Circulating serum anti-C1q antibody: correlation with clinical and histopathological activity in patients with proliferative lupus nephritis

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Introduction
In systemic lupus erythematosus (SLE) the prevalence of anti-C1q antibodies (Abs) varies from 30 to 50% and is associated with high clinical activity and, particularly, with renal involvement. Moreover, in the absence of anti-C1q auto-Abs, no lupus nephritis occurs, whereas at least 50% of patients with anti-C1q auto-Abs have or develop lupus nephritis. For lupus nephritis, anti-C1q Abs are as specific as high-avidity dsDNA Ab and capable of closing a diagnostic gap in some cases.

Patients and methods
The present study was conducted on 40 patients with SLE. Patients were classified into group I (20 patients with active proliferative lupus nephritis (LN)), group II (10 patients with inactive LN), and group III (10 patients without nephritis). Laboratory investigations were carried out, including complete blood picture, renal functions (blood urea, serum creatinine, and creatinine clearance), complete urine analysis and urine analysis for dysmorphic red blood cells (RBCs), measurement of 24 h urinary proteins, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), and anti-dsDNA, and measurement of serum anti-C1q. Renal biopsy was taken from all patients of group I.

Results
Anti-C1q Abs were significantly higher in group I than in other groups. There were statistically significant positive correlations between anti-C1q Ab level, anti-dsDNA, and percentage of dysmorphic RBCs in urine in group I. There was also a statistically significant positive correlation between anti-C1q Ab level and cellular crescents, leukocyte infiltration, and endocapillary cellularity in the activity index.

Conclusion
Anti-C1q Ab can be used as an indicator of renal activity in patients with lupus nephritis.

Keywords:
anti-C1q antibodies, nephritis activity, proliferative lupus nephritis

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Introduction

Renal involvement is observed in most SLE patients at some point during the history of the disease, with a significant proportion having an adverse outcome. Kidney involvement contributes significantly to morbidity and mortality in SLE patients. Renal disease may present as asymptomatic hematuria/proteinuria, nephrotic syndrome, or nephritic syndrome. This may be accompanied by varying degrees of hypertension and renal dysfunction [1].

In the pathogenesis of SLE, the complement plays an ambivalent role [2]. The dominant way of activation in SLE is the classical way initiated by interaction of the C1q component with immune complexes. The components of the classical way (C1, C4, and C2) are usually lowered in active SLE [3].

C1q, the first component of the classical pathway of complement activation, contains six distinct globular heads and a unique collagen-like region. Several functions have been assigned to C1q. They include principally the initial step of complement activation by the binding of the globular heads of the C1q molecule to the Fc portions of immune complexes and the participation in the clearance of self-antigens generated during programmed cell death [4,5].

In SLE the prevalence of anti-C1q antibodies (Abs) varies from 30 to 50% and is associated with high clinical activity and, particularly, renal involvement [6]. Moreover, in the absence of anti-C1q auto-Abs, no lupus nephritis occurs, whereas at least 50% of patients having anti-C1q auto-Abs have or develop lupus nephritis [7,8]. For lupus nephritis, anti-C1q Abs are as specific as high-avidity dsDNA Ab and capable of

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closing a diagnostic gap in some cases [9]. During the therapy of SLE the levels of anti-C1q Abs tend to drop, as proved in one rituximab study [10]. Thus, this study was conducted with the aim to explore any relationship between circulating anti-C1q Ab level and clinical or histopathological activity in patients with proliferative lupus nephritis.

Patients and methods

This study was carried out in accordance with the ethical standards of the Faculty of Medicine, Alexandria University, after obtaining the approval of the ethical committee, and also in accordance with the Helsinki Declaration of 1975, as revised in 2000.

The present study was conducted on 40 patients with SLE who fulfilled at least four of the American College of Rheumatology criteria for diagnosis of SLE. Patients were selected from the internal medicine ward of the Main University Hospital, Alexandria University, after taking their informed consent. Patients with diabetes mellitus, CKD due to any cause, active infection, or any inflammatory disease were excluded. Patients were classified into group I (20 patients with active proliferative LN), group II (10 patients with inactive LN), and group III (10 patients without nephritis).

Laboratory investigations were obtained from all subjects involved in our study, including complete blood picture, renal functions (blood urea, serum creatinine, and creatinine clearance), complete urine analysis and urine analysis for dysmorphic RBCs, measurement of 24 h urinary proteins, ESR, ANA, and anti-dsDNA, and measurement of serum anti-C1q using an ELISA kit [11].

Renal biopsy was taken from all patients of group I and histopathological examination was performed (light microscopic examination using hematoxylin and eosin, Periodic acid–Schiff, and trichrome stains).

