

**EXPERT
OPINION**

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Role of serum anti-C1q antibodies as a biomarker for nephritis activity in pediatric and adolescent Egyptian female patients with SLE

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Objective: To evaluate serum anti-C1q antibodies as a biomarker of systemic lupus erythematosus (SLE) flare and as a proposed noninvasive alternative to renal biopsy which is still the “gold standard” to determine renal activity in SLE.

Methods: Serum anti-C1q antibodies were measured in our patients (all were females), they were followed at the nephrology and pediatric nephrology units at the Faculties of Medicine of Cairo University and Misr University for science and technology (MUST). Our study included 120 patients in the pediatric and adolescent age group and they were categorized into three groups with (mean \pm SD of 16.7 ± 3 , 16.1 ± 2 , 15.9 ± 3) respectively: Group 1 including 40 patients with SLE and active lupus nephritis; Group 2 including 40 patients with SLE and without active lupus nephritis, but with some extra renal activity mainly arthritis; and Group 3 including 40 healthy subjects.

Results: Anti-C1q antibodies were found to be significantly higher in patients with active lupus nephritis than those without active nephritis than control individuals with a median (range) of [27.5 (14 – 83), 9 (2.5 – 30), 7 (2 – 13)] respectively. In those with active lupus nephritis, anti-C1q was found to correlate significantly with other parameters assessing lupus nephritis activity like C3 ($r = -0.33$, $p < 0.04$), C4 ($r = -0.32$, $p < 0.044$), daily urinary protein excretion ($r = 0.32$, $p < 0.036$), renal SLEDAI ($r = 0.64$, $p < 0.001$), and activity index ($r = 0.71$, $p < 0.001$).

Conclusions: Anti-C1q antibodies can be used as a considerable marker for LN activity in that age group with 97.5% sensitivity and 65% specificity with the cutoff level 12 U/l. These levels are clearly higher than those for traditional markers of disease activity such as C3/C4 consumption and anti-dsDNA.

Keywords: anti-C1q antibodies, anti-dsDNA, C3, C4, ELISA, juvenile systemic lupus erythematosus, lupus nephritis, renal SLEDAI, urinary proteins

Expert Opin. Med. Diagn. (2012) 6(6):489-498

1. Introduction

Despite aggressive immunosuppression, the ability to control severe systemic lupus erythematosus (SLE) glomerulonephritis (GN) remains unsatisfactory. Treatment with intravenous or oral cyclophosphamide followed by maintenance immunosuppression with azathioprine or mycophenolate mofetil (MMF) yields complete and partial remissions in less than 50% of patients after 6 months [1]. Similar outcomes

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Table 1. Comparison between mean age of patients in all groups.

| Variables | Group 1, n = 40 | Group 2, n = 40 | Group 3, n = 40 | p |
|-----------------------|-----------------|-----------------|-----------------|--------|
| Age (mean ± SD) years | 16.7 ± 3 | 16.1 ± 2 | 15.9 ± 3 | > 0.05 |

Table 2. Comparison between the studied groups as regard laboratory data.

| Variables | Group 1, n = 40 (mean ± SD) | Group 2, n = 40 (mean ± SD) | Group 3, n = 40 (mean ± SD) | F | P | Post hoc (LSD) [‡] |
|--|--------------------------------|--------------------------------|--------------------------------|-----|---------|-----------------------------|
| HB (11 – 15) g/dl | 9.2 ± 3 | 9.9 ± 2 | 10.8 ± 2 | 0.6 | > 0.05 | |
| TLC (4 – 11) (10 ³ × mm ³) | 8.8 ± 2 | 7.4 ± 2 | 6.8 ± 1.7 | 0.9 | > 0.05 | |
| Platelets (150 – 450) (10 ³ × mm ³) | 191 ± 58 | 158 ± 60 | 189 ± 50 | 1.1 | > 0.05 | |
| ESR (3 – 14) mm/h | 88 ± 11 | 51 ± 10 | 12 ± 3 | 0.8 | < 0.001 | 1 versus 2 and 3 |
| Glucose random < 200 mg/dl | 120 ± 38 | 112 ± 20 | 109 ± 11 | 1.6 | > 0.05 | |
| Urea (8 – 21) mg/dl | 52 ± 25 | 29.6 ± 20 | 20 ± 8 | 1.9 | > 0.05 | |
| Creatinine (0.3 – 1.2) mg/dl | 1.5 ± 0.2 | 1.2 ± 0.3 | 1.1 ± 0.3 | 1.6 | > 0.05 | |
| 24 h Protein < 0.3 g | 1.9 ± 0.7 | 0.22 ± 0.4 | 0.11 ± 0.12 | 1.3 | < 0.001 | |
| C3 (90 – 140) U/l | 53 ± 20 | 83 ± 16 | 85 ± 19 | 34 | < 0.001 | 1 versus 2 and 3 |
| C4 (10 – 40) U/l | 14.7 ± 4 | 35.7 ± 10 | 39.4 ± 8 | 40 | < 0.001 | 1 versus 2 and 3 |
| Anti C1q U/l, Median (IQR) | 27.5 (14-83) | 9 (2.5-30) | 7 (2-13) | 13* | < 0.001 | 1 versus 2 and 3 |
| CRP(< 0.5 mg/l) | 13(32.5%) | 11(27.5%) | - | - | > 0.05 | |

