Serum neopterin level in patients with active systemic lupus erythematosus and its correlation with complement 3 and 4

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Abstract: Introduction: Previous reports indicated that patients with systemic lupus erythematosus have significantly higher levels of serum neopterin. **Aim:** We aimed to study the role of serum neopterin level in assessment of SLE activity. **Patients and Methods:** Seventy five (75) subjects were enrolled. These included 30 patients with active SLE (group I), 30 patients with inactive SLE (group II), and 15 healthy control subjects (group III). Diagnosis of SLE based on presence of four or more than of these criterias including malar rash, discoid rash, photo sensitivity, oral ulceration, arthritis, serositis, kidney involvement, neurological disorders, haematological disorders, positive test for ANA and anti ds DNA. The SLE activity was assessed by SLE activity index. Serum complement 3 (C3), complement 4 (C4), and anti-double stranded DNA (anti-ds DNA) were measured for all subjects (n=75). as well the serum neopterin level measured in all subjects (n=75) by enzyme linked immunosorbent assay (ELISA). **Results:** The mean age of included subjects was 18± 32 years, all subjects were females. Patients in groups I, II were matched for age and sex with subjects in group III. The mean values of serum neopterin in groups I, II and III were 33.9 ng/ml, 3.45 ng/ml and 1.95 ng/ml respectively. Patients with active SLE have significantly higher neopterin levels compared with inactive SLE patients (P < 0.001). Moreover inactive SLE patients have significantly higher neopterin levels than healthy control subjects (0.001). Although serum neopterin had significant negative correlation with C3, it had significant positive correlation with SLE activity index and 24 hours urinary protein (P< 0.001). **Conclusion:** Serum neopterin can segregate patients with active SLE. Serum neopterin measurement may help in assessment of SLE activity and progression. Moreover it may judge the efficacy of SLE treatment.

Keywords: Serum; neopterin; patient; systemic lupus; erythematosus; complement

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by chronic inflammation and the production of autoantibodies directed against numerous antigen which target multiple organ systems including joints, skin and kidneys. The relapsing- remitting pattern of disease, along with the clinical heterogeneity makes SLE not only one of the challenging autoimmune disorders to diagnose but also to treat and assess drug efficacy. (**Hochberg, et al 2011**)

Neopterin (6-D-erytro-trihydroxypropylpterin) formed from intra cellular guanosine triphosphate produced by human monocyte-derived macrophages upon stimulation with the cytokine interferon gamma (INT-γ) released from activated T- lymphocytes. Also other interferons, interleukin-1α (IL-1α), tumor necrosis factor- α (TNF-α) and lipopolysaccharides affect Neopterin production. (**Voet, et al 2004**)

In vivo increased concentration of neopterin have been found in patients with diseases associated with the activation of cell- mediated immunity (e.g., during allograft rejection, acute viral infection, intracellular bacteria, parasites, autoimmune disease and malignant tumor cells). The Neopterin level provides appropriate information regarding the extent and activity of the pathological process. (**Sucher, et al., 2010**)

The complement has been recognized one as pivotal part of innate and adaptive immune system and it had three well- known physiological activities including host defense against infection, bridging interface between innate and adaptive immunity, and disposal of waste immune complex or apoptotic cells. (**Klos, et al., 2013**)

Serum level of neopterin was significantly increased in SLE while the complement C3, C4 levels was significantly lower than those of healthy controls, neopterin is one of the parameters that showed significantly higher levels in SLE with mild activity. (**Hafez, et al 2004**)

2. Subject and Methods

This study was carried out on sixty female patients suffering from systemic lupus erythematosus (SLE) attending to outpatient and inpatient clinics of

Internal Medicine Department, Al-Azhar University Hospitals. And 15 healthy female individual of matched age and sex as a control group apparently free from any relevant disease, their ages ranged from (19-39) years. All patients were females their ages ranges from (18-40) years and the disease duration ranges from (6months – 5 years).

Subjects in the study have been classified in three groups:

Group I: 30 patients with active systemic lupus erythematosus.

Group II: 30 patients with inactive systemic lupus erythematosus.

Group III: 15 healthy female individual of matched age and sex as a control group apparently free from any relevant disease, their ages ranged from (19-39) years.

