International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
DOI: 10.22192/ijarbs Coden: IJARQG(USA) Volume 5, Issue 1 - 2018

**Research Article**


**DOI:** http://dx.doi.org/10.22192/ijarbs.2018.05.01.009

# Correlation of Serum Neopterin level with Complement C3, C4 in assessment of Systemic Lupus Erythematosus Activity

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## Abstract

**Background:** Systemic Lupus Erythematosus has a continued disease activity throughout the natural course of the disease, assessment of that is often complex and time consuming, to date no measures have been created specifically for SLE, for that studying serum neopterin and comparing with other established parameters C3, C4 may add benefit for SLE follow up. **Aim:** 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. **Patients and method:** 75 subjects 60 patients with (SLE) 30 of them are active and another 30 with no activity and 15 subjects healthy as a control group. **Results:** 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 **conclusion:** our marker serum neopterin can be used to segregate patients with active SLE. Also may help in assessment of SLE activity and progression in SLE patients as well as the assessment of the efficacy of various treatment regimens.

**Keywords:** Systemic lupus erythematosus activity, Serum Neopterin, Lupus nephritis, Correlation

## Introduction

Systemic lupus erythematosus (SLE) is a multisystem 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. (**1**) Human monocyte- derived macrophages upon stimulation with the cytokine interferon gamma (INF-γ) released from activated T- lymphocytes produce a substances called Neopterin (6-D-erytro-trihydroxypropylpterin) formed from intra cellular guanosine triphosphate. Also other interferons, interleukin-1α (IL-1α), tumor necrosis factor- α (TNF-α) and lipopolysaccharides affect Neopterin production. **(2)**

The concentration of neopterin have been increased in vivo 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. **(3)**

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.**(4)**

The significantly increased of serum neopterin level in SLE while the complement C3,C4 levels was significantly lower than those of healthy controls make neopterin is one of the parameters that showed significantly higher levels in SLE with mild activity. **(5)**

## 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, and Tanta and 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).

Diagnosis of SLE was based on the American Rheumatism Association (ARA) criteria for classification of SLE ***(6)***.

The activity of the disease was measured by Systemic Lupus Disease Activity Index (SLEDAI).

**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.

**Methods:**

The Study will take about six months, through which, subjects were subjected to the followings:

**(a) Full history taking including:** (Photosensitivity, Falling of hair, Oral ulceration, Morning stiffness, its duration and location, 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, erythematosus rash, Cardiovascular examination for pericarditis, Raynaud phenomenon, Chest examination to detect pleurisy, pleural effusion, Neurological examination for stroke, seizures, headache, cortical dysfunction).

**(c)Routine laboratory investigations:** (Complete blood count, C-Reactive protein, Liver & kidney function tests, 24-hour urine protein, Urine analysis, Erythrocyte sedimentation rate (ESR), Serum cholesterol and triglycrides, Anti-nuclear antibodies, Complement 3 (C3) and complement 4 (C4) level, Anti-double strand DNA antibodies (Anti ds AB).

**(d)Specific laboratory investigation:** Serum neopterin by ELISA.

***Notes:***

➢ Written informed consent will be obtained from all subjects. The study will be approved by the Ethics Committee of Faculty of Medicine Al Azhar University.

**Measurement of serum neopterin:**

Serum neopterin was measured using a solid phase enzyme- linked immunosorbent assay (ELIZA) kit supplied by Cellular Comminication Investigations Immunotech, France (7).

**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.

**1- Mean value** $\left(\bar{X}\right)$ **:** the sum of all observations divided by the number of observation:

$$\left(\bar{X}\right) = \frac{\Sigma x}{n}$$

Where $\Sigma$ = sum & n = number of observations.

**2-Standard Deviation [SD]:**

It measures the degree of scatter of individual varieties around their mean:

$$SD = \sqrt{\frac{\Sigma \left|x - x\right|^{-2}}{n-1}}$$

**3. Analysis of variance [ANOVA] tests:** According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data.

**4-Chi-square**: the hypothesis that the row and column variables are independent, without indicating strength or direction of the relationship. Pearson chi-square and likelihood-ratio chi-square. Fisher's exact test and Yates' corrected chi-square are computed for 2x2 tables.

**Chi-square test:**

For comparison between two groups as regards qualitative data.

$$\mathbf{x^2} = \sum \frac{(O-E)^2}{E}$$

Where:

$\Sigma$ = Summation.
O = Observed value.

