Significance of low molecular weight Clq in systemic lupus erythematosus

R Hoekzema, A J G Swaak, M C Brouwer, A van Rooijen,* E J Nieuwenhuys, C E Hack

Abstract

The significance of high serum concentrations of low molecular weight Clq (LMW-Clq) in patients with systemic lupus erythematosus (SLE) was studied. Concentrations of LMW-Clq were increased in SLE, but not in rheumatoid arthritis or acute poststreptococcal glomerulonephritis. Concentrations of LMW-Clq in SLE serum samples correlated with titres of anti-dsDNA and were inversely related to concentrations of normal Clq and C3. Serial studies in six patients, who had rising anti-dsDNA titres and who developed a major exacerbation requiring admission to hospital, showed that LMW-Clq increased in parallel with anti-dsDNA, reaching peak values of more than 2000% of normal just before or at the time of clinical relapse and decreasing during convalescence. Most marked increases in LMW-Clq were noted in the three patients in whom Clq concentrations remained normal, whereas increases were less in the three patients who had strongly depressed concentrations of normal Clq. A study of Clq biosynthesis by macrophages cultured from patients with SLE and high serum concentrations of LMW-Clq did not show impaired secretion of normal Clq in favour of LMW-Clq, but indicated that serum concentrations of LMW-Clq may reflect the synthetic rate of Clq in vivo. The results show that increased serum concentrations of LMW-Clq may be helpful in diagnosing SLE and suggest that serial determination of LMW-Clq in serum may have predictive value in monitoring patients with SLE.

In a previous study we reported increased concentrations of low molecular weight Clq (LMW-Clq) in serum samples from 54 patients with SLE who had not been selected for their disease activity. This antigenically defective molecule, which does not participate in complement activation, was originally found in homozygous subjects with an inherited deficiency of functional Clq and a tendency to develop SLE-like syndromes. Low molecular weight Clq was also found at lower concentrations in serum samples from normal controls. Furthermore, recent studies with cultured blood monocytes from normal donors and subjects genetically deficient in Clq indicated that in vitro LMW-Clq is an important by-product of Clq synthesis. These observations raise the following questions about the significance of LMW-Clq in SLE. Are high serum concentrations of LMW-Clq specific for SLE or a common finding in immune complex mediated disorders? Do they reflect increased or impaired synthesis of Clq? Are serum concentrations of LMW-Clq related to serological or clinical indices of disease activity and does LMW-Clq itself behave as such an index?

The aim of the work described here was to answer these questions.

Patients and methods

PATIENTS AND SERUM SAMPLES

Eighty two patients with SLE fulfilling the revised American Rheumatism Association (ARA) criteria were entered into the study. Blood samples from 71 of these patients were obtained within six weeks after the appearance of one or more of the following symptoms: skin lesions, including rashes, palpable purpura, and digital infarctions (present in 34 patients); arthralgia or arthritis (in 32 patients); haematological abnormalities—that is, haemolytic anaemia, thrombocytopenia or leucopenia (in 38 patients); pleuritis (in 22 patients); renal symptoms manifested by a decrease of glomerular filtration rate of more than 20%, appearance of or an increase in red cell casts in the urinary sediment, or the appearance of or an increase in proteinuria (in 33 patients); central nervous system disease, in most cases manifested by the occurrence of psychotic episodes, and in occasional patients by aseptic meningitis or convulsions (in 21 patients). Anti-dsDNA antibodies, measured by the Farr assay, in these 71 serum samples were increased. In addition, blood samples were obtained from the other 11 patients with SLE, who had no symptoms of SLE at that time. In addition, we studied 38
patients with polyarthritus, all with classic or definite rheumatoid arthritis according to the ARA criteria, and 21 children (ages 2–18 years) with acute glomerulonephritis, whose diagnosis was based on a combination of clinical criteria and laboratory findings. Raised anti-streptolysin titres were present in 15 of these children. From all these patients one serum or plasma sample was tested. Serial samples were also tested from six other patients with SLE who fulfilled the revised ARA criteria. Samples of serum, citrate, or EDTA plasma from patients and from 60 healthy donors were frozen at −70°C until use.