All patients and controls has been subjected to the following: (a) Full history taking including **(**photosensitivity, falling of hair, oral ulceration, morning stiffness its duration, location and neurological symptoms as headache, seizures and stroke**).** (b) Complete clinical examination with stress on the following: joints examination, skin examination including **(**oral or nasal ulcers, hair loss and erythematosus rash**)**, cardiovascular examination for pericarditis, Raynauds phenomenon, chest examination to detect pleurisy and pleural effusion and neurological examination for stroke, seizures, headache and cortical dysfunction**., (c)** Routine laboratory investigations: CBC, CRP, ESR, liver & kidney function tests, urine analysis, 24-hour urine protein, S cholesterol and triglyceride, ANA, Ads DNA and C3, C4., **(d)** Specific laboratory investigation:

Serum neopterin by ELISA.

Expected physiological ranges:

Normal: 0.3-3.0 ng/ml (note: to convert to nmol/l, multiply ng/ml by 3.95).

As with all diagnostic tests, differences in physiological ranges may be from laboratory to laboratory due to patient demographics, laboratory techniques and population sampling. These ranges should only be used as a guideline.

Statistical presentation and analysis of the present study:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.16. Data were presented as mean, SD, number and percentage. Chi-square test was used to compare qualitative data between the two groups of patients. Independent sample T-test was used to compare means of both groups. One way analysis variants(ANOVA) test: for comparison between multiple groups with quantitative continuous variables. P-value considered significant when it ≤ 0.05. Regression analysis was done and or calculated for independent risk factors.

3. Results

Our study was carried out on 75 female subjects. Of them, 15 were employed as the healthy control group and 60 subjects as the patients groups. 30 of them are with active systemic lupus erythematosus (SLE) and 30 are with inactive systemic lupus erythematosus. The patients with active SLE their ages ranged between (18-37) years with a mean of (22.7+2.21) and the duration of the disease ranged between (5 months-5 years) with a mean (2.46+1.45)The patients with inactive SLE their ages ranged between (19-40 years) years with a mean of (25.8+6.36) and the duration of the disease ranged between (1 month-5 years) with a mean (2.60+1.11) The healthy control persons were females, their ages ranged from (19-39) years with a mean of (25.8+5.04).
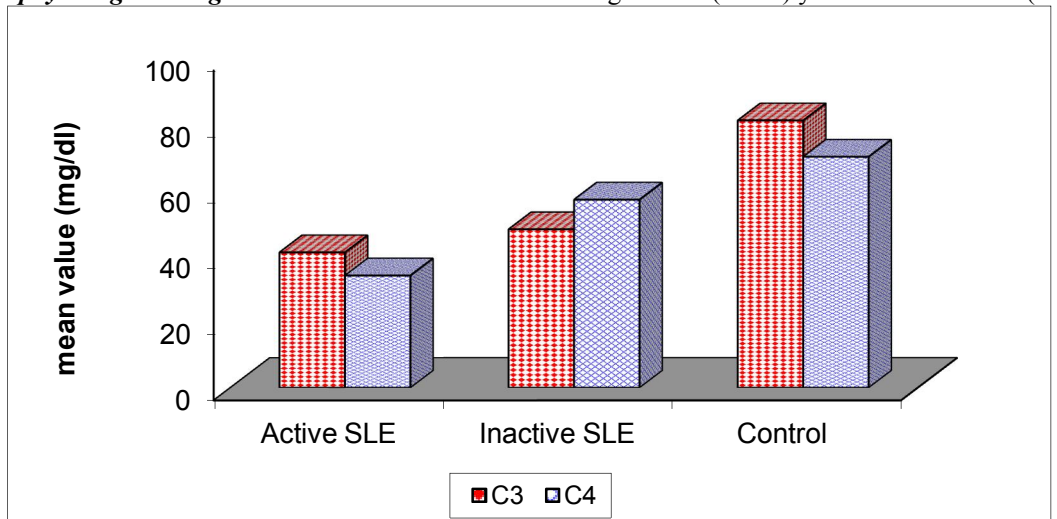
Figure (1): The mean value of C3 and C4 in the three groups.

Table (1): Distribution of laboratory parameters among SLE patients and controls.