*Kruskal–Wallis test.

[‡]Least significant difference.

IQR: Inter quartile range (0.25 – 75th percentile).

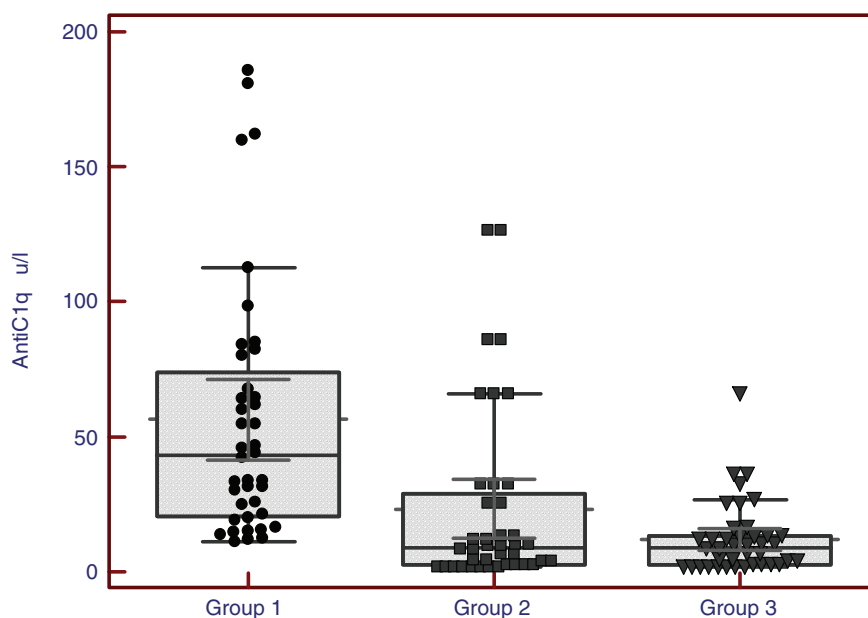


Figure 1. Comparison between anti-C1q antibodies in the three groups.

are seen when mycophenolate mofetil (MMF) is used for both induction and maintenance therapy [2].

Because kidney biopsies are not repeated at every flare, a noninvasive predictor of renal pathology would be very useful in choosing therapy. This approach to treatment represents a fundamental change from a reactive to a proactive paradigm

and will require biomarkers that accurately predict SLE nephritis activity, pathology, and prognosis to guide therapeutic decisions [3].

A biomarker that can forecast lupus nephritis flare well before thresholds of proteinuria, renal function, and urine sediment that signal clinical flare are reached would be a

Table 3. Correlation between anti-C1q antibodies versus all variables among cases (group 1).

| Variables | Anti-C1q | |
|---------------------|--------------|-------------------|
| | r | p |
| Age | 0.19 | > 0.05 |
| HB | 0.09 | > 0.05 |
| TLC | 0.11 | > 0.05 |
| Platelets | 0.14 | > 0.05 |
| ESR | 0.026 | > 0.05 |
| Glucose | -0.02 | > 0.05 |
| Urea | 0.1 | > 0.05 |
| Creatinine | 0.24 | > 0.05 |
| 24 h urine proteins | 0.33 | < 0.03 |
| C3 | -0.33 | < 0.04 |
| C4 | -0.32 | < 0.04 |
| Renal SLEDAI | 0.65 | < 0.001 |
| Activity index | 0.71 | < 0.001 |
| Chronicity index | 0.15 | < 0.33 |

valuable tool. Such a predictive biomarker could be followed serially, and based on biomarker levels, treatment could be initiated before the development of significant inflammatory injury in the kidney. This is likely to result in more complete remissions and less chronic kidney damage than waiting to treat until the flare is fully developed [4].