Statistical analyses

Data were analyzed using SPSS software package (version 18.0; SPSS, Chicago, Illinois, USA) [12]. Quantitative data were expressed as range, mean, SD, and median and qualitative data as frequency and percentage. Qualitative data were analyzed using exact tests such as Fisher's exact, and the Monte Carlo test was applied to compare different groups. Quantitative data were analyzed using the *F*-test (analysis of variance) to compare the three categories of outcome. Non-normally distributed quantitative data were analyzed using the Mann–Whitney test for comparing two groups, whereas for more than two groups the Kruskal–Wallis test was applied. Spearman's coefficient and Pearson's coefficient were used to analyze the correlation between any two variables. *P* value was assumed to be significant at 0.05.

Results

In the present study, in group I blood urea and serum creatinine were significantly higher, whereas creatinine clearance was significantly lower. Urine analysis revealed significantly higher hematuria and dysmorphic RBCs in group I than in other groups, and nephrotic range proteinuria was detected in 15% of patients in group I.

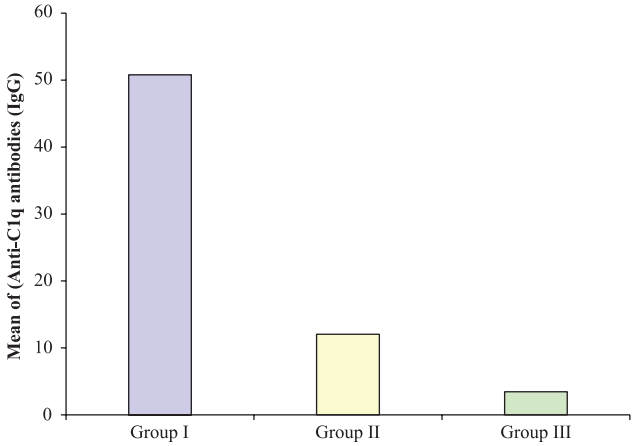
As regards the immunological parameters, ANA and anti-dsDNA levels were significantly higher in group I than in other groups. The mean value of ANA in group I was 296.0 ± 172.36 U/ml (range: 80.0–640.0 U/ml, median: 320.0 U/ml), that in group II was 132.0 ± 80.11 U/ml (range: 40.0–320.0 U/ml, median: 120.0 U/ml), and that in group III was 164 ± 93.24 U/ml (range: 40.0–320.0 U/ml, median: 160.0 U/ml). There was a statistically significantly higher level of ANA in group I than in groups II and III. No significant difference was present between group II and group III.

The mean value of anti-dsDNA in group I was 202.28 ± 119.09 U/l (range: 83.0–600.0 U/l, median: 170.0 U/l), that in group II was 119.16 ± 71.29 U/l (range: 26.0–218.0 U/l, median: 93.35 U/l), and that in group III was 132.49 ± 98.65 U/l (range: 27.9–293.3 U/l, median: 127.45 U/l). There was a statistically significant difference in anti-dsDNA level between group I and group II. No significant difference was present between group I and group III or between group II and group III.

In the present study, anti-C1q Abs were significantly higher in group I than in other groups. They were detected in 60% of patients with active nephritis, compared with 30% of patients with inactive nephritis and in 10% of those with no nephritis. The mean value of anti-C1q Abs in group I was 50.79 ± 62.0 U/ml (range: 2.6–185.8 U/ml, median: 17.30 U/ml), that in group II was 12.05 ± 18.34 U/ml (range: 0.5–62.0 U/ml, median: 5.65 U/ml), and for group III was 3.45 ± 3.95 U/ml (range: 0.1–13.60 U/ml, median: 2.05 U/ml) (Fig. 1).

In the current work, there were statistically significant positive correlations between anti-C1q Ab level and ESR, serum creatinine level, 24 h urinary proteins, anti-dsDNA, and percentage of dysmorphic RBCs in urine, and statistically significant negative correlations between anti-C1q Ab level and hemoglobin level and creatinine clearance, in group I (Table 1).

Figure 1



Level of anti-C1q antibody in different groups.

As regards renal biopsy, there was a statistically significant positive correlation between anti-C1q Ab level and cellular crescents, leukocyte infiltration, and endocapillary cellularity in the activity index, and with interstitial fibrosis in chronicity index; however, there was a negative correlation between anti-C1q Ab level and glomerular sclerosis in chronicity index (Table 2).

Table 1 Correlation between anti-C1q with creatinine, 24-h urinary protein, ANA, and anti-dsDNA in each group

Studied variable	Anti-C1q					
	Group I		Group II		Group III	
	r	*P*	*r*	*P*	*r*	*P*
Creatinine	0.856*	<0.001	0.318	0.370	−0.341	0.334
24 h urinary proteins	0.818*	<0.001	0.418	0.229	−0.164	0.651
ANA	0.417	0.067	0.103	0.776	0.111	0.761
Anti-dsDNA	0.842*	<0.001	0.442	0.200	−0.030	0.934

r, Pearson's coefficient; *Statistically significant at $P \leq 0.05$.

