A Review of Anti-C Reactive Protein Antibodies in Systemic Lupus Erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE), the prototype autoimmune disease, is characterized by the production of a plethora of autoantibodies with various roles in the development of disease-related tissue damage. C-reactive protein (CRP) is an acute phase reactant with a pentameric structure. Under acidic or alkaline conditions, or when urea levels are high and/or calcium levels are low, the pentamer (pCRP) dissociates irreversibly into monomeric CRP (mCRP) and exposes new epitopes (neo-CRP). Importantly, anti-mCRP (but not anti-pCRP) antibodies have been described in patients with SLE, their prevalence varying from 4% to 78% in different cohorts. Numerous studies have investigated the relationship between autoantibodies directed against CRP (anti-CRP) and disease activity as well as their association with lupus nephritis (LN), frequently reporting discrepant findings. The main objective of the present review is to describe the role of anti-mCRP antibodies in SLE according to the currently available data.

Keywords: systemic lupus erythematosus, lupus nephritis, anti-CRP antibodies, SLEDAI

INTRODUCTION

Systemic lupus erythematosus (SLE) is considered to be the prototype autoimmune disease in humans.¹ The pathogenesis of SLE involves the release of a wide range of autoantibodies, inducing extensive tissue damage in multiple organs.^{2,3}

C-reactive protein (CRP) is an acute phase reactant of the pentraxin family of serum proteins, known as a serum marker of inflammation.²⁻⁵ It belongs to the innate as well as adaptive immune system, serving several functions including the efficient removal of apoptotic cells or various antigens and interaction with the complement system.^{2,4,6} Under acidic or alkaline conditions, or when urea levels are high or calcium levels are low,⁴ the pentamer (pCRP) dissociates irreversibly into monomeric CRP (mCRP)⁷ and exposes new epitopes (neo-CRP).^{4,7} This process also occurs in vivo in inflamed tissues.⁸ Interestingly, anti-mCRP but not anti-pCRP antibodies have been described in patients with SLE.⁸

TABLE 1. Different prevalence rates of anti-CRP antibodies in SLE and other immune-inflammatory rheumatic diseases

References	Patients	Prevalence of anti-mCRP in SLE	Results
Bell <i>et al.</i> , 1998 ¹⁰	50 SLE 40 SCLE 40 DLE 20 SSc (anti-Scl-70 antibody positive) 20 SSc (anticentromere antibody positive) 20 localized scleroderma 19 PBC 20 EMS 10 bone marrow transplantation-induced chronic GVHD 40 HC	78% (39/50) in SLE 30% (12/40) in SCLE 10% (2/20) in SSc (anti-Scl-70 positive) 5% (1/20) in SSc (anticentromere positive) 16% (3/19) in PBC 3/40 in DLE without systemic involvement 0/20 in localized scleroderma 0/10 in GVHD 0/20 in EMS 2.5% (1/40) in HC	Bell <i>et al.</i> found a high prevalence of IgG antibodies to mCRP in 78% of SLE, but a lower prevalence (30%) in SCLE patients. There was no correlation between anti-mCRP with others antibodies (anti-DNS, anti-Ro, anti-La, anti-U1-RNP, anti-Sm, anti-histone, anti-CL).
Minatani <i>et al.</i> , 2001 ¹⁵	125 SLE 24 SSc 16 PM/DM 77 pSS 102 RA 12 MCTD 49 HC	32% (40/125) in SLE 22% (9/24) in SSc 19% (3/16) in PM/DM 43% (33/77) in pSS 29% (30/102) in RA 33% (4/12) in MCTD 43% (3/7) in overlap syndrome	Not only patients with SLE, but also other autoimmune conditions, such as SSc, SS, RA, and overlap syndrome, presented a high incidence of anti-mCRP. A direct correlation was found with other markers such as serum IgG levels, anti-SS-A, anti-SS-B, and anti-U1 RNP antibodies.
Sjöwall <i>et al.</i> , 2002 ⁴	56 sera with from 31 anti-dsDNA positive patients (27 SLE, 4 autoimmune hepatitis) 16 pSS sera 15 RA 31 CD 37 UC	48% (13/27) in SLE on at least one determination 36% (20/56) in anti-dsDNA sera 13% (2/16) in pSS sera The rest of the patients were negative.	Sjöwall <i>et al.</i> confirmed the presence of anti-mCRP in anti-dsDNA antibody positive SLE. Few anti-CRP positive samples from patients with pSS. No positivity for anti-CRP was found in RA, CD, or UC sera.
Sjöwall <i>et al.</i> , 2004 ¹⁶	10 SLE 100 HC	70% (7/10) in SLE on at least one determination	High frequency of anti-CRP in SLE Positive association with anti-dsDNA antibodies, but negative with complement factors (C1q, C3, C4) and lymphocyte count.
Rosenau and Schur, 2006 ¹⁷	413 patients (190 SLE, 103 RA, 120 other CTD) 50 HC	23% (43/190) in SLE 23% (23/103) in RA 11.6% (14/120) in other CTD	Presence of anti-CRP in several connective tissue diseases and inflammatory diseases, including SLE and RA, but at a lower prevalence than previously described.
Figueredo <i>et al.</i> , 2006 ¹	137 SLE 127 non-SLE with persistent aPL 30 idiopathic VTE without APS 80 HC	51% (70/137) in SLE patients 54% (68/127) in non-SLE, aPL positive 5% (4/80) in HC	High prevalence of anti-CRP in SLE. In anti-CRP positive patients, increased levels of anti-dsDNA and aPL antibodies (52% and 68%, respectively) were detected compared to those without anti-CRP (26% and 31%, respectively).
Mathsson <i>et al.</i> , 2007 ¹⁸	125 SLE sera 100 HC	40% (50/125) in SLE	Elevated levels of anti-CRP compared to HC. No difference between anti-CRP and serum samples with or without ANA-autoantibodies, high CRP, or circulating IC.
Shoenfeld <i>et al.</i> , 2007 ¹⁹	150 SLE (100 quiescent disease, 50 active disease) 112 HC	10% in quiescent disease 4% in active disease 4% HC	Anti-CRP antibodies were significantly elevated only in patients with quiescent disease. Overall, Shoenfeld reported a low prevalence in SLE patients.
Kessel <i>et al.</i> , 2008 ²⁰	98 SLE 80 HC	37% (34/98) in SLE	High frequency of anti-CRP, but not reaching a statistical significance

