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ORIGINAL ARTICLE

Nonrenal and renal activity of systemic lupus erythematosus: a comparison of two anti-C1q and five anti-dsDNA assays and complement C3 and C4

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Abstract Associations of different assays for antibodies to C1q (anti-C1q) and to dsDNA (anti-dsDNA) and of complements C3 and C4 with disease activity in patients with systemic lupus erythematosus (SLE) were studied. The clinical manifestations of 223 SLE patients were recorded, and the disease activity was assessed by the SLEDAI score. Anti-C1q were determined by two enzyme-linked immunosorbent assays (ELISA) and anti-dsDNA by a radioimmunoassay (RIA), a *Crithidia* immunofluorescence (IF) assay and three ELISA assays using human telomere DNA, plasmid DNA circles, or calf thymus DNA as antigens, respectively. Complement C3 and C4 were determined by nephelometry. Control sera were obtained from 98 blood donors. In patients with SLE**,** the prevalence of anti-C1q was 17–18% and that of anti-dsDNA was 36–69%. Anti-C1q, anti-dsDNA, and complement C3 and C4 correlated well with the overall activity of SLE ($r = 0.323$–0.351, 0.353–0.566, and −0.372–0.444, respectively; $P < 0.001$). Sensitivity, specificity, positive predictive value, and negative predictive value for active lupus nephritis among SLE patients were 40–44, 92, 29, and 91–92% for anti-C1q and 48–68, 29–66, 11–16, and 86–91% for anti-dsDNA, respectively. Patients with active nephritis had higher levels of anti-C1q and lower levels of C3 and C4 than patients with inactive nephritis ($P = 0.003$–0.018). The corresponding associations of anti-dsDNA were somewhat weaker ($P = 0.023$–0.198). Hematological parameters reflecting disease activity correlated clearly better with anti-dsDNA and complement C3 and C4 than with anti-C1q. Anti-C1q is inferior to anti-dsDNA as a diagnostic test in SLE and in the evaluation of overall clinical activity of the disease. Anti-C1q together with complement C3 and C4 may offer useful additional information to monitor lupus nephritis activity. There are no practical differences between different assays for anti-C1q and anti-dsDNA.

Keywords Anti-C1q · Anti-dsDNA · Systemic lupus erythematosus · Lupus nephritis · SLEDAI

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Introduction

Antibodies to double-stranded DNA (anti-dsDNA) are classical marker antibodies for SLE. They are reasonably sensitive and specific in the diagnosis of SLE, and raised titers of these antibodies along with hypocomplementemia are reported to be associated with the activity of the disease [1–3]. Therefore, many rheumatologists and nephrologists use anti-dsDNA and complement C3 and C4 in the follow-up of SLE as an aid to decide whether to increase, maintain, or decrease ongoing immunosuppressive medication.

There is controversy about the most relevant, simple, and practical biological marker to evaluate the activity of SLE [4–7]. Anti-dsDNA are usually determined by the Farr assay (radioimmunoassay, RIA), immunofluorescence (IF), or various enzyme-linked immunosorbent (ELISA)

techniques. Several studies have reported differences in the performance of different assays in terms of sensitivity and specificity in diagnosing SLE or in assessing the activity of the disease [8–10]. In addition, the lack of specificity of anti-dsDNA and complement C3 and C4 for exacerbations of SLE and for renal flare has led to search for clinically more useful biomarkers [6, 7, 11].

Antibodies to C1q, to the first component of the classical pathway of complement activation, have been detected in the serum of patients with SLE with a prevalence of 34–47% [12–16]. Anti-C1q has been reported to be associated with the overall clinical activity of SLE [17], specific nonrenal manifestations [18] and, especially, with renal involvement and renal flares [19]. It has been suggested that the presence of anti-C1q is a prerequisite for the development of lupus nephritis [20, 21] and that anti-C1q may be a clinically valuable marker to monitor for renal SLE [22–25]. However, and so far, testing anti-C1q does not have a definitive place in clinical practice.