**MONOCYTES**

Blood (30 ml) from patients with SLE was collected in siliconised vacutainer tubes (Becton and Dickinson, Meylan, France) containing tri-sodium citrate at a final concentration of 0.38% (w/v). Within four hours after collection plasma was separated from cells by centrifugation (five minutes, 4000 g at room temperature) and stored at −70°C. Monocytes were purified from the cell pellets essentially as described by de Boer et al., with the exception that Ficoll was replaced by Percoll (Pharmacia Fine Chemicals A/B, Uppsala, Sweden). The purity of monocytes obtained by this procedure ranged from 60 to 90% as determined by size analysis differentiation (Coulter counter with Channelizer) and yields ranged from 5 to 20×10⁶ monocytes. The cells were cultured in 24-well multitubes (Nunclon, Roskilde, Denmark) at 5×10⁶ cells/well in Iscove’s modified Dulbecco’s medium, supplemented with 10% (v/v) heat inactivated (one hour, 56°C) fetal calf serum (Sera-Lab, Sussex, UK), 10 μg/ml of L(+)-ascorbic acid (Merck, Darmstadt, FRG), penicillin, and streptomycin. Culture supernatant was harvested and medium replenished after 24 hours and then twice a week.

Each time that cells were obtained from patients, blood was also collected from healthy donors with similar sex and age (the difference in age between patient and donor was not more than four years). The monocytes from these donors were studied for Clq production at the same time as those from the patients.

**MONOCLONAL ANTIBODIES AGAINST Clq**

The following two monoclonal antibodies (MAbs) against Clq were used in this study: MAb 130, which is directed against an epitope on the fibril-like strands (arms) of Clq close to the globular heads, and which can bind normal Clq, pepsin digested Clq, and also collagenase digested Clq, but cannot bind LMW-Clq produced by cultured monocytes, nor the dysfunctional LMW-Clq found in some patients with a hereditary Clq defect; MAb 101, which hardly binds normal Clq, but does bind the LMW-Clq produced by cultured monocytes. Monoclonal antibody 101 also binds the LMW-Clq that is present in some patients with a genetic Clq deficiency (unpublished observations).
controls was determined by the Wilcoxon-Mann-Whitney test.

**Results**

**CHARACTERISTICS OF RADIOIMMUNOASSAY FOR LMW-Clq**

Although MAb 101 used for the LMW-Clq radioimmunoassay preferably binds LMW-Clq, binding of normal Clq does occur to some extent (Hoekzema et al, unpublished data). Therefore, all sera and monocyte culture supernatants were first depleted of Clq by an incubation with another MAb (130), specific for normal Clq, which had been coupled to Sepharose beads as described under 'Patients and methods'. Conditions of immunoabsorption were chosen in such a way that all normal Clq was removed from 50 μl of normal human serum. Low molecular weight Clq in serum from a patient with a genetic Clq deficiency was not removed by this absorption procedure (data not shown). Figure 1 shows that this radioimmunoassay procedure resulted in a reproducible dose-response curve for LMW-Clq in normal human serum. When a solution of purified normal Clq (250 μg/ml) was used as starting material, no significant binding was found. The antigen detected in this radioimmunoassay had the physicochemical properties of LMW-Clq—that is, a sedimentation coefficient of 4S in sucrose gradient ultracentrifugation and an apparent molecular weight of 130 000 in gel filtration (not shown).

In the following experiments concentrations of LMW-Clq in serum samples and monocyte culture supernatants were calculated by reference to standard curves of normal human serum as in fig 1, arbitrarily defined as containing 100% LMW-Clq.

**SERUM CONCENTRATIONS OF NORMAL AND LMW-Clq IN PATIENTS AND IN NORMAL DONORS**

Concentrations of normal and LMW-Clq were determined as described under 'Patients and methods' in serum samples from 82 patients with SLE, and compared with concentrations in serum samples from 38 patients with rheumatoid arthritis, 21 patients with acute glomerulonephritis, and 60 healthy controls (fig 2). In comparison with controls (median 102.5%), concentrations of LMW-Clq were increased in SLE (median 163.5%, p<0.0001) but not in rheumatoid arthritis (median 110%, p=0.7565). In acute glomerulonephritis serum concentrations of LMW-Clq were decreased (median 78%, p=0.0116). Normal Clq was decreased in SLE (median 47.5%, p<0.0001) and acute glomerulonephritis (median 92%, p=0.0002) but showed a tendency towards increased concentrations in rheumatoid arthritis (median 125%, p=0.0502) when compared with controls (median 113.5%).

