Metabolism of Human C1q

STUDIES IN HYPOGAMMAGLOBULINEMIA, MYELOMA, AND SYSTEMIC LUPUS ERYTHEMATOSUS

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ABSTRACT The in vivo metabolism of radioiodine-labeled C1q was determined in patients with hypogammaglobulinemia, multiple myeloma, systemic lupus erythematosus (SLE), and in healthy controls. Marked differences in metabolic behavior were observed with a much more rapid disappearance of plasma radioactivity in patients as compared with controls. Estimated plasma volumes at 10 min after injection (time 0) were normal in controls and the SLE patient, mean 40 ml/kg, whereas they were grossly elevated, 57–82 ml/kg, in the hypogammaglobulinemic and myeloma patients, indicating significant loss of C1q-^{125}I during the initial mixing period. Absence of a distinct initial equilibration phase of radioactivity loss from the plasma suggested significant reversible interaction of the labeled C1q with plasma proteins and density gradient studies provided evidence for in vivo uptake into the circulating trimolecular first component complex (C1q, r, s). In controls and the SLE patient 0.51–0.75 of the C1q was retained in the plasma space while only 0.28 or less was in the others. The daily plasma pool fractional C1q catabolism was 0.65–0.67 in controls compared with 0.95–4.80 in the patients. C1q synthetic rates in controls were 4.64 and 4.34 mg/kg per day while higher rates, 4.94–37.40 occurred in the patients.

These experiments clearly indicate that the metabolism of C1q is markedly influenced by serum IgG concentrations, probably related to the reversible interactions of C1q with IgG, and also affected by interactions with C1r and C1s. The decreased serum C1q often present in hypogammaglobulinemia and myeloma relates to an increased catabolism and higher extravascular distribution rather than impaired C1q synthesis. In contrast, a second distinctly different basis for decreased C1q occurs in SLE; increased utilization by an ongoing immunopathogenic process.

INTRODUCTION

Serum C1q is the subunit of the first component of complement (C1) which is endowed with the capacity to recognize immunoglobulins and to initiate the complement reaction. It is a basic glycoprotein of molecular weight 400,000 with an electrophoretic mobility of a slow gamma globulin and has been isolated in a highly purified and functionally active form (1). Originally defined by its ability to induce precipitation of soluble gamma globulin complexes (2, 3) C1q has receptors directed to sites on the heavy polypeptide chains of immunoglobulins (Ig)[1] G and M but not A, D, or E (4).[2] The binding affinity to IgG molecules varies in dependence on their heavy chain subclass; it is greater for G3 than for G1 and G2 and apparently zero for G4.

Decreased serum C1q has been observed in a limited number of diseases. In active systemic lupus erythematosus (SLE) it may be low and correlated with the total serum complement (5–7). Precipitation of the serum cryoglobulins which are frequently present in SLE was

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[1] *Abbreviations used in this paper:* Ig, immunoglobulin(s); SLE, systemic lupus erythematosus; TCA, trichloroacetic acid.

[2] Ishizaka, T., and K. Ishizaka. 1969. Personal communication.

first shown by Christian, Hatfield, and Chase to be dependent on the presence of C1q (8). In addition, some patients with active chronic "hypocomplementemic" nephritis have reduced serum C1q (9). Complement-dependent immunopathogenic processes are thought to be operative in both of these diseases and the decreased serum C1q has been attributed to increased utilization by the underlying pathogenic process (5–7, 9).

In addition to the above diseases, even more consistent reductions of C1q occur in patients with certain immunoglobulin deficiencies in whom hemolytic total complement and other component levels are normal. Müller-Eberhard and Kunkel found low C1q concentrations in serum from three individuals with Bruton's agammaglobulinemia (2). A profound decrease in C1q was subsequently reported in a 3 wk female with Swiss agammaglobulinemia (10, 11). These observations have been recently extended by studies employing the quantitative radial diffusion technique (12–14).

Our previous study revealed a direct relationship between the serum concentration of C1q and IgG, but not IgA or IgM (12). The lowest C1q concentrations were found in patients with deficient IgG synthesis. In addition, close to one-half of multiple myeloma and Waldenström's macroglobulinemia sera had low C1q while markedly elevated concentrations were observed in heavy chain disease sera of the IgG_3 subclass (12). Gewurz and associates (13) found a reduction of C1q to 27% in three infants with Swiss-type agammaglobulinemia and 75% of normal in other agammaglobulinemic syndromes. In their report, the C1q reduction was felt to be related to the type of agammaglobulinemia rather than to the extent of IgG deficiency (13).

