Elevated Levels of IL- 6 in serum of SLE patients correlated with High-sensitivity CRP and ESR.

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Abstract

Systemic Lupus erythematosus (SLE) is an autoimmune disease more prominent in women characterized by wide variety of auto antibodies production, some of which are pathogenic, immune complex deposition and various clinical systemic manifestation that effect various organ. The aim of this study is to investigate the correlation between IL-6, high sensitivity CRP, ESR and organ involvement in SLE patients and to assess if IL-6 could be related to disease activity and to organ involvement. Total of 50 patients with SLE(48female.2Male) and 30 healthy control were studied. SLE patients were divided into two groups 42 patients had active disease and 8 had inactive disease at p= 0.000. The mean level of IL-6 in SLE patients and healthy control groups was (541.1; 5.31 pg/ml) respectively, the difference was statistically significant at (p=0.000).There was positive correlation between serum IL-6 and SLEDAI (r= 0.422**, p= 0.002).Associations of IL-6 levels in patients with active and inactive disease in different organs were high significant at p= 0.000, The mean levels of IL-6 in patients with Lupus nephritis was (936.270pg/ml) the difference was higher significantly than

other organs (p=0.000). The mean levels of hs CRP for SLE patients was (6.08 mg/l) and the difference was statistically significant (p= 0.000) than healthy control groups, There was strong positive correlation between IL-6 and hs CRP in serum of SLE patients (r= 0.969**, p= 0.000). But the difference was not significant between hs CRP and ESR (r= 0.249, p = 0.08), The mean levels of hs CRP in SLE patients was (8.844 mg/l) significantly higher in patients with lupus nephritis than other organs p= 0.000.

Key words: SLE, IL-6, hs CRP, ESR.

INTRODUCTION

Systemic lupus erythemat-osus (SLE) is rheumatic autoimmune disease (Brink,*et al*.,1999) characterized by the consequence of it is complex immunopathology , involving B lymphocyte hyperactivity, the production of a wide spectrum of auto antibodies and the failure of lymphocytes to suppress auto reactive B cell clones. SLE is up to 10 times more common in women than men, and typically has a predilection for women in their child –bearing years (Cervera ,*et al.,* 2003). Even though the etiology of SLE is unknown, many predisposing factors have been found, including genetic, environmental, infections, and hormonal factors (Alindon , 2000) . Lupus is a complex disease with varying manifestations. Cytokines are important mediators of intercellular communication and or start the interaction of immune cells during immune response. Certain cytokine may serve as biomarkers to monitor disease activity and predict disease severity (Kunz,*et al.* 2009). In SLE several cytokines are involved in general immune dysregulation and also in local inflammation which leads tissue injury and organ damage (Lee, *et*

al.,2010) Such immune disturbances may, be explained by the dysregulation of cytokines, which have important regulating the functions of cells within the normal immune system.(Linker,*et al.*, 1991; Brink,*et al.*,1999).Interlukin-6 is a proinflammatory cytokine which is synthesized principally by monocytes, fibroblasts and endothelial cells.IL-6 can also be found in both T and B lymphocytes (Hiran,1998) .which is multifunctional cytokine produced in response to inflammatory stimuli, including IL-1 and tumors necrosis factor α , with pivotal roles in regulating the host immune response to infection. Thus IL6 has been found to be a potent stimulator of the differentiation and activation of lymphoid and myeloid cells (Kishimoto,*et al.,* 1988).).IL-6 is also a key regulator of various other cellular processes, including erythropoiesis(Ershler, *et al.*, 2000; Ershler,2003),neuronal celldifferentiation(Satoh,*etal*,1998), bone metabolism(Kurihara,*et al.*,1990) and the production of acute phase proteins within the liver(Andus, *et al.*, 1987)in response to factors released by macrophages and adipocytes (Lau,*et al.*,2004) , one type is protein is known as CRP. The acute phase response develops in wide range of acute and chronic inflammatory conditions. These conditions cause release of IL-6 and other cytokine that trigger the synthesis of CRP and fibrinogen by the liver. The levels of C- reactive protein (CRP) rise significantly in infection as well as in many rheumatologic diseases, include-ing rheumatoid arthritis RA (Ganapathi,*et al.*, 1991; Wolfe, 1997) and vasculitis (Cantini,*et al., 1998*). Several studies investigating the role of CRP in patients with SLEhave concluded that CRP levels rise significantly in SLE patients with active