In this study, we wanted to further investigate the clinical significance of anti-dsDNA, anti-C1q, and complement C3 and C4 in patients with SLE. We compared the performance of 2 anti-C1q assays by ELISA with that of anti-dsDNA by RIA, IF and 3 ELISA assays using human telomere DNA, plasmid DNA circles, or calf thymus DNA as antigens, respectively, and complement C3 and C4 levels to detect SLE patients with active disease including active nephritis.

Materials and methods

Patients and controls

All patients with a clinical diagnosis of SLE, who attended or had attended the Helsinki University Central Hospital, were identified from the hospital registry. We included 223 patients, all of whom satisfied the criteria for SLE [26].

Demographic features and past and present clinical characteristics of all SLE patients were recorded by personal interview, clinical examination, and chart review by two rheumatologists (SE-K and HJ) according to a detailed protocol, which also included Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [27].

The mean age of the patients was 46.8 years (SD 14.4 years, range 18–87) and 92% of them were females. The duration of SLE from the time of onset of first manifestations of the disease was 16.6 years (SD 18.8 years, range 0.2–45.5 years) and from the onset of clinical diagnosis 13.0 years (SD 9.7 years, range 0.03–39.4 years). The mean number of classification criteria was 5.9 (SD 1.5, range 4–10). A history of nephritis as defined by the ACR criteria was detected in 86 (38.6%) of the 223 SLE patients. In 83 (37.2%) patients, lupus nephritis had been verified by biopsy.

Control subjects consisted of 98 blood donors. The sera from the 223 patients and from the 98 controls were stored at −20°C until tested. Missing data reflected small amounts of sera in unselected SLE patients.

The study was approved by the ethical committee of Helsinki University Central Hospital.

Laboratory methods

Anti-C1q antibody assays

Antibodies to C1q were determined by using two commercial ELISA kits: Anti-C1q Autoantibodies (EK-AC1QA; Bühlmann laboratories AG, Basel, Switzerland) and Anti-C1q (ORG 549; Orgentec Diagnostika GmbH, Mainz, Germany), as recommended by the manufacturers. Both tests used isolated human C1q as antigen, and in both tests, the sera were tested at dilution 1:100.

In the Bühlmann test, the technical cutoff for a positive test result as recommended by the manufacturer was 15 U/l. In our 98 control sera, the median anti-C1q value was 7.7 U/ml (range 5.0–237.9 U/ml). To achieve comparability to previous reports describing that about 6% of normal subjects are anti-C1q positive, the cutoff was set at 77 U/l, when 6.1% of the controls had higher values [19, 20].

In the Orgentec test, the cutoff value suggested by the manufacturer was 10 U/ml and the median anti-C1q in our control sera was 3.3 U/ml (range 0.4–44.6 U/ml). For similar analytical purposes as with the Bühlmann test, the cutoff was set at 16 U/ml, when 6.1% of the controls had higher values.

Anti-double-stranded DNA antibody assays

Anti-dsDNA was analyzed by one radioimmunoassay (RIA), by one immunofluorescence assay, and by three different ELISA assays. Originally, the samples were analyzed by a Farr immunoprecipitation assay using [^{125}I]-labelled bacterial DNA as antigen (Anti-dsDNA test, Medix Biochemica, Kauniainen, Finland). The cutoff value of this test was <5 mg/l. The test is not produced any more; thus, we could not determine the cutoff value for it in our control sera.

The indirect immunofluorescence (IF) technique for anti-dsDNA was performed using *Crithidia luciliae* slides as substrates (Fluorescent nDNA Test System, Immuno-Concepts, N.A. Ltd, Sacramento, CA). For screening, sera were diluted 1:10 and the secondary antibodies (FITC–conjugated anti-human IgG;A;M, Dako, Glostrup, Denmark) 1:200 in phosphate buffered saline, pH 7.2 (PBS). At the screening dilution, none of the 30 blood donor sera tested was positive. This dilution was used as the cutoff titer.

