Abdulhamid Mustafa[4]

[1, 2, 4] Rheumatology and Rehabilitation Department, Faculty of medicine, Al Azhar University- Cairo- Egypt
[3]Medical Biochemistry and Molecular Biology Department, Faculty of medicine, Cairo University – Cairo – Egypt

ARTICLE INFO

Article History:
Received 6th August, 2020
Received in revised form 15th September, 2020
Accepted 12th October, 2020
Published online 28th November, 2020

Key words:
SLE, CD72, SLEDAI, Nephritis

ABSTRACT

Introduction: B cell receptor (BCR) -mediated signals are enhanced when CD72 expression is deficient on B cells in autoimmune diseases. The significance of soluble CD72 (sCD72) has not been well explained yet.
Methods: Soluble CD72 was analyzed in the serum of 37 Systemic lupus erythematosus (SLE) patients, 27 had lupus nephritis and 10 had no nephritis. Correlations between sCD72 and SLE disease activity index (SLEDAI) and other activity indices were assessed.
Results: Soluble CD72 was found to be increased in SLE patients with lupus nephritis with (P <0.001). Statistically significant correlation found between serum CD72 level and low serum C3 (P <0.001), serum creatinine (P <0.001), SLEDAI (P 0.001), activity index (P 0.003), and chronicity index (P <0.001).
Conclusion: Soluble CD72 is significantly increased in SLE patients with renal involvement. Increased sCD72 may become a potential biomarker for renal involvement, disease activity and prognosis in SLE.
Conflict of interest: authors declare no conflict of interest and this article have not been published or submitted for publication elsewhere.

INTRODUCTION

Systemic lupus erythematosus is a chronic autoimmune disease affecting multiple organs. A complex interaction of genetics, environment, and hormones leads to immune dysregulation and breakdown of tolerance to self-antigens, resulting in autoantibody production, inflammation, and end-organs damage (Moulton *et al*., 2017).SLE is highly heterogeneous disorder that may affect any organ but tends to affect the skin, kidneys, blood cells, nervous system, serosal sacs and joints more frequently.(Bertsias *et al*., 2013)

Lupus nephritis (LN) is one of the most severe organ manifestations of the SLE. Most patients with SLE who develop LN within 5 years of an SLE diagnosis and, in many cases, LN is the presenting manifestation resulting in the diagnosis of SLE. LN remains a substantial cause of morbidity and death among patients with SLE. Clearly, early and accurate diagnosis of LN and prompt initiation of therapy are of vital importance to improve outcomes in patients with SLE (Anders *et al*., 2020).CD72, type II membrane protein and well established for its regulatory function, being an inhibitory co-receptor of B cell receptor (BCR) (Tsubata, 2012).CD72 regulates distinct autoimmune diseases either positively or negatively. As B cell depletion therapy clearly reveals crucial roles of B cells in the regulation of various autoimmune diseases, CD72 may be a novel therapeutic target for treatment of autoimmune diseases (Tsubata, 2019).We carried out our study to assess serum level of CD72 in SLE patients and to find out if there is a correlation between its serum level, disease activity and lupus nephritis or no.

PATIENTS AND METHODS

The ethical approval was obtained from the hospital ethical research committee. Thirty seven patients diagnosed with SLE

Corresponding author:* **TI Adrosy
Rheumatology and Rehabilitation Department, Faculty of medicine, Al Azhar University- Cairo- Egypt

attending the rheumatology outpatient clinic and inpatient department in Sayyed Galal University hospital in the period from November 2016 to June 2018 were enrolled after informed consent. Demographic data regarding the age, sex, and theonset of the disease and date of diagnosis were all collected. Our patients were identified as SLE according to 2015 ACR/SLICC Revised Criteria for Diagnosis of Systemic Lupus Erythematosus (IrajSalehi, 2015).All Patients were subjected to careful history taking,complete clinical examination, laboratory investigations (complete blood count (CBC) with differential, C- Reactive Protein (CRP), serum creatinine, urine analysis, Complement 3, 4 (C3 & C4), Anti-nuclear antibody (ANA), Anti double stranded deoxyribonucleic acid (Anti ds-DNA), 24 hour urinary proteins), renal biopsy (if indicated), (SLE-DAI) (Touma, 2012) and Serum CD72.Class of nephritis was determined according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS)(Fanouriakis *et al*., 2020)