		Active SLE	Inactive SLE	Control	f. test	p. value	Active SLE & Inactive SLE	Active SLE & Control	Inactive SLE & Control
C3		41.8+14.9	48.3+13.4	81.9+23.2	15.336	0.009	0.024	0.001	0.001
ESR		77+30.7	49.6+18.1	18.6+4.64	16.151	0.001	0.001	0.001	0.002
C4		34.2+10.4	57.8+14.3	70.7+22.6	12.529	0.002	0.009	0.001	0.007
Anti DNA	No	6(20%)	22(73.3%)	20(100%)	12.225	0.004			
	Yes	24(80%)	8(26.7%)	-					
	Total	30(100%)	30(100%)	20(100%)					

Table(1): Distibution of laboratory parameters among SLE patients and controls
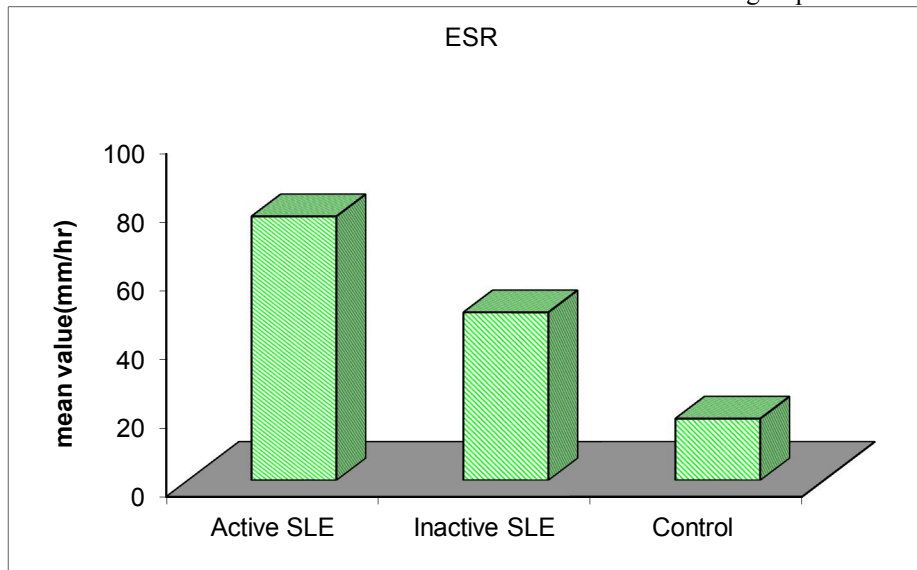**p.value ≤0.001 is highly significant.
*p.value ≤0.05 is significant.

The mean serum C3 level was significant lower for the whole SLE patients than for the control group where:

• The mean serum C3 was significantly lower for whole SLE patients as compared to controls. And in active and inactive groups compared to the controls P values<0.009, <0.001, <0.001. respectively;

however there was no significant difference between active and in active groups P value<0.24.

2. The mean serum C4 level was significant lower for the whole SLE patients as compared to the control groups; Also the active and inactive as compared to the controls P values <0.002, <0.001, <0.007 respectively. as well mean C4 level were lower in active than inactive group P value<0.009.

Figure (2): The mean value of ESR in the three groups.

3. The erythrocyte sedimentation rate (ESR) was highly significant for whole SLE patients than for the control group (P<0.001) where:

• ESR level was significantly high for all patients with SLE compared to the control group; also high in active and in active compared to the controls P values <0.001, <0.002, <0.002 respectively. There is a significant increase in ESR level in active compared to inactive group P value <0.001.

4. The anti- ds DNA was positive in 24 patients with active SLE (80%) and in 8 patients with inactive SLE (26.7%). The number and percentage of presence of anti-ds DNA was significant for all SLE patients than the controls (P<0.004).

Table (2): Correlation coefficients between C3, C4 and Anti ds DNA among SLE patients.

	Anti DNA			
	Active SLE		Inactive SLE	
	r.	p. value	r.	p. value
C3	-0.352	0.042	-0.258	0.095
C4	-0.296	0.030	-0.334	0.041