Table 1 Anti-C1q and anti-dsDNA in patients with SLE and active lupus nephritis

Autoantibody (method, manufacturer)	All SLE patients (positive)	Active lupus nephritis	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Anti-C1q (ELISA, Bühlmann)	38/209 (18.2%)	11/25	44	92	29	92
Anti-C1q (ELISA, Orgentec)	35/208 (16.8%)	10/25	40	92	29	91
Anti-ds DNA (RIA, Medix Biochemica)	103/212 (48.6%)	15/25	60	53	15	86
Crithidia luciliae (IF, ImmunoConcepts)	89/209 (42.6%)	13/25	52	52	11	90
Anti-dsDNA (ELISA, Biohit)	143/208 (68.8%)	17/25	68	29	12	88
Anti-dsDNA (ELISA, FEIA, Phadia)	108/209 (51.7%)	16/25	64	50	15	91
Anti-dsDNA (ELISA, Farrzyme, Binding Site)	75/209 (35.9%)	12/25.	48	66	16	90

Active nephritis was defined as the presence of proteinuria (>150 mg/l) and/or hematuria (>3 RBCs/high power field) in a patient with biopsy-verified lupus nephritis

PPV positive predictive value, *NPV* negative predictive value

The ELISA assays used human telomere DNA (Anti-dsDNA test, Biohit Plc, Helsinki, Finland) [10], plasmid DNA circles (EliA dsDNA test using ImmunoCap 250 analyzer; Phadia, Uppsala, Sweden), or calf thymus DNA (Farrzyme High avidity anti-dsDNA kit, Binding Site, Birmingham, UK) as antigens, respectively. The assays were performed according to the instructions of the manufacturers. The median values for blood donors were 10.4 IU/ml (range 2.9–123.0 IU/ml), 1.2 IU/ml (range <1.0–11.0 IU/ml), or 12.0 IU/ml (range 12.0–29.1 IU/ml) for the Biohit, Phadia, or Binding Site assays, respectively. The cutoff values were set at the 95th percentile for the controls were 33.4, 6.6, or 25.7 IU/ml, respectively, in the three assays.

Other laboratory measurements

Routine laboratory tests determined from the SLE patients at the time of the study included Westergren sedimentation rate, hematocrit, complete blood count, plasma creatinine, glomerular filtration rate (GFR). and urinary dipstick for proteinuria and hematuria. Complement C3 and C4 were measured by nephelometry.

Characteristics of lupus nephritis patients

The mean age of the 83 patients with a history of biopsy-verified lupus nephritis was 43.4 years (SD 15.0, range 18–87 years). Of the 83 latest renal biopsies performed median 8.3 years (range 0–33.5 years) before this study, 11 were classified as WHO II, 14 as WHO III, 41 as WHO IV, 12 as WHO V, 3 as WHO VI, and 2 had not been classified. The median creatinine value at the time of the study was 77.0 μmol/l (range 40–1,008 μmol/l), and the median GFR was 81.1 ml/s (range 7.4–172.5 ml/s). In 20 (24.1%) of the 83 patients, GFR was less than 50 ml/s. Active lupus nephritis was defined as the presence of at least 2+ proteinuria (>150 mg/l) and/or hematuria (3 or more red cells/high power field) by a urinary dipstick performed at the time of study in a patient with a history of biopsy-verified lupus nephritis.

Statistical methods

Spearman`s rank correlation was applied in studying correlations between the different assays and the activity of SLE as assessed by SLEDAI. The Mann–Whitney *U* test was used to compare the levels of the antibodies and complement C3 and C4 in patients with or without specific clinical characteristics including active nephritis. Odds ratios were calculated using logistic models. All *p* values were two-tailed, and differences at ≤0.05 were considered significant.

Results

Prevalence of the antibodies in patients with SLE

When the cutoff for positivity was set at the 94% percentile, the prevalences of anti-C1q in SLE by the two assays were 16.8 and 18.2%, respectively (Table 1). In general, the prevalences of anti-dsDNA were clearly higher than anti-C1q in the SLE patients. The most sensitive test (68.8%) was the anti-dsDNA assay using human telomere DNA as antigen, and the two least sensitive tests were the anti-C1q assays.

