Studies of Serum C-Reactive Protein in Systemic Lupus Erythematosus

RALPH C. WILLIAMS Jr, MOLLY E. HARMON, RUFUS BURLINGAME, and TERRY W. DU CLOS

ABSTRACT. ***Objective***. To examine the relationship of serum C-reactive protein (CRP) levels to other indicators of disease activity during the course of systemic lupus erythematosus (SLE).

Methods. In 124 patients serum CRP was measured retrospectively by ELISA and in some instances by radial immunodiffusion. Serum CRP levels were compared to laboratory, clinical, and radiographic assessments of disease activity. In many patients, serial CRP levels were measured over months or years to determine whether elevations of serum CRP reflected apparent changes in other disease activity variables. CRP was also measured in lyophilized aliquots of 24 h urine samples from SLE patients and controls with other renal disorders. Parallel determinations of interleukin 6 (IL-6) were made by ELISA in healthy controls and SLE patients.

Results. Of the 124 SLE patients studied, most showed elevations in serum CRP levels in the course of their disease. No inverse or direct correlation was noted between serum CRP and levels of nucleosome antigen or serum IgM or IgG anti-DNA antibody. In patients with renal involvement and proteinuria, CRP was often detected in 24-h urine samples. A strong correlation ($p < 0.001$) was noted between CRP and IL-6 levels in healthy subjects, but no correlation was recorded between serum CRP and IL-6 in SLE.

Conclusion. Contrary to previous reports, most patients with SLE in our study showed elevations of serum CRP during the course of their illness, and extremely high serum CRP was recorded in some patients. CRP was also found in concentrated urine samples from patients with renal involvement and often paralleled elevated serum levels. In patients, no correlation was seen between CRP serum levels and serum IL-6, whereas a strong correlation between CRP level and IL-6 was recorded in healthy subjects. (J Rheumatol 2005;32:454–61)

Key Indexing Terms:
C-REACTIVE PROTEIN
INTERLEUKIN 6
SYSTEMIC LUPUS ERYTHEMATOSUS
DISEASE ACTIVITY

Many variables have been advanced to assist clinicians in estimating degree and extent of inflammation and tissue injury in generalized or intermittently recurrent inflammatory diseases such as systemic lupus erythematosus (SLE). Active disease in SLE is frequently accompanied by high levels of circulating IgG anti-dsDNA, low levels of C3 and C4, elevated sedimentation rates, or increasing proteinuria. Results of C-reactive protein (CRP) assays — generally regarded as a very sensitive indicator of tissue injury — have often not paralleled acute inflammatory episodes[1-7]; moreover, the value of CRP elevations to monitor disease activity in SLE remains controversial[8-13]. Several investigators have suggested that episodes of superimposed infection or serositis, when they occurred in SLE, were much more likely than disease flares to result in CRP elevations[5,7,10]. We studied serum samples from 124 patients with definite SLE by American College of Rheumatology (ACR) criteria who were seen at the University of Florida Health Sciences Center (Gainsville, FL, USA), during a 10-year period from 1988 to 1998, and from additional patients over the subsequent 4 years at the University of New Mexico Health Sciences Center, Albuquerque, New Mexico. Our analysis indicates that most of the patients studied showed serum CRP elevations during the course of their illness; however, elevations did not correlate with either disease activity or interleukin 6 (IL-6) levels.

From the Department of Medicine, Division of Rheumatology, University of New Mexico (UNM) School of Medicine, Albuquerque, New Mexico; and Inova Diagnostics, Inc., San Diego, California, USA.

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R.C. Williams Jr, MD, Emeritus Professor of Medicine, UNM School of Medicine; M.E. Harmon, BS, Laboratory Technician, UNM School of Medicine; R. Burlingame, PhD, Inova Diagnostics; T.W. Du Clos, MD, PhD, Professor of Medicine, Division of Rheumatology, UNM School of Medicine.

Address reprint requests to Dr. R.C. Williams, Department of Medicine, Division of Rheumatology, UNM School of Medicine, UNM Hospital ACC5, 2211 Lomas Blvd. NE, Albuquerque, NM 87131.