**p.value ≤0.001 is highly significant. *p.value ≤0.05 is significant.
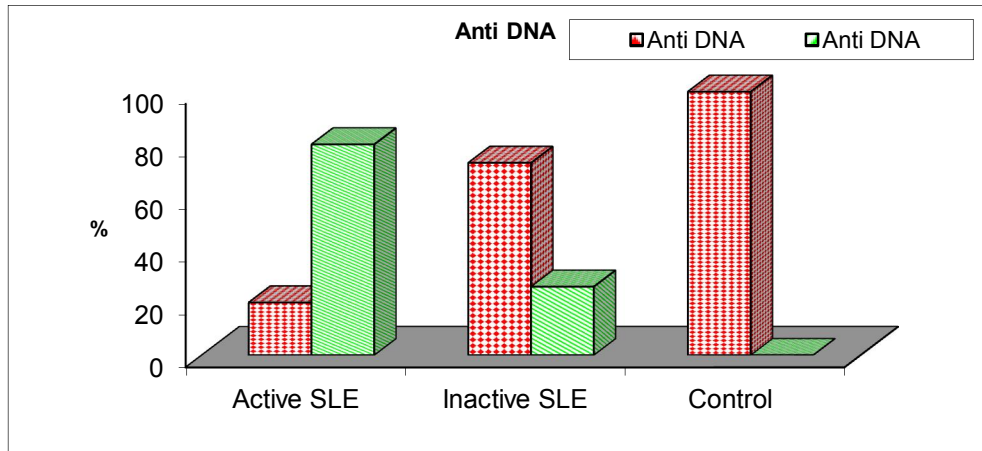
Figure (3): The percentage of the presence the Anti-ds DNA antibodies in the three groups

Table (2) shows that there is a negative significant correlation was found between antibodies to DNA and C3, C4 in patients with active SLE. In patients with inactive SLE there is negative insignificant correlation between C3 and anti- ds DNA, however the correlation between C4 and Anti ds DNA was negative and significant.

Table (3) shows that there is a negative significant correlation between Anti ds DNA and C3 and C4 in all SLE patients.

Table (3): The correlation between Anti ds DNA and C3 and C4 in whole patients.

	Anti- ds DNA	
	r.	p. value
C3	**-0.362**	**0.042**
C4	**-0.296**	**0.049**

**p.value ≤ 0.001 is highly significant. *p.value ≤ 0.05 is significant.
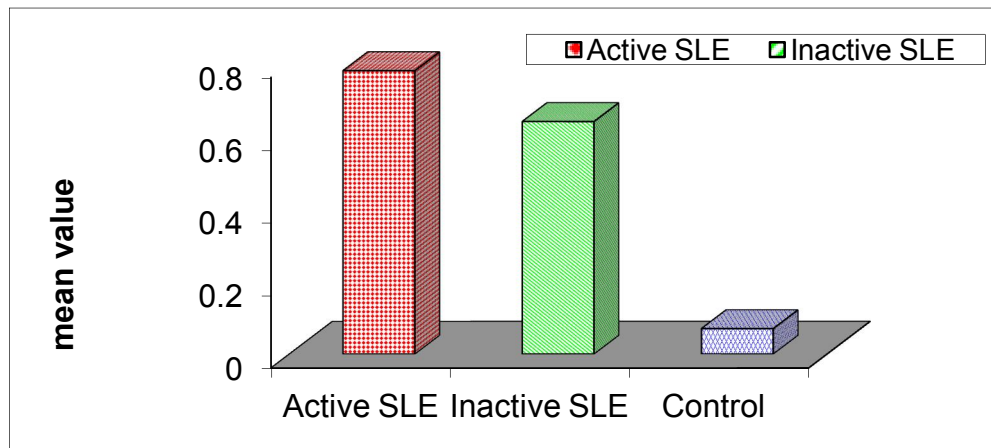
Figure (4): The mean values of 24 hour urine protein level in the three groups

Table (4): Means and standard deviations of proteinuria level among SLE patients and control group.

24 h PTN	Active SLE	Inactive SLE	Control
Mean	0.78	0.64	0.07
+SD	0.12	0.16	0.013
f. test	**5.336**		
p. value	**0.003**		
Scheffe test			
Active SLE & Inactive SLE		**Active SLE & Control**	**Inactive SLE & Control**
0.006		**0.001**	**0.001**

**p.value ≤ 0.001 is highly significant. *p.value ≤ 0.05 is significant.

The mean value of proteinuria was significantly higher for the whole SLE compared to the control group; and significantly higher in active and inactive compared to the controls P.value <0.003, <0.001, <0.001. respectively. Also mean value of proteinuria is significantly higher in active compared to in active group P.value <0.006.

Table (5): Means and standard deviations of serum neopterin level among SLE patients and control group.