In patients with active nephritis, the prevalence of anti-C1q was 40–44% and that of anti-dsDNA 48–68% (Table 1). The corresponding figures in patients with inactive nephritis were 9.3–16.7% and 30–68%, respectively. The prevalences of positive anti-C1q by the 2 assays were higher in active versus inactive nephritis (OR 3.9 and 6.6; 95% CI 1.4–11.4 and 1.9–22.1), but no differences were found in the corresponding prevalences of anti-dsDNA by any of the 5 assays (OR 1.0–2.1; 95% CI 0.4–5.8). Four

(15%) of the 26 patients with active nephritis were negative by all anti-C1q and anti-dsDNA assays.

In general, specificity for active lupus nephritis was higher for anti-C1q than for anti-dsDNA (92% vs. 29–66%). Positive predictive values (PPV) were also higher for anti-C1q (29%) than for anti-dsDNA (11–16%). Negative predictive values (NPV) vary similar (88–92%).

Correlations of the assays and overall activity of SLE

Correlation coefficients between the antibody and complement levels and the SLEDAI score are summarized in Table 2. The results of the two anti-C1q assays correlated very well with each other ($r = 0.891$) and reasonably well with those of the anti-dsDNA assays ($r = 0.306$–0.571). The SLEDAI score correlated somewhat better with anti-dsDNA than with anti-C1q ($r = 0.353$–0.566 and 0.323–0.351, respectively). The anti-dsDNA RIA ($r = 0.566$) assay had the highest and the two anti-C1q assays ($r = 0.323$–0.351) the lowest correlation with SLEDAI. All values were, however, significant at the 0.01 level. The correlation between SLEDAI and low levels of complement C3 and C4 were −0.372 and −0.444, respectively ($P < 0.001$). The correlation coefficients of anti-C1q with complement C3 and C4 were −0.328 to 0.343 and −0.252 to 0.262, respectively. The corresponding figures for anti-dsDNA were −0.195 to 0.367 and −0.197 to 0.325, respectively. Anti-C1q, anti-dsDNA, and complement C3 and C4 did not significantly correlate with creatinine values or GRF.

Association of the tests with active nephritis

The differences in the antibody levels in patients with active versus inactive nephritis are shown in Table 3. The strongest associations were found by anti-C1q (0.008–0.016) and the weakest by anti-dsDNA using human telomere DNA and *Crithidia luciliae* slides as antigens (0.196–0.198). Active nephritis correlated very well with low levels of complement C3 ($P = 0.003$) and C4 ($P = 0.018$).

Association of then assays with hematological manifestations

Correlation coefficients were determined between the antibody and complement values and the hematological manifestations reflecting disease activity. Sedimentation rate correlated quite well with anti-dsDNA ($P = 0.001$–0.064), C3 ($P = 0.07$) but not with C4 ($P = 0.140$) or anti-C1q ($P = 0.758$–0.939). Low leukocyte count correlated significantly with anti-dsDNA by almost all ELISA assays ($P = 0.004$–0.136), C3 ($P < 0.001$), C4 ($P = 0.01$), and with anti-C1q ($P = 0.008$ and 0.145). Low thrombocyte values correlated most strongly with C3 and C4 ($P < 0.001$) and not so well with anti-dsDNA ($P = 0.036$–0.895) and not at all with anti-C1q ($P = 0.391$–0.736). Lymphopenia was associated with C3 ($P = 0.041$) and anti-dsDNA ($P = 0.002$–0.127) but not with C4 ($P = 0.360$) or anti-C1q ($P = 0.093$–0160). Low hematocrit associated with C3 ($P = 0.002$), C1q ($P = 0.039$–0.054), anti-dsDNA ($P < 0.001$–0.134) but not with C4 ($p = 0.682$).

Discussion

In daily clinical practice, the overall activity of SLE is evaluated by specific disease-associated symptoms and signs and by basic laboratory tests, which usually include sedimentation rate, hematocrit, complete blood count, creatinine (GFR), and urine dipstick. Additional tests in selected patients may include anti-dsDNA, complement C3 and C4, and other less conventional commercial assays including anti-C1q. In our study, anti-dsDNA and C3 and C4 correlated better with the SLEDAI score and with hematological parameters reflecting disease activity than anti-C1q. On the other hand, active lupus nephritis was more strongly associated with anti-C1q and complement assays than anti-dsDNA.