Early treatment may also permit a decrease in the total exposure to immunosuppressive medications, thereby reducing toxicity [5].

The traditional clinical biomarkers for SLE, including complement components 3 and 4 (C3, C4) and anti-double-stranded DNA antibodies (ADNA) have low sensitivity (49 – 79%) and specificity (51 – 74%) for concurrent renal flare and do not reliably predict impending flare when measured serially, with sensitivities and specificities around 50 and 70%, respectively [6].

C1q is the first component of the classical pathway of complement activation and its main function is to clear immune complexes from tissues and self-antigens generated during apoptosis [7]. Hereditary deficiency of this component is a known risk factor for the development of SLE [8].

In 1984, antibodies directed to C1q (anti-C1q) were reported in the serum of patients with SLE, with a prevalence ranging from 34% to 47%, and in patients with hypocomplementemic urticarial vasculitis syndrome with a prevalence of 100% [9].

Recently, it has been suggested that the presence of anti-C1q is a required condition for the development of lupus nephritis. Some investigators have also proposed that monitoring anti-C1q might be valuable for the clinical management of SLE patients as a noninvasive biological marker of renal disease [10].

The complement system plays an important role in SLE pathogenesis because tissue damage is strongly mediated by immune complex deposition [11]. Paradoxically, hereditary

classical complement component deficiencies are frequently associated with SLE development as a result of an impairment in the clearance of apoptotic debris [12]. Homozygous C1q deficiency is the strongest genetic risk factor related to SLE, and 93% of C1q-deficient patients develop SLE or lupus-like manifestations. However, the majority of SLE patients frequently have secondary complement deficiency caused by the presence of anti-C1q antibodies [13].

Of note, anti-C1q antibodies have been detected in up to 65% of adult SLE patients and associated with disease activity, especially with lupus nephritis [14]. However, there are only two studies that evaluated anti-C1q antibodies in juvenile SLE (JSLE), and these studies had discordant results and did not have a comparative healthy control group. In 1997, Ravelli *et al.* [15] found serum anti-C1q antibody in 17 of 29 (59%) JSLE patients and this was not associated with active nephritis. More recently, Kozyro *et al.* [16] reported the presence of anti-C1q antibody in 7 of 12 (58%) lupus nephritis patients. Six of these seven patients were in renal flare.

1.1 Aim of the work

The aim of this study was to evaluate serum anti-C1q antibodies as a biomarker of SLE flare and as a proposed non-invasive alternative to renal biopsy which is still the “gold standard” to determine renal activity in SLE.

2. Subjects and methods

The present study was carried out in accordance with the ethical standards of the updated Declaration of Helsinki which was approved by the Medical Ethics Committee at the Faculties of Medicine of Cairo University and Misr University for Science and Technology (MUST) during the period from January 2011 till January 2012. An informed consent was taken from the parents of all subjects.

All patients (all females) were followed at the nephrology and pediatric nephrology units at the Faculties of Medicine of Cairo University and Misr University for Science and Technology (MUST). Our study included 120 patients in the pediatric and adolescent age group and they were categorized into three groups with mean \pm SD of 16.7 ± 3 , 16.1 ± 2 , and 15.9 ± 3 respectively:

Group 1 including 40 patients with SLE and active lupus nephritis.

Group 2 including 40 patients with SLE and without active lupus nephritis, but with some extra renal activity mainly arthritis.

Group 3 including 40 healthy subjects.

All the patients were subject to thorough clinical examination including assessment of the vital signs (heart rate, blood pressure), body weight, lower limb edema, and signs of uremia.

