Anti-C1q antibodies in lupus nephritis: Detection and Relationship with Disease activity

Manar Raafat[1], Malak Nabil[1], Sameh AbouZeid[1] and Azza S. Hassanein[2,3]

Nephrology[1] and Hematology[2] Departments, Theodor Bilharz Research Institute, Cairo, Egypt
AL-Ghad International College for Applied Medical Sciences for Girls, Jeddah, Saudi Arabia[3]
sameh.kidney@gmail.com

Abstract: Background: Systemic Lupus Erythromatosis (SLE) is a multisystem autoimmune disorder with a broad spectrum of clinical presentations. Glomerulonephritis is one of the commonest and most serious manifestations of SLE. Several autoantibodies, especially those against double stranded DNA (anti-dsDNA), are believed to play a major role in the induction of glomerular inflammation. C1q is a multifunctional protein that binds to immune complexes deposited on tissues, including the kidney and aids in their solubilization and removal. C1q also plays a role in apoptotic cell debris removal. The binding of anti-C1q antibodies and other proteins to C1q is potentially of concern as it may impede the ability of C1q to carry out its normal anti-inflammatory functions such as immune complex clearance and removal of apoptotic debris. **The aim of the present study**: to evaluate the presence of anti-C1q antibodies in patients with SLE, with and without renal involvement, and to correlate their presence and levels with disease activity and occurrence of nephropathy. **Method:** Forty SLE patients were recruited in the study, they were divided in two groups according to their clinical status and laboratory investigations, group 1 was comprised 15 SLE patients without evidence of nephritis while Group 2 comprised 25 SLE patients who were diagnosed to have lupus nephritis. Sera were tested for anti C1q by ELISA technique. **Result:** A statistical significant difference between group 1 and 2 as regard anti- C1q (p = 0.002) was noticed. In those with lupus nephritis, anti-C1q was found to correlate significantly with other parameters assessing lupus activity such as ESR (p =0.017), creatinine clearance, (p =0.029), proteinuria (p =0.003), and Anti-dsDNA (p =0.014). **Conclusion:** Anti-Clq autoantibodies correlate with renal disease activity and with renal flare-ups like other standard parameters, such as proteinuria, complement levels anti-dsDNA . Anti-C1q antibodies can be considered as a reliable sensitive and specific biomarker to diagnose nephritis flare in patients with SLE.

[Manar Raafat, Malak Nabil, Sameh AbouZeid and Azza S. Hassanein, Anti-C1q antibodies in lupus nephritis: Detection and Relationship with Disease activity**.** *Life Sci J* 2014;11(12):940-946]. (ISSN:1097-8135). http://www.lifesciencesite.com. 163

Keywords: C1q , SLE, Anti-dsDNA

1. Introduction:

Systemic Lupus Erythromatosis (SLE) is a multisystem autoimmune disorder with a broad spectrum of clinical presentations. Due to the heterogeneity of the disease and the absence of a single diagnostic test, the diagnosis of SLE remains challenging.[1]

Glomerulonephritis is one of the commonest and most serious manifestations of SLE. Renal involvement in SLE carries significant morbidity and mortality.[2] Early diagnosis and rapid treatment of lupus nephritis are crucial to improve survival in SLE patients.[3]

Several autoantibodies, especially those against double stranded DNA (anti-dsDNA),are believed to play a major role in the induction of glomerular inflammation.[4,5] Raised titers of anti-dsDNA and hypocomlementemia are reported to be associated with the activity of the disease.[6,7] However, the lack of specificity of these biological markers for renal exacerbations has led to the search for other autoantibodies that might contribute to nephritis and help diagnose a renal flare.

,It has been suggested that antinucleosome antibodies are a more sensitive marker of SLE than anti-dsDNA [8,9], particularly the IgG3 isotype which might constitute a selective biological marker of active SLE and lupus nephritis.[10] The complement system plays an important role in the onset as well as throughout the course of SLE.