E = Expected value=

$$\frac{\text{vertical total X Horizontal total}}{\text{grand total}}$$

**5. Linear Correlation Coefficient [r]:**

$$r = \frac{\Sigma \left(X - \bar{X}\right)\left(y - \bar{y}\right)}{\sqrt{\left\{\Sigma \left(X - \bar{x}\right)2 \right\}\left\{\Sigma \left(y - \bar{y}\right)2\right\}}}$$

Where:

X= Independent variable.
Y= Dependent variable

## Results

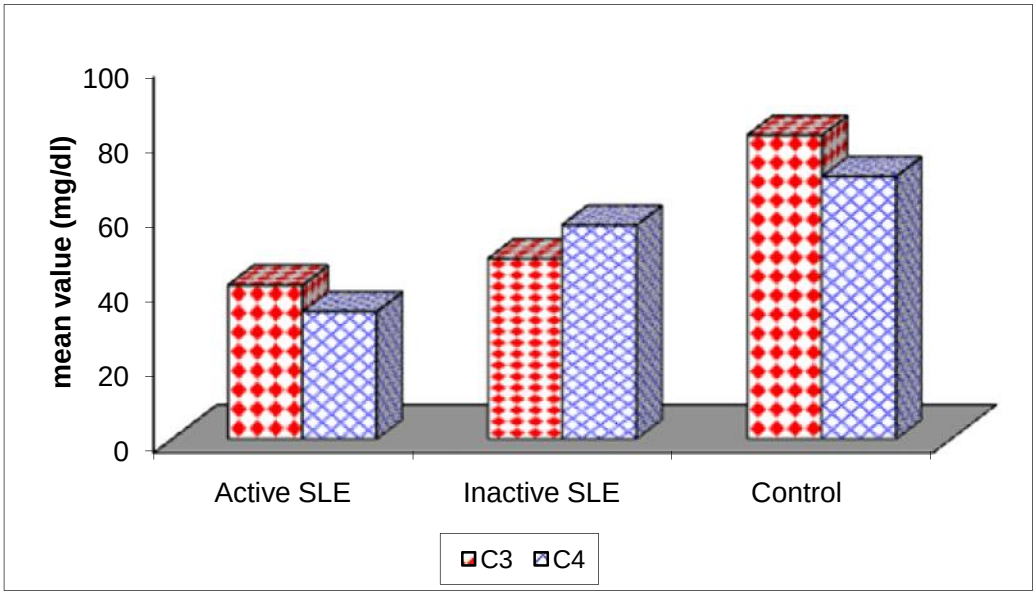
Our study was carried out on 75 female subjects. Of them, 15 were employed as the healthy control group and 60 subjects as the patients groups. 30 of them are with active systemic lupus erythematosus (SLE) and 30 are with inactive systemic lupus erythematosus. The patients with active SLE their ages 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) (Table 1)

**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%) | | | | | |

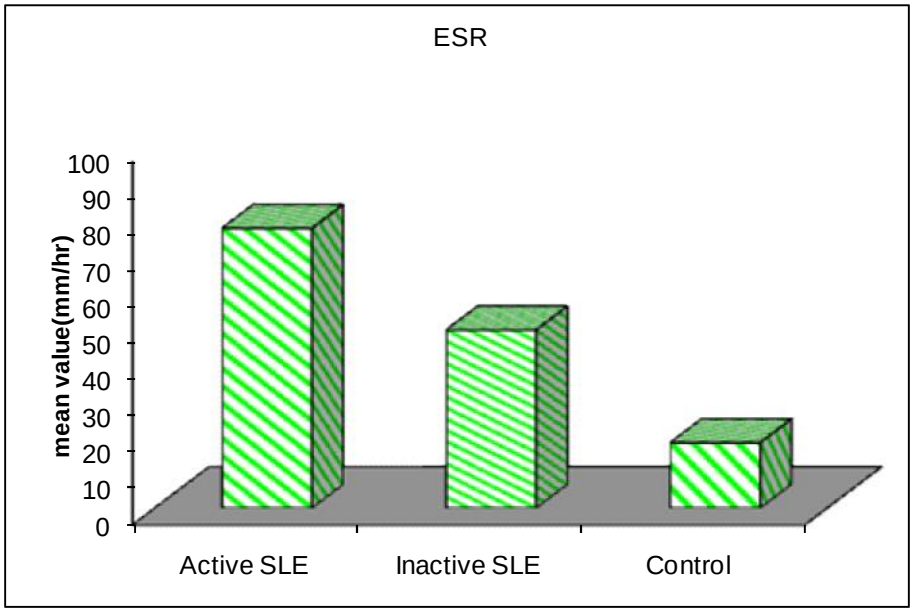
****p. value ≤0.001 is highly significant. *p.value ≤0.05 is significant.**

**Figure (1):** The mean value of C3 and C4 in the three groups.




The mean serum C3, C4 level was significant lower for the whole SLE patients than for the control group (P<0.002).