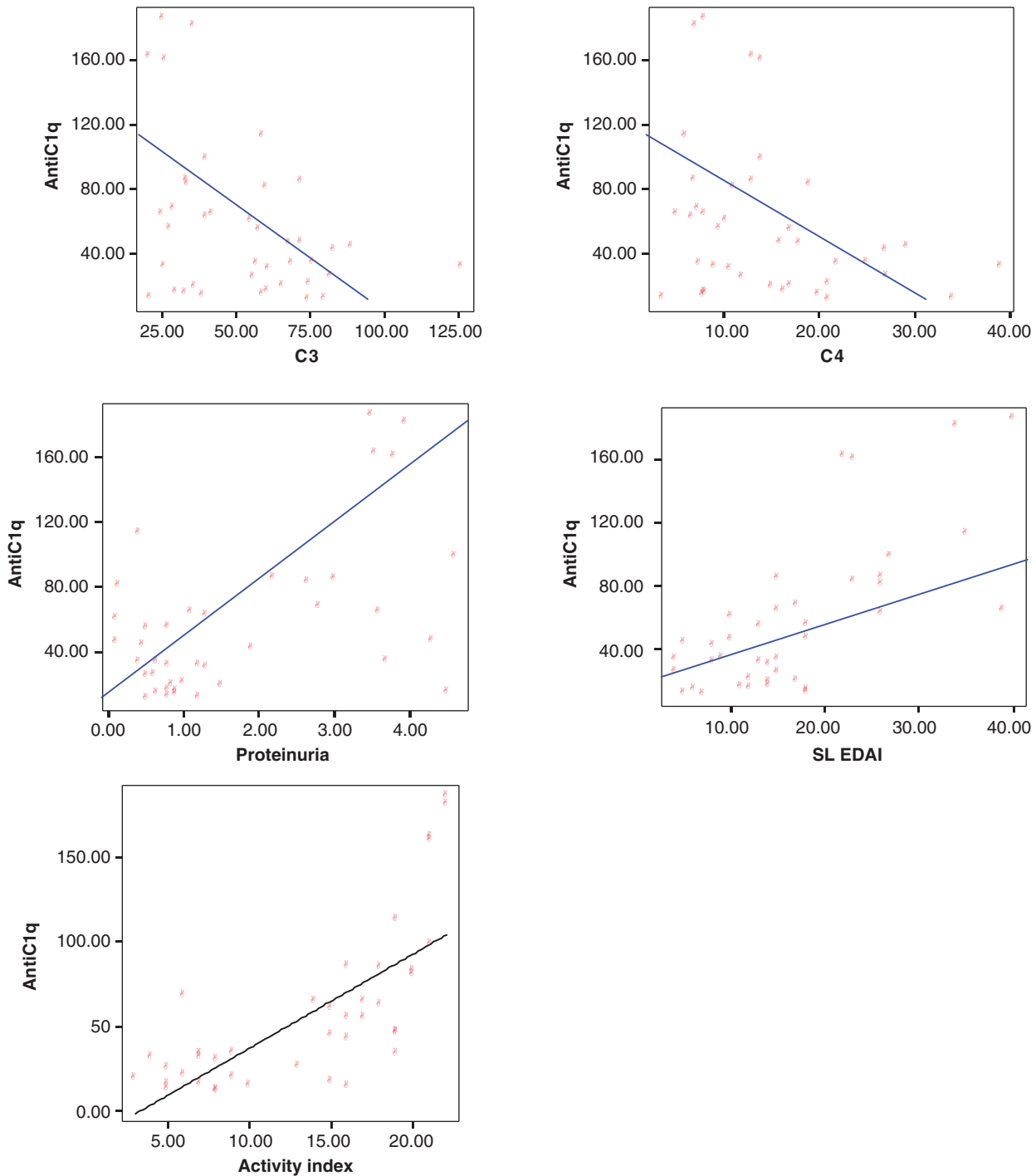


Figure 2. Correlation between anti-C1q antibodies versus C3, C4, Proteinuria, and renal SLEDAI and Activity index in cases (group 1).

