

Study of Dyslipidemia in Patients with Systemic Lupus Erythematosus and its Correlation to Disease Activity

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Abstract:

Background: Cardiovascular events and accelerated atherosclerosis in patients with active systemic lupus erythematosus results in significant increased morbidity and mortality. The non-traditional risk factors induce alteration in lipoprotein metabolism and the constant inflammatory and immune activity can lead to accelerated atherosclerosis. **Aim:** To assess prevalence of dyslipidemia in systemic lupus erythematosus patients and to study the relation of dyslipidemia to disease activity.

Patients and methods: The presented study included 60 SLE adult patients (56 females and 4 males) and they were classified according to disease activity into two groups: Active Lupus: Included 30 lupus patients. Inactive Lupus: Included 30 lupus patients. 20 healthy subjects with matched age, sex and BMI were included as healthy controls. Methods: Patients underwent clinical assessment. Total cholesterol, (LDL, HDL) and triglyceride were measured.

Results: Cholesterol, LDL, and TG levels were elevated in the active group compared to that in the inactive group and healthy controls. This elevation was significant ($P < 0.001$). But HDL level decreased in the active group compared to the inactive and healthy controls groups. The decrease of HDL was the active group is significant ($P < 0.001$). **Conclusion:** The elevated levels of Total cholesterol, LDL, and TG and decreased level of HDL in SLE patients are considered an independent risk factor for cardiovascular disease. The dyslipidemia and inflammatory process predispose to premature atherosclerosis and disease activity contribute to dyslipidemia and hence cardiovascular risk associated with SLE.

Keyword: SLE, Dyslipidemia, Cholesterol, TG

Introduction:

Systemic lupus erythematosus (SLE) is an autoimmune, chronic, relapsing, inflammatory, and often multi-systemic disorder of connective tissue, characterized by involvement of the skin, joint, kidney and serosal membranes ⁽¹⁾.

Patients with SLE have higher mortality and morbidity rate compared to general population. The major causes of death remain to be infection, lupus nephritis (LN), and cardiovascular disease (CVD) ⁽²⁾.

CVD in autoimmune rheumatic diseases is caused by traditional (increasing age, male gender, hypertension, smoking, hypercholesterolemia, diabetes) and the so-called non-traditional risk factors ⁽³⁾. There are statistically significant increases in coronary heart disease and stroke in SLE patients that cannot be fully explained by Framingham risk factors ⁽³⁾. These non-traditional factors are disease related, such as disease activity, glucocorticoid, hydroxychloroquine (HCQ) used to control disease activity, impaired renal

function, presence of antiphospholipid antibodies, and immune cell activation. A modification of Framingham risk score, where each item is multiplied by two, estimates more accurately the risk for coronary artery disease in lupus patients ⁽³⁾.

Additional mortality in SLE patients shows a bimodal pattern, with an early peak due to the consequence of active lupus and a later peak attributable mainly to atherosclerosis ⁽⁴⁾.

Abnormal plasma concentration of lipids is common in patients with SLE. Dyslipidemia usually refers to elevated total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and decreased high-density lipoprotein (HDL) level ⁽⁴⁾.

Lupus nephritis (LN), a common and potentially life-threatening manifestation of SLE, occurs in almost half of the lupus patients ⁽⁵⁾. Patients with LN have a higher TC, TG, and LDL and lower HDL and

apolipoprotein B levels, than patients without renal manifestation ⁽⁶⁾.

Dyslipidemia is more severe in lupus nephritic patients than those with a similar degree of chronic kidney disease despite disease inactivity, low level of proteinuria, and low dose steroid usage ⁽⁷⁾. Hyperlipidemia can affect all parts of the nephron causing endothelial cell injury, glomerular filtration defect with hyperfiltration and tubule-interstitial lipid deposition ⁽⁷⁾.

If other systemic disorders such as diabetes mellitus and thyroiditis are also present, they can also cause changes in lipid metabolism. Age-related and postmenopausal changes also matter ⁽⁸⁾.