The complement system plays an important role in the onset as well as throughout the course of SLE.[11]

The first component of complement C1 is comprised of three subcomponents C1q, C1s and C1r. The C1 complex plays a pivotal role in the activation of the classical pathway of complement. Classical complement activation has both inflammatory and anti-inflammatory functions.[12]

C1q is a multifunctional protein[13], and binds to immune complexes deposited on tissues, including the kidney[14], and aids in their solublization and removal.[15] C1q also plays a role in apoptotic cell debris removal.[16]

Forty years ago, the possibility of antibodies against C1q in SLE patients was raised. [17]The

binding of anti-C1q antibodies and other proteins to C1q is potentially of concern as it may impede the ability of C1q to carry out its normal anti-inflammatory functions such as immune complex clearance and removal of apoptotic debris.[18,19]

Note only is C1q important for complement activation, but it can also help to clear away potentially dangerous nuclear autoantigens from apoptotic cells. Thus, the absence of C1q leads to the development of anti-DNA antibodies and to clinical SLE.[20] In the context of multiple roles for C1q, researchers have hypothesized that anti-C1q autoantibodies affect patients with SLE not only by injuring the kidneys, but also by enhancing the development of anti-DNA and other glomerular – targeting nuclear autoantibodies, because there is too little C1q available for effective clearance of these dangerous antigens.[20] Indeed, researches have demonstrated an inverse correlation between anti-C1q autoantibodies titers and plasma C1q levels. [21] Thus, these autoantibodies play a dual role : not only can they amplify local injury, but they can also accelerate the development of antinuclear autoantibodies by interfering with C1q clearance functions.[20,22]

Aim of the work

The aim of the present study to evaluate the presence of anti-C1q antibodies in patients with SLE, with and without renal involvement, and to correlate these markers' presence and levels with activity of the disease and nephropathy.

2. Subjects and Methods:

Forty SLE patients were recruited in the study from those attending nephrology department of Theodor Bilharz Research Institute (outpatient clinic and inpatient ward).They were 34 females and 6 males.

Patients were divided into two groups according to clinical presentations and laboratory investigations:

1- group I: comprised of 15 SLE patients (13 females and 2 males) without evidence of nephritis.

2- Group II: comprised of 25 SLE patients (21 females and 4 males) who were diagnosed to have lupus nephritis according to American College of Rheumatology (ACR) criteria : proteinuria > 500mg/day and/or red cell casts. The diagnosis of renal involvement was confirmed by renal biopsy.

The biopsies were classified according to the international Society of Nephrology/ Renal Pathology Society, Class III and IV are considered more active while classes I,II and IV are considered less active.

Exclusions criteria: SLE patients with proteinuria other than lupus nephritis as pregnancy and fever or patients with renal impairment due to any other cause than lupus nephritis as diabetic nephropathy. Also patients with HCV, HBV and other connective tissue diseases other than SLE.

Ethical consideration: a written consent was taken from all the participants after explaining details, benefits as well as risks to them.

All patients were subjected to the following:

1- Complete history and physical examination.

2- Routine laboratory investigations complete blood count, erythrocyte sedimentation rate, serum urea, serum creatinine, C-reactive protein, creatinine clearance, urine analysis and 24 hour protein excretion.

3- Immunological profiles including antinuclear antibody (ANA) by indirect immune-fluorescence principle, Anti-ds DNA by solid phase immunoassays and complement level (C3 and C4) by using BN ProSpee nephelometery.

4- Serum level of anti – C1q antibodies by indirect solid phase enzyme immunoassay (ELISA) for the quantitative measurement of IgG class autoantibodies against anti- C1q in immune serum or plasma.

Statistical analysis

Results were expressed as means ± standard deviation of the means (SD) or number (%). Comparison between different parameters in the two studied groups was performed using unpaired t test. Comparison between parameters in different pathological classes was performed using ANOVA. Comparison between categorical data was performed using Chi square test. Correlation between different parameters in the cases group was performed using Pearson correlation. The data were considered significant if p value was equal to or less than 0.05 and highly significant if p value < 0.01. Statistical analysis was performed with the aid of the SPSS computer program (version 12 windows).

3. Results:

Forty systemic lupus erythromatosis patients from nephrology department of TBRI were included in the present study (34 females and 6 males). They were classified into two groups, 15 without nephritis and 25 with evidence of lupus nephritis (8 patients have class III, 11 patients have class IV and 6 patients have class V nephritis). All patients were analysed for the presence of anti-C1q Abs.