The present study was undertaken to define the basis for the reduced C1q concentrations in patients with immunoglobulin abnormalities and SLE by determining the in vivo metabolism of radioiodine-labeled protein. In addition, attention was directed to the possible in vivo uptake of the injected C1q into the native trimolecular C1 complex.

METHODS

Study group. A total of seven adults were studied. Two male physicians served as controls. The experimental group consisted of two patients with acquired hypogammaglobulinemia, two with multiple myeloma, and one with active SLE. A brief summary of the pertinent clinical and laboratory information concerning these subjects is presented in Table I. All were in a stable clinical condition during the studies save for the patient with IgG myeloma (case 7) who required transfusions of packed red cells because of gastrointestinal bleeding.

Preparation of isolated, radioactive-labeled C1q for intravenous injection. C1q was isolated from the fresh serum of healthy adults by a recently described procedure (1). All buffers were autoclaved and contained 5×10^{-5} M kanamycin.

The purified C1q was trace labeled with ^{125}I by the chloramine T method as described by McConahey and Dixon (15). After extensive dialysis to remove nonprotein-bound

TABLE I

Clinical and Laboratory Data

Case	Diagnosis	Sex	Age	C1q	IgG	IgA	IgM	Study initiated	Treatment	Comment
					mg/ml					
1	Control	M	34	0.182	8.50	2.55	0.59	6/20/69	—	—
2	Acquired hypogamma	M	53	0.132	2.61	0.117	0.078	6/23/69	—	Atrophic gastritis, malabsorption, previous Giardia lamblia infection
3	IgA myeloma	F	52	0.091	1.13	0.216	0.096	6/23/69	Prednisone (20 mg) and cyclophosphamide (100 mg/day)	Multiple osteolytic lesions, no proteinuria
4	Acquired hypogamma	M	19	0.094	0.76	0.0	0.116	6/23/69	15 cm^3 Cohn F II (16.6% humangamma globulin)/2 wk	Recurrent respiratory infections since age 1, brother's immunoglobulins normal
5	SLE	M	25	0.134	18.0	5.83	0.85	6/27/69	Prednisone (40 mg), azathioprine (100 mg), and hydroxychloroquine (600 mg/day)	Proteinuria, 1–1.5 g/24 hr, low total C, C3 and C4, cryoglobulins
6	Control	M	37	0.151	11.88	2.55	2.26	6/30/69	—	—
7	IgG myeloma	M	58	0.240	24.30	1.25	0.56	7/5/69	Transfusions of packed red blood cells	Proteinuria 1 g/24 hr, G.I. bleeding and fever 38°C during study
Normal range, *mg/ml*				0.134–0.246	6.20–14.00	0.68–3.14	0.93–3.20			

isotope, the C1q-^{125}I was centrifuged at 49,000 rpm for 60 min in a Spinco model L-2 ultracentrifuge (Spinco Div., Beckman Instruments, Inc., Palo Alto, Calif.) to remove aggregated protein. This step was also necessary as a precaution to insure that any bacterial contaminants were removed since it had been previously observed that Millipore filtration (0.45 μ pore size [Millipore Corporation, Bedford, Mass.]) caused retention of a large proportion of C1q and, therefore, could not be used for sterilization. Subsequent to ultracentrifugation the supernatant fluid was removed sterilely and diluted with sterile pyrogen-free saline to a protein concentration of 80 μg/ml. Sterile human albumin was then added as a carrier at a final concentration of 1 mg/ml and the material placed in sterile rubber-stoppered vacuum vials which were kept thereafter between 0 and 4°C. After anaerobic and aerobic cultures and rabbit pyrogen testing (16) of the labeled C1q were negative, it was judged to be suitable for in vivo use.