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MATERIALS AND METHODS

One hundred twenty-four patients with definite SLE by ACR criteria[14] provided the clinical population studied. All patients in this study were examined by the same physician (RCW), and their records and concomitant laboratory and radiographic reports studied for any indication of subclinical infection as well as clear evidence of disease activity. In a number of patients, serial serum samples collected over several years of followup were available. The patients included 46 Black and 51 Caucasian patients. Twenty-two were Hispanic and 3 were of Asian background. Two were

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Native American. The patient group included 108 women and 16 men. Ages ranged from 13 to 79 years (mean 34) for female patients, and 14 to 67 years (mean 33) for male patients. Among the entire SLE group studied, 73 had evidence of SLE renal involvement, 30 showed obvious clinical or imaging evidence of central nervous system lesions, 17 had concomitant serositis, and 31 had arthritis. Six patients had vasculitis or vasculitic complications, and 8 showed pulmonary involvement. Relative SLE disease activity was calculated at the time each serum sample was collected by one of the authors (RCW) using the SLE Disease Activity Index (SLEDAI).

No patient studied was judged to have concomitant clinically apparent infections at the time of serum sample collection. These characteristics are summarized in Table 1.

Healthy controls. A total of 70 healthy controls of both sexes ages 18 to 65 years were used as a reference standard. No control subject had clinical evidence of concomitant infection or inflammatory conditions. Fifty control serum samples were collected in Florida between 1988 and 1998 during the time that the Florida patients were studied. Twenty control samples were also collected in New Mexico from healthy donors with no clinical evidence of infection or disease. All control sera were kept frozen at –70°C until thawed just prior to CRP assay.

CRP determinations. CRP levels were determined retrospectively on serum samples kept frozen in separate aliquots at –70°C until tested. CRP was determined by ELISA for CRP quantitation as described[15-17]. Assays were performed using 1:400 and 1:4000 serum dilutions in duplicate with Immulon 2 microtiter plates (Dynatech Laboratories, Alexandria, VA, USA); plates were coated with 100 µl of sheep anti-human CRP antibody (Cappel, Durham, NC, USA) at 0.5 µg/ml in phosphate buffered saline (PBS); in some instances test sera were studied at 1:200 and 1:2000 dilutions. The plates were blocked, washed, and incubated with a dilution of human serum or a standard amount of purified human CRP. Following 90-min incubation, plates were washed and incubated with horseradish peroxidase (HRP)-conjugated rabbit anti-CRP (Binding Site, San Diego, CA, USA). The substrate, consisting of 10 mg/ml ABTS (2, 2'-azino-bis 3-ethylbenzothiazoline-6-sulfonic acid) and 0.005% H_2O_2 in McIlvaine's citric acid-phosphate buffer, pH 4.6, was then added and plates were read in an ELISA reader at 415 nm. Results represent the average of duplicate wells.

In all samples where relatively high CRP values had been found by initial ELISA tests (values of > 50 µg/ml) the serum level of CRP was performed using radial immunodiffusion in which rabbit anti-CRP antiserum was mixed with 2% agarose and standards of 0.1, 1, 5, 10, 20, 50, 100, and 200 µg/ml of purified CRP employed to construct a standard curve. Wells containing dilutions of test sera were measured for halos of precipitation at 48 and 72 h, and measured rings of precipitation were employed to estimate serum CRP levels, using the standard curve. Values from radial immunodiffusion assays coincided with values previously determined by ELISA with good concordance and agreement within 10% in all instances. Repeated determinations of serum CRP on the same sample using either the ELISA or radial diffusion method showed no more than 5–6% variability within determinations.

Table 1. Clinical profiles of 124 patients with SLE studied for serum CRP levels.

	Patients		
	Female	Male	All
Race			
Native American	1	1	
White	44	7	
Black	42	4	
Hispanic	19	3	
Asian	2	1	
SLE disease characteristics			
Renal disease*			73
Central nervous system**			30
Concomitant serositis			17
Arthritis			31
Vasculitis			6
Pulmonary			8

* Renal disease manifested by significant proteinuria, microscopic hematuria, casts or red blood cell casts, reduced creatinine clearance, renal biopsy, or renal failure. ** Central nervous system involvement as shown by magnetic resonance imaging, computed tomography, or autopsy evidence of lesions.