The demographic, clinical and laboratory data are summarized in tables 1,2 and 3.

Table (1): Comparison between the two studied groups according to demographic data:

	Group 1(n=15)	Group 2(n=25)	*P* value
Age	29.4 ± 7.02	27.68 ± 7.03	0.458 (NS)
Gender (F/M)	13/2 (86.7%/13.3%)	21/4 (84%/16%)	0.819 (NS)
Duration of disease (yrs.)	1.55 ± 1.13	2.20 ± 1.59	0.168 (NS)

Data are expressed as mean ± SD or number % NS= *P* >0.05= not significant (NS)

Table (2): Comparison between the two studied groups according to clinical manifestations:

	Group 1(n=15)	Group 2(n=25)	*P* value
Dermatological manifestations			
Malar rash	15 (100%)	12 (48%)	0.003**
Discoid rash	0 (0%)	1 (4%)	0.433 (NS)
Photosenstivity	11 (73.3%)	19 (76%)	0.850 (NS)
Hair fall	14 (93.3%)	15 (60%)	0.022*
Oral ulcer	8 (53.3%)	15 (60%)	0.680 (NS)
Articular manifestations			
Artheralgia	13 (86.7%)	16 (64%)	0.120 (NS)
Fever/malaise	8 (53.3%)	7 (28%)	0.109 (NS)
Seizure	2 (13.3%)	2 (8%)	0.586 (NS)
Psychosis	0 (0%)	0 (0%)	---
Serositis (pleural effusion)	0 (0%)	7 (17.5%)	0.163 (NS)

Data are expressed as number (%) NS= *P* >0.05= not significant. *p<0.05= significant **p< 0.01= highly significant.

Table (3): Comparison between the two studied groups according to laboratory manifestations:

	Group 1(n=15)	Group 2(n=25)	*P* value
Complete blood picture:			
Hb	10.61 ± 1.02	10.31 ± 1.62	0.516 (NS)
RBCs	3.87 ± 0.53	4.06 ± 0.39	0.203 (NS)
WBCs	7.09 ± 3.93	6.21 ± 2.09	0.361 (NS)
Platelet count	243.87 ± 45.81	206.96 ± 70.44	0.079 (NS)
S. creatinine	0.58 ± 0.12	1.76 ± 1.63	0.001**
BUN	11.77 ± 2.94	39.88 ± 38.80	0.001**
Urea	27.33 ± 7.11	67.32 ± 68.99	0.008**
Protein 24 hrs.	121.33 ± 23.29	2587.00 ± 2439.50	0.001**
Cr. clearance	107.07 ± 7.46	67.80 ± 28.66	0.001**
CRP	6.63 ± 5.31	6.92 ± 6.06	0.876 (NS)
ESR	67.27 ± 39.00	88.08 ± 27.80	0.056 (NS)
C3	1.13 ± 0.17	0.63 ± 0.49	0.001**
C4	0.74 ± 0.61	0.26 ± 0.42	0.012*
Anti-dsDNA	59.19 ± 23.96	169.71 ± 162.47	0.003**

Data are expressed as mean ± SD NS=p>0.05= not significant. *p< 0.05= significant.
**p< 0.01= highly significant.
There was a statistical significant difference between group 1 and 2 as regard creatinine, BUN, urea, cr. Clearance, protein in urine/24 hours, C3, C4 and anti-dsDNA.

Table (4): Comparison between the mean values of anti-C1q in the two studied groups:

Group 1(n=15)	Group 2(n=25)	*P* value
9.64 ± 16.73	59.09 ± 56.37	0.002**

Data are expressed as mean ± SD NS=p>0.05= not significant. *p< 0.05= significant.
**p< 0.01= highly significant.
There was a statistical significant difference between group 1 and 2 as regard anti- C1q abs.

Table (5) : Correlation between anti-C1q and different studied parameters in group 2:

	Pearson Correlation	Sig. (2-tailed)
Urea	0.099	0.637 (NS)
BUN	0.129	0.540 (NS)
S_creat	0.221	0.288 (NS)
ESR	0.471	0.017*
Cr.Clear	-0.438	0.029*
24hr.pro	0.57	0.003**
C3	0.047	0.825 (NS)
C4	-0.328	0.110 (NS)
AntidsDNA	0.484	0.014*

NS= *p*> 0.05= not significant. *p< 0.05= correlation is significant at the 0.05 level (2-tailed).
**p< 0.01= correlation is significant at the 0.01 level (2-tailed).