SLE disease activity was measured in all patients, using the SLE disease activity index renal (SLEDAI) [17]. Lupus activity was defined arbitrarily as renal SLEDAI > 4. The diagnosis of nephritis was established according to the presence of proteinuria > 0.5 g/24 h, presence of cellular casts, persistent

hematuria >10 red blood cells under high-power field, and renal failure. The mean renal SLEDAI for group 1 was 12 while the mean renal SLEDAI for group 2 was 4. The renal histopathology was described according to the World Health Organization (WHO) classification [18].

Table 4. Correlation between anti-C1q antibodies versus all variables among group without active lupus nephritis (group 2).

| Variables | Anti-C1q | |
|---------------|--------------|---------------------|
| | r | p |
| Age | 0.08 | > 0.05 |
| HB | 0.02 | > 0.05 |
| TLC | 0.16 | > 0.05 |
| Platelets | 0.15 | > 0.05 |
| ESR | 0.16 | > 0.05 |
| Glucose | -0.17 | > 0.05 |
| Urea | 0.10 | > 0.05 |
| Cr | 0.20 | > 0.05 |
| 24 h Proteins | -0.30 | > 0.05 |
| C3 | -0.42 | < 0.001HS |
| C4 | 0.07 | > 0.05 |

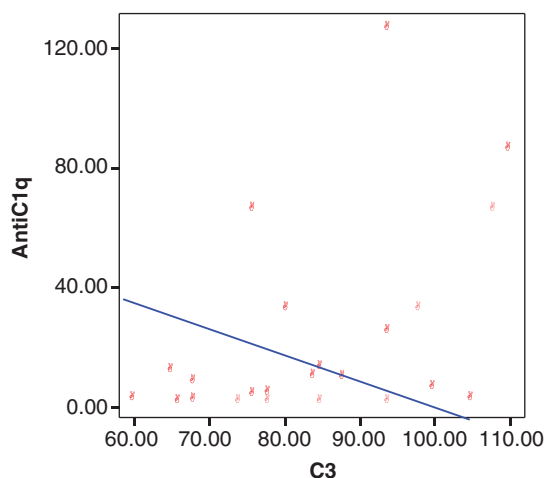


Figure 3. Correlation between anti-C1q antibodies and C3 among group without active lupus nephritis (group 2).

The following laboratory investigations were done to the subjects of the study:

- 1) Complete blood count,
- 2) Erythrocyte sedimentation rate,
- 3) Serum creatinine, blood urea, serum sodium, and serum potassium
- 4) Serum C3, C4
- 5) Anti-dsDNA (Qualitative)
- 6) Urine analysis
- 7) Twenty-four hours urinary proteins
- 8) Serum anti-C1q by ELISA technique
- 9) Renal biopsy for all the 80 SLE patients in group 1 and group 2 (renal biopsy was performed in group 2 when they had active disease in the past). The renal histopathology in both groups ranged between class IV and class V (diffuse proliferative glomerulonephritis and membranous

glomerulonephritis according to the WHO classification). The renal biopsy and blood sampling for detection of anti-C1q antibodies in group 1 patients were done simultaneously at the same time. Group 1 patients were on active treatment during this time also.

Anti-C1q antibodies were detected by ELISA (ORGENTEC Diagnostika GmbH, Mainz, Germany) with duplicated samples. Tests were performed strictly according to manufacturer protocols, including the suggested cutoff values of 20 U.

2.1 Sample collection and treatment

2.1.1 Specimen

Three milliliters of blood was drawn by venipuncture, left to clot and serum was separated by centrifugation at $2500 \times g$ for 10 min. Hemolyzed and lipemic sera were avoided.

2.1.2 Specimen storage

Specimens were capped and stored at -20°C for few months until the time of the assay. Repeated thawing and freezing were avoided.

2.2 Immunoassay of the test

The Anti-C1q ELISA kit (ORGENTEC Diagnostika GmbH, Mainz, Germany) – Highly purified human C1q is bound to microwells. Antibodies against this antigen, if present in diluted serum, bind to the respective antigen. Washing of the microwells removes unspecific serum and plasma components. Horseradish peroxidase (HRP)-conjugated antihuman IgG immunologically detects the bound patient antibodies forming a conjugate/antibody/antigen complex. Washing of the microwells removes unbound conjugate. An enzyme substrate in the presence of bound conjugate hydrolyzes to form a blue color. The addition of an acid stops the reaction forming a yellow end-product. The intensity of this yellow color is measured photometrically at 450 nm. The amount of color is directly proportional to the concentration of IgG antibodies present in the original sample.