Serum neopterin	Active SLE	Inactive SLE	Control
Mean	33.9	3.45	1.95
+SD	8.36	0.81	0.67
f. test	15.633		
p. value	0.001		
Scheffe test			
Active SLE & Inactive SLE	**Active SLE & Control**		**Inactive SLE & Control**
0.001	0.001		0.001

***p.value ≤0.001 is highly significant. *p.value ≤0.05 is significant.*

- The normal range of serum neopterin using ELISA technique is between (0.3-3) ng/ml.
- Serum neopterin level in patients with active SLE ranges between (5.5-82.5) ng/ml.
- Serum neopterin level in patients with inactive SLE ranges between (1.7-5.6) ng/ml.
- Serum neopterin level in the normal control ranges between (1-3) ng/ml.

Our study shows that:
- The mean value of serum Neopterin in whole SLE patients (21.9 ng/ml) range between (1.7-82.5).
- The mean values of serum neopterin for the active and inactive groups was 33.9 ng/ml and 3.45 ng/ml respectively where they were highly significant than the mean value of the control group (1.95 ng/ml) (P<0.001).
- Also the differences between the three groups are highly significant (P<0.001).

From above, we conclude that for our marker serum neopterin, there was highly significant increase of its values for the patients with active SLE as compared with the healthy control group with P-value of 0.001**. In a same manner, S. Neopterin for inactive SLE group compared with healthy control group shows highly significant correlation with p. value of 0.001**

In the group of active SLE:
- Serum neopterin shows negative correlation with C3where this correlation is highly significant (P<0.001).
- Serum neopterin shows positive correlation with ESR and where there is a highly statistically significance (P<0.001).
- Serum neopterin shows negative correlation with HB however there is no statisticallysignificance (P<0.1).
- Serum neopterin shows positive correlation with proteinuria where there is statisticallysignificance (P<0.01).
- Serum neopterin shows negative correlation with the other laboratory parameters (C4, HB, WBC and platelets count) without any statistical significance.
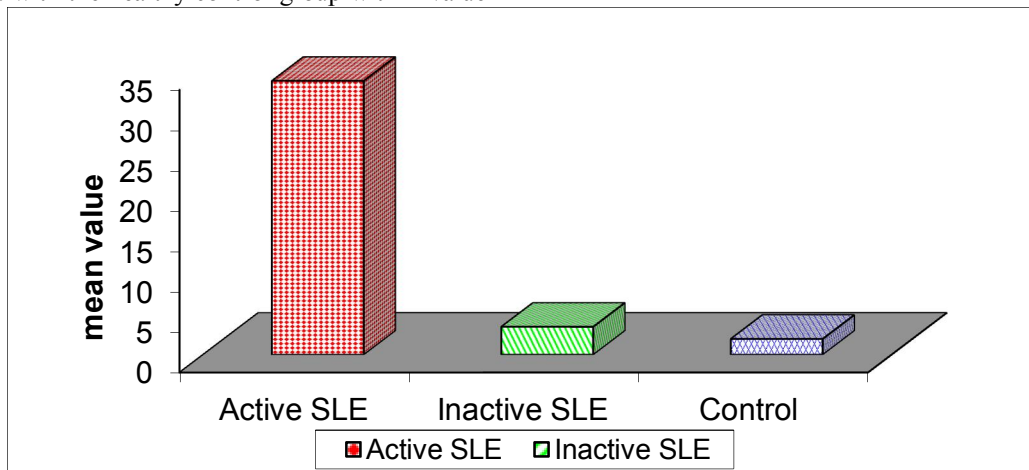
Figure (5): The mean values of serum Neopterin level in the three groups

Table (6): Correlation coefficients between serum neopterin levels and some laboratory parameters among active and inactive SLE patients.

	Serum neopterin			
	Active SLE		Inactive SLE	
	r.	p. value	r.	p. value
C3	-0.585	0.001	-0.199	0.299
C4	-0.259	0.166	-0.319	0.091
Anti DNA	0.037	0.829	0.024	0.900
ESR	0.616	0.001	-0.062	0.750
SLEDAI score	0.830	0.001	-0.166	0.389
HB	-0.284	0.128	-0.164	0.415
PLT	-0.268	0.152	-0.118	0.541
24 PTN	0.445	0.014	0.024	0.904
WBC	-0.293	0.116	-0.359	0.056

**p.value ≤ 0.001 is highly significant. *p.value ≤ 0.05 is significant.

In the group of inactive SLE:

• Serum neopterin show positive correlation with Anti ds DNA however there is no statistically significance.