Table (6) : Comparison between mean values of anti-C1q, Cr clearance and 24 hrs. protein measured before and after treatment in group 2.

	Before (n= 25)	After (n= 25)	*P* value
Serum anti-C1q (U/ml)	59.09 ± 56.37	45.14 ± 53.86	0.026*
Cr. Clearance (m/min.)	68.05 ± 24.28	67.80 ± 28.66	0.947 (NS)
Protein 24 hrs (mg/day)	2587.24 ± 2439.54	1735.96 ± 1595.03	0.015*

Data are expressed as mean ± SD. NS= *p*> 0.05= not significant. *p< 0.05= significant.

Table (7) : Correlation between anti-C1q and 24 hours protein and creatinine clearance measured after treatment in group 2.

	anti-C1q	
	Pearson Correlation	Sig. (2-tailed)
24 hours protein	0.534	0.006**
Creatinine clearance	-0.435	0.030*

*p< 0.05= correlation is significant at the 0.05 level (2-tailed).
**p< 0.01= correlation is significant at the 0.01 level (2-tailed).

Table (8) : Comparison between mean values of anti-C1q, anti-C1q follow up in different pathological classes.

	Class III (n= 8)	Class IV (n= 11)	Class V (n= 6)
Anti-C1q before #	26.20 ± 48.24	97.16 ± 48.23 (p= 0.003) [a]	33.15 ± 40.18 (p= 0.013) [b]
Anti-C1q follow up	23.45 ± 45.74	75.54 ± 58.12 (p= 0.030) [a]	18.33 ± 24.31 (p= 0.029) [b]

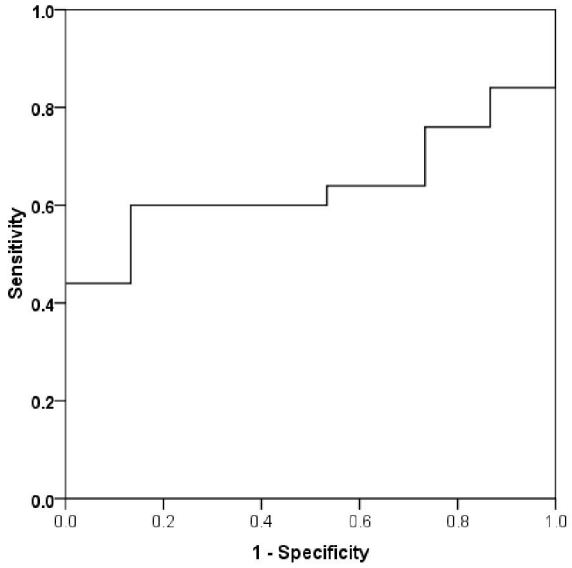
Data are expressed as mean ± SD. [a] significant relative to class III. [b] significant relative to class IV.

Table (9) : Validity of anti-dsDNA and anti-C1q antibodies in prediction of lupus nephritis in group 2 patients.

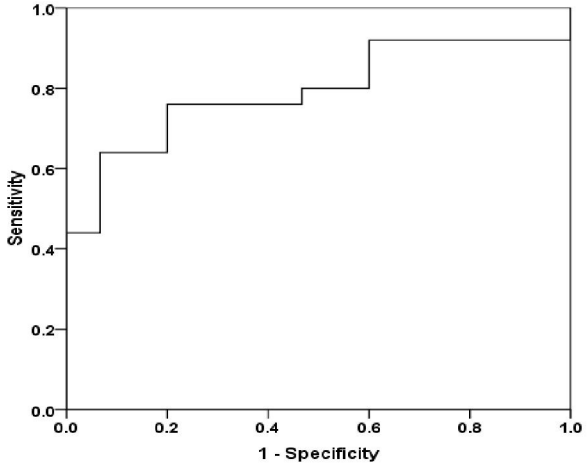
Variables	**Anti-dsDNA**	Anti-C1q
Area under the Roc curve	**0.640**	**0.792**
Cutoff	**> 629**	**> 12.9**
Sensitivity	**60.00**	**64.00 %**
Specificity	**86.67**	**93.33 %**
PPV	**88.2**	**94.1**
NPV	**56.5**	**60.9**