Serological assays. All SLE serum samples tested for CRP levels were also tested for anti-dsDNA, anti-Sm, anti-chromatin, anti-SSA, anti-SSB, anti-RNP, anti-Scl-70, and anti-Jo-1 using the Luminex Profile 8 (Inova Diagnostics, Inc., San Diego, CA, USA). The tests were performed according to manufacturer's instructions. Results of the anti-dsDNA assay, an ELISA employing dsDNA coated on ELISA plates, were expressed in a scale: 0–200 was considered negative; 201–300, weak positive; 301–800, moderately strong positive; and > 801 strongly positive.

Serum nucleosome levels. We studied serum nucleosome antigen levels in many SLE patients seen in Florida between 1988 and 1998. Their serum nucleosomal antigen levels have been reported[18]; in many instances high levels of nucleosomal antigen appeared to correlate with increased SLE disease activity levels[18]. In the present study, we examined whether CRP levels inversely correlated to concomitantly determined serum nucleosome levels, since CRP binds to small nuclear ribonucleoprotein[19], nucleosomes[20] and apoptotic cells[21], which may affect clearance of these antigens.

We also measured serum IgM in many SLE serum samples, since the report by Gershov and co-workers[21] also suggested that naturally occurring IgM antibodies present in serum often bound to apoptotic cells, and we wondered whether low serum IgM might correlate with elevated levels of nucleosomal antigen previously quantitated in these same SLE sera[18].

Healthy controls. Most of the 70 control serum samples showed no detectable CRP or very low values, 0–1.0 µg/ml. The mean value of CRP in the 70 controls tested was 0.78 ± 4.3. Because we employed a very sensitive ELISA, we arbitrarily considered any value above the normal mean ± 2 SD to be elevated in patients.

Urinary excretion of CRP. In many of the patients studied here, we had also previously collected 24-h urine samples for measurement of creatinine clearance and urinary loss of IgG anti-F(ab)'$_2$ and anti-DNA antibody[22]. Lyophilized aliquots of these 24-h samples were reconstituted with a small (1 ml) volume of normal saline and used for determination of urinary CRP excretion. Serum CRP values of samples collected at times when these urine samples were originally collected were available in 17 SLE patients. CRP determinations were also made in 24-h urine aliquots of lyophilized urine collected during the previous study[22] from 12 disease control patients with other forms of kidney disease (diabetic nephropathy, chronic glomerulonephritis, amyloidosis, nephrotic syndrome).

Studies of serum IL-6 levels. Since IL-6 is known to be a potent stimulus for CRP production by the liver[23], we measured serum IL-6 levels by ELISA in 51 normal sera samples as well as in 52 SLE serum samples where we had already determined serum CRP values. Immulon 4HBX ELISA plates were coated with monoclonal mouse antibody to human IL-6 (Endogen, Woburn, MA, USA) using a coating dilution of 1:500 in PBS. Plates were incubated overnight at 4°C and then washed 4× with PBS-Tween 20 (0.05%). Plates were then blocked with 1% BSA in PBS using 300 µl per well and incubated 1 h at room temperature. After blocking, plates were washed 3 times and then standards of IL-6 and test serum dilutions added to the ELISA plates using 100 µl per well and incubated at room temperature for 2 h. After washing with PBS 5×, plates were treated with 1:5000 biotinylated rat anti-human IL-6, incubated 2 h at room temperature, washed 5×, and developed with avidin horseradish peroxidase conjugate diluted 1:1000. After 30 min, plates were washed 5× and TMB

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added for 15 min before stop solution (2.5 N H_2SO_4 50 µl/well) was added and plates read in the ELISA reader at 450 nm.

RESULTS

In the SLE serum samples collected over a 14-year period, 70% showed elevated CRP values (> 9.4 µg/ml). Only 30.0% showed normal serum CRP levels. In 29 SLE patients, more than one serum sample collected over a period of several years of followup was available; in some patients, 7 to 9 separate samples drawn over a 7–10 year period were available for assay. Most of these serum samples showed CRP elevations. Mean serum CRP among the SLE sera studied was 53 µg/ml (SD 76). Serum CRP values were frequently markedly elevated, with values ranging from moderate elevations of 10 µg/ml to many values over 50–100 µg/ml. Of the 35 (28%) SLE patients who showed no serum CRP elevation, half were considered not to be experiencing clinically active lupus at the time of sample collection.