In most laboratories, anti-dsDNA are determined by the Farr assay, IF, or various ELISA techniques with different types of DNA as antigens. Most ELISA assays use DNA extracted from mammalian thymic tissues. In the *Crithidia luciliae* IF assays, the antigen is eukaryotic kinetoplast DNA, and many Farr and ELISA assays use bacterial or plasmid DNA. Different methods have different sensitivities and specificities. The Farr assay detects high-avidity antibodies, has high specificity for SLE and correlates well with disease activity [28]. Many laboratories have, however, moved away from the Farr assay to ELISA assays that are practical to perform and are nowadays the most commonly used methods for quantifying antibodies to dsDNA. ELISAs are more sensitive in detecting low affinity anti-dsDNA but also less specific for SLE [8, 9]. *Crithidia luciliae* IF assay shows high specificity for SLE but has relatively low sensitivity [28]. In our study, the ELISA assay using telomeric DNA as antigen was somewhat more sensitive for SLE and for active lupus nephritis than the other assays, but its specificity was low. With regard to two other ELISA assays, the Farr assay and IF, no practical differences were found in relation to sensitivity and specificity for either nonrenal and renal activity of SLE.

The prevalence of anti-C1q in our patients with SLE was low as compared to previous studies. This is explained by elevated levels of anti-C1q in healthy blood donors, which resulted in a high cutoff value for positivity. Most previous studies have used cutoffs recommended by the manufacturer.

Table 2 Spearman rank correlation coefficients between antibody titers and complement C3 and C4 values and the activity of SLE as assessed by the SLEDAI score in 223 patients*

	Anti-C1q (ELISA, Bühlmann)	Anti-C1q (ELISA, Orgentec)	Anti-ds DNA (RIA, Medix)	*Crithidia luciliae* (IF, ImmunoConcepts)	Anti-dsDNA (ELISA, Biohit)	Anti-dsDNA (FEIA, Phadia)	Anti-dsDNA (Farrzyme, Binding Site)	Complement C3 (Nephelometry)	Complement C4 (Nephelometry)	SLEDAI score
Anti-C1q (ELISA, Bühlman)	1.000	0.891	0.481	0.358	0.492	0.571	0.502	0.343	0.252	0.351
Anti-C1q (ELISA, Orgentec)		1.000	0.473	0.306	0.456	0.535	0.444	0.328	0.262	0.323
Anti-ds DNA (RIA Medix)			1.000	0.475	0.659	0.709	0.561	0.195*	0.250#	0.566
Critidia luciliae (IF, ImmunoConcepts)				1.000	0.583	0.538	0.552	0.310	0.235	0.405
Anti-dsDNA (ELISA, Biohit)					1.000	0.785	0.546	0.349	0.325	0.452
Anti-dsDNA (FEIA, Phadia)						1.00	0.619	0.367	0.246	0.435
Anti-dsDNA (Farrzyme, Binding Site)							1.000	0.314	0.197	0.353
Complement C3 (Nephelometry)								1.000	0.583	0.372
Complement C4 (Nephelometry)									1.000	0.444
SLEDAI score										1.000

All but 2 values were significant at the 0.01 level

ELISA enzyme-linked immunosorbent assay, *RIA* radioimmunoassay, *IF* immunofluorescence, *FEIA* fluoroimmunoenzymatic assay

* $P = 0.086$

$P = 0.014$

Table 3 Differences in autoantibody titers and levels of complement C3 or C4 in 26 patients with active lupus nephritis versus in 57 patients with inactive lupus nephritis

Antibody assay	*P* value
Anti-C1q (ELISA, Bühlmann)	0.008
Anti-C1q (ELISA, Orgentec)	0.016
Anti-dsDNA (RIA, Medix Biotech)	0.023
Anti-dsDNA (IF, ImmunoConcepts)	0.196
Anti-dsDNA (ELISA, Biohit)	0.198
Anti-dsDNA (FEIA, Phadia)	0.093
Anti-dsDNA (Farrzyme, Bining Site)	0.157
Complement C3	0.003
Complement C4	0.018

Active or inactive nephritis was defined as history of biopsy-verified lupus nephritis and the presence or absence of proteinuria (>150 mg/l) and/or hematuria (>3 RBCs/high power field) at the time of the study, respectively

When we used these technical cutoffs, the prevalences of anti-C1q in SLE were 38.3 and 21.2% and in blood donors 37.8 and 23.5%, respectively. The high values of the controls were surprising but remained in repeated tests and with more stringent washings. According to our figures, low to moderately elevated levels of anti-C1q are common in healthy people. We suggest a higher cutoff for positivity than recommended by manufacturers of anti-C1q kits similarly as in a recent report [19], and this emphasizes the fact that every laboratory should establish its own cutoff values before using the test in the clinical routine.