Seventy one patients with SLE had had one or more clinical symptoms within six weeks before the time of blood sampling. Low molecular weight Clq concentrations in these patients were not particularly associated with one or more clinical manifestations. Low molecular weight Clq concentrations in patients with these symptoms were: 174% (101–667%) (median range) in patients with pleuritis; 167% (96–667%) in patients who had haematological abnormalities; 160% (96–421%) in patients with skin lesions; 154% (96–400%) in patients who...
Low molecular weight C1q in SLE

Table 1 Correlation between serum concentrations of low molecular weight C1q and other serological indices

<table>
<thead>
<tr>
<th>Indices correlated with LMW-C1q</th>
<th>Control</th>
<th>RA*</th>
<th>AGN*</th>
<th>SLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clq</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-66 (n=60)</td>
<td>-0-05 (n=38)</td>
<td>0-09</td>
<td></td>
<td>-0-22</td>
</tr>
<tr>
<td>p&lt;0-001</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>(n=82)</td>
</tr>
<tr>
<td>C3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-53 (n=60)</td>
<td>-0-47 (n=38)</td>
<td>-0-62</td>
<td></td>
<td>-0-34</td>
</tr>
<tr>
<td>p&lt;0-001</td>
<td>NS</td>
<td></td>
<td></td>
<td>(n=69)</td>
</tr>
<tr>
<td>C4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-51 (n=60)</td>
<td>-0-26 (n=38)</td>
<td></td>
<td>-0-12</td>
<td></td>
</tr>
<tr>
<td>p&lt;0-001</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td>(n=69)</td>
</tr>
<tr>
<td>Anti-dsDNA (Farr)</td>
<td>NT*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA (IFT)*</td>
<td>NT</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AGN=acute glomerulonephritis; IFT=immunofluorescence technique; LMW-C1q=low molecular weight C1q; NT=not tested; RA=rheumatoid arthritis; SLE=systemic lupus erythematosus.

had arthritis or arthralgia; 143% (96–667%) in patients with central nervous system disease; and 160% (96–667%) in patients with renal disease.

RELATION OF LMW-C1q TO OTHER SEROLOGICAL INDICES

In the 60 healthy controls highly significant correlations were found between concentrations of LMW-C1q and Clq (r=0-6611, p<0-001), C3 (r=0-5279, p<0-001), and C4 (r=0-5137, p<0-001), indicating that in the absence of complement activation the synthetic rates of these components are probably coupled (table I).

In contrast, in SLE serum samples concentrations of LMW-C1q were inversely correlated with concentrations of Clq (n=82, r=−0-2239, p<0-05) and C3 (n=69, r=−0-3375, p<0-01). When concentrations of LMW-C1q or Clq were compared with titres of anti-dsDNA it was found that LMW-C1q but not normal Clq correlated with anti-dsDNA measured by the Farr assay (n=71, r=0-2481, p<0-05) or by the immunofluorescence technique (n=71, r=0-2688, p<0-05). In serum samples from patients with rheumatoid arthritis and acute glomerulonephritis, no correlation was found between concentrations of LMW-C1q and Clq.
Figure 3 shows the longitudinal profile of normal and LMW-C1q in serum of patients D, S, and P, who developed a severe deterioration of renal function during a major flare. In these patients the exacerbation was heralded not only by rising anti-dsDNA titres (not shown in fig 3), but also by markedly depressed serum C1q, starting several months before clinical signs of nephritis were apparent. Concentrations of C1q returned to normal during convalescence except in patient S who died of sepsis as a complication of severe skin ulceria. Serum concentrations of LMW-C1q fluctuated in a manner opposite to those of normal C1q and more similar to titres of anti-dsDNA: they ‘peaked’ in the period of severe relapse and decreased during convalescence.

When profiles of LMW-C1q were studied in three other patients who had normal serum concentrations of C1q in the period of rising anti-dsDNA that preceded major flares, unexpected results were obtained: the increase in LMW-C1q was much more pronounced in these patients, reaching values of more than 20 times the normal concentration (fig 4). None of these patients had severe renal disease, though patients H and W had mild renal symptoms about two weeks after the anti-dsDNA peak.

Figure 4 Profiles of C1q and low molecular weight C1q (LMW-C1q) in serum during exacerbations of systemic lupus erythematosus (SLE). Serial determinations of serum concentrations of normal and LMW-C1q in three patients with SLE who developed a major exacerbation after a period of rising anti-dsDNA, accompanied by normal C1q concentrations in serum. Time zero (t=0) indicates the moment of highest anti-dsDNA titres in these patients. Patient G had an erythematous skin rash, arthralgia, severe leucopenia, and haemolytic anaemia. No signs of renal disease were noted. Patient H had leucopenia, thrombopenia, and pleuritis, and patient W had skin rashes, thrombocytopenia, and arthralgia. Both patients H and W had mild renal symptoms (an increase in serum creatinine up to 300 µmol/l and proteinuria of 1 g/24 h, respectively) about two to three weeks after the anti-dsDNA peak. NHS = normal human serum.