The range of CRP values recorded in the entire group of SLE patients is illustrated in Figure 1. Parallel levels of IgG anti-DNA antibody measured in the same serum samples are similarly shown (see vertical axis). We looked for an inverse correlation between measured levels of serum CRP and IgG anti-DNA antibody using Spearman's correlation rank order analysis. This evaluation showed no positive or inverse correlation between serum CRP and IgG anti-DNA levels in the SLE patients studied ($p > 0.7$). Similarly, no direct or inverse correlation was found between CRP values and any of the other antinuclear antibody specificities measured in the same samples (anti-Sm, anti-RNP, anti-SSA, anti-SSB, anti-Scl-70, or anti-chromatin) and no significant relationship was recorded.

In another set of analyses, we investigated whether high levels of CRP were associated inversely with low serum

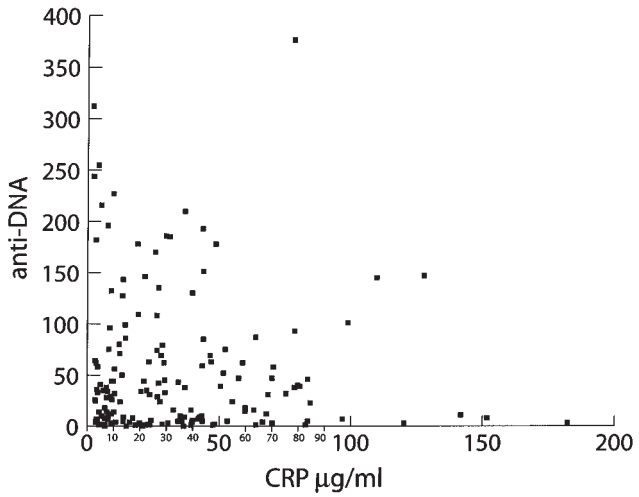

Figure 1. Levels of IgG anti-DNA antibody (y axis) versus levels of CRP (µg/ml) in the same patients (x axis).

levels of nucleosome antigen, as determined in many of the same SLE sera previously[18]. Analysis showed no inverse or positive relation between serum nucleosomal antigen levels and serum CRP values. When quantitative levels of serum IgM in SLE were compared with serum IgG anti-DNA, serum nucleosome levels, and serum CRP values, no direct or inverse correlation was noted using Spearman's rank correlation coefficient or by applying Kruskal-Wallis analysis of variance of median values.

When parallel values for serum CRP and IL-6 were examined in 52 SLE sera and 51 healthy controls, a positive correlation between serum CRP level and IL-6 was apparent in healthy controls ($p < 0.001$); however, no correlation was noted between serum CRP and IL-6 in SLE (Figure 2).

Serial studies of individual SLE patients provided interesting results indicating wide ranges of serum CRP levels in many patients over the course of their disease. Table 2 shows representative serial values based on 13 patients for serum CRP in parallel with individual patients' disease progression. Elevated values were often observed but did not appear to correlate with any one type of disease manifestation or complication. Moreover, lower CRP values closer to normal were sometimes recorded when SLE patients were still having active manifestations of disease.

The data presented in Table 2 support the observation that CRP elevation is frequent in SLE. Zuniga, *et al*[24] observed that CRP is often deposited in glomeruli of kidney biopsies of SLE patients with lupus nephritis; moreover, there may be a relationship between the IgG H-chain subclass of gamma-globulin deposited in the kidney and the Fc-gamma-RIIa-R131 variant with low affinity for IgG2 but high affinity for CRP[25] and the IgG deposited in lupus glomeruli. Accordingly, we examined the relationship of our serum CRP values and patient clinical status with respect to SLE renal involvement: whether active nephritis, onset of renal failure due to nephritis, or remission of prior active nephritis at time of sampling was reflected by parallel CRP determinations. This analysis included 49 CRP determinations in patients with concurrent clinically active lupus nephritis, 48 in patients with renal failure due to lupus nephritis, and 20 in patients in remission from prior active nephritis. These data are shown in Table 3 and indicate slightly higher average CRP values in SLE patients with kidney failure than in those with concurrent active SLE nephritis. The mean serum CRP in those with previous but no concurrent active kidney involvement was lower (24.2 µg/ml). However, no statistical difference was present between the various SLE groups with or without renal involvement ($p > 0.8$).