The specific activity of the labeled protein was 77.4 μCi/mg. Over 97% of the radioactivity was protein bound as determined by duplicate precipitation in 10% trichloroacetic acid (TCA). To determine the specifity of labeling excess anti-C1q was incubated with the labeled C1q for 16 hr at 4°C. The resulting precipitate was isolated by centrifugation at 2500 rpm for 30 min and washed three times in saline. The rabbit anti-C1q–C1q-^{125}I precipitate contained 92% of the total radioactivity. As an additional check, direct radioimmunoelectrophoresis of the C1q-^{125}I was performed using as carrier: (*a*) the same preparation of unlabeled protein (1 mg/ml), (*b*) heavy chain disease serum Mat (12) which has an elevated C1q (0.410 mg/ml), and (*c*) normal human serum (case 1). The immunoelectrophoresis conditions were those described by Morse and Christian (17) except for the use of 1% agarose instead of 0.7% agar. Specific rabbit anti-C1q and goat anti-whole human serum (Hyland Div., Travenol Laboratories, Inc., Costa Mesa, Calif.) were used. The precipitin lines developed over a 24-hr period and the slides were then washed with multiple changes of normal saline followed by distilled water, photographed, dried, and stained with amido black. The slides were incubated for 1 wk with Kodak K. K. X-ray film (Eastman Kodak Co., Rochester, N. Y.) which was then developed. Only the C1q precipitin line was present on the radioautograph further indicating the labeling specificity and purity of the C1q preparation (Fig. 1).

Immunochemical quantitation. A highly potent rabbit antiserum to human C1q was prepared as previously described (12) and used in the single radial diffusion quantitation of serum C1q in the study subjects and for specificity testing of the labeled C1q. The serum concentration of C3, C4, and C5 were also measured by single radial diffusion (18). Measurement of IgG, A, and M was done by a modified Oudin tube method as described by Claman and Merrill (19).

Total complement. Titers of total hemolytic complement were measured in 50% hemolytic U (CH_{50}) by the method of Mayer and Kabat (20).

Administration of labeled C1q and sample collections. Lugol's solution, 30 drops/day, was taken from 24 hr before to 48 hr after completion of the study by all subjects. From 29 to 37 μCi C1q-^{125}I was administered i.v. to the controls and patients from disposable plastic syringes. The amount of material injected was determined by the difference in syringe weight before and after injection.

Heparinized and clotted blood samples were obtained at 10 min after the C1q injection, at intervals up to 8 hr and daily thereafter for 7–9 days. Fresh serum and plasma were stored at −70°C in an electric freezer. In addition, 2-ml portions of plasma were kept in sterile 12 × 74 mm plastic tubes at 4°C before counting.

During the initial 72 hr of the study, fecal loss of ^{125}I was determined in four patients (cases 2, 3, 4, and 6) and found to be negligible in every instance. Urines were collected for each 24 hr period, the volumes recorded, and portions stored at 4°C for isotope analysis.

These studies were carried out over a 23 day period from 6/20/69 to 7/12/69. The first study was done in a control (case 1) and the other control (case 6) received the labeled C1q on 6/30/69. In this way the effect of storage at 4°C on the subsequent in vivo behavior of labeled protein could be evaluated. The starting dates of the individual studies are indicated in Table I.

Measurement of radioactivity in 2-ml vol of plasma, urine, and homogenized stool was done in a Nuclear-Chicago automatic gamma scintillation counter (Nuclear-Chicago, Des Plaines, Ill.) equipped with a 1 inch NaI scintillation crystal. Both the total and TCA precipitable radioactivity were determined in all plasma samples. Proteinuria of approximately 1 g/day was present in cases 5 and 7 and their urine TCA precipitable radioactivity was also measured and found to be less than 0.5% in each patient. The patient with SLE (case 5) had a cryoprecipitate consisting of IgG and C1q. After determination of isotope in 2 ml of plasma, the cryoprecipitate which developed after 72 hr at 4°C was isolated by centrifugation, washed three times in ice-cold saline, and analyzed for radioactivity in parallel with the supernatant plasma which lacked cryoprecipitable protein.