Table 2 Correlation between activity and chronicity index with anti-C1q in the active lupus nephritis group

Activity index	Active lupus nephritis	
	r	*P*
Activity index		
Cellular crescents	0.821*	<0.001
Leukocyte infiltration	0.532*	0.016
Endocapillary cellularity	0.798*	<0.001
Wire loping	0.165	0.488
Glomerular fibrinoid necrosis	0.160	0.500
Interstitial inflammation	0.318	0.172
Chronicity index		
Glomerular sclerosis	−0.522*	0.018
Fibrous crescents	0.301	0.197
Interstitial fibrosis	0.464*	0.040
Tubular atrophy	0.375	0.104

*Statistically significant at $P \leq 0.05$.

Discussion

Patients of group I were significantly younger than those in the other two groups. The mean age distribution in our study was similar to that of most other studies that showed that patients with nephritis were younger than those without nephritis [12].

This could be attributed to the fact that SLE, with or without renal involvement, is mainly a disease afflicting young women in the child-bearing period [13]. Most patients develop nephritis early in the course of the disease and it is uncommon to have onset of renal involvement more than 10 years after the appearance of SLE [14].

In the present study the degree of proteinuria was correlated with disease activity. Moroni *et al.* [15] reported that renal relapse associated with increase proteinuria and/or serum creatinine and appearance of red or white blood cell casts is a reliable predictor of relapse of LN.

In the present study, ANA was significantly higher in group I than in the other groups. Others reported that elevated levels of ANA are correlated with the presence of active glomerulonephritis [16].

In the present work, anti-dsDNA was significantly higher in group I than in group II. Many studies reported a relation between serum anti-dsDNA Ab level and renal involvement in SLE [17].

The participation of anti-dsDNA Abs complexes in the pathogenesis of LN may be through activation of complement and clotting systems. Anti-dsDNA Abs were thought to cause glomerulonephritis by forming complexes with DNA that are passively trapped in the glomeruli [18].

In the present study, anti-C1q Abs were significantly higher in group I than in other groups. They were detected in 60% of patients with active nephritis, compared with 30% of patients with inactive nephritis and 10% of those with no nephritis. Similar findings were reported in previous studies [19,20].

Horvath *et al.* [21] found a clear-cut positive correlation between the presence of high-titer C1q-Ab and SLE activity based on clinical and laboratory data. Almost half (29/70) of the SLE patients in the active stage, but only 10/66 of the patients in the inactive stage, had high anti-C1q levels.

In present study, significant correlations were found between anti-C1q Abs and several parameters of clinical and serological activity in SLE patients. Many investigators have similarly reported that

anti-C1q Abs were correlated with disease flare and active renal involvement and can be used as an index of LN activity [22–24].

Thus, the correlation between anti-C1q and renal involvement in our study and in other studies may suggest that the detection of anti-C1q Abs is a marker of disease activity, particularly in renal flare.

It is still confusing how anti-C1q Abs could cause renal disease in SLE. An indirect evidence for the role of these Abs in the pathogenesis of lupus nephritis is the observation of Chen *et al.* [25], who found that higher titers of anti-C1q Abs were present in patients with LN and C1q deposition in the kidney tissue.

First evidence of the pathogenic role of anti-C1q Abs came from the study of Mannik and Wener [26], who extracted the Abs from autopsied kidneys. Anti-C1q Abs were present in higher concentration in the glomeruli compared with serum.

Anti-C1q Abs have a definite role in the pathogenesis of lupus glomerular injury. They may either contribute to the formation of circulating immune complexes that are deposited in the kidneys or contribute to local formation of immune complexes on the glomerular basement membrane [19,27].

It is noticed that, although some SLE patients have anti-dsDNA and anti-C1q Abs, renal involvement is not observed, which may be explained by the presence of inadequate amount of C1q to pass the threshold of complement activation [28]. This may also explain why the presence of anti-C1q Abs has been identified in the serum of patients with other connective tissue diseases without renal involvement, or even in the normal population. These observations may suggest that SLE is different from other conditions, and anti-C1q Abs have the potential to cause renal affection [29].

Coremans *et al.* [30] reported in a follow-up study conducted every month in SLE patients that anti-C1q Abs are more prevalent in renal flares than in nonrenal flares and their level follows disease activity more closely in renal lupus than in nonrenal lupus. These findings are in agreement with another study that reported that determination of anti-C1q Abs is a better tool to indicate the occurrence of renal flares in SLE than determination of anti-dsDNA Abs [31].

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Conflicts of interest

There are no conflicts of interest.

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