Several mechanisms have been proved or suggested among factors that may increase risk of dyslipidemia in SLE and by turn increase risk of CVD. Interestingly, immune and inflammatory reactions seem to have a role in the pathogenesis of atherosclerotic vascular damage ⁽⁹⁾. This raises the exciting possibility that SLE itself may be atherogenic through chronic activation of the immune system and inflammatory process. In fact, autoantibodies such as anti-phospholipid, anti-b2-glycoprotein1, anti-ox-LDL-c and anti-lipoprotein lipase and elevated inflammatory markers such as CRP and IL-6 are common finding of SLE. It is therefore reasonable to postulate that the interaction of disease associated factors induce specific alteration in lipoprotein metabolism which is aggravated by drugs and associated conditions frequently observed in lupus patients ⁽⁹⁾.

Subjects and methods

The presented study included 60 SLE adult patients (56 females and 4 males) selected from Internal Medicine Departments and Rheumatology outpatient Clinic of Al-Hussein University Hospitals between May 2017 and January 2018. Twenty healthy subjects with matched age, sex and BMI were included as healthy controls.

Patients were classified according to disease activity into the following groups:

Active Lupus: Comprised 30 lupus patients.

Inactive Lupus: Comprised 30 lupus patients.

Methods:

Patients were subjected to full medical history taking, clinical examination, as well as laboratory investigations. The revised criteria of the American College of Rheumatology ⁽¹⁰⁾. Were used for diagnosis of SLE.

Assessment of Disease Activity of SLE Patients:

The Systemic Lupus Activity Measure (SLAM) index was recorded for each patient. This scoring system is based on a comparative study done by Liang and his colleagues ⁽¹⁰⁾.

The Lupus Activity Index is a concise measure comprised of a 0-3 visual analog scale for 4 symptoms (fatigue, rash, joint involvement, serositis) and 4 signs (neurologic, renal, pulmonary, and hematologic involvement).

All subjects were subjected to

A- Detailed history taking.

B- Full clinical examination.

C- Routine laboratory investigations; erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fasting and 2 hours postprandial blood glucose, complete blood count (CBC), complete urine analysis, and liver and kidney function test.

D- Measurement of proteins in 24 hour urine (g/24hrs).

E- Antinuclear antibodies (ANA) and Anti-double stranded deoxyribonucleic acid antibodies (**anti-dsDNA**). Done by immunofluorescence technique. Titer of 1/40 or more is considered positive. (Done for SLE patients only).

F-Serum complement levels (**C3, C4**). Done by nephelometry (Normal level of C3 is 84-160 mg /dl and for C4 12- 36 mg /dl): (Done for SLE patients only)

G-Total cholesterol in mg/dl by enzymatic colometric assay. H-Total triglyceride in mg/dl by enzymatic colometric assay. J-LDL cholesterol by mg/dl by enzymatic colometric assay. K-HDL in mg/dl by enzymatic colometric assay.

Sample collections: After 12 hours fast 8 ml venous blood was obtained from all participate.

They were divided into; 1 ml on EDTA (1 mg/ml) for CBC, 5 ml into plain tubes and serum samples were separated into 2 aliquots for investigations.

Serum total cholesterol, triglycerides, and HDL-c concentration were measured ⁽¹¹⁾. The

material was supplied by Spinreact (Spain) for total cholesterol and triglycerides and by STANBIO (USA) for HDL-c. LDL-c concentration was calculated ⁽¹²⁾.

Statistical analysis:

Statistical Package for Social Science (SPSS) version 17 was used. Quantitative data were expressed as mean ± SD and qualitative data were expressed as number and percentage of the total. The mean and standard deviation

(SD) were calculated. Comparing the mean ± SD of 2 groups was done using the unpaired t test. Determining the extent that a single observed series of proportions differs from a theoretical or expected distribution was done using the Chi square test. Receiver operator characteristic (ROC) curve was used and sensitivity and specificity for various cut off points were plotted. P was considered non-significant if >0.05, significant if <0.05 and highly significant if <0.01 and <0.001.