infection (Pereira, *et al.*, 1980; Bertouch, *et al.*, 1983). The majority of reports demonstrated increased levels of IL-6 in patients with active SLE that do not correlate with acute phase proteins (Spronk ,*et al.*,1992; Lacki ,*et al*., 1997) , other found elevated IL-6 levels only in cases with increased C- reactive protein, concluding that it is part of the acute phase response (Lacki , *et al.*,1997).Previous studies on correlations between disease and IL-6 in SLE did not differentiate between activity in different organs or system. The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) are the two most common laboratory measurements of systemic inflammation in clinical practice. These two tests are used for the diagnosis and monitoring of a variety of conditions, in particular rheumatic diseases and infections. The ESR measure-ment is a simple measurement of the velocity (in mm/hr) of sedimentation of erythrocytes in anticoagulated freshly drawn blood in standardized vertical tube. Inflammatory cytokines (IL-6), tumor necrosis factor-α (TNF-α) and IL-1 stimulate the liver to produce acute phase reactant proteins (fibrinogen, immunoglobulin's, hapto-globin, CRP and others). These proteins, in particular fibrinogen and immunoglobulin's, increase the dielectric constant in the blood, allowing erythrocytes to form rouleaux and increasing the velocity of their descent in the tube (Holley, *et al.,1999*). The CRP, on the other hand, is a highly Conserved pentameric peptide produced in the liver in response to inflammatory cytokines. It was discovered in 1930 in the sera of patients with pneumonia (Tillet , *et al.*, 1930) and plays a role in the recognition and elimination of foreign pathogens and cellular

debris. There has been debate as to the accuracy and sensitivity of the ESR and CRP in conditions such as rheumatoid arthritis RA (Walshl , *et al*.,1979; Pincus , *et al.*,2005) SLE (Pepys ,*etal*,1982; Suh , *et al*.,2006) . A variety of systemic conditions, such as age, sex, anemia, and pregnancy may influence CRP and ESR measurements (Kanfer ,*et al.*,1997; Kushner, *et al.*, 2006).In the present study we investigate the relationship between levels of IL-6 and hs CRP with r erythrocyte sedimentation rate (ESR). Also investigate whether serum levels of IL-6 is higher in Iraqi patients with SLE-than healthy control and its correlation with the clinical activity in patients with different activity scores as measured by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) as the same time with organ involvement in SLE patients.

MATERIAL AND METHODS

Patients

Fifty patients with SLE (48female, 2 male, Mean age (32.36± 9.405) years, ranged (15 -55) who fulfilled the criteria of the American College of Rheumatology ACR (Tan, *et al*. 1982 Hochberg ,1997) for the classification of SLE at least four or More of the 11 ACR criteria were studied. No patients fulfilling these criteria were excluded. Thirty healthy control unrelated to the patients, without inflammatory or autoimmune disease as normal control subjects (28female,2male) mean age was (38.7± 7.240) were studied.

Specimens

Specimens of venous blood10cc from all patients were taken , Sera were separated by centrifugation at 3000 rpm for 3 minutes and separated as soon as possible from the clot of red cells

and were kept in aliquots at-80°C centigrade until the time of assay.