2.3 Statistical analysis of the data collected

Analysis of data was done by IBM computer using SPSS (statistical program for social science version 15.0) (SPSS, Inc., Chicago, IL, USA) for Windows[®]. as follows:

Description of quantitative variables as mean, SD, and range

Description of qualitative variables as number and percentage

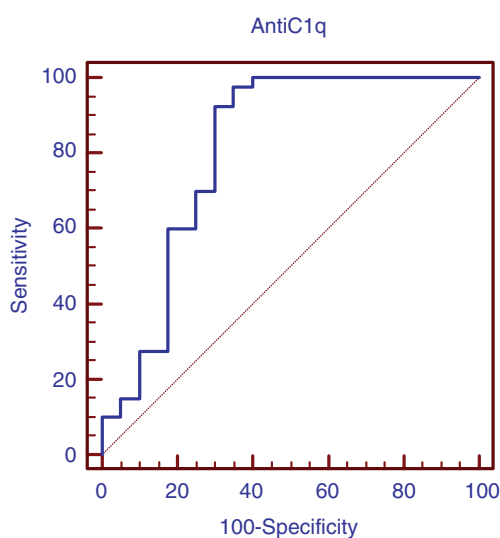
Chi-square test was used to compare qualitative variables between groups. Fisher exact test was used instead of chi-square when one expected cell or more are less than 5. Unpaired *t*-test was used to compare two groups as regard quantitative variable. Paired *t*-test was used to compare quantitative variables in the same group.

Table 5. Correlation between anti-C1q antibodies versus all variables among controls (group 3).

| Variables | Anti-C1q | |
|--------------|----------|--------|
| | r | p |
| HB | -0.09 | > 0.05 |
| TLC | 0.02 | > 0.05 |
| Platelets | 0.08 | > 0.05 |
| ESR | 0.18 | > 0.05 |
| Glucose | 0.17 | > 0.05 |
| Urea | -0.03 | > 0.05 |
| Cr | 0.02 | > 0.05 |
| 24 h Protein | 0.16 | > 0.05 |
| C3 | 0.11 | > 0.05 |
| C4 | -0.04 | > 0.05 |

Table 6. Validity of anti-C1q antibodies in prediction of lupus nephritis in group 1 patients.

| Variables | |
|------------------------|----------|
| Area under the curve | 0.81 |
| Best cut off | > 12 |
| Sensitivity | 97.5% |
| Specificity | 65% |
| PPV | 74% |
| NPV | 96% |
| Standard error | 0.052 |
| Significance level (p) | < 0.0001 |

**Figure 4. ROC curve for anti-C1q in lupus nephritis.**

One-way ANOVA test (analysis of variance) was used to compare more than two groups as regards quantitative variable. Kruskal–Wallis test was used instead of one-way ANOVA in nonparametric data. Spearman correlation test

was used to rank different variables positively or inversely. ROC (receiver operator characteristic) curve was used to find out the best cut of value and validity of certain variable. p value > 0.05 was considered as insignificant, p < 0.05 significant, and p < 0.01 highly significant [19].

3. Results

Serum anti-C1q antibodies were measured in our patients (all were females), they were followed at the nephrology and pediatric nephrology units at the Faculties of Medicine of Cairo University and Misr University for Science and Technology (MUST). Our study included 120 patients in the pediatric and adolescent age group and they were categorized into three groups with mean \pm SD of 16.7 ± 3 , 16.1 ± 2 , and 15.9 ± 3 respectively: Groups 1, 2 and 3.

Anti-C1q antibodies were found to be significantly higher in patients with active lupus nephritis than those without active nephritis than control individuals with a median (range) of [27.5 (14 – 83), 9 (2.5 – 30), 7 (2 – 13)] respectively. In those with active lupus nephritis anti-C1q was found to be significantly correlating with other parameters assessing lupus nephritis activity like C3 ($r = -0.33$, $p < 0.04$), C4 ($r = -0.32$, $p < 0.044$), daily urinary protein excretion ($r = 0.32$, $p < 0.036$), renal SLEDAI ($r = 0.64$, $p < 0.001$), and activity index ($r = 0.71$, $p < 0.001$).