Data calculation. The urine/plasma radioactivity[3] clearance method (21, 22) as modified by Waldmann, Wochner, Drews, and Strober was used for determination of plasma volume, daily fractional catabolism of C1q and the C1q turnover rate (23, 24). A summary of these calculations is outlined as follows: (*a*) Plasma volume (ml/kg) = radioactivity administered/radioactivity per milliliter plasma at 10 min after injection (time 0) × body wt. in kilograms. (*b*) Total body radioactivity = radioactivity administered − cumulative radioactivity excreted. (*c*) Fraction of total body C1q intravascular = plasma volume × plasma radioactivity/radioactivity retained in body. This was determined after equilibration of labeled protein among body compartments was complete, e.g., 24 hr. (*d*) Total circulating C1q = plasma volume × plasma concentration of protein. (*e*) Total exchangeable pool of C1q = total circulating protein/fraction of protein that is intravascular. (*f*) Fraction of circulating C1q catabolized per day = radioactivity excreted in each 24 hr period/mean circulating radioactivity during the same period. (*g*) Turnover rate = total circulating C1q × fraction of circulating C1q catabolized per day. The latter fraction was determined for each day and the mean values for the steady-state days was used in determining the turnover rate.

The concentration of serum C1q in each subject was measured on days 1, 3, and 6 and the mean value determined. The variation from the mean was less than 10% in every instance, hence, the assumption of a steady state was considered valid and the daily C1q synthetic rate was therefore equal to the turnover rate (mg/kg per day).

Density gradient studies. Density gradient ultracentrifugation was utilized to evaluate the possible in vivo incorporation of the injected C1q-^{125}I into the circulating trimolecular C1 complex. Two different buffers were used: (*a*) a stan-

[3] Plasma protein-bound (TCA precipitable) radioactivity was used for the calculations.

TABLE II

C1q Metabolic Data

Case	Diagnosis	Plasma volume	Plasma pool C1q	Total "exchangeable" C1q	Fraction in plasma pool	Daily fractional plasma pool catabolism	Daily plasma pool turnover rate
		ml/kg	*mg/kg*	*mg/kg*			*mg/kg*
1	Control	38	6.92	13.54	0.51	0.67	4.64
2	Acquired hypogamma	57*	5.28	19.04	0.28	1.90	10.04
3	IgA myeloma	72*	3.64	19.15	0.19	2.65	9.65
4	Acquired hypogamma	65*	3.76	28.18	0.13	4.80	18.05
5	SLE	39	5.21	8.52	0.61	0.95	4.94
6	Control	44	6.64	8.78	0.75	0.65	4.34
7	IgG myeloma	80‡	10.70	66.45	0.16	1.86	37.40

* Corrected to 40 ml/kg for calculation of plasma pool protein.
‡ Corrected to 47 ml/kg for calculation of plasma pool protein.

dard complement-veronal buffer containing 1.5×10^{-4} M Ca^{++} and 5×10^{-4} M Mg^{++}, and (*b*) an EDTA-veronal buffer in which Ca^{++} and Mg^{++} were omitted and 0.05 M Na_3 EDTA was added. Samples of serum and plasma obtained at 10 min (time 0)–8 hr after injection of the labeled C1q were diluted 1:1 in buffer and 0.1 ml portions were applied to 4.5-ml gradients of 7–31% sucrose. The individual samples were run simultaneously in both buffers at 50,000 rpm for 6 hr at 4°C in a Spinco model L ultracentrifuge (Spinco Div., Beckman Instruments, Inc.) with a SW50 rotor.

Fractions were collected with a Buchler gradient fractionation device and analyzed for radioactivity and for protein by the Folin method. As a reference for s rate estimations purified C1q-^{125}I was added to fresh heparinized human plasma in vitro and run in gradients containing EDTA-veronal and standard complement buffer.

RESULTS

Serum C1q and immunoglobulin concentrations in the control and experimental subjects are listed in Table I. A decreased C1q was present in every patient except case 7 (IgG myeloma). Three of the four patients with low C1q also had decreased serum IgG ranging from 0.76 to 2.61 mg/ml while an elevated IgG of 18.00 mg/ml was present in the patient with SLE.

Significant differences in the in vivo behavior of the labeled C1q were observed between controls and experimental subjects and also within the experimental group. A major variation occurred in the estimated plasma volumes determined by dividing the total radioactivity administered by the radioactivity per milliliter of plasma at 10 min after injection (Table II). The controls and patient with SLE had volumes in the normal range of 38–44 ml/kg while the remaining four patients had moderately to grossly elevated values of 57–82 ml/kg. The highest volume was present in the patient with IgG myeloma (case 7) who had an initial hematocrit of 30%. This reduction in red cell volume could only partially explain his estimated plasma volume of 82 ml/kg Hematocrits were normal and stable in all other subjects. Since accurate plasma volumes are essential for determining total plasma pool C1q and in turn the protein's distribution, fractional catabolism, turnover, and synthetic rates, it was necessary to correct the plasma volumes to 40 ml/kg in cases 2, 3, and 4 and to 47 ml/kg in case 7 for these calculations.[4]

The plasma disappearance curves of the labeled C1q are illustrated in Figs. 1–3. In patients the C1q survival was clearly shorter as compared with controls.