PPV: Positive predictive value. NPV: Negative predictive value

ROC curve for Anti-dsDNA in lupus nephritis (group 2 patients)



ROC curve for anti-C1q in lupus nephritis (group 2 patients)



4. Discussion:

Systemic lupus erythematosus is a systemic autoimmune disease characterized immunologically by a variety of autoantibodies, B-cell hyperactivity, and immune complex (IC) formation.[23] Complement, especially C1q, the first component of the classical pathway of complement, is considered to be involved in the pathogenesis of SLE. This is based on the following: First, almost all patients with C1q deficiency develop a lupus-like syndrome, with homozygous C1q deficiency being the strongest disease susceptibility gene for the development of SLE.[24]Second, a substantial number of patients with SLE develop hypocomplementemia with depletion of C1q and other components of the classical pathway of complement [25]; and C1q is deposited in affected tissues.[26]

C1q is a complex molecule consisting of a collagenous portion with globular heads, morphologically resembling a bundle of tulips. C1q is the first componentof the classical pathway of complement activation, and its main function is to clear immune complexes (ICs) from tissues and self antigens generated during apoptosis (27). The hereditary deficiency of this component is a known risk factor for the development of SLE.[27]

The current study was designed to evaluate the diagnostic and prognostic performance of anti-C1q antibodies in a cohort SLE patients with and without

LN, and to correlate findings with other disease variables, and standard laboratory investigations used to assess renal function, SLE nephritis and activity indices.

In our study of a cohort of 40 consecutive patients with SLE, we observed that anti-C1q antibodies are associated with SLE global activity and specifically with nephritis. We also showed that anti-C1q antibody titers significantly decreased as the patients' condition improved with clinical treatment.

In our study, anti-C1q antibodies were found to be significantly higher in patients with active lupus nephritis with a median range of [59.09 ± 56.37] than those without nephritis with a median (range) of [9.64 ± 16.73] P < o.o1 with 64.00 %sensitivity and 93.33 % specificity with the cut off level >12.9, PPV 94.1 and NPV 60.9.

In those with active lupus nephritis anti-C1q antibodies were found to be significantly correlating with other parameters assessing lupus nephritis activity compared to patients without lupus nephritis like ESR (P =0.017*), creatinine clearance (P = 0.029*), proteinuria (P = 0.003**) and Anti-dsDNA (P = 0.014*) but not significant correlation was found with BUN, serum creatinine, C3and C4.

Our results support the study done by Moroni *et al.,* which showed 87% sensitivity and 92% specificity for anti- C1q in predicting SLE nephritis activity.[28] It also agrees with the study by Sinico *et al.,* which showed a strong association of anti-C1q with active SLE nephritis. Anti-C1q in the latter study had a better predictive value for active nephritis than other parameters such as C3/C4 consumption and anti-dsDNA.[29]

In study done by El-Hewala *et al.,* for detection of more active LN among biopsy proven LN patients, sensitivity and specificity for anti- ds DNA Ab was 85% and 64%, for anti-C1q Ab was 70% and 55% and 75% and 91% for both antibodies. Detection of both anti-C1q Ab and anti- ds DNA Ab could predict

94% of those more active LN and exclude 67% 0f those who had lower activity of LN proven by biopsy.[30]

On the other hand results by Katsumata *et al*, showed that anti-C1q antibodies are associated with SLE global activity but not specifically with active lupus nephritis. A potential weakness of Katsumata *et al*, study arises from the variation in treatment protocols among the patients, reflecting different clinical presentations. Follow up durations also varied among the patients, because reevaluation samples were collected at certain time points cross-sectionally. In addition, because almost all of the patients in the latter study were Japanese, it is not clear whether anti-C1q antibodies have a different effect on lupus nephritis in patients with different ethnic backgrounds.[31]

The titers of anti-C1q antibodies in SLE patients showing a variety of clinical manifestations significantly decreased as the disease condition improved with treatment, as previously reported .[11,32] These findings also support the view that anti-C1q antibodies are associated with SLE global activity. It is possible that anti-C1q antibodies could be useful as a surrogate marker of SLE disease activity in patients positive for this antibody.