O'Neill <i>et al.</i> , 2010 ⁸	39 SLE (high disease activity) 42 SLE (low disease activity) 25 preflare/flare 16 LN 24 SLE with CVD 34 HC	26.3% in SLE - high activity 12.8% in SLE - low activity 28% in preflare/36% in flare 21.7% in SLE with CVD	Anti-CRP levels were higher in SLE patients with persistent high activity compared to control groups. They also marked higher at the time of SLE flare. The first report to establish the presence of anti-CRP, but also anti-Apo A-I and anti-HDL antibodies in SLE patients in the 12 months prior to their CVD event.
Janko <i>et al.</i> , 2011 ²¹	39 SLE 35 HC	61.5% in SLE 2.7% in HC	A great prevalence of anti-CRP in SLE. No correlation with anti-dsDNA antibodies.
Pradhan <i>et al.</i> , 2013 ²²	100 SLE 100 HC	26% (26/100) in SLE	Higher titers of anti-dsDNA antibodies in anti-CRP positive patients.
Jung <i>et al.</i> , 2014 ¹³	99 SLE 60 incomplete lupus 48 HC	18% (18/99) in SLE 8% (5/60) in incomplete lupus 6% (3/48) in HC	Anti-CRP exhibited a positive but weak correlation with anti-dsDNA antibodies, CRP, and complement C3, whereas a strong association was seen with anti-chromatin antibodies.
Son <i>et al.</i> , 2018 ¹²	34 SLE 36 HC	52.9% (18/34) in SLE 27.8% (10/36) in HC	No significant correlations were detected between anti-CRP and complements or anti-dsDNA antibodies.

HC – healthy controls; anti-CRP – anti C-reactive protein antibodies; SLE – subacute cutaneous lupus erythematosus; SSc – systemic sclerosis; PBC – primary biliary cirrhosis; GVHD – graft-versus-host disease; EMS – eosinophilia-myalgia syndrome; PM/DM – polymyositis/dermatomyositis; MCTD – mixed connective tissue disease; PSS – primary Sjögren's syndrome; RA – rheumatoid arthritis; CD – Crohn's disease; UC – ulcerative colitis; CTD – connective tissue diseases; aPL – antiphospholipid antibodies; VTE – thromboembolic disease; APS – antiphospholipid syndrome; IC – immune complex; ANA – anti-nuclear antibody; anti-Apo A-I – anti-apolipoprotein A-I; anti-HDL – anti-high-density lipoprotein; CVD – cardiovascular disease; anti-dsDNA – anti-double stranded DNA antibodies