Another distinctive feature of the plasma disappearance curves was the presence of a single phase of radio-

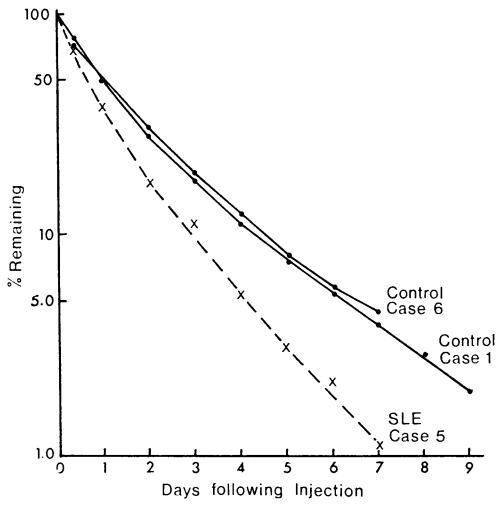

FIGURE 1 Protein-bound plasma radioactivity in the controls and patient with SLE. The initial sample obtained 10 min after injection is 100% and the percentage remaining at various times up to 9 days is plotted on a semilogarithmic scale. A majority (0.61 ± 0.05) of the C1q-^{125}I activity in the SLE plasma was associated with the cryoprecipitate throughout the study.

[4] As the plasma volumes in the controls and SLE patient averaged 40 ml/kg body wt. (Table II) this value was taken as the "normal." A value of 47 ml/kg was assigned to case 7 on the basis of his reduced red cell mass (hematocrit = 30%).

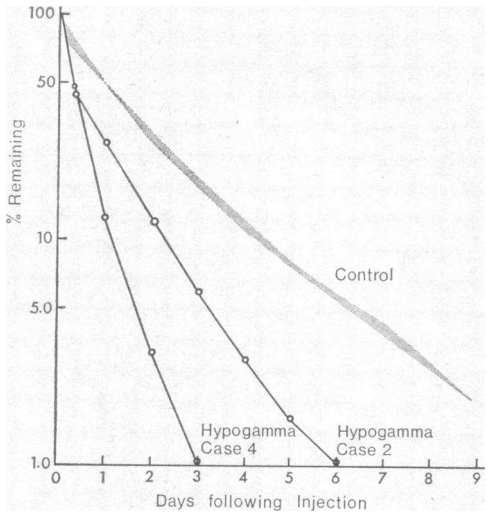

FIGURE 2 Plasma radioactivity curves of the two patients with hypogammaglobulinemia plotted as in Fig. 1.

activity loss rather than a distinct two-phase loss as previously observed in the metabolism of other complement proteins. This indicates that an initial rapid intra- to extravascular equilibration of the labeled C1q did not occur and is best illustrated by the activity curves in the controls and patient with SLE (Fig. 1).

The plasma and total body C1q activity curves were essentially parallel in the controls and SLE patient indicating a prompt excretion of the ^{125}I released from the catabolized labeled C1q in these subjects. In contrast, considerable divergence between the plasma and total body radioactivity curves occurred in the hypogammaglobulinemic and myeloma patients indicating retention of label as either free iodine or more likely

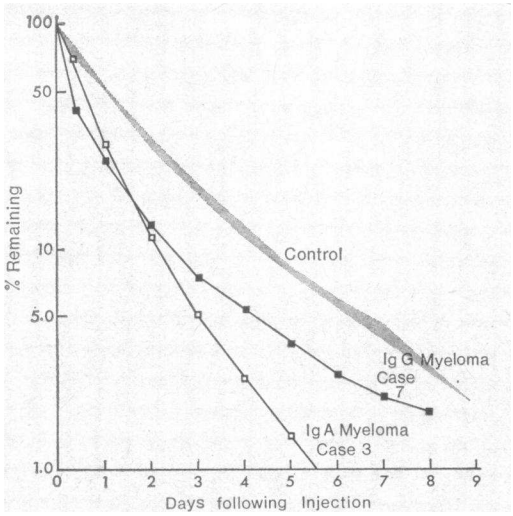

FIGURE 3 Plasma radioactivity curves of the two patients with multiple myeloma plotted as in Figs. 1 and 2.