Results

Table (1): Cholesterol level among the studied groups

Groups	Cholesterol (mg/dl)				ANOVA	
	Range	Mean	±	SD	F	P-value
Active group	146 - 376	272.767	±	58.533	16.544	<0.001*
Inactive group	165 - 324	249.767	±	46.804		
Control group	156 - 265	194.100	±	26.213		
TUKEY'S Test						
A&I		A&C		I&C		
0.156		<0.001*		<0.001*		

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control

Table 1 shows that cholesterol level is elevated in active group compared to that in inactive group and healthy controls. This elevation is significant (*P* < 0.001).

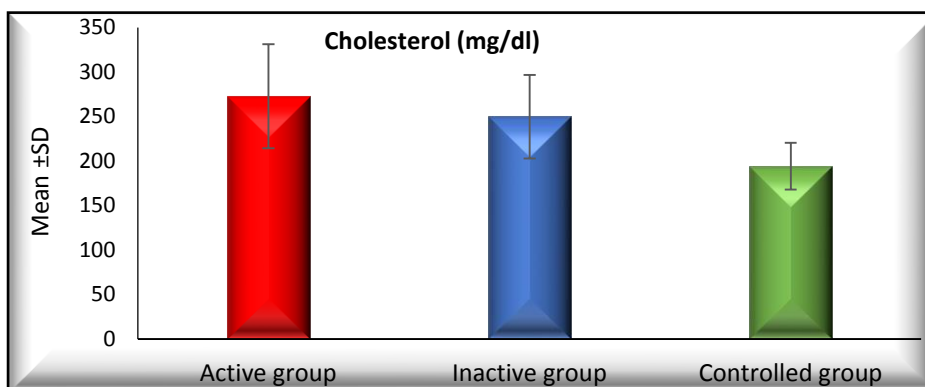


Fig (1): Shows the correlation between cholesterol levels in active, inactive, and healthy controls.

Table (2): TG level among the studied groups

Groups	TG (mg/dl)				ANOVA	
	Range	Mean	±	SD	F	P-value
Active group	105 - 388	271.300	±	91.306	19.891	<0.001*
Inactive group	135 - 382	246.133	±	76.325		
Control group	126 - 168	142.100	±	11.534		
TUKEY'S Test						
A&I		A&C		I&C		
0.383		<0.001*		<0.001*		

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control

Table 2 shows that TG level is elevated in active group compared to that in inactive and healthy controls groups. This elevation is significant (*P* < 0.001).

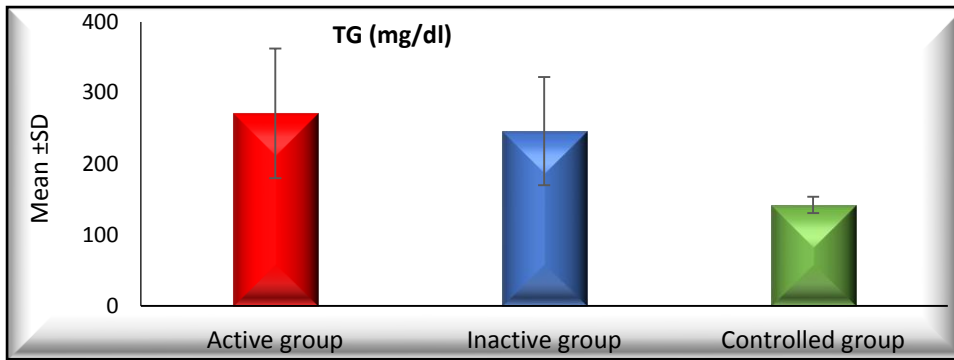


Figure (2): Shows the correlation between TG level in active, inactive, and healthy controls groups.

Table (3): LDL level in the active group compared to that in the inactive and healthy controls groups.