The presence of anti-CRP autoantibodies in SLE patients was first mentioned by Robey *et al.*⁹ Bell *et al.* have described increased levels of anti-CRP antibodies that recognize mCRP subunits.^{7,10} Similarly to other lupus autoantibodies, they can be considered neo-epitope-specific.⁷ Another study showed that amino acids 35–47 represent major epitopes recognized by anti-CRP autoantibodies in lupus nephritis (LN).² Monomeric CRP binds IgG immune complexes (IC) and may have an important role in inflammation and apoptosis.⁴ High levels of anti-mCRP antibodies may reportedly relate to increased SLE disease activity.⁸ Moreover, circulating antibodies directed against CRP together with anti-C1q were suggested to contribute to the pathogenic mechanisms of active LN.^{7,11} Anti-CRP antibodies have been described as potential biomarkers or therapeutic targets in SLE, more particularly in LN.^{2,12} Anti-CRP antibodies are not specific to SLE and are also found in Sjögren's syndrome, rheumatoid arthritis (RA), antiphospholipid syndrome, as well as in children with PFAPA syndrome (Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis).^{13,14}

The main objective of the present review is to describe the role of anti-mCRP antibodies in SLE including their relationship with disease activity and lupus nephritis.

ANTI-CRP ANTIBODIES IN SLE AND OTHER AUTOIMMUNE DISEASES

With respect to the presence of anti-CRP antibodies, studies have demonstrated various prevalence rates in SLE,

such as those presented in Table 1. The prevalence of anti-CRP antibodies varied between 4% and 78%. According to the currently available literature data, anti-CRP antibodies may be found in SLE as well as in other autoimmune diseases or healthy individuals.^{1,4,8,10,15–17}

Regarding the relationship of anti-mCRP with clinical and laboratory parameters in SLE, Minatani *et al.* revealed significantly lower levels of anti-CRP in patients with persistent proteinuria, cellular casts, or hypoalbuminemia.¹⁵ Rosenau and Schur described no association between anti-CRP antibodies and CRP levels or erythrocyte sedimentation rate (ESR),¹⁷ while Jung *et al.* observed an inverse correlation with the total platelet count.¹³

Pradhan *et al.* showed reduced complement levels in anti-CRP positive versus anti-CRP negative Indian patients.²² Studying a group of 100 SLE patients with quiescent disease, Shoenfeld *et al.* reported a positive correlation between anti-CRP and anti-serum amyloid P protein (SAP), and also between anti-CRP and anti-mannose-binding lectin (MBL).¹⁹

Jakuszek *et al.* showed that higher levels of anti-CRP were associated with significantly lower levels of white blood cells. The study also demonstrated that elevated anti-mCRP levels were associated with notably higher TNF- α levels in SLE. During treatment, a significant decrease in anti-CRP was noted.³ A research conducted by Figueredo *et al.* found that the anti-CRP positive patients had a higher frequency of antiphospholipid syndrome (APS), exhibiting a higher frequency of aPL and anti-dsDNA antibodies. Complement C3, C4, and C1q levels were lower in anti-

TABLE 2. The possible correlation between anti-CRP antibodies and disease activity in SLE

References	Assessment of disease activity	Results
Sjöwall <i>et al.</i> , 2004 ¹⁶	SLEDAI, mSLEDAI	Positive correlations between anti-CRP and disease activity.
Figueredo <i>et al.</i> , 2006 ¹	Retrospective Systemic Lupus Activity Measure	No association with disease activity.
Shoenfeld <i>et al.</i> , 2007 ¹⁹	ECLAM or SLEDAI score	No correlation between anti-CRP and disease activity. This may happen because of the methodology on the determination and cut off levels of anti-CRP.
Kessel <i>et al.</i> , 2008 ²⁰	SLEDAI	No notable correlation between the presence of IgG anti-CRP antibodies and SLEDAI scores.
Tan <i>et al.</i> , 2008 ²³	SLEDAI	Significantly higher SLEDAI rates in patients with anti-mCRP versus those without.
O'Neill <i>et al.</i> , 2010 ⁸	BILAG	Anti-CRP levels were not higher in patients with persistently high disease activity than in patients with low disease activity.
Pradhan <i>et al.</i> , 2013 ²²	SLEDAI	No statistically significant difference was found in SLEDAI evaluation.
Jung <i>et al.</i> , 2014 ¹³	SLEDAI	Anti-CRP presented a weak correlation with the SLEDAI score.
Pesickova <i>et al.</i> , 2015 ⁷	SLEDAI	Anti-CRP correlated with the overall activity of SLE.
Son <i>et al.</i> , 2017 ¹²	SLEDAI	No significant correlations were detected with the SLEDAI score.