Comparative levels of serum CRP and 24-h urine excretion of protein and CRP in 17 SLE patients are presented in Table 4. Twelve patients showed excretion of small amounts of CRP in urine. Most of the patients who showed detectable urinary CRP by sensitive ELISA method also had moderate

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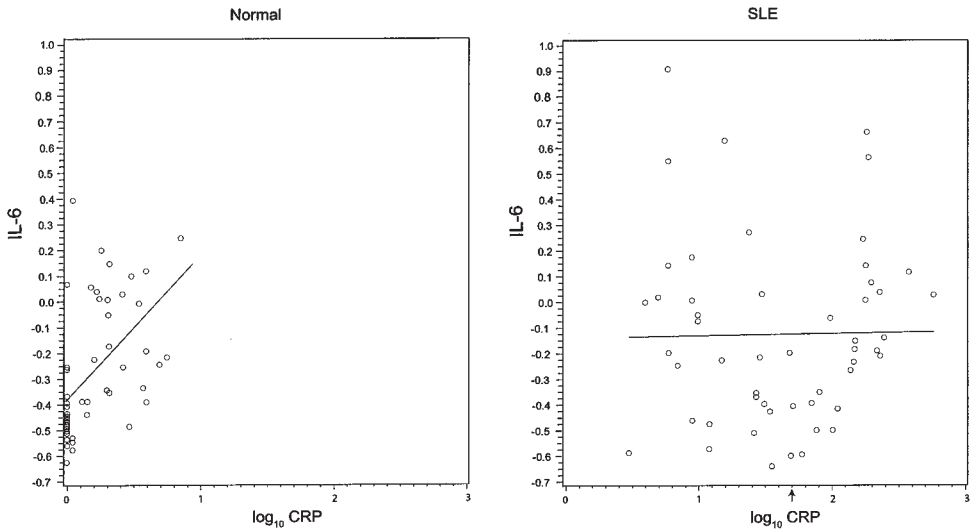

Figure 2. A. Serum IL-6 (µg/ml) plotted versus $\log_{10}$ of serum levels of CRP, similarly plotted in 51 healthy controls. A correlation coefficient of 0.7 was recorded ($p < 0.001$). B. The same analysis when log to base 10 for serum CRP was plotted against serum levels of IL-6 in 52 patients with SLE. No significant correlation was present. Values to the right of the arrow represent SLE patients with diverse clinical manifestations.

or marked elevations in serum CRP as determined in samples collected concurrently. Serum CRP values ranged from 150 to 11 µg/ml (Table 4) in the patients showing detectable CRP in lyophilized urine samples (Patients 1–21). Control patients with similar degrees of proteinuria but with other types of renal disease also showed urinary CRP. Unfortunately, with these controls no simultaneous serum samples were available for parallel serum CRP determinations.

Representative data on urinary CRP excretion in control patients with other forms of renal failure are shown in Table 5.

DISCUSSION

Our results indicate that most SLE patients show serum CRP elevations during the course of their disease. Wide fluctuations in serum CRP values during the evolution of the disease process appear to be present in a large number of our patients. Our patients showed a broad range of clinical presentations; many had severe disease and either active or endstage renal disease or relatively high SLEDAI scores. No patient had concomitant active or documented infection, and clinical profiles of SLE patients examined here do not suggest a clear pattern; many SLE patients with renal failure showed intermittent marked serum CRP elevations.

Although previous authors have pointed out that active SLE may be associated with no elevation of CRP[1-3], we cannot, in the large patient group studied, confirm this impression. If CRP acts as a scavenger for apoptotic nuclear-derived material presented to the circulation during evolution of disease, then one might expect to record low serum CRP values when serum nucleosomal antigen values are elevated in the course of the disease. This pattern was not borne out by our findings.