Groups	LDL (mg/dl)				ANOVA	
	Range	Mean	±	SD	F	P-value
Active group	79 - 188	146.233	±	30.450	13.277	<0.001*
Inactive group	69 - 187	136.500	±	33.558		
Control group	66 - 149	101.900	±	25.470		
TUKEY'S Test						
A&I		A&C		I&C		
0.437		<0.001*		0.001*		

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control.

Table 3 shows that LDL level is elevated in active group compared to that in inactive and healthy controls groups. This elevation in active group is significant ($P < 0.001$).

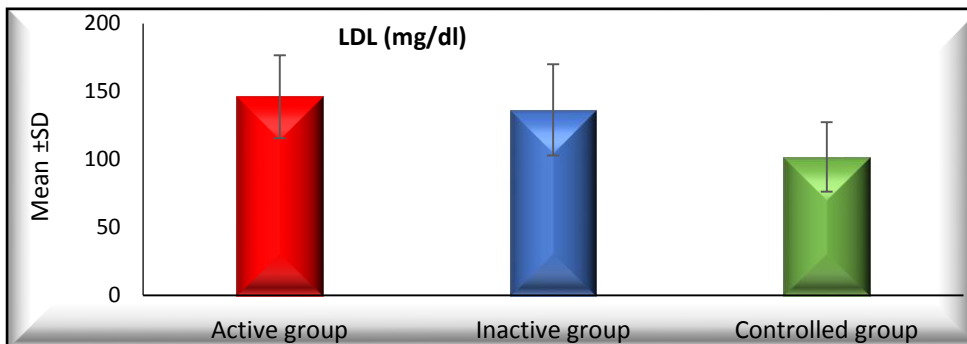


Figure (3): Shows the between LDL levels in active, inactive, and healthy controls groups.

Table (4): HDL level in the active group compared to that in the inactive and healthy controls groups.

Groups	HDL (mg/dl)				ANOVA	
	Range	Mean	±	SD	F	P-value
Active group	19 - 57	35.800	±	11.146	15.976	<0.001*
Inactive group	24 - 73	42.200	±	14.880		
Control group	38 - 77	56.500	±	11.533		
TUKEY'S Test						
A&I		A&C		I&C		
0.134		<0.001*		0.001*		

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control.

Table 4 shows that HDL level is decreased in active group compared to that in inactive and healthy controls groups. This decrease in active group is significant ($P < 0.001$).

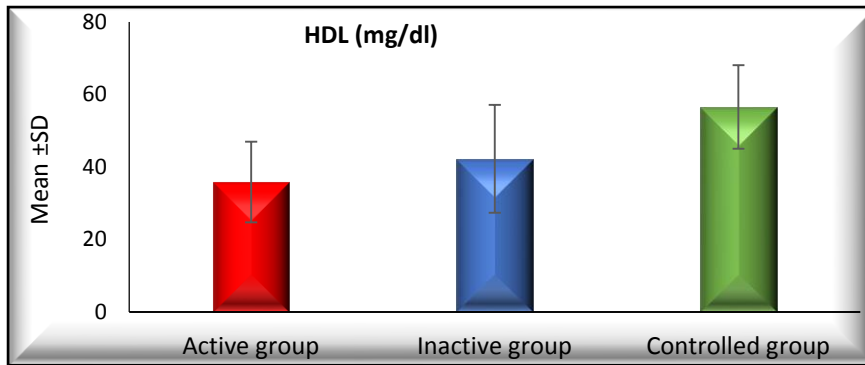


Figure (4): Shows the correlation between HDL levels in active, inactive, and healthy controls groups.

Table (5): CRP level in the active group compared to that in the inactive and healthy controls groups.

Groups	CRP (mg/l)			ANOVA	
	Range	Mean	± SD	F	P-value
Active group	11 - 42	23.633	± 7.622	123.903	<0.001*
Inactive group	3 - 9	6.067	± 1.780		
Control group	4 - 9	5.800	± 1.508		
TUKEY'S Test					
A&I		A&C		I&C	
<0.001*		<0.001*		0.980	

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control.