All serum samples used in our study had been stored at −20°C, and thus, we do not know whether unfrozen samples would give lower values. Freezing and thawing may increase the amount of aggregated IgG in the samples, and this could increase positivity in the anti-C1q assays. All sera of SLE patients and of controls were, however, stored in the same way.

The prevalence of anti-dsDNA in our controls and patients with SLE was clearly different from that of anti-C1q; only a few healthy controls had high values, and the majority of SLE patients were anti-dsDNA positive. The sensitivities of the different anti-dsDNA assays were between 40 and 70%, which is in accordance with the literature [3]. It, thus, appears that anti-C1q is insensitive and clearly inferior as a diagnostic test for SLE as compared to anti-dsDNA.

In patients with lupus nephritis, the activity of the renal disease correlated better with anti-C1q and complement C3 and C4 than with anti-dsDNA, and patients with active nephritis were clearly more often anti-C1q positive than patients with inactive nephritis. Curiously, although anti-dsDNA correlated with the activity of SLE, the differences in the prevalences of these antibodies in patients with active versus inactive nephritis were small. These findings support the evidence of superior specificity of anti-C1q over anti-dsDNA for renal flares [24, 25].

The sensitivity of anti-C1q for active nephritis was lower than for anti-dsDNA, but specificity was clearly higher. Anti-C1q and especially anti-dsDNA had low PPV for active nephritis, but NPVs were high by all tests. In other studies, the PPVs of anti-C1q for active nephritis have been higher than in our study and NPVs similar [17, 20, 22, 24]. This is obviously explained, in addition to setting cutoffs for positivity differently, by different patient populations. In our cross-sectional study, patients with lupus nephritis were unselected, had an ongoing effective medication and had a rather low disease activity. Low PPVs and high NPVs indicate that anti-C1q and anti-dsDNA may not be satisfactory to detect a renal flare, but in the presence of normal values of the tests, active nephritis is rare. Negative results by all assays, however, do not exclude active nephritis, and there are reports of patients with active proliferative lupus nephritis having negative anti-C1q [29]. In our study, 15% of the patients with active nephritis were negative by all anti-C1q and anti-dsDNA assays.

What is the possible role of anti-C1q in the pathogenesis of lupus nephritis? C1q is important in the clearance of immune complexes and self antigens generated during cell death [30, 31], and a recent study suggests that the real target might be apoptotic cells [32]. Defective clearance of apoptotic cells, which may become antigenic, is an important hypothesis about the pathogenesis of SLE [33], and primary (hereditary) deficiency of C1q is a known risk factor for the development of the disease [34, 35]. Hypocomplementemia in SLE can also be a secondary event resulting from binding of antibodies to the collagen-like region of C1q. These antibodies may either contribute to the formation of circulating immune complexes that are deposited in the kidney or contribute to the local formation of immune complexes on the glomerular basement membrane. Moreover, by interfering with the activation of the complement system, anti-C1q may hinder immune complex solubilization contributing further to the deposition of immune complexes in the kidney. The antibodies may also directly bind to C1q bound to the glomerular immune complexes and thus increase the damage [36].

In conclusion, we found that the prevalence of anti-C1q was low in patients with SLE, which was explained by elevated levels of anti-C1q in healthy controls leading to reasonably high cutoff values. We also found that anti-C1q and complement C3 and C4 were better markers for lupus nephritis activity than anti-dsDNA, and that anti-dsDNA and complement C3 and C4 were better than anti-C1q to evaluate the overall and nonrenal activity of SLE. Futhermore, no practical differences between different assays for anti-dsDNA and anti-C1q were found.

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