Laboratory measurement

Interlukine-6 levels were evaluated using enzyme linked immune-sorbent assay(ELISA) with commercially available kits EPROTECE, USA (900-M16 Lot#0412016).Disease activity was assessed according to (Sdaile , *et al*., 1996; Bombardier ,; Active SLE when SLEDAI >12 points and inactive when SLEDAI <12 points. Erythr-ocytes Sedimentation Rate was measured using Westergren method (Dacie & Bain 2001) .High sensitivity CRP ELISA (Cat. No.DE740011) was measured using Enzyme Immunoassay for the Quantitative high sensitive determination of C-reactive protein in human serum by 5 calibrations (0-0.4-1-5-10 µg/ml).

Statistical analysis

The results were evaluated by the analysis of the variance (ANOVA) , p-values at levels ($p<0.05$) was considered to be statistically significant. This calculation was carried out according to Statistical Package for Social Science (SPSS version 16), Group differences on normally distributed numerical variables were assessed by the independent samples-test (Groups 1 and 2) and ANOVA (Groups 1,2) and the least significant difference (LSD) at level less than 0.05 by using Gene State 2009 and correlation(r) were used when appropriate at 0.01.

RESULTS AND DISCUSSION

The characteristics of 50 patients suffering from SLE were studied in Table (1).

The majority of the SLE patients 96%were female and the mean

age was (32.5 year). No statistically significant difference were observed between those age, sex ,ESR ,and disease duration, we found only age to be significantly associated with ESR (r = -0.287 , p= 0.04) Table(4).With regard to Disease activity(SLEDAI) our patients can be divided into two groups,42 (84%) patients had active disease and 8(16%) patients had inactive disease ,this difference was statistically significant (p=0.000). table(1). The mean level of IL-6 which is first target in our study was significantly higher in SLE patients with active and inactive disease at (p<0.05) (541.19± 399.12 pg/ml) p= 0.000) compared with the mean levels of healthy controls groups (5.319± 2.354 pg/ml) p=0.000. Table (2). There was positive correlation between serum of IL-6 and SLEDAI (r=+0.422**, p= 0.002) while the correlation between hs CRP and SLEDAI was (r= 0.437*, p=0.001) Table (3). Our data indicate that mean level of IL-6 was significantly higher in patients with Lupus nephritis (936.27± 259.19pg/ml) p=0.000, rang from (609.72-1603.13pg/ml) and lower in patients with other organ(Skin , Liver, Lung, CNS, Spleen, Heart, Abdominal pain, Pancreatic, Thrombocytopenia and Joints) were (148.103- 366.644- 565.692- 67.06- 477.634- 331.788 – 206.58-411.59- 262.075 and 53.854 pg/ml) respectively Figure A. Further analyses were performed to determine the mean levels of hs CRP in SLE patients which was the second target in our study .We found significantly higher hs CRP levels in SLE patients with both active and in active disease at p<0.05 (6.08± 2.66mgl) p=0.000 when compared with the mean level of healthy controls (1.15± 0.89 mg/l) p=0.000 Table (2). Table (3) Shows the levels of hs CRP that correlated

significantly with IL-6(r=+ 0.969**, p=0.000). No significant correlation between hs CRP and ESR were seen (r=- 0.249, p=0.249) Table (4), As the same No significant correlation between hs CRP and other variables Age, Duration disease(r= 0.109, 0.118) Table (4) respectively. Figure B shows that the mean levels of hs CRP were significantly higher (p=0.000) in patients with lupus nephritis (8.84± 1.51 mg/l) ranged from (6.170 -10.5 mg/l) at p<0.05, than patients with other organ involvements (skin, Liver, , Lung, CNS, Spleen, Heart, Abdominal pain, Pancreatic, Thrombocytopenia and Joints) were(3.35-4.87- 5.60-3,05- 5.00-4.95-4.12-5.08-4.37and 3.02 mg/L) p= 0.000 respectively. In our study IL-6 is apheliotropic cytokine with wide range of biological activities that plays an important role in immune regulation and inflammation (horwitz , *et al*., 1994), which is one of the most important B cell stimulation factors that induces the differentiation of T cell into effectors' cells (Hiep , *et al*.,1991).which is highly expressed in Kidneys in human lupus glomerulonephritis (Malide , *et al*.,1995; Sabry , *et al*.,2005) , While some authors found elevated IL-6 levels only in cases with increased C-reactive protein ,concluding that it is part of acute phase response (Spronk,*et al*.,1992; Alaa,A,*etal*, 2005). Results of our study in agreement with most of these reports since IL-6 level is significantly increased in Iraqi patients with SLE and Lupus nephritis (Mean 936.27±259.19 pg/ml) when compared to healthy controls. Our finding revealed that hsCRP rise to significantly higher levels in lupus patients with active and in active disease than those healthy controls. It is thought that IL-6 is