• Serum neopterin show positive correlation with ESR however there is no statistical significance.

• Serum neopterin shows positive correlation with HB however there is no statistical significance.

• Serum neopterin shows positive correlation with proteinuria however there is no statistical significance.

• Serum neopterin shows negative correlation with the other laboratory parameters (C3, C4, HB, platelets count) without any statistically significance.

4. Discussion

The aim of our study is to evaluate the level of serum neopterin in patient with systemic lupus erythematosus (SLE) as a marker of disease activity and correlation with other parameters of disease activity.

Assessment of disease activity is done by systemic lupus erythematosus disease activity index (SLEDAI) as a global index and reflecting all aspects of activity, its weightened scale for 24 parameters and score ranges from zero to 105 **(Galdman et al 2002).**

In this study evaluation of serum neopterin and comparison between active and inactive patients had done on 75 patients with (SLE). 30 of them are active and another 30 with no activity 15 subjects healthy as a control group we found that serum Neopterin was higher in active group than inactive group. And also significant difference between the patients with systemic lupus erythematosus group than controls group our results shows that the mean value of serum

Neopterin in whole SLE patients (21.9 ng/ml) range between (1.7-82.5).

The mean values of serum neopterin for the active and inactive groups was 33.9 ng/ml and 3.45 ng/ml respectively where they were highly significant than the mean value of the control group (1.95 ng/ml) (P<0.001). Also the differences between the three groups are highly significant (P<0.001). From above, we conclude that for our marker serum neopterin, there was highly significant increase of its values for the patients with active SLE as compared with the healthy control group with P-value of 0.001**. In a same manner, S. Neopterin for inactive SLE group compared with healthy control group shows highly significant correlation with p. value of 0.001**And this agree with study of **(Mahmoud et al., 2005)** that said that serum neopterin and STNFRII were the only measured parameters that show significant evaluation in mild neuro psychic lupus erythematosus in comparison to those without neuro psychic lupus erythematosus also significant increase in patients with lupus nephritis.

Also our study agree with **(Wais et al.,2003)** study that show significant difference between SLE patients and healthy controls., also between active and inactive patients with SLE patients and also concluded that patients with clinical remission show on going systemic immune-inflammatory activity measured with TNF, STNFII and serum neopterin.

Serum neopterin level showed higher sensitivity than other SLE markers (80%) and second highest specificity after anti-dsDNA antibodies (73%). These findings confirmed that there is a continuous low grade activation of the cellular immune system in patients with SLE even if the disease is inactive and without being associated with clinical symptoms. Which is agree with study of **(Jin et al., 2005)** that

show the level of serum neopterin in active SLE patient significantly higher than in controls.

The present study demonstrated that serum neopterin level was significantly lower in active SLE patients receiving combined therapy of prednisolone and cytotoxic drugs compared to those receiving either prednisolone alone or cytotoxic drugs alone. Comparison of active SLE patients receiving prednisolone alone to those receiving cytotoxic drugs alone did not show any statistical significance. Thus, serum neopterin level can therefore be considered as a reflection of the treatment efficacy in suppressing disease activity. Drugs, like steroids, affect the proportion of lymphocyte subpopulations and the expression of cell surface molecules and thus could potentially influence neopterin production **(NEl Ghandour et al., 2007).**

Determination of serum anti-ds DNA titter and complement levels (C3, C4) are the most common and useful tests for assessing the 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. p.value ≤0.001 is highly significant. p.value ≤0.05 is significant. The table shows that there is a negative significant correlation was found between antibodies to DNA and C3, C4 in patients with active SLE. In patients with inactive SLE there is negative insignificant correlation between C3 and anti-ds DNA, however the correlation between C4 and Anti ds DNA was negative and significant.

Anti-dsDNA and antiSm antibodies are highly specific for idiopathic SLE. Combination of anti-dsDNA, serum complement 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. **(Mok CC. et al., 2010).**

However both these tests have limitation in that elevated anti-dsDNA antibodies and hypocomplementemia do not occur in all patients and their correlation with disease activity is not absolute. Patients can have persistently elevated anti-dsDNA antibodies titer without evidence of clinical disease for several months. Serum neopterin shows negative correlation with C3where this correlation is highly significant (P<0.001).

Serum neopterin shows positive correlation with ESR and where there is a highly statistically significance (P<0.001).