Table 5 shows that CRP level is elevated in active group compared to that in inactive and healthy controls groups. This increase in CRP level in active group is significant (p<0.001).

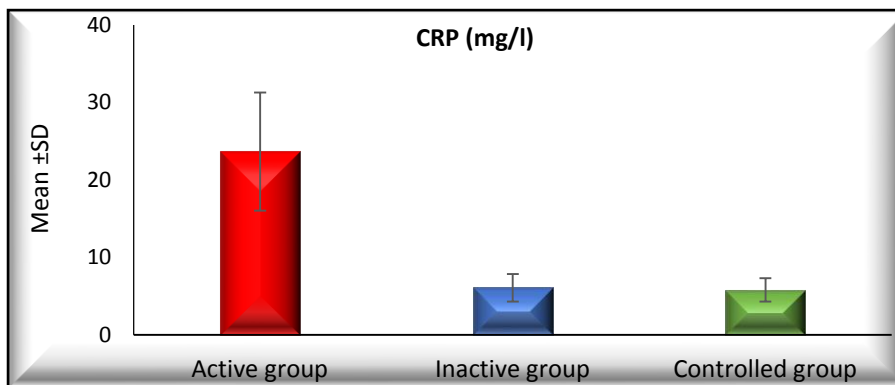


Figure (5): Shows the correlation between CRP levels in active, inactive, and healthy controls groups.

Table (6): C3 level in the active group compared to that in the inactive and healthy controls groups.

Groups	C3 (mg/dl)			ANOVA	
	Range	Mean	± SD	F	P-value
Active group	50 - 110	74.200	± 13.345	78.891	<0.001*
Inactive group	94 - 188	144.933	± 29.496		
Control group	93 - 165	124.400	± 20.314		
TUKEY'S Test					
A&I		A&C		I&C	
<0.001*		<0.001*		0.006*	

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control.

Table 6 shows that C3 level is decreased in active group compared to that in inactive and healthy controls groups. This decrease in C3 level in active group is significant (P< 0.001).

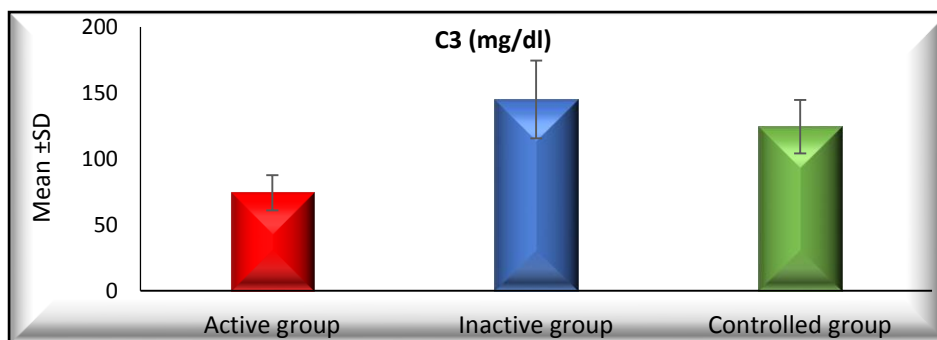


Figure (6): Shows the correlation between C3 levels in active, inactive, and healthy controls groups.
 Table (7): C4 level in the active group compared to the inactive and healthy controls groups.

Groups	C4 (mg/dl)				ANOVA	
	Range	Mean	±	SD	F	P-value
Active group	5 - 16	9.267	±	2.924	46.451	<0.001*
Inactive group	10 - 39	25.533	±	8.361		
Control group	12 - 38	24.200	±	9.146		
TUKEY'S Test						
A&I		A&C		I&C		
<0.001*		<0.001*		0.792		

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control.

Table 7 shows that C4 level is decrease in active group compared to inactive and healthy controls groups. This decrease in C4 level in active group is

Table (8): Platelet level in the active group compared to the inactive and healthy controls groups.