Table 2 Correlation between concentrations of C1q and low molecular weight C1q (LMW-C1q) in serum and monocyte cultures of patients with systemic lupus erythematosus (SLE)

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Serum</th>
<th>Culture (day 20)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LMW-C1q t</td>
<td>C1q t</td>
</tr>
<tr>
<td>1</td>
<td>100</td>
<td>116 0.86</td>
<td>820</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>100 1.80</td>
<td>820</td>
</tr>
<tr>
<td>3</td>
<td>98</td>
<td>87 1.13</td>
<td>510</td>
</tr>
<tr>
<td>4</td>
<td>116</td>
<td>1.87</td>
<td>510</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>0.94</td>
<td>240</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>121 1.49</td>
<td>570</td>
</tr>
<tr>
<td>7</td>
<td>259</td>
<td>140 1.85</td>
<td>730</td>
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<tr>
<td>8</td>
<td>246</td>
<td>174 1.41</td>
<td>540</td>
</tr>
<tr>
<td>9</td>
<td>321</td>
<td>162 1.98</td>
<td>700</td>
</tr>
<tr>
<td>10</td>
<td>355</td>
<td>182 1.95</td>
<td>560</td>
</tr>
</tbody>
</table>

*Expressed as percentage of the concentration in normal human serum.
†Expressed as percentage of the concentration in normal human serum, secreted in 24 hours.
‡Ratio LMW-C1q/C1q.

Figure 5 Secretion of C1q and low molecular weight C1q (LMW-C1q) by macrophages cultured from patients with systemic lupus erythematosus (SLE) and from controls. Blood mononuclear from 10 patients with SLE (○) and 10 healthy controls matched for age and sex (●) were allowed to differentiate into C1q producing, macrophage-like cells by culture. Amounts of functional C1q (assessed by C1q haemolytic assay) and LMW-C1q (assessed by radioimmunoassay) that had accumulated in culture medium in 24 hours were measured at different times in culture and expressed as percentage of the amount present in normal human serum (NHS). Mean (2 SD) is indicated.
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both patients this was accompanied by moderate depression in C1q concentrations (fig 4).

SECRETION OF NORMAL AND LMW-C1q BY CULTURED MONOCYTES

To investigate whether a dysfunction of C1q synthesis is present in C1q producing cells from patients with SLE, blood monocytes were cultured from 10 patients with SLE and 10 healthy controls matched for sex and age, as described under 'Patients and methods'. None of the patients had a major relapse or depressed serum C1q, but seven of the 10 patients had a LMW-C1q serum concentration ≥180% of normal, and serum concentrations of LMW-C1q and C1q correlated significantly (p<0.001) in these patients (table 2). During the period of in vitro maturation into C1q synthesising macrophages samples were taken from the culture supernatants and tested for functional C1q (by haemolytic assay) and LMW-C1q (by radioimmunoassay). Figure 5 indicates that impaired synthesis of C1q could not be shown in SLE monocytes by comparison with controls. On the contrary, the monocyte derived macrophages from patients tended to secrete more C1q than cells from controls. Table 2 shows the significant correlation (p<0.001) between amounts of functional and LMW-C1q that had been secreted by cells from patients with SLE as well as the excessive production of LMW-C1q, as judged by LMW-C1q/C1q ratios in comparison with sera. No correlations were present between concentrations of LMW-C1q or C1q in serum and those in culture supernatant or between ratios in serum and those in culture supernatant. Similar results were obtained with cultures from healthy controls matched for age and sex (not shown).

Discussion

In a previous study we reported that serum samples from patients with SLE contain increased concentrations of LMW-C1q when compared with samples from healthy donors.7 The possibility was considered that serum concentrations of LMW-C1q reflect the rate of biosynthesis of normal C1q in these patients. At that time it was not clear whether LMW-C1q represents a product of C1q-synthesising cells, however, and the study on patients with SLE did not include serial measurements of LMW-C1q at varying stages of disease activity.