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




(ESR) was highly significant for whole SLE patients than for the control group (P<0.001).

**Figure (3):** The percentage of the presence the Anti-ds DNA antibodies in the three groups

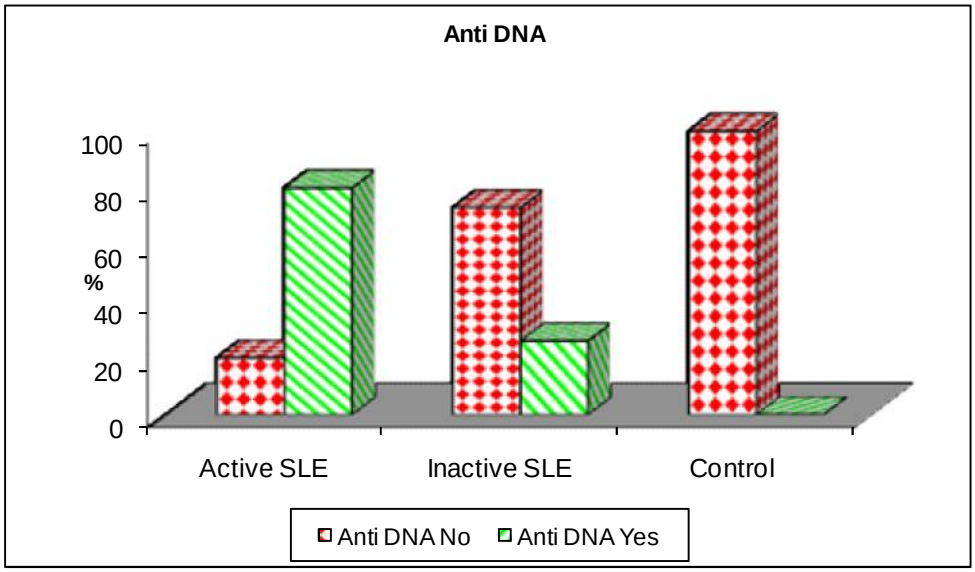



**Table (2):** Correlation coefficients between C3, C4 and Anti ds DNA among SLE patients.

| | 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.**

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.

**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.**

The table shows that there is a negative significant correlation between Anti ds DNA and C3 and C4 in all SLE patients.

**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.**

**Figure (4):** The mean values of 24 hour urine protein level in the three groups

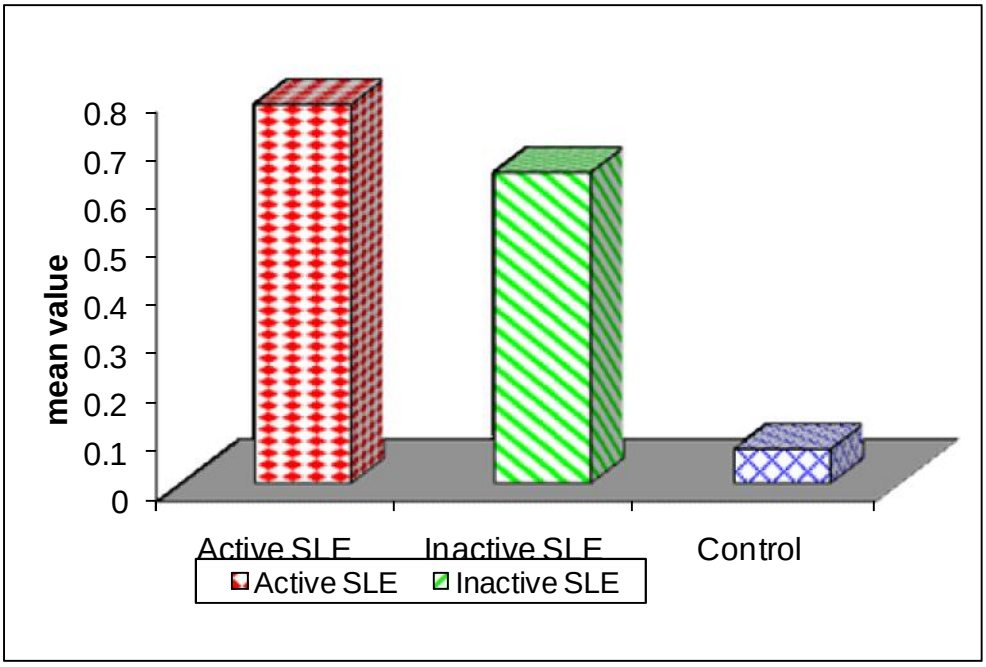
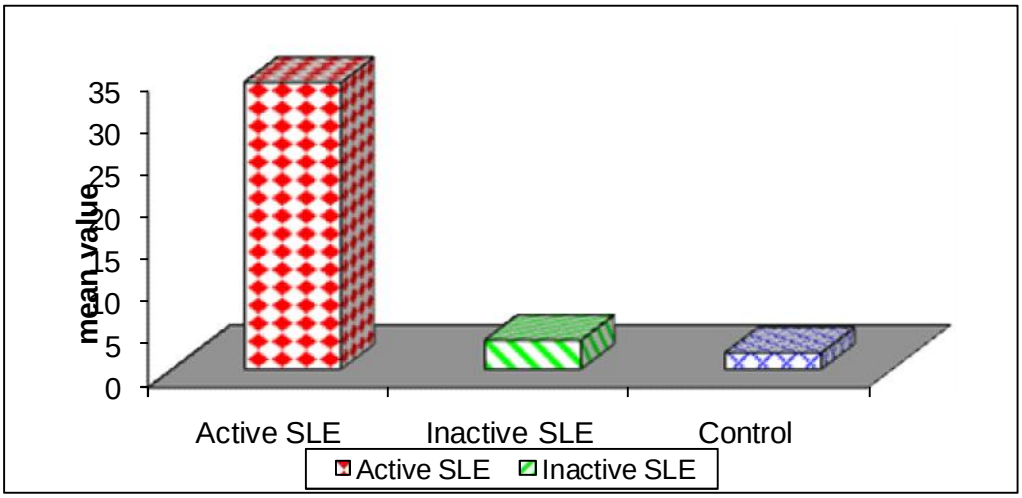