Table 1 shows that there was no statistically significant difference between the studied groups with respect to age.

Table 2 and Figure 1 show that anti-C1q antibodies were highest among cases compared to the other two groups with statistically significant difference in-between by using Kruskal–Wallis test.

Table 3 and Figure 2 show statistically significant positive correlations between anti-C1q antibodies versus 24 h proteins and renal SLEDAI and Activity index, while they show negative correlation between anti-C1q antibodies versus C3 and C4 by using Spearman correlation test. On the other hand, there is no significant correlation as regard other variables.

Table 4 and Figure 3 show statistically significant negative correlation between anti-C1q antibodies versus C3 in group 2 by using Spearman correlation test. On the other hand, there is no significant correlation as regard other variables.

Table 5 shows no statistically significant correlation between anti-C1q antibodies versus different variables by using Spearman correlation test.

Table 6 and Figure 4 show that anti-C1q antibodies is considered better positive marker than negative in case of lupus nephritis with higher sensitivity.

Table 7 and Figure 5 show that C3 is considered better positive marker than negative in case of lupus nephritis with high sensitivity.

Table 8 and Figure 6 show C4 is considered better positive marker than negative in case of lupus nephritis with high sensitivity.

Table 7. Validity of C3 in prediction of lupus nephritis in group 1 patients.

| Variables | |
|------------------------|----------|
| Area under the curve | 0.87 |
| Best cut off | ≤ 61 |
| Sensitivity | 67.5% |
| Specificity | 95% |
| PPV | 93% |
| NPV | 75% |
| Standard error | 0.041 |
| Significance level (p) | < 0.0001 |

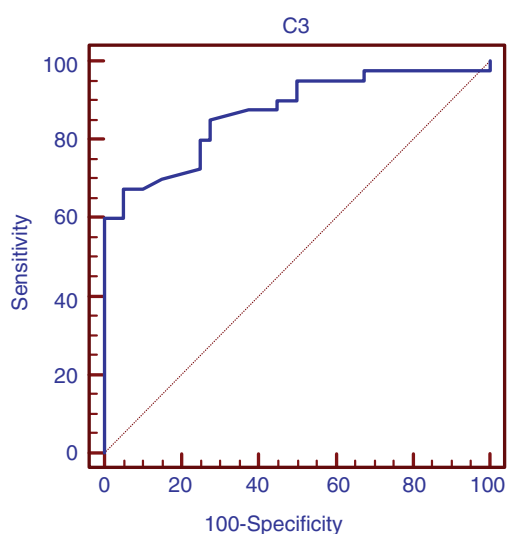


Figure 5. ROC curve for C3 in lupus nephritis.

Table 8. Validity of C4 in prediction of lupus nephritis in group 1 patients.

| Variables | |
|------------------------|----------|
| Area under the curve | 0.96 |
| Best cut off | ≤ 22 |
| Sensitivity | 85% |
| Specificity | 100% |
| PPV | 100% |
| NPV | 87% |
| Standard error | 0.021 |
| Significance level (p) | < 0.0001 |

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 [20]. 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 [21]. Second, a substantial number of patients with SLE develop hypocomplementemia with depletion of C1q and other components of the classical pathway of complement [22]; and C1q is deposited in affected tissues [23].

Glomerulonephritis is a frequent and often severe feature of SLE and is one of the major determinants of poor outcome. Reliable markers for diagnosing and monitoring lupus nephritis are therefore critically important.

The association of anti-C1q antibodies with lupus nephritis has been demonstrated by the discovery of anti-C1q antibodies in lupus nephritis kidneys [24].

The clinical relevance of anti-C1q antibodies in adult patients with active SLE nephritis was raised in several clinical studies [25-28,28-31], however a lower frequency of anti-C1q antibodies with high specificity was found in patients with juvenile onset SLE, in the study done by Jesus *et al.* [32], but remarkably in this study, there was no definite segregation in number between the groups of juvenile SLE patients with and without lupus nephritis activity, the authors did not clarify how many patients had nephritis activity and how many were without at the time of sampling, and also the patients and controls were not equal in number.