The initiating signals for calling forth CRP production may be deranged or blunted during the course of SLE in some patients. When we compared serum levels of IL-6 to serum CRP in normal controls and SLE patients, an interesting divergence was noted. Analysis of paired serum IL-6 and CRP levels obtained on the same sample did show a strong positive correlation between CRP level and IL-6 in 51 healthy controls ($p < 0.001$, correlation coefficient 0.7). However, no such correlation was present in 52 SLE patients studied (Figure 2). Which lymphokine system or which mediator molecules are abnormal with regard to CRP elevations in SLE is not yet clear.

Recent studies by several other groups have also indicated that serum CRP levels may be elevated in SLE. Al-Mekaimi and co-workers[13] found that 71% of 31 SLE patients studied from a hospital-based rheumatology clinic in Kuwait showed high CRP levels, with very high levels in 13%. On the other hand, Nishiya and Hashimoto[12] found elevated serum CRP levels in only occasional patients among a group of 36 SLE patients studied, and Haga and co-workers reported serum CRP elevations of greater than 10 µg/ml in only 17 of 95 SLE patients studied for various serological parameters of inflammation including calprotectin levels[26]. A possible explanation suggested for normal levels of serum CRP during SLE could be that production and effective signaling of IL-1 and IL-2 might be defective in the disease; this could account for absence of CRP elevations in some patients[27]. Spronk and co-workers studied plasma IL-6 levels in conjunction with CRP serially in 16 SLE patients and found that elevations of IL-6 before SLE disease exacerbations did occur in a subgroup of SLE

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Table 2. Serial studies of serum CRP, nucleosome antigen, and IgG anti-dsDNA antibody levels in patients with SLE.

Patient	Race, Sex, Age, yrs	Date of Serum Sample	Serum Nucleosome Levels*	CRP**	IgG Anti-dsDNA	Clinical Course
1	HF, 25	11/02/92	0.035	25	1600	No evidence for renal involvement; arthritis rash
		03/05/93	0.030	11	1418	Proteinuria, membranous glomerulonephritis WHO Class V on biopsy
		11/13/95	0.012	8	1517	After 4 cytoxan treatments, no joint symptoms, persistent proteinuria
2	WF, 48	11/18/94		8	173	Patient with disease onset 1992 with arthritis
		09/19/97		147	1277	Developed lupus vanishing lung syndrome; no arthritis
		01/09/98		178	485	After pulse cytoxan x 6, pulmonary function improved
3	HF, 18	03/10/92	0.671	74	263	8 mo previously developed polyarthritis, butterfly rash, nephritis and cerebritis; 1 mo after initial blood sample began pulse cytoxan; over 18 mo remission
		03/02/98	0.003	2	59	In remission for 6 years
13	HF, 20	01/23/97		1	640	General malaise, intermittent joint pain; no rash, but ESR 65 mm/h
		01/09/98		23	847	Onset of shortness of breath, malaise; on corticosteroid prednisone 15 mg/day
		02/04/98	1.685	3	1822	Intrapulmonary hemorrhage with increased skin lesions. No renal involvement. ESR 50
		03/12/98	1.301	46	836	Acutely ill; anemic; still has pulmonary hemorrhage; on 40 mg prednisone
17	BF, 50	06/14/91	0.025	21	300	Multiple joint polyarthritis; no renal or skin manifestations
		10/21/94	0.032	24	125	Joint symptoms persist. Thyroiditis
		02/14/97	0.078	7	79	Thyroid inflammation resolved
		08/9/97	0.021	7	82	Chronic arthritis in multiple joints
		02/9/98	0.864	578	250	Pulmonary infiltrates; congestive heart failure
21	WF, 18	08/22/95	0.590	62	290	Malar rash, arthritis, chronic seizure
		09/1/95	0.650	59	435	Arthritis; on 15 mg prednisone
		09/27/96	0.750	145	1098	Arthritis persists; MRI shows chronic dural thickening
23	WF, 48	08/23/94	0.350	4	108	Chronic renal failure for 2 yrs; on dialysis
		05/23/95	0.487	25	32	SLE clinically inactive
		05/29/96	0.542	210	368	Abdominal pain and chest pain related to SLE
		10/02/96	0.375	10	55	No clinical SLE activity; on dialysis
26	WF, 37	10/18/93	0.540	13	950	Active vasculitis and cerebritis; on 20 mg prednisone, pulse cytoxan
		09/9/94	0.020	18	598	Vasculitis better; prednisone dose 10 mg
		07/19/96	0.032	47	700	Bouts of arthritis. Now has 4+ proteinuria
36	BF, 38	09/13/96	0.381	15	598	Symptomatic polyarthritis involving multiple joints. Recent malar rash
		11/17/97	0.016	16	632	Arthritis improved on hydroxychloroquine. No renal involvement; no corticosteroids
53	WF, 19	10/31/92	0.484	9	1650	Recent onset SLE with butterfly rash, arthritis; renal biopsy showed active proliferative GN WHO Class IV
		03/11/94	0.118	63	469	Status post 4 IV cytoxans and prednisone 10–20 mg/day. Joint symptoms persist
60	BF, 34	07/15/94	0.679	101	989	Onset of SLE 2 mo previously. Arthritis, rash; kidney biopsy showed membranous GN, WHO class V
		09/9/94	0.091	63	233	Lupus less active; received 4 IV cytoxan treatments
		02/25/95	0.487	130	397	Bouts of polyarthritis persist. IV cytoxan treatments every 3 mo
		02/15/96	0.207	87	638	Active SLE despite regular cytoxan IV
		04/17/96	2.761	11	950	Active SLE, polyarthritis
87	BF, 48	09/10/89	0.037	45	293	Extensive facial and hand dermatitis. No renal involvement
		04/22/94	0.046	7	969	Skin involvement persists. Improved on hydroxychloroquine
		11/02/94	1.870	377	781	Nocturnal seizures; MRI showed fresh and old brain infarcts
		03/19/96	0.012	39	504	SLE considered inactive except for skin lesions
		01/30/98	0.013	16	393	No SLE activity except skin lesions
64	BF, 37	11/05/89	0.083	227	98	Initial symptoms pleuritic pain and arthritis
		11/18/94	0.003	56	103	Arthralgias and fatigue persist
		09/12/96	1.035	35	350	Cutaneous vasculitis involving both elbow regions
		03/14/97	0.009	14	75	Occasional bouts of joint pain. Not much SLE activity