Serum neopterin shows negative correlation with HB however there is no statistically significance (P<0.1).

Serum neopterin shows positive correlation with proteinuria where there is statistically significance (P<0.01).

Serum neopterin shows negative correlation with the other laboratory parameters (C4, HB, WBC and platelets count) without any statistical significance.

Predictive value of various serological tests in SLE depends on many factors such as criteria used for define and measure disease activity, effect of drug therapy, immunological methods used to measure serologic parameters and the type of study, whether cross sectional or long term prospective study. Hence comparison of the results of various studies is difficult **(Col et al., 2010).**

The present study show that there is a significant difference between active and in active SLE patients as regard presence of anti-ds DNA agree with **(Abd Elsamad et al., 2000).**

However some authors observed that raised anti-dsDNA titer of no significant and may be found raised in quiescent diseases and may decrease in association of flares in systemic lupus erythematosus patients. **(Ho Aet al., 2001)**

In the present study it was found that is a significant difference between the active group and in active group with SLE as regard complement (C3) level (p<0.05). Agree with study **(schurbert et al., 1999),** who found highly significant difference 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.

However other 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. **(Rahman A, Hiepe F., 2002)**

The present study showed that significant difference in complement (C4) in patients with SLE comparing active and in active groups. Level of C4 concentration was lower in the active groups than of in active groups of SLE. Agree with study of **(Abd Elsammad et al., 2000).**

So several studies showed that the level of (C3, C4) low in active SLE patients comparing with that of inactive patients. **(Ramos et al., 2004)**

While some study said that the level of complement (C3, C4) shows no significant difference between active and inactive SLE patients. And does not reflect the activity of the disease. **(Elwy et al., 2010)**

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, also due to poor general condition, cachexia and anorexia, in addition to bone marrow suppression by aggressive cytotoxic therapy **(Rahman A, Hiepe F., 2002).**

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 platelet clearance mediated by anti-platelet auto-antibodies **(Kyttaris VC et al., 2005).** ESR was significantly higher comparing active SLE patients to patients in remission and healthy controls, and was significantly higher comparing patients in remission to controls. Plasma levels of C3 and C4 were significantly decreased comparing SLE patients to healthy normal subjects, also, significant decrease in their levels were found comparing active SLE patients with patients in remission. 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 (**Wais T et al., 2003**).

As regard level of ESR. Our study revealed a significant difference between active and inactive SLE patients. The level of ESR was higher in active group than in inactive group. This agree with study of (**Stojan G et al., 2013**).

While some authors found no relation between ESR level and disease activity in SLE. (*Zanana* **N et al., 1995**)

The most recent speak about ESR level is associated with the disease activity in SLE.

In our study we found that presence of proteinuria show significant difference in disease activity an SLE patients. This study agree with study of (**Michelle petri et al., 2007**) who found that patient with activity of disease show high concentration of proteinuria especially those who have renal involvement.

However some authors found that no significant difference in proteinuria and disease activity in patients with systemic lupus erythematosus.

Serum neopterin show a positive correlation with ESR, anti-ds DNA antibodies and proteinuria level in systemic lupus erythematosus patients and a negative correlation with complement level (C3, C4) in patients with systemic lupus erythematosus agree with study of (**N-Elghandour et al., 2007**).

The physiological role and disordered production of cytokines needs still further investigations in order to get a better understanding of the nature of dysfunction immune system in SLE patients.

We suggested that serum neopterin level may be a helpful marker for predicting disease activity and prognosis in patients with SLE. Its level may predict the risk of organ damage at an early stage. This should be confirmed by a prospective long term study in a larger group of patient.

In patient with SLE, serum neopterin may be used to evaluate the SLE disease activity and efficacy of treatment, so we recommended its use in follow up of such patients.

In conclusion the present results showed that increased serum neopterin level were found in patients with SLE disease and were correlated with certain clinical and laboratory immunoinflammatory parameters. So the estimation of serum neopterin levels seems beneficial in the assessment of disease activity and progress in SLE patients as well as the assessment of the efficacy of various treatment regimens used.

Recommendation

We recommend that serum neopterin levels can be used in patient with systemic lupus erythematosus in order to predict the risk of disease activity at an early stage.

In patients with SLE, neopterin may be used to evaluate the treatment efficiency, so we recommend its use in follow up of such patients.

Future studies should include the group of patients with SLE. which could study the predictive values of neopterin in such patients.

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