Serum cluster of differentiation 72 (CD72)

Using human B-cell CD72 enzyme-linked immunosorbent assay (ELISA) Kit of CUSABIO Company (Catalog Number: CSB-EL004955HU).Serum samples were collected using a serum separator tube and stored at -80°C. Fresh standard was prepared and discarded after use.

Calculation of the results

Detection range: 0.9ng/ml-60ng/ml.Sensitivity: The minimum detectable dose of human CD72is typically less than 0.225ng/ml.Specificity: This assay has high sensitivity and excellent specificity for detection of human CD72.

RESULTS

The present study included 27 female patients with SLE who were in active diseases state and had an established nephritis (LN) with mean age 30.2±10.2. In addition, 10 female SLE patientsfree of nephritis (Non-LN) with mean age 32.4±9.5, were included as a control group. Table 1 shows the clinical characteristics of the included patients. There were statistically significant associations between lupus nephritis and fatigue (p <0.001), ADLs (p =0.001), fever (p =0.01), dyspnea (p =0.018), lower limb edema (p =0.003), confusion (p =0.022), and the presence of burning urine (p =0.002) being all more evident in LN group of patients. On the other hand, there were no statistically significant associations between lupus nephritis and other SLE features (SLE headache, Malar rash, Oral ulcers, Discoid rash, Photosensitivity, Hair loss, Chest pain, DVT, Seizures, Sicca, Dysphagia, Raynaud's Phenomenon, Appetite loss, Nausea, Decreased urine, Itching, Sleep disturbance, HTN, Coma, Muscle weakness, Peripheral neuropathy, Vaginal discharge and Arthritis).

Table 1 showing the statistically significant clinical characteristics of the included patients.

Variable	LN (N =27)		Non-LN (N =10)		P value
	Yes N (%)	No N (%)	Yes N (%)	No N (%)	
Fatigue	24 (88.9%)	3 (11.1%)	0	10 (100%)	<0.0001
ADLs	24 (88.9%)	3 (11.1%)	3 (30%)	7 (70%)	0.001
Fever	6 (22.3%)	21 (77.7%)	7 (70%)	3 (30%)	0.011
Dyspnea	15 (55.6%)	12 (44.4%)	1 (10%)	9 (90%)	0.018
LL edema	21 (77.7%)	6 (22.3%)	2 (20%)	8 (80%)	0.003
Confusion	0	27 (100%)	2 (20%)	8 (80%)	0.022
Burning urine	11 (40.7%)	16 (59.3%)	0	10 (100%)	0.022

In Figure1, Indices of disease activity of both study groups are blotted and shows that there were statistically significant associations between lupus nephritis and SLEDAI (p <0.001), activity index (p <0.001), and chronicity index (p <0.001). Patients with lupus nephritis had significantly higher SLEDAI, activity index, and chronicity index than the non LN group. There were no statistically significant associations between lupus nephritis and hemoglobin level (p =0.09), RBCs count (p =0.079), WBCs count (p =0.75), neutrophil count (p =0.61), lymphocyte count (p =0.93), and platelet count (p =0.41). As shown in table 2, there were statistically significant associations between lupus nephritis and increased creatinine level (p =0.002), 24 hours urinary protein (p =0.013), proteinuria (p <0.001), urinary RBCs (p =0.004), urinary pus cell (p =0.004), and urinary casts (p =0.001).