* Optical density (OD) on ELISA reading using assay with 4H7 monoclonal antibodies. All levels above 0.1 considered elevated; marked elevations showed OD readings of > 0.500 up to 2.00. ** Normal levels 0.78 ± 4.3 μg/ml. + Anti-DNA ELISA readings: negative 0–200; weak positive 201–300; moderate positive 301–800; strongly positive > 801. H: Hispanic; W: White; B: Black.

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Table 3. Average CRP values in SLE patients with kidney disease.

Patient Status	CRP No. of Determinations	CRP Average Measure, µg/ml
Inactive kidney disease	20	24.2
Active nephritis	49	52.8
Renal failure	48	81.6

Inactive kidney disease vs active nephritis: $p > 0.5$. Inactive disease/active nephritis vs renal failure: p not significant.

patients who had elevated CRP and serositis during disease exacerbation[28].

Our findings indicate that, using a sensitive ELISA method for serum CRP quantitation, CRP is often moderately elevated when a large group of SLE patients is studied. No particular subgroup of patients seemed to show elevated levels. Serial studies of serum CRP levels in many patients showed wide variations in quantities of CRP detected in serum. The recent report by Zuniga, *et al*[24] of CRP deposition in the renal tissues of patients with SLE nephritis provides a new outlook on the participation of this usual marker for tissue inflammation in diseases such as SLE. Our

Table 4. Comparison of CRP levels in serum and 24-h urine samples of patients with SLE, in parallel with urine CRP values in control patients with other forms of renal disease.

SLE Patient	Race, Sex, Age, yrs	Type of Kidney Involvement, WHO Class	Serum CRP, µg/ml	24-h Urine Protein Excretion, mg/24 h	Creatinine Clearance, ml/min	Urine, CRP of Urine Concentrate, µg/ml	24-h Excretion of IgG
1	BF, 25	V*	87	3350	19	0.103	569
2	BF, 28	ND	45	9443	30	0.082	3985
3	WF, 40	V	35	6228	39	0.068	5724
4	WM, 23	IV	50	5300	8	0.060	1267
5	WF, 21	IV	54	1859	10	0.035	216
6	BF, 20	ND	150	2138	12	0.021	359
7	BF, 20	V	42	696	9	0.006	40
8	BF, 39	III	58	1273	69	0.005	131
9	WF, 24	III	47	842	62	0.004	36
10	WF, 21	IV	52	2430	104	0.003	214
11	BF, 30	IV	38	884	13	0.003	84
12	WF, 36	V	11	2475	85	0.002	109
13	BF, 20	V	7	2059	92	0	296
14	WM, 40	IV	33	1612	20	0	242
15	BM, 30	V	3	9000	47	0	945
16	BF, 38	V	44	3106	14	0	2019
17	BF, 39	V	0	2173	120	0	196