the main cytokine responsible for CRP induction (Swaak, *et al*. ,1989; Swaak, *et al*.,1996 and Peterson, , *et al*.,1996) Since the CRP is produced by the liver and adipocytes in response to various acute and chronic inflammatory processes, and is referred to as an ' acute-phase protein'. It is synthesis in hepatocytes is stimulated by arise in IL-6, among other cytokines, and it binds to polysaccharides of many bacteria, fungi, and certain parasites. CRP can activate the complement system and may have role in the clearance of apoptotic cells (Ledue ,*et al.*, 1998; Barnes ,*et al.*, 2005). The behavior of CRP in SLE has been surprising and subject to controversy, several older studies investigating the role of CRP in patients with SLE using conventional method of CRP measurements, concluded that while CRP levels rose significantly in SLE patients with infection (Pereira ,*et al.*, 1980 ;Bertouch , *et al.*, 1983). Hence investigators found an elevation of serum CRP in active SLE even in absence of infection (AL-Mekaimi, *et al.*, 1997;. Williams , *et al.*, 2005) Although three recent studies Barnes , *et al.*,(2005); Bertoli , *et al.*,(2008) and Lee ,*et al.*,(2008) have inspected the association of hs CRP levels and organ- specific lupus activity patients ,reported significantly higher hs CRP levels in SLE patients with organ. Lee, *et al.*,(2008). Reported significantly higher medians hs CRP levels and organ damage than in those without.Un like some of the older studies, however, the CRP level in their patients with active was not undetectable. We believe that this is explained by the fact that hs CRP methods detect much lower levels of rise in CRP in active SLE that would have been missed by less sensitive methods (Barnes, *et al.*, 2005; Firooz, e*t al.*, 2011) . Other investigators

have also reported relationship between elevation of hs CRP and specific organ involvement in they found significantly higher hs CRP values in SLE patients with myocarditis, cardiac murmur, interstitial pulmonary fibrosis, pulmonary hypertension, gastrointestinal manifestations, and anemia than in those without (Lee, *et al.*, 2008). In other study, it has been suggested that an elevated CRP can occurred in SLE patients in the presence of serositis,(Borg , *et al.*,1990; Mochizuki ,*et al.*,1999 ; Lee ,*et al*.,2008) polyarthritis, (Spronk *et al.*,1992 ; Zuniga , *et al.*,2003), nephritis(Zuniga ,*et al.*,2003; Firooz, *et al.*,2011). Swaak, *et al.*, 1996 found a positive association between IL-6 and CRP levels. .Clinical support for this association is provided by the observation that an elevated CRP level is relatively common in patients with chronic renal failure before and after dialysis (Zimmermann , *et al.*, 1999; Ortega, *et al.,2002*). Further support for this linkage is found in the observation that CRP is deposited in the glomeruli of kidney biopsy specimens from patients with lupus Nephritis and CRP may amplify kidney damage by binding to Fcγreceptor IIa-R131, Which has low affinity for IgG2 but high affinity for CRP (Zuniga ,*et al*.,2003). Arguably, the serum hs CRP levels are elevated in patients with lupus nephritis, particularly in those with end-stage renal disease and decreased renal clearance of CRP and/or proinflammatory cytokines (IL-6) may play a role in the elevation of serum CRP. As several studies have shown that damage in SLE ispredicted by disease activity over the follow-up period (Stoll,*et al.*, 2004; Becker, *et al.*, 2006).The association between hs CRP and organ damage is explained by the finding that hs CRP reflects lupus