The current cross-sectional study was designed to evaluate the diagnostic performance of anti-C1q antibodies in a cohort of pediatric and adolescent 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, anti-C1q antibodies were found to be significantly higher in patients with active lupus nephritis than those without active nephritis than control individuals with a median (range) of [27.5 (14 – 83), 9 (2.5 – 30), 7 (2 – 13)] (Table 2, Figure 1) respectively. In those with active lupus nephritis anti-C1q antibodies were found to be significantly correlating with other parameters assessing lupus nephritis activity like C3 ($r = -0.33, p < 0.04$), C4 ($r = -0.32, p < 0.044$), daily urinary protein excretion ($r = 0.33, p < 0.036$), and renal SLEDAI ($r = 0.65, p < 0.001$), and activity index ($r = 0.71, p < 0.001$). That refers to anti-C1q as a considerable marker for LN activity in that age group with 97.5% sensitivity and 65% specificity with the cutoff level 12 U/l and positive predictive value of 74% and negative predictive value of 96% (Table 6, Figure 4). These levels are clearly higher than those for traditional markers of disease activity such as C3/C4 consumption and anti-dsDNA. When we compared the validity of anti-C1q antibodies in prediction of lupus nephritis in group 1 patients, with C3 and C4, anti-C1q antibodies had the highest sensitivity with 97.5% and standard error of prediction of 0.052 (Table 6, Figure 4), compared to C3 with sensitivity of 67.5%, standard

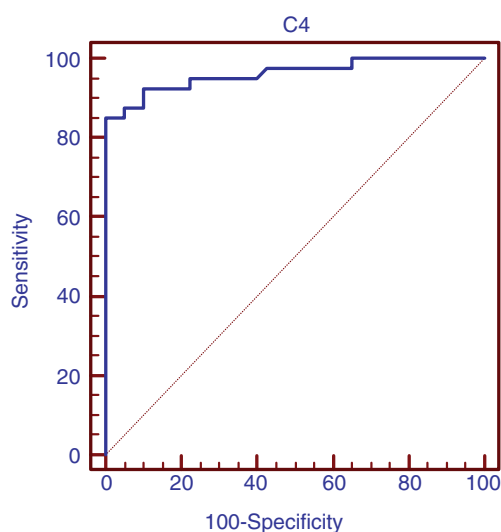


Figure 6. ROC curve for C4 in lupus nephritis.

error of prediction of 0.041 (Table 7, Figure 5) and C4 with sensitivity of 85%, standard error of prediction of 0.021 (Table 8, Figure 6).

These results support the study done by Moroni *et al.*, which showed 87% sensitivity and 92% specificity for anti-C1q in predicting SLE nephritis activity [27]. 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 [31].

The wide variation in clinical presentation of SLE in pediatric and adolescent patients, together with the myriad of associated autoantibodies, calls for a trend toward determining “organ-specific” autoantibodies for diagnosis, prognosis and possibly specific therapeutic intervention [33]. Albeit

unlikely that anti-C1q as a noninvasive biomarker can replace gold standard renal biopsies, it may help to avoid unnecessary invasive biopsies in this particular age group, especially in the context of treatment follow-up. The relatively high sensitivity shown in our study renders anti-C1q antibodies an optimal screening tool for SLE active nephritis. The importance of avoiding potentially toxic drugs with special concern for future fertility in adolescents cannot be overemphasized [34].

In view of relatively limited number of involved patients, further evaluation of such findings in large cohorts of SLE patients with different disease severity is recommended to validate the clinical value of anti-C1q in diagnosis and prognosis of renal disease in SLE. We also recommend in further similar bigger studies to involve study of correlation between anti-C1q antibodies level and anti-dsDNA titer as we measured the anti-dsDNA in qualitative method only. Observations done in our study, in addition to previous studies in different age groups, give cumulative evidence for the important role of anti-C1q in pathogenesis of active SLE nephritis. This in turn opens the way to advancing specific therapeutic targets in C1q-mediated renal injury in SLE.

5. Conclusion

Anti-C1q autoantibodies correlate with renal disease activity and with renal flare-ups like other standard parameters, such as proteinuria and complement levels and renal SLEDAI. Anti-C1q antibodies can be considered a reliable sensitive and specific biomarker to diagnose nephritis flare in pediatric and adolescent Egyptian females with SLE, in addition to, and possibly replacing, other confirmed disease activity indices.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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