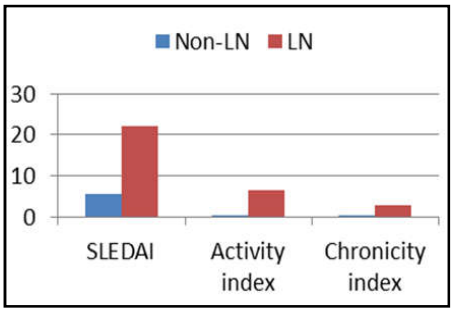

Figure 1 Indices of disease activity of the included patients

Table 2 Kidney function tests and Urinary Protein of the included patients (Data are presented as mean ±SD and median (range)

Variables	Non-LN (N =10)	LN (N =27)	P-value
Serum creatinine (mg/dL)	0.9±0.15	2.16 ±1.1	0.002
Urine protein	0.26±0.12	3.097 ±0.32	0.013
Proteinuria	0	27 (100%)	<0.0001
Urinary RBC	0	15 (55.6%)	0.004
Urinary pus cells	0	15 (55.6%)	0.004
Urinary casts	0	18 (66.6%)	0.001

There was statistically significant association between lupus nephritis and low C3 level (p =0.001), patients with lupus nephritis had lower C3 level. In contrary, there were no statistically significant associations between lupus nephritis and CRP (p =0.54), C4 level (p =0.706), ANA positive, and Anti-ds DNA positive (p =0.23). All the study cases are ANA and Anti-ds DNA positive. There was statistically significant association between lupus nephritis and CD72 level (p =0.001), patients with lupus nephritis had higher CD72 serum level.

There was a statistically significant correlation between serum level and CD72 and SLEDAI, both activity and chronicity indices, low RBCs count, high serum creatinine level and low C3 serum level. Figure2 shows the positive correlation between serum level of CD72 and SLEDAI in the lupus nephritis group. This correlation was statistically significant with P= 0.001.Serum level of CD72 showed statistically significant difference with both activity index and chronicity in the lupus nephritis group. (P= 0.003) and (P= 0.001) respectively.

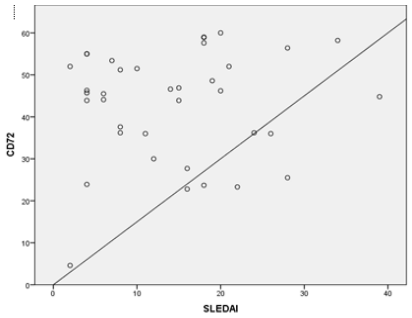

Figure 2 Correlation between CD72 and SLEDAI

DISCUSSION

CD72 is a type 2 membrane protein of around 45 kDa mostly expressed in B cells. CD72 contains a C-type lectin like domain (CTLD) in the extracellular region and an immunoreceptor tyrosine-based inhibition motif (ITIM) in the cytoplasmic region. Upon phosphorylation, CD72 ITIM recruits and activates SH2-containing protein tyrosine phosphatase 1 (SHP-1), which then negatively regulates signaling through BCR by dephosphorylating BCR proximal signaling molecules such as Syk. (Tsubata, 2019)

Therefore, we conducted the present prospective study to assess serum level of CD72 in SLE patients and correlating it with disease activity and nephritis. The present study included 27 patients with SLE who were in active diseases state and had an established nephritis. In addition, 10 SLE patients, who were free of renal disease, were included as a control group.Age is one of the major factors affecting the clinical manifestations and prognosis of SLE patients. SLE may develop at any age, although its peak incidence occurs during the reproductive age years. (Tamirou, 2019)