There is a general agreement in different literatures that the more active classes of biopsy proven LN are classes III and IV while other classes namely classes I, II, V and V are considered less active that need limited immunosuppressive therapy.[33]

In the current study anti- C1q antibody level is significantly in more active (biopsy proven grade III and IV) than less active LN (biopsy proven grade V). This goes hand in hand with study done by Fang *et al.,* who found strong +ve association between anti-C1q Ab and the detection of proliferative LN.[32]

Conclusion

Anti-Clq autoantibodies correlate with renal disease activity and with renal flare-ups like other standard parameters, such as proteinuria , complement levels anti-dsDNA . Anti-C1q antibodies can be considered a reliable sensitive and specific biomarker to diagnose nephritis flare patients with SLE.

In view of relatively limited number of involved patients in the current study further evaluation of such findings in large cohorts of SLE patients with different severity is recommended to validate the clinical value of anti-C1q in diagnosis and prognosis of renal disease in SLE.

References:

1. Yu C ; Gershwin ME and Chang C: Diagnostic criteria for systemic lupus erythromatosus : A critical review. J Autoimmune.(2014); 48-49:10-13. (PubMed)
2. Mok CC: Biomarkers for lupus nephritis: a critical appraisal. J Biomed Biotechnol (2010); 2010:638413.
3. Houssiau FA ; Vasconcelos C ; D'Cruz D *et al.,*: Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis : lessons from long – term followup of patients in Euro-lupus Nephritis Trial. Artheitis Rheum (2004) ; 50: 3934-40.
4. Lefkowith JB and Gilkeson GS.: Nephritogenic autoantibodies in lupus: current concepts and continuing controversies. Arthritis Rheum (1996); 39:894–903.
5. Hahn BH. Antibodies to DNA. N Engl J Med (1998); 338:1359–68.
6. Isenberg DA, Ravirajan CT, Rahman A *et al.,*: The role of antibodies to DNA in systemic lupus erythematosus – a review and introduction to an international workshop on DNA antibodies held in London, May 1996. Lupus (1996); 6:290–304.
7. Swaak AJ, Aarden LA, Statius van Eps LW *et al.,*: Anti-dsDNA and complement profiles as prognostic guides in systemic lupus erythematosus. Arthritis Rheum (1979); 22:226–35.
8. Bruns A, Blass S, Hausdorf G *et al.,*: Nucleosomes are major T and B cell autoantigens in systemic lupus erythematosus. Arthritis Rheum (2000) ; 43:2307–15.
9. Amoura Z; Koutouzov S and Piette JC. The role of nucleosomes in lupus. Curr Opin Rheumatol (2000) ; 12:369–73.A
10. Amoura Z ; Koutouzov S; Chabre H *et al.,*: Presence of antinucleosome autoantibodies in a restricted set of connective tissue diseases: antinucleosome antibodies of the IgG3 subclass are markers of renal pathogenicity in systemic lupus erythematosus. Arthritis Rheum (2000); 43:76–84. B
11. Trendelenburg M; Lopez- Trascasa M; Potlukova E *et al.,* High prevalence of anti- C1q antibodies in biobsy-proven active lupus nephritis. Nephrol. Dial. Transplant. (2006); 21: 3115-21.
12. Eggleton P; Ukoumunne OC; Cottrell I *et al.,*: Autoantibodies against C1q as a diagnostic measure of lupus nephritis : systematic review and meta-analysis. J Clin. Cell Immunol. (2014) ; 5 (2) 33:36