activity. In the current study, IL-6 is associated with SLEDAI scores, and a broad range of clinical manifestations, many of which are components of disease activity measures. Therefore, we believe that lupus activity occurring over a decade of disease processes also mediates the association of hsCRP with organ In our present study, serum levels of IL-6 were found to be elevated in all patients with SLE associated with different organ although which the mean level was different from one organ to another. This controversy could be explained by the fact that SLE is genetic disease (Kelly ,*et al.*, 2003) and we can assume that the difference in the genetics of different populations may be responsible for the difference in clinical presentation. Our observations showed no statistically signification correlation between hs CRP and ESR since it is an indirect measure of inflammation and is influenced by a variety of factors. (Brigden, 1999; Costenbader, *et al.*, 2007). Conditions such as gender, age, renal disease, anemia, heart failure, and obesity, among others, can cause wide fluctuations in ESR levels.(Bedell, *et al.*, 1985; Brigden,1998 ;Brigden,1999 and Ballou, *et al.*, 2005) While CRP is a direct measurement of an acute-phase plasma protein,it might be a more reliable measure of inflammation(Dilber, *et al.*,2003), its levels are also influenced by a variety of factors (Firooz, *et al.*,2011).

Conclusion

Thus, our data allow us to speculate that, Iraqi SLE patients with lupus nephritis have altered cytokine profile different from their healthy control subject. IL-6 is significantly increased in Iraqi SLE patients with Lupus nephritis compared to the healthy control subject and this level is well correlated with SLE disease

activity. Although IL-6is thought to be the main cytokine responsible for CRP production, further investigations are awaited especially since IL-6 could be a target for therapeutic purposes. These studies might clarify some important relationships that otherwise remain unexplained. These findings highlight hs CRP as a strong marker for increased disease activity and organ damage accrued over the course of SLE.

TABLE (1): General Characteristics of the studied group.

Sex	Cases N= 50	Control = 30
Female	48.00	28.00
Male	2.00	2.00
Age(years)	32.510±9.402	38.66±7.42
Duration of SLE	6.240±5.607	
Activity of disease depending on score*		
SLEDAI <12	48/50 (84%)	
SLEDAI >12	8/50 (16%)	

*Total score <12 = Active group

Total score >12 =In active group

SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

Table (2): The mean levels of IL-6, hs CRP, ESR and SLEDAI in patients with SLE and in healthy controls.

Variable	Group	N	Mean	SD	SE	Rang	P<0.05
IL-6*	SLE	50	541.19	399.125	56.444	45.5- 1603.12	0.000
	Control	30	5.319	2.354	0.429	o.564- 8.8	
Hs CRP	SLE	50	6.087	2.661	0.376	2.75-10.5	0.000
	Control	30	1.15	0.89	0.162	0.056-3.29	
SLEDAI	Active	42	21.333	5.358	0.826	12 – 34	0.000
	Inactive	8	10	1.511	0.534	7 – 11	
ESR	SLE	50	59.6	34.405	4.86	5- 135	0.000

*IL-6,Interlukine-6;hsCRP,High-sensitivityC- reactive protein; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; ESR, Erythrocyte sedimentation rate.

Table (3): Pearson correlation between IL-6 and hsCRP in patients with SLE.

Variable	Hs CRP	SLEDAI
	R	r
IL-6	0.969**	0.422**
P<0.05	0.000	0.002
Hs CRP	1	0.437**
P<0.05		0.001

**Correlation is significant at the 0.01 level (2- tailed)

Table (4): Pearson correlation between different variables in SLE patients.