In the present study, the mean age of the patients was 32.4 ±9.5 years in nephritis group and 30.22 ±10.2 years in the control group.In line with our findings, Sliem and colleagues performed a case control study involving 59 SLE Egyptian patients and found that the mean age of the included patients was 28.6 years (Sliem, 2010).In our study, all of the included patients were females. It was not intended to collect only female cases but by coincidence, all our patients during this period were ladies and this is matched with the disease nature. Similarly, El-Garf and colleagues conducted a prospective study to analyze the clinical features of Egyptian SLE patients admitted to the Rheumatology and Rehabilitation inpatient Department, Cairo University Hospitals, during the period from the years 2000 to 2013. The results showed that 93.2% of the patients were females (El-Garf, 2017).In our study, patients with lupus nephritis had significantly higher prevalence of fatigue, dyspnea, lower limb edema, confusion, and burning urine. Moreover, patients with active lupus nephritis had numerically higher prevalence of chest pain, deep venous thrombosis, seizures, and Raynaud's phenomena; despite it did not reach the level of statistical significance. This goes in agreement with findings ofFaezi and colleagues assessed the characteristics of Persian SLE patients with lupus nephritis and an SLE subpopulation without lupus nephritis. The results revealed that patients with lupus nephritis had significantly higher prevalence of CNS manifestations (confusion and convulsion), musculoskeletal manifestations (arthritis and myositis), fatigue, chest pain, and dyspnea (Faezi, 2017). Because no single measure can describe status in all SLE patients, standardized indices for assessing SLE disease activity have been created. In addition to the Physicians' Global Assessment (an estimate of activity rated on a 0 to 3 visual analog scale), the most commonly used measures include the SLE Disease Activity Index (SLEDAI). Our study showed that the mean of SLEDAI was significantly higher in patients with lupus nephritis than SLE patients without renal involvement. And same results were obtained from Burling and colleagues (Jarrett, 2016).Regarding the primary outcomes of the present study, there were statistically significant differences between cases and controls in terms of mean CD72 ($p < 0.001$). The mean CD72 level was significantly higher in patients with lupus nephritis than SLE patients without nephritis. In concordance with our findings, Vadasz *et al*., evaluated and compared the presence of soluble CD72 in the serum of patients with SLE and healthy individuals in order to ascertain whether soluble CD72 serum level is increased in SLE patients. The serum level of soluble CD72 in 159 SLE patients was found to be significantly increased compared to that of 80 healthy individuals; the levels were also significantly higher in patients with lupus nephritis than that in patients without ($p < 0.001$) (Vadasz *et al*., 2016).To the best of our knowledge, our study is the second study that assessed the role of soluble CD72 level in lupus nephritis. Although the exact mechanisms by which CD72 contribute to the development of lupus nephritis are largely unclear, this association is thought to be a consequence to the regulatory role of CD72 on B cell functions.CD72 is a B cell coreceptor that is expressed in all stages of B cell development except plasma cells. Polymorphism of the CD72 gene has been found to be associated with the susceptibility to develop human SLE. Some polymorphic isoforms of CD72 appear to increase antibody production, this when the expression of these isoforms are trapped in endoplasmic reticulum and thereby fail to regulate B cell antigen receptor (BCR) signaling. Human CD72 is preferentially expressed on human naïve mature B cells but much lower on activated plasma cells. In this respect, activated plasma cells were found at high frequencies in active rather than in SLE patients in remission (Vadasz *et al*., 2016).The present study also investigated the association between measures of disease activities of SLE patients and the serum CD72 level. We found a significant correlation between serum CD72 level andC3, serum creatinine, SLEDAI, activity index, and chronicity index. This goes in agreement with Vadasz and colleagues (Vadasz *et al*., 2014). CD72 expression on activated B cells of SLE patients was significantly lower than that of normal controls. The lower expression of CD72 on activated B cells from SLE patients correlates with SLE disease activity, lupus nephritis, the presence of anti-dsDNA antibodies, and low levels of complement (Han, 2016). Similarly; another study investigated the expression of the CD72 molecule in SLE with lupus nephritis. There were significant correlations between CD72 expression and C3, serum creatinine, and SLEDAI (Han, 2016).

We acknowledge that the present study has number of limitations. The sample size of the included patients was relatively small which may affect the generalizability of our findings. Moreover, the study was single-center experience. Due to the descriptive nature of the present study, making a causal relationship between soluble CD 72 and SLE was limited in the present study as well.