**Table (5):** Means and standard deviations of serum neopterin level among SLE patients and control group.

| 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.

**Figure (5):** The mean values of serum Neopterin level in the three groups




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**

.**Table (8):** 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

## 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**(7).**

In this study evaluation of serum neopterin and comparison between active and inactive patients had done on75 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 serum 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 **(8),(9)** 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, clinical remission show on going systemic immune-inflammatory activity measured with TNF,STNFRII and serum neopterin.

One of the main findings of the current study was increased levels of serum neopterin in SLE patients (active and inactive) compared to normal subjects, and in patients with active disease compared to inactive ones. 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 was agree with study of **(10)** that show the level of serum neopterin in active SLE patient significantly higher than in controls.

Serum neopterin level in our study 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**(11).**

The most common and useful tests for assessing the disease activity and predicting flares in SLE is the determination of serum anti-ds DNA titter and complement levels (C3, C4). The current work demonstrated a significant increase in anti-dsDNA antibodies levels in active SLE patients in comparison to patients in remission. p.value $\leq 0.001$ is highly significant. p.value $\leq 0.05$ is negatively 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.

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**(12).**
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. Some patients has a persistently elevated anti-dsDNA antibodies titer without evidence of clinical disease for several months.

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 **(13).**

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 **(14).**However some authors observed that raised anti-dsDNA titer of no significant and may be found raised in quiescent diseases **(15)**

In the present study there is a significant difference between the active group and inactive group with SLE as regard complement (C3) level ($p<0.05$). And this agree with study **(16),** 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. In contrast to (17) 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.

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 **(14).**

Although the many years of study of the disease, 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. Particular attention has recently been focused on neopterin as an important indicator for assessing SLE activity (18), (19). 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 **(17).**

Leucopenia in SLE patients may be explained by bone marrow failure, disease activity, peripheral destruction and sepsis or occurs as a part of drug toxicity-induced medullary hypoplasia. The increased platelet clearance mediated by anti-platelet auto-antibodies is the most common mechanism of thrombocytopenia in SLE patients**(20).**

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 and this agree with (21) but (22)found that no relation between ESR level and disease activity in SLE. 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 their consumption in immune complex formation and reduction of their synthesis. These results indicated that complement dysfunction may be an important factor in the pathophysiology of SLE (9).

In our study we found that presence of proteinuria show significant difference in disease activity an SLE patients. This study agree with study of (23) 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 an egative correlation with complement level (C3, C4) in patients with systemic lupus erythematosus agree with study of (11), 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 ahelpful 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 aprospective long term study in a larger group of patient. Also 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.

## Conclusion

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

## Acknowledgments

The authors thank members of our laboratory in Al- Hussein University Hospital and also for members of Tanta dialysis unit for aid in preparation of this manuscript.

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| DOI:10.22192/ijarbs.2018.05.01.009 | |

How to cite this article:
Farag Khalil, Mohammad A. Khedr. (2018). Correlation of Serum Neopterin level with Complement C3, C4 in assessment of Systemic Lupus Erythematosus Activity. Int. J. Adv. Res. Biol. Sci. 5(1): 46-56.
DOI: http://dx.doi.org/10.22192/ijarbs.2018.05.01.009