BILAG – British Isles Lupus Assessment Group; ECLAM – European Consensus Lupus Activity; SLEDAI – Systemic Lupus Erythematosus Disease Activity Index; anti-CRP – anti C-reactive protein antibodies

CRP positive lupus patients.¹ A notable correlation between the anti-CRP and the mean lupus disease duration has been reported by Son *et al.* (specifically, longer disease duration corresponded to higher anti-CRP levels).¹²

ANTI-CRP ANTIBODIES AND DISEASE ACTIVITY IN SLE

Several studies have investigated the presence of serum antibodies directed against mCRP in patients suffering from SLE and the correlations between the levels of these antibodies and disease activity scores.¹ As presented in Table 2, research focusing on the connection between anti-CRP antibodies and SLE activity frequently assessed the latter through the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),¹⁶ but also used the British Isles Lupus Assessment Group (BILAG)⁸ and European Consensus Lupus Activity (ECLAM)¹⁹ indexes.

Some authors found a positive correlation regarding the high levels of anti-CRP and high SLEDAI.^{7,8,16,23} These results support the relationship between anti-CRP antibodies and disease activity.^{1,23} In contrast, other data suggested that this may not be a useful indicator of disease activity. Jung *et al.*¹³ reported a weak correlation between the two parameters, while Son *et al.*¹² identified no relationship, similarly to the results obtained by Shoenfeld *et al.*¹⁹ Pradhan *et al.* classified SLE patients as having either mild, moderate, or severe disease activity (based on SLEDAI scores) and found no significant difference between these subgroups regarding anti-CRP antibody titers.²²

Although CRP is a valuable indicator of high disease activity in RA, in lupus patients it may mark the onset of comorbid conditions such as neoplasia and infections. Importantly, high CRP titers in SLE patients require further investigations in order to exclude an overlap syndrome with other autoimmune diseases such as RA or PM.^{24–26} It is considered that CRP is not a useful marker for lupus flares.²⁴ Albeit, certain studies have reported a significant relationship between CRP levels and other proinflammatory molecules in SLE, as well as a correlation with disease activity scores.^{27–30} Interestingly, at a genetic level, CRP genotype (rs1205) was negatively correlated with CRP levels and was associated with a lower risk of developing SLE.^{31,32} The significance of high CRP titers and anti-CRP antibodies in active forms of lupus remains requires further investigation.^{22,33,34}

ANTI-CRP ANTIBODIES IN LUPUS NEPHRITIS

Apart from being described in SLE, anti-CRP antibodies seem to be increased particularly in patients with kidney involvement. Several studies have evaluated the possible association between anti-CRP and LN.^{7,35} In this respect, relevant data is shown in Table 3.

It is well known that one of the most severe complications of SLE is renal involvement, being an important cause of morbidity and mortality.^{7,11} Similarly to anti-dsDNA antibodies, anti-CRP antibodies can bind cellular fragments and necrotic cells, which are then ingested by phagocytes, followed by a release of pro-inflammatory cytokines.⁶ Cer-