In this study we used a particular radioimmunoassay to measure LMW-C1q concentrations in serum. LMW-C1q was bound to MAb 101 and measured by a subsequent incubation with 125I labelled purified rabbit antibodies to C1q. Although normal C1q hardly bound to MAB 101, at higher concentrations it interfered with the assay. Therefore, we removed normal C1q from serum samples by absorption with MAB 130 before determining LMW-C1q concentrations. Although MAB 130 neither binds the LMW-C1q produced by cultured monocytes8 nor the LMW-C1q found in some patients with a genetic C1q deficiency, it can bind other low molecular weight forms of C1q, in particular those forms generated by enzymatic degradation of normal C1q.13 We did not analyse the composition of the C1q molecules removed from sera by MAb 130. Therefore, the possibility still remains that in addition to the normal C1q and the LMW-C1q described in this study, other forms of C1q, generated by enzymatic degradation, may circulate in patients with SLE. In a recent study we showed that the LMW-C1q detected by MAb 101 is produced by cultured monocytes and contains normal A, B, and C chains as well as an abnormal AC dimer.9 This LMW-C1q is indistinguishable from the serum LMW-C1q present in normal subjects and at higher concentrations in patients with SLE.7 9 Therefore, we believe that the LMW-C1q described in this study is formed as a by-product of C1q synthesis and that serum LMW-C1q concentrations reflect C1q synthesis in vivo.

The results shown here confirm our previous finding—that is, that high serum concentrations of LMW-C1q seem to be specific for SLE: concentrations higher than 170% of normal were not found in patients with rheumatoid arthritis or in those with poststreptococcal acute glomerulonephritis. Although LMW-C1q will have to be measured in other disorders, these data indicate that the determination of LMW-C1q may prove a helpful addition to the revised ARA criteria in diagnosing SLE.10 The correlation (p<0.05) between concentrations of LMW-C1q and anti-dsDNA titres in SLE sera suggested to us that they may fluctuate in a comparable manner—that is, rise in periods of active disease and decrease during convalescence.2 4 This was confirmed by a prospective study in six patients who experienced a major flare: in these patients serum concentrations of LMW-C1q started to rise several weeks or even months before admission into hospital was required. Similar fluctuations were found for serum titres of anti-dsDNA and the rise in LMW-C1q and anti-dsDNA occurred simultaneously.

Remarkable were the differences of LMW-C1q profiles in patients with SLE with and without disease, especially in relation to concentrations of normal C1q. It is well known that serum C1q is lower in patients with nephritis,1 4 16 which is usually attributed to increased catabolism of this complement component. Indeed, experiments in vivo17 and in vitro18 19 showed that after binding to aggregates of IgG (as a model for circulating immune complexes) C1q is rapidly cleared and degraded by cells of the mononuclear phagocyte system, suggesting that the fate of C1q and immune complexes in vivo may be closely connected. If the turnover of C1q is accelerated in SLE, one would expect increased catabolic and synthetic rates, as found in other disorders with depressed serum C1q, such as paraproteinaemia.20 21 The few studies on the metabolism of C1q in SLE do not confirm this, however, as they report normal or only slightly accelerated catabolism.20 22 23 Therefore, the possibility has to be considered that impaired biosynthesis of C1q contributes to low serum concentrations of C1q in renal SLE, as has been shown for

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complement component C3. The high peak values (up to more than 2000%) of LMW-Clq with normal or slightly depressed Clq found in patients G, H, and W, who had no renal disease, (fig 4) would then be compatible with a greater ability of these patients to accelerate biosynthesis of Clq than patients D, S, and P with renal disease (fig 3), who had very low or undetectable Clq and a less pronounced rise in LMW-Clq. Analysis of LMW-Clq concentrations in the 71 patients with SLE, from whom blood samples were obtained within six weeks after the appearance of clinical symptoms, did not show significantly lower LMW-Clq concentrations in patients with renal disease than in those without renal symptoms. Apparently, more serial measurements of LMW-Clq concentrations in patients with active SLE are needed in combination with detailed Clq turnover studies to show whether there are differences in Clq synthesis between patients with various manifestations of SLE. Also, the possibility that the less pronounced rise of LMW-Clq in patients with nephritis results from loss through proteinuria will have to be excluded.

The inability to show impaired biosynthesis of Clq by culture derived macrophages from 10 patients with SLE does not exclude an impairment in vivo. Firstly, none of these particular patients had active disease according to clinical and laboratory indices: decreased synthesis of Clq in vivo may be temporary and restricted to a certain phase in the disease course, as has been shown for C3 (27). Secondly, cultured cells from healthy donors as well as from patients with SLE (table 2) secreted excessive amounts of LMW-Clq in comparison with functional Clq. This suggests that the in vitro situation itself may impede the production of normal Clq, possibly masking any differences between patients and controls. We are currently investigating this phenomenon.

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