* Most patients had renal biopsies. B: Black; W: White. ND: Biopsy not performed.

Table 5. Control patients with other chronic renal disease and proteinuria.

Patient	Race, Sex, Age, yrs	Type of Kidney Disease	24-h Urine Protein Excretion, mg/24 h	Creatinine Clearance, ml/min	Urine, CRP of Urine Concentrate, µg/ml	24-h IgG Urinary Excretion
1	WM, 51	Membranous glomerulonephritis	23,940	30	0.0542	1676
2	WM, 45	Diabetic nephropathy	13,420	13	0.046	658
3	BF, 60	Nephrotic syndrome diabetes	10,036	32	0.090	1295
4	WM, 69	Membranous glomerulonephritis	9938	140	0.075	447
5	WM, 3	Nephrotic syndrome, minimal change	6324	80	0.003	326
6	WF, 62	Amyloidosis	5132	28	0.015	308
7	WF, 24	Wegener's granulomatosis	3455	12	0.003	366
8	BM, 20	Chronic glomerulonephritis	2594	87	0.019	205
9	WF, 55	Chronic glomerulonephritis, post-transplant	2568	18	0.055	241
10	WF, 61	Membranous glomerulonephritis	3940	684	0.007	197
11	WF, 8	Congenital renal deformity	762	6	0.003	38
12	WF, 28	Chronic glomerulonephritis	2785	40	0.007	200

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studies of urinary CRP excretion detectable in lyophilized aliquots of 24-h urine samples collected when concurrent serum CRP values were also available indicate that CRP is also detectable in SLE urines, particularly in conjunction with marked serum CRP elevation. Since the study by Zuniga and co-workers indicates that renal deposition of CRP occurred in damaged kidneys, it was not surprising that we were able to document urinary loss of CRP in such patients. In the future, direct correlations between serum CRP and renal deposition as well as renal excretion of CRP will be of interest.

Recent studies indicate that CRP often localizes in the kidney in glomerular injury[29]. Moreover, a report by Jabs, *et al*[30] indicates that renal cortical tubular epithelial cells can be shown to express CRP mRNA within 6 h after stimulation with conditioned medium. In this latter study a majority of needle biopsies of acutely rejecting kidney transplants showed CRP mRNA expression. Du Clos and co-workers[31] demonstrated that CRP treatment of lupus mice (NZB × NZW) F1 mice immunized with chromatin significantly prolonged survival along with a transient decrease in IgG antibody levels to histones, DNA, and DNP. These findings appeared to indicate that CRP could modify the course of this murine autoimmune disease. Moreover, a fascinating recent report by Szalai and co-workers[32] indicates that NZB × NZW F1 mice expressing a human CRP transgene had less proteinuria and longer survival than was observed in NZB/NZW control mice. In the human CRP transgenic NZB/NZW mice, IgM and IgG accumulation in renal glomeruli was delayed, and it appeared that in these mice transgenic for human CRP, the presence of CRP protected the animals by increasing blood and mesangial clearance of immune complexes.

Recently, there has been increasing interest in CRP as a marker for cardiovascular disease in apparently healthy individuals as well as SLE[33,34]. In the SLE patients studied here, many had chronic renal failure and a few severe coronary artery disease, but marked elevations of serum CRP in this group did not predict or always accompany cardiac complications. A prospective study with this in mind should be of interest.

It seems clear that mechanisms regulating CRP production in perplexing disorders such as SLE deserve additional careful scrutiny. It may well be that in a complex interactive immunologic disease such as SLE, CRP could help to down-regulate elements of inflammation. Considerably more work in this area is needed.

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