Groups	Platelet (x1000)				ANOVA	
	Range	Mean	±	SD	F	P-value
Active group	71 - 120	92.633	±	12.439	135.464	<0.001*
Inactive group	103 - 198	140.567	±	21.847		
Control group	165 - 410	271.700	±	70.345		
TUKEY'S Test						
A&I		A&C		I&C		
<0.001*		<0.001*		<0.001*		

A&I= active and inactive, **A&C**= active and control, **I&C**= inactive and control.

Table 8 shows that platelet level is decreased in active group compared to inactive and healthy controls groups. The decrease level of platelet in active group is significant (P<0.001).

Discussion

Patients with SLE have higher mortality and morbidity rate compared to the general population. The major causes of death remain to be infection, lupus nephritis (LN), and cardiovascular disease (CVD) ⁽³⁾.

There is increased cardiovascular mortality in SLE. Accelerated atherosclerosis leading to coronary artery disease (CAD) and other cardiac manifestations have increasing importance for the management and outcome of SLE. Several traditional and disease-related risk factors, as well as corticosteroids are suggested to be involved in lupus-associated

atherosclerosis and its clinical manifestations ⁽³⁾.

Traditional risk factors, such as altered lipid levels, aging and smoking, do not fully explain this increased risk of CVD, and strongly suggesting that autoimmunity contributes to accelerated atherosclerosis ⁽³⁾.

Altered immune system function is recognized as the primary contributor to both the initiation and progression of atherosclerosis. Many mechanisms of autoimmunity, including changes in cytokine

levels and innate immune responses, autoantibodies, dysfunctional lipids, and oxidative stress, could heighten atherosclerotic risk. In addition, multiple SLE therapeutics seems to affect the development and progression of atherosclerosis both positively and negatively⁽¹³⁾.

The aim of this study was to evaluate the plasma lipid (cholesterol, HDL, LDL, and triglyceride) and its relation to systemic lupus erythematosus activity.

The present study revealed elevated levels of serum TG, LDL and TC in active group compared to that revealed in the inactive group or healthy control. This elevation was statistically highly significant ($P < 0.001$).

Also, the study revealed decreased serum HDL level in the active group compared to that in inactive group or healthy controls. The degree of decreased HDL level is significant ($P < 0.001$).

The findings in the current study are ongoing with general consensus of the so called "Lupus pattern" of dyslipoproteinemia which defined by elevated levels of TC, LDL and TG, and lower HDL levels⁽¹⁴⁾.

Lupus pattern is reported to be associated with atherosclerotic risks⁽¹⁵⁾.

The findings in active lupus group in this study are supported by several previous studies⁽¹⁶⁻¹⁹⁾ and one study⁽⁷⁾ demonstrated that increased expression of TGs and low levels of HDL (lupus dyslipidemia) were associated with disease activity in SLE and suggested their use as markers of disease activity.

Dyslipoproteinemia in lupus patients are attributed to various etiologies. Autoimmunity and inflammation are among players⁽⁹⁾.

It seems reasonable to accept that inflammatory conditions of the disease itself would induce specific alterations in the lipid profile. It is known that TNF- α which presents in a high concentration in SLE patients; promote a significant increase in circulating TG due to increase hepatic synthesis of VLDL. In addition; TNF has the ability to inhibit LPL⁽¹⁶⁾.

The production of a large variety of autoantibodies is a prominent pathogenic feature of SLE and it had been proved that it lead to autoimmune hyperlipidemia. The binding of autoantibodies to LPL impair its enzymatic activity, and titers of anti-LPL antibody correlate with TG levels, disease activity, and markers of inflammation⁽⁹⁾.

Chronic activation or damage to endothelium in SLE may trigger the inflammatory cascade and thereby promote atherogenesis. Several forms of endothelial insult are being recognized in SLE, including hypercholesterolemia, hyperhomocysteinemia, mechanical stress from hypertension, increased oxidative stress and immunologic injury as a result of immune complex deposition⁽²⁰⁾.