TABLE 3. Anti-CRP antibodies in lupus nephritis

References	Patients with SLE and LN versus control	Prevalence of anti-CRP in LN	Results
Sjöwall <i>et al.</i> , 2004 ¹⁶	10 SLE (4/10 renal involvement)	100% (4/4)	All patients with LN tested positive for anti-CRP at flare.
Figueredo <i>et al.</i> , 2006 ¹	137 SLE 28 LN 70 anti-CRP positive	27% (19/70) with LN	In anti-CRP positive patients, the high prevalence of active nephritis approached a statistical significance compared to those without.
Tan <i>et al.</i> , 2008 ²³	96 LN 49 nonrenal SLE 60 HC	59.4% (57/96) in LN 40.8% (20/49) in nonrenal SLE 0/60 in HC	Tan <i>et al.</i> concluded that anti-mCRP antibodies are significantly higher in active LN, being associated with disease activity and renal tubulointerstitial lesions.
Sjöwall <i>et al.</i> , 2009 ³⁶	38 LN 100 HC	45% (17/38) 16% (6/38) positive at follow-up	Sjöwall <i>et al.</i> are the first to establish a statistically significant correlation between anti-CRP and renal biopsy activity in patients with LN. They also investigated poor response to therapy.
Yang <i>et al.</i> , 2012 ³⁷	3 LN 1 HC	3/3 in LN	The first study to suggest that anti-mCRP might play a role in the pathogenesis of SLE as anti-mCRP could suppress the binding between mCRP and C1q.
Sjöwall <i>et al.</i> , 2013 ¹¹	5 active LN 1 HSP 1 P-i nephritis 1 renal cancer	4/5 in LN 0/1 in HSP not analyzed in P-i nephritis	Anti-CRP appeared at the highest disease activity of nephritis; neither before, nor after the flare.
Jung <i>et al.</i> , 2014 ¹³	99 SLE (10/99 renal disease) 48 HC	absent	No parallel between anti-CRP and renal involvement. This may be caused by poor renal manifestations.
Pesickova <i>et al.</i> , 2015 ⁷	57 LN (46 active renal disease, 11 inactive renal disease.) 29 newly diagnosed LN, 122 HC	26.3% (15/57) in LN 33% (15/46) in active LN 0% (0/11) in inactive renal disease 44.8% in newly diagnosed active LN	Anti-CRP significantly higher in LN versus HC. Anti-CRP antibodies were detected exclusively in patients with active renal disease versus inactive renal disease.
Jakuszko <i>et al.</i> , 2017 ³	103 patients (74 LN 29 SLE without LN) 31 primary GN 31 HC	75.7% in LN 44.8 % in non-renal SLE 19.3% in GN 35.4% in HC	High prevalence of anti-CRP in LN versus other groups (patients without LN, primary GN and HC).
Son <i>et al.</i> , 2017 ¹²	34 SLE (5 LN) 36 HC	Due to limited number of patients, anti-CRP linked to LN was not analyzed	No significant correlation with the occurrence of LN.

P-i nephritis – pauci-immune nephritis; HSP – Henoch-Schönlein purpura; GN – glomerulonephritis; HC – healthy controls; anti-CRP – anti C-reactive protein antibodies

tain studies have demonstrated experimentally that anti-CRP antibodies may be involved in the pathogenesis of LN by interfering with the physiological function of CRP in the clearance of apoptotic debris and in complement activation.⁵ Research performed on biopsy specimens support the link between anti-CRP antibodies and renal biopsy activity index.^{5,7}

Pesickova *et al.* focused on patients with renal involvement (confirmed by biopsy), demonstrating that the prevalence of anti-CRP antibodies in SLE patients was exclusively observed in active LN and not in patients with inactive renal disease.⁷ The study also presented an important negative correlation between anti-CRP and

C3. Elevated levels of anti-CRP were seen in anti-dsDNA positive patients. Moreover, anti-CRP antibodies were significantly associated with unfavorable results (lack of response to treatment, LN flare, or end-stage renal disease) at two years, suggesting their potential role as a marker of active LN.⁷ This statement comes in accordance with the findings of Sjöwall *et al.* who described a decrease of anti-CRP levels in active LN patients who were in transition to remission. Additionally, the levels of anti-CRP antibodies were significantly associated with LN activity based on renal biopsy characteristics.³⁶ Jakuszko *et al.* suggested that anti-mCRP antibodies could be a valuable biomarker in LN, which could be used as a prognostic marker in LN.³

Contrary to the findings reported in the above mentioned studies, Jung *et al.* detected no correlation with LN.¹³ Similarly, the results obtained by Son *et al.* did not support the relationship between anti-CRP antibodies and LN.¹²

Ahn *et al.* stated that CRP levels may be a predictive marker for end-stage renal disease.³⁸ Furthermore, it seems that indices such as neutrophil-to-lymphocyte ratio (NLR, demonstrating increased values in LN) and platelet-to-lymphocyte ratio can demonstrate a positive correlation with CRP.³⁹ However, whether or not these relationships are maintained in the presence of anti-CRP antibodies (or influenced by the latter) could be a subject of future research.

CONCLUSIONS

Pentameric CRP experiences conformation changes in vitro but also in vivo in inflamed tissues, giving rise to monomeric CRP. This process also occurs in patients diagnosed with SLE. Albeit a higher prevalence has been reported by certain studies on SLE compared to other autoimmune diseases, anti-CRP antibodies do not meet the criteria for a reliable disease activity or severity. Nevertheless, many studies have reported strong correlations with kidney involvement. Further robust scientific evidence is required to confirm the clinical and prognostic relevance of anti-mCRP antibodies in SLE.

CONFLICT OF INTEREST

Nothing to disclose.

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