Control Variables		Age	Duration	CRP	ESR
Age	r	1	0.233	0.109	-0.287
	p		0.112	0.46	0.048
Duration	r	0.233	1	0.118	0.162
	p	0.112		0.423	0.271
CRP	r	0.109	0.118	1	0.249
	p	0.46	0.423		0.081
ESR	r	-0.287	0.162	0.249	1
	p	0.048	0.271	0.081	

r = correlation coefficient.

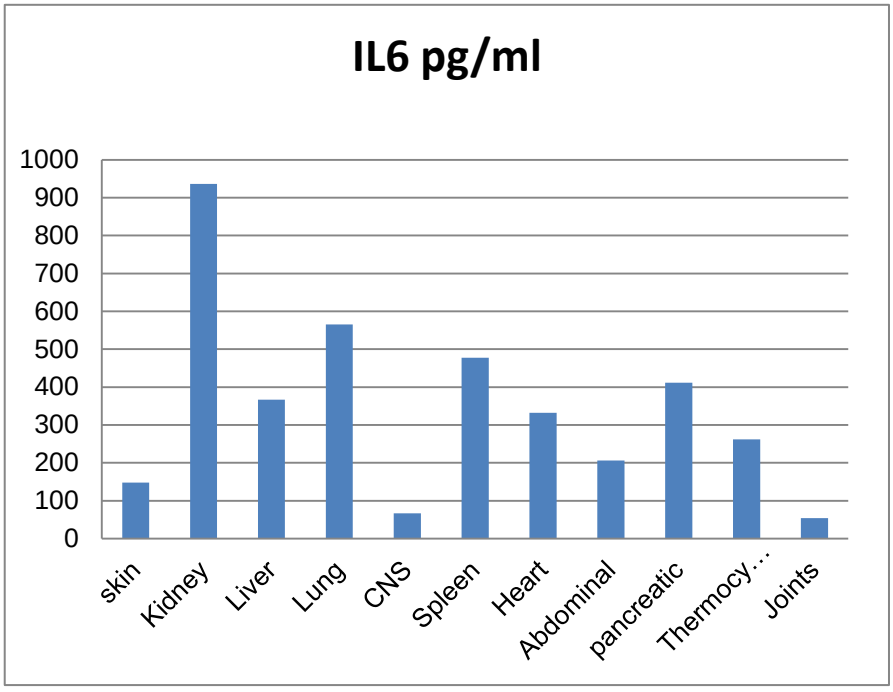

Figure A: The positive association between IL-6pg/ml and organ involvement in SLE patients.