In contrast to the findings of the current study; some other studies^(21, 22) reported relatively low LDL, low HDL, high VLDL, and high TG levels. They attributed these finding to impaired LPL activity which degrades VLDL, with subsequent conversion to LDL. Also Das reported high levels of VLDL and TG and low level of HDL in inactive lupus patients and decrease in LDL during active disease, the so called "active lupus pattern", suggesting a defect in VLDL metabolism⁽²³⁾.

Determinations of serum anti-ds DNA titer and complement levels (C3, C4) are the most common and useful tests for assessment of disease activity and predicting flares in SLE.

The current work demonstrated a significant increase in anti-dsDNA antibodies levels in active SLE patients in comparison to patients in remission. Anti-dsDNA and anti-Sm antibodies are highly specific for idiopathic SLE. Combination of anti-dsDNA, serum complements C3 and C4, ESR and CRP supported by relevant tissue histology, probably provides the most useful information on disease activity, particularly in patients with lupus nephritis. However, results of any laboratory test should always be interpreted with reference to the clinical presentation⁽²⁴⁾.

The present study show that there was a statistically significant difference between active and inactive SLE patients regarding anti-ds DNA levels, which agrees with (**Abd-ElSamad et al., 2000**)⁽²⁵⁾.

However some authors observed that raised anti-dsDNA titer is of no significance and may be found raised in quiescent diseases⁽²⁶⁾.

In the present study there was a statistically significant difference between the active group and inactive group with SLE as regarding serum complement (C3) level ($p < 0.05$). This agrees with the findings of **Rahman and Hiepe (2002)**, where highly significant difference was reported between active SLE patients with reduced C3 level comparing with inactive SLE patients ($p < 0.001$) and they

concluded that C3 provides the best assessment of disease activity in patients with SLE⁽²⁷⁾.

On other hand some authors observed that C3 level was low in active stage of SLE especially during clinical exacerbation but its concentration was often normal in mild to moderate active stage⁽²⁸⁾.

The present study showed a statistically significant decrease in level of serum complement (C4) in patients with SLE activity. Level of C4 concentration was lower in the active groups than in the inactive group of SLE. Similar results were reported by⁽²⁵⁾.

Plasma levels of C3 and C4 were significantly decreased on comparing SLE patients to healthy normal subjects. Significant decrease in their levels was also found on comparing active SLE patients with patients in remission.

In spite of many years of study of the SLE, the pathology or disease process in systemic lupus erythematosus remains unclear. Various laboratory tests were used for detection of the activity of the disease as ESR, plasma complements concentrations, and formation of autoantibodies⁽²⁹⁾. The present study showed significant decrease in RBC, WBC and platelet counts in patients with active SLE compared to patients in remission, as well as, to the healthy controls. Decreased RBC count could be explained by impaired renal function with decreased erythropoietin formation, and also due to poor general condition, cachexia and anorexia, in addition to bone marrow suppression by aggressive cytotoxic therapy⁽²⁸⁾.

Leucopenia in SLE patients occurs as part of drug toxicity-induced medullary hypoplasia. Also, it may be due to disease activity, bone marrow failure, peripheral destruction and sepsis. The most common mechanism of thrombocytopenia in SLE patients is believed to be increased RBCs, platelets clearance mediated by anti-platelet auto-antibodies⁽²⁹⁾. ESR was significantly higher on comparing active SLE patients to patients in remission and healthy controls, and was significantly higher on comparing patients in remission to controls. This could be attributed to reduction of their synthesis and, also, their consumption in immune complex formation. These results indicated that complement dysfunction may be an important factor in the pathophysiology of SLE⁽²⁹⁾.

Conclusion: Dyslipidemia in SLE includes elevated levels of total cholesterol, TG, and LDL and decreased level of HDL. Elevation of TC, TG, LDL and decrease HDL are considered an independent risk factor for CVD share in premature atherosclerosis in these patients. Some SLE complication and disease activity contributes to dyslipidemia and hence cardiovascular risk associated with SLE.

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