C1q-^{125}I, in an extravascular compartment (Fig. 4).

Another difference was found in the distribution of C1q, i.e., plasma/total exchangeable protein (Table II). In the controls and patient with SLE from 0.51 to 0.75 of the protein remained intravascularily compared with from 0.13 to 0.28 in the other patients.

Values for the total plasma and exchangeable C1q are shown in Table II. While the plasma concentration, compared to controls, was reduced in every patient except case 7, the total exchangeable C1q was higher in the hypogammaglobulinemia and myeloma patients and lower in the patient with SLE.

When the daily catabolism of the labeled C1q was calculated from the urine activity loss for each 24 hr period, a constant value was evident only when expressed as a fraction of the mean plasma pool and not of the total body or extravascular radioactivity as illustrated by the patient with IgA myeloma (Fig. 5). This indicates that C1q catabolism was occurring primarily within or at least in close association with the plasma pool. In all patients, the daily fractional plasma pool catabolism was increased, ranging from 0.95 in the patient with SLE to 4.80 in the 19 yr old male with hypogammaglobulinemia, compared with 0.67 and 0.65 in the controls (Table II). The standard deviation from the mean was from 2 to 13% in every subject except for the patient with IgG myeloma who was not stable clinically as indicated previously.

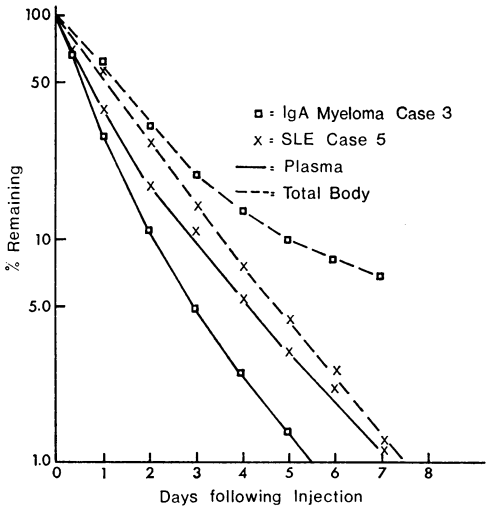

FIGURE 4 Total body and plasma radioactivity curves in the patient with SLE compared with the patient with IgA myeloma. The curves for both the total body and plasma activity are parallel in the patient with SLE indicating prompt excretion of released isotope. In contrast, a marked divergence of the curves is apparent in the patient with myeloma compatible with a large extravascular pool of labeled C1q which is not in rapid equilibrium with the plasma space.

The concentration of serum C1q remained constant throughout the individual studies and the assumption of a steady state was considered valid in all subjects with the possible exception of case 7. Under these circumstances the amount of circulating C1q catabolized per day was equal to the synthetic rate expressed as milligrams per kilogram. The rates in the controls were 4.64 and 4.34 mg/kg per day and ranged from 4.94 to 37.40 in the patients (Table II).

The density gradient studies provided evidence for the in vivo incorporation of injected C1q-^{125}I into a higher molecular weight complex (Fig. 6). In the presence of 0.005 M EDTA the radioactivity peak occurred in the upper or slow (11S) region of the gradients. In contrast a faster sedimenting radioactivity peak of approximately 18S was consistently present when the standard buffer containing Ca^{++} and Mg^{++} was employed.