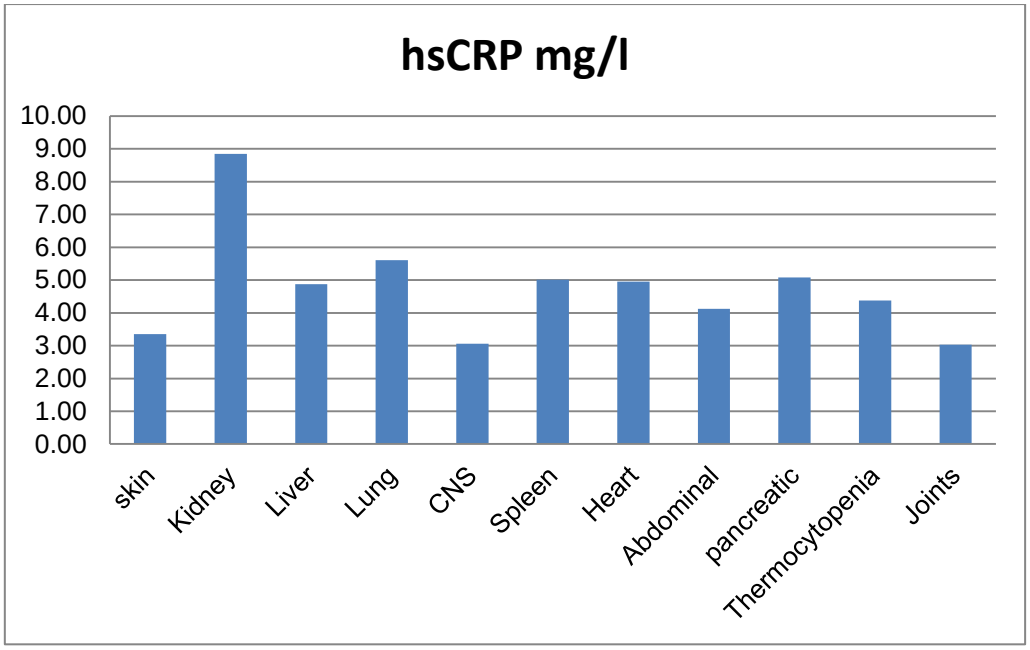

Figure B: The Mean levels of hsCRP in SLE patients that association with different organs involvements.

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قياس مستويات المحرك الخلوي IL-6 في مصل المرضى المصابين بداء الذئب الاحمراري وعلاقته ب CRP,ESR

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الخلاصة

داء الذئب الاحمراري (SLE) هو أحد أمراض المناعة الذاتية أكثر وضوحا في النساء ويتميز بانتاج تشكيلة واسعة من الأجسام المضادة ، وترسيب المعقدات المناعيه ومختلف الاعراض جهازية السريرية التي تؤثر على اعضاء مختلفه من الجسم .

هدف الدراسة هو البحث عن العلاقة بين كل من المحرك الخلوي IL-6-، ومعدل الترسيب(ESR) hs-CRPو وعلاقتهم بالاعضاء المشمولة في المرضى المصابين ، وتقييم ما إذا IL-6- يمكن أن يكون ذي علاقة بشدة المرض(SLEDAI) ومشاركة الأعضاء. وقد تناولت الدراسة 50 مريضا مصابا بداء الذئب الاحمراري(SLE)(48اناثا، 2 ذكورا)ا و 30من الاصحاء، حيث تم تقسيم هؤلاء المرضى إلى مجموعتين كان 42 مريضا ينتمون الى المجموعة الشديده(النشطه)و 8 مرضى الى المجموعة الساكنه(غير نشط)عند (P =)0.004. كان متوسط مستوى تركيز(IL-6) في مرضى داء الذئب و الاصحاء (541.19، 5.319 بيكوغرام / مل) على التوالي، وكانت الفروق ذات دلالة إحصائية عند (P = 0.000) عندما كان P <0.05.

تحققت الدراسه من وجود علاقة إيجابية طرديه بين كل من المصل (IL-6) وSLEDAI (r = 0.422 **، P = 0.002) وكان مستوى متوسط (IL-6) في المرضى الذين يعانون من التهاب الكلية هو(936.27بيكوغرام / مل)حيث كان الفرق أعلى بكثير من الأجهزة الأخرى (P = 0.000).بينما كانت تراكيز مستويات البروتين التفاعلي (hs-CRP) لمرضى الذئبة الحمراء هي (6.0879 ملجم / لتر) وكان الفارق معنويا (P = 0.000) عن الاصحاء، حيث تحققت الدراسه من وجود ارتباطا طرديا قويا بين(IL-6) و hs-CRP في مصل الدم لمرض بداء الذئبة (r = 0.969 **، P = 0.000). ولكن الفرق لم يكن كبيرا بين hs-CRP وESR (r = 0.249، P = 0.08)، حيث كان متوسط مستويات البروتين التفاعلي(CRP) لدى مرضى الذئبة الذين يعانون من التهاب الكلية هو (8.844 ملغم / لتر) أعلى بكثير في المرضى الذئبة من الأجهزة الأخرى P = 0.000