13. Eggleton P ; Reid KB and Tenner AJ : C1q- how many functions ? How many receptors? Trends Cell Biol. (1998); 8: 428-431. (PubMed)
14. Lewis EJ; Busch GI and Schur PH: Gamma G globulin subgroup composition of the glomerular deposits in human renal diseases. J Clin. Invest. (1970) ; 49: 1103-1113. (PubMed)
15. Gasque P : Complement : a unique innate immune sensor for danger signals. Mol. Immunol. (2004) ; 41 : 1089-1098.
16. Botto M and Walport MJ : C1q, autoimmunity and apoptosis. Immunology. (2002) ; 205 : 395-406.
17. Agnello V ; koffler D ; Eisenberg JW *et al.,*: C1g preciptins in the sera of patients with systemic lupus erythematosus and other hypocomplementemic states : characterization of high and low molecular weight types. J Exp. Med. (1971) ; 134 : 228s-241s (PubMed)
18. Donnelly S ; Roake W; Brown S *et al.,*: Impaired recognition of apoptotic neutrophils by the C1q/calreticulin and CD91 pathway in systemic lupus erythromatosus. Arthritis Rheum. (2006) ; 54 : 1543-1556. (PubMed)
19. Kovacs H; Campbell ID; Strong P *et al.,*: Evidence that C1q binds specifically to CH2-like immunoglobulin gamma motifs present in the autoantigen calreticulin and interferes with complement activation. Biochemistry. (1998) ; 37 :17865-17874. (PubMed)
20. Holers VM : Anti-C1q autoantibodies amplify pathogenic complement activation in systemic lupus erythromatosus. (2004); J. Clin Invest. 114: 616-619.
21. Siegert CM; Daha ML; Westedet *et al.,*: IgG autoantibodies against C1q are correlated with nephritis, hypocomplementemia and dsDNA antibodies in systemic luous erythromatosus (1991) J. Rheumatol. 18: 230-234.
22. Sinico RA; Radice A;Ikehata M *et al.,*: Anti-C1q autoantibodies in lupus nephritis: Prevelence and Clinical significance. (2005); Ann. N. Y. Acad.Sci. 1050: 193-200.
23. . Lipsky PE.: Systemic lupus erythematosus: an autoimmune disease of B cell hyperactivity. Nat Immunol. (2001); 2:764-6.
24. Barilla-LaBarca ML and Atkinson JP: Rheumatic syndromes associated with complement deficiency.Curr Opin Rheumatol. (2003); 15:55-60.
25. Agnello V. Association of systemic lupus erythematosus and SLE-like syndromes with hereditary and acquired complement deficiency states. Arthritis Rheum (1978) ; 21:S146-52
26. Jennette JC and Hipp CG: Immunohistopathologic evaluation of C1q in 800 renal biopsy specimens. Am J Clin Pathol (1985); 83:415-20.
27. Marto N; Bertolaccini ML; Calabuig E *et al.,*: Anti-C1q antibodies in nephritis: correlation between titres and renal disease activity and positive predictive value in systemic lupus erythematosus. Ann Rheum Dis (2005); 64:444–8.
28. Moroni G ; Radice A ; Giammarresi G *et al.,*: Are laboratory tests useful for monitoring the activity of lupus nephritis? A 6-year prospective study in a cohort of 228 patients with lupus nephritis. Ann Rheum Dis (2009) ; 68:234-7
29. Sinico RA; Rimoldi L; Radice A *et al.,*: Anti-C1q autoantibodies in lupus nephritis. Ann. NY. Acad. Sci. (2009); 1173:47-51.
30. El-Hewala A; Ghada SN; Eman EE *et al.,*: Anti-C1q and anti-ds DNA antibodies in systemic lupus erythromatosus : Relationship with disease activity and renal involvement in Sharkia governorate, Egypt. The Egyptian Rheumatologist (2011); 33: 203-208.
31. Katsumata Y *et al.,*:Anti-C1q Antibodies Are Associated With Systemic Lupus Erythematosus Global Activity but Not Specifically With Nephritis ARTHRITIS & RHEUMATISM Vol. 63, No. 8, August 2011, pp 2436–2444
32. Fang QY; Yu F; Tan Y *et al.,* Anti-C1q antibodies and IgG subclass distribution in sera from Chinese patients with lupus nephritis. Nephrol Dial Transplant (2009); 24: 172–8.
33. Segal M and Johnson R: Renal involvement in systemic lupus erythromatosus. In: Wilcox CS; Tisher CC, editors. Handbook of nephrology and hypertension 6th ed., vol. 7. Lippincott: Williams and Wilkins. (2009); p. 63-71.

12/16/2014