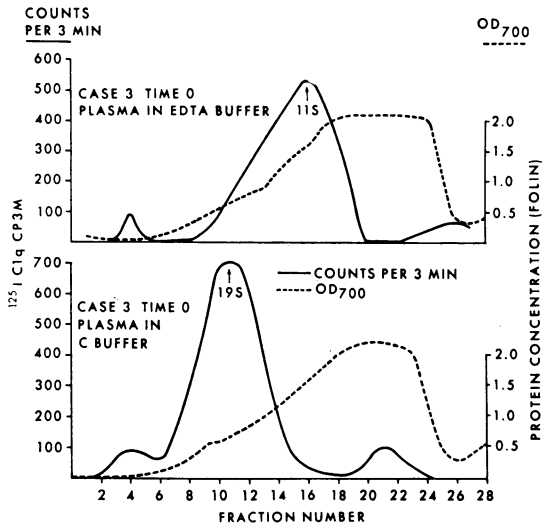

FIGURE 6 Density gradient ultracentrifugation of plasma samples obtained 10 min (time 0) after injection in the patient with IgA myeloma. In buffer containing Ca^{++} and Mg^{++} the peak C1q radioactivity localizes to the 19S region of the gradient indicating in vivo uptake into the C1q, r, s complex. The radioactivity peak is in the 11S region in the presence of EDTA buffer. When labeled C1q was added in vitro to fresh serum, plasma, or whole blood (with optimal Ca^{++} and Mg^{++}) there was no evidence for its uptake into the native C1q, r, s complex in contrast to consistent uptake in vivo. An explanation for this difference in behavior is not available. The minor radioactivity peak at fraction 4 may represent binding with IgM and the slower peak subunits of C1q.

DISCUSSION

The association between decreased serum C1q and hypogammaglobulinemia was described in one of the initial studies (2) of this complement protein and subsequently in an infant with Swiss-type agammaglobulinemia (10, 11). This observation has been recently confirmed and extended by studies from different laboratories in larger numbers of patients with hypogammaglobulinemic syndromes and a variety of other immunoglobulin disorders including myeloma, Waldenström's macroglobulinemia, and heavy chain disease (12–14). The correlation between the concentration of serum C1q and IgG, but not IgA or M, the presence of lower C1q in patients with deficiencies of IgG synthesis and the presence of a normal C1q concentration in a patient with intestinal lymphangiectasia who had a serum IgG of 0.90 mg/ml but normal IgG synthesis, led us to postulate that synthesis of these proteins could be linked (12). Gewurz and associates also suggested that the lowered C1q present in their agammaglobulinemic patients was secondary to a deficiency in C1q synthesis (13).

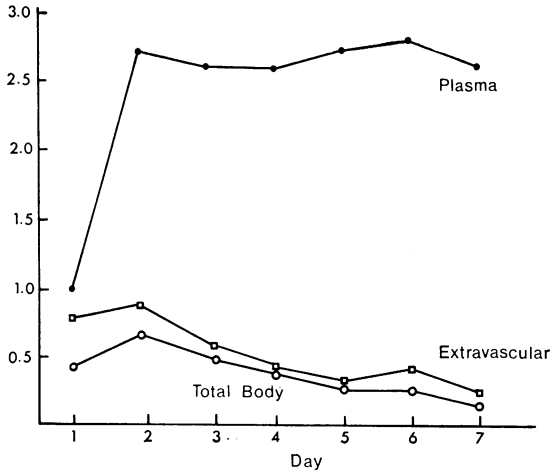

FIGURE 5 The ratios of urine radioactivity during each 24 hr period over the mean radioactivity during the same period in the plasma, extravascular, and total body compartment are plotted in the IgA myeloma patient against time. The constancy of plasma C1q catabolism indicates that protein breakdown occurred either within or in close association with the plasma space. Similar results were also present in the other subjects.

The present metabolic studies clearly indicate that the decreased serum C1q associated with IgG deficiency is not related to impaired C1q synthesis. Two distinctly different mechanisms leading to hypercatabolism of C1q were evident and in turn were responsible for the lowered serum concentrations.

In the patients with acquired hypogammaglobulinemia and myeloma, the C1q-^{125}I disappeared very promptly from the plasma space. This was apparent from the over-estimated plasma volumes in these four subjects, the shortened plasma disappearance times and the

altered distribution of the labeled C1q with only 28% or less remaining intravascularily (Table II).

The lack of a parallel decline in plasma and total body radioactivity indicates that in these subjects a large proportion of the C1q was in an extravascular compartment which was not in rapid equilibrium with the plasma pool. The constant fractional catabolism of the plasma pool C1q (but not the extravascular or total body) indicated that breakdown of protein occurred primarily within the space even though its distribution was altered.