CONCLUSION

In conclusion, soluble CD72 level is a promising diagnostic and prognostic biomarker in patients with lupus nephritis. The present study showed that the soluble CD72 level is significantly higher in patients with lupus nephritis and it is significantly correlated with measures of disease activities and inflammatory markers. As such, it is suggested that the use soluble CD72 level may increase the significance of traditional markers in predicting disease severity and nephritis development. It can also help in refining lupus prognosis. However, due to the descriptive nature of the present study, making a causal relationship between soluble CD 72 and SLE is still challenging, thus further studies on the exact role of CD72 in SLE pathogenesis are needed.

References

1. Anders HJ, Saxena R, Zhao MH *et al*., 2020. Lupus nephritis. Nat Rev Dis Primers; 6(1):7.
2. Bertsias GK, Pamfil C, Fanouriakis A *et al*., 2013. Diagnostic criteria for systemic lupuserythematosus: has the time come? Nat Rev Rheumatol; 9:687-94.
3. El-Garf AK, Gheith RE and Badran SN. 2017. Clinical pattern in Egyptian systemic lupus erythematosus patients with pleuropulmonary involvement. Egypt Rheumatol; 39(2):83-88.
4. Faezi ST, HosseiniAM, Paragomi P *et al*., 2017. Clinical picture of lupus nephritis in patients with systemic lupus erythematosus (SLE): Results of a large survey. Rheumatol Res; 2(2):51-59.
5. Han J, Sun L, Fan X, *et al*., 2016. Role of regulatory B cells in neuroimmunologic disorders. *J Neurosci Res*; 94(8):693-701.
6. IrajSalehi A. 2015. 2015 ACR/SLICC Revised Criteria for Diagnosis of Systemic Lupus Erythematosus. Autoimmune Dis Ther Approaches; Open Access 2(1):114.
7. Jarrett P, Thornley S, and Scragg R. 2016. Ethnic differences in the epidemiology of cutaneous lupus erythematosus in New Zealand. Lupus; 25(13):1497-1502.
8. Moulton VR, Suarez-Fueyo A, Meidan E *et al*., 2017. Pathogenesis of Human Systemic Lupus Erythematosus: A Cellular Perspective. Trends Mol Med; 23(7):615-635.
9. Fanouriakis A, Kostopoulou M, Cheema K *et al*., 2020. 2019 Update of the Joint European League against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ ERA–EDTA) recommendations for the management of lupus nephritis Ann Rheum Dis; 0:1–11.
10. Sliem H, Tawfik G, Khalil KA *et al*., 2010. Pattern of systemic lupus erythematosus in Egyptian patients: the impact of disease activity on the quality of life. *Pan Afr Med J*; 6:14.
11. Tamirou F, Arnaud L, Talarico R, *et al*., 2019. Systemic lupus erythematosus: state of the art on clinical practice guidelines RMD Open; 4:1.
12. Touma Z, Urowitz MB, Taghavi-Zadeh S *et al*., 2012. Systemic lupus erythematosus disease activity Index 2000 Responder Index 50: sensitivity to response at 6 and 12 months. Rheumatology (Oxford); 51(10):1814–1819.
13. Tsubata T. 2012. Role of inhibitory BCR co-receptors in immunity. Infect. Disord. Drug Targets; 12(3):181–190.
14. Tsubata T. 2019. CD72 is a Negative Regulator of B Cell Responses to Nuclear Lupus Self-antigens and Development of Systemic Lupus Erythematosus. Immune Net w; 19(1):e1.
15. Vadasz Z, Goldeberg Y, Halasz K *et al*., 2016. Increased soluble CD72 in systemic lupus erythematosus isin association with disease activity and lupus nephritis. Clinical Immunology; 164:114-118.
16. Vadasz Z, Haj T, Balbir A *et al*., 2014. A regulatory role for CD72 expression on B cells in systemic lupus erythematosus. Semin Arthritis Rheum; 43(6):767–671.

How to cite this article:

Taha Ibrahim Taha Mohamad AlAdrosy *et al* (2020) 'Serum Level of Cluster of Differentiation 72 In Systemic Lupus Erythematosus Patients And Correlation With Nephritis And Disease Activity (case control study)', *International Journal of Current Medical and Pharmaceutical Research,* 06(11), pp 5400-5403.

****