The reversible protein-protein interactions between C1q and IgG have been defined by in vitro studies employing analytical ultracentrifugation techniques (4). In conditions of IgG excess, a single C1q molecule may reversibly combine with five to six IgG molecules. The basis for the prompt plasma disappearance of labeled C1q in the two individuals with hypogammaglobulinemia and the patient with IgA myeloma presumably relates to their decreased serum IgG concentrations which limited the normal C1q-IgG interactions thereby allowing the injected labeled protein to be rapidly cleared from the intravascular space.

This explanation cannot account for the very similar in vivo behavior of the labeled C1q in the patient with IgG myeloma and over 24 mg/ml IgG. His estimated plasma volume was 82 ml/kg compared with an expected 47 ml/kg. Thus in the initial 10 min mixing period approximately 40% of the injected C1q left the plasma space. This was not related to any physicochemical alteration of the preparation during storage since the initial and the sixth studies in the controls provided the expected estimated plasma volumes of 38 and 44 ml/kg. His myeloma protein was in the IgG_1 subclass.[5]

The mean concentrations of C1q and IgG in normal adults are 0.185 mg/ml and 10.0, respectively, as determined by the immunodiffusion methods used in this laboratory (7, 19). Applying the estimated molecular weights of 400,000 for C1q and 160,000 for IgG and Avogadro's number, approximately 25×10^{13} molecules C1q and 25×10^{16} IgG/ml are normally present with a molar C1q: IgG ratio of approximately 1: 1000. It would therefore appear that even with marked reductions of serum IgG below 1 mg/ml as in cases 3 and 4, a surfeit of IgG molecules would be present capable of interacting with C1q. However, the application of in vitro data concerning C1q-IgG interactions to the actual in vivo events is hazardous at best. It has been shown that C1q preferentially binds with the IgG heavy chains of subclass 3 and 1, to a lesser extent with IgG_2 and little, if at all, with IgG_4 molecules (4). It is likely that the quantitative distribution of IgG subgroups is of importance in the metabolism of C1q.

A second mechanism for the decreased C1q was suggested in the patient with SLE. In this instance, the increased turnover could be related to the underlying active disease process which, in addition to a decreased C1q, was manifested by a low total complement, decreased C4 and C3, the presence of serum cryoproteins, an abnormal urine sediment, and mild arthralgias. By immunoelectrophoresis of the washed concentrated cryoprecipitate, which contained a high fraction of the plasma C1q-^{125}I (mean 0.61 ± 0.05) throughout the study, only IgG and C1q were detected. Hanauer and Christian found both IgG and IgM in addition to C1q in their studies of SLE cryoproteins which were analyzed with antisera to individual cryoproteins from six patients (25). We did not attempt to raise specific antiserum to our patient's cryoprecipitate.

Morse, Müller-Eberhard, and Kunkel (5) first reported low serum C1q in SLE as have Hanauer and Christian, using radial immunodiffusion (6). In both studies this decrease was associated with disease activity and low total complement titers. Kohler and ten Bensel found that the most consistent complement abnormality in SLE was a decreased fourth component which often occurred with normal total complement activity and normal concentrations of C1q, C3, and C5 and in the absence of overt disease (7). Subsequent metabolic studies have demonstrated an increased turnover of C4 in patients with SLE even when their disease is inactive and their levels of C4 are normal (26). It is probable that the increased C1q turnover present in the patient with SLE was due to utilization by the disease process, a mechanism distinctly different from that present in the hypogammaglobulinemic and myeloma patients.

More profound decreases of serum C1q have been documented in individuals with Swiss-type lymphopenic agammaglobulinemia compared with the two hypogammaglobulinemic patients in the present study (11, 13, 14). Of great interest is the fact that normal C1s concentrations are present in Swiss-type patients by both hemolytic and radial diffusion quantitation suggesting that the synthesis and/or catabolism of these subunits of C1 are independent (11, 14). In all likelihood the synthesis of C1q and C1s is independent. However, the fact that density gradient studies indicated uptake of injected C1q-^{125}I into the circulating trimolecular C1 complex suggests that the catabolism of all three subunits of C1 is interrelated. The possibility also remains that a C1q synthesis defect may be present in Swiss-type lymphopenic agammaglobulinemia whereas it is clearly not in the immunoglobulin disorders included in this study.

[5] Determined by Dr. Howard Grey.

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