

# Serum Amyloid P Component-DNA Complexes Are Decreased in Systemic Lupus Erythematosus. Inverse Association with Anti-dsDNA Antibodies

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**ABSTRACT. Objective.** To study serum levels of serum amyloid P component (SAP) and SAP-DNA complexes in a population-based cohort of patients with systemic lupus erythematosus (SLE).

**Methods.** The study population comprised 82 unselected patients of predominantly Scandinavian ancestry with SLE according to current classification criteria. Serum samples were collected at baseline and serially for up to 2 years. SAP component and SAP-DNA complexes were measured by ELISA. Associations between SAP-DNA and clinical manifestations or serological findings were analyzed. Ninety healthy, age-matched blood donors served as controls.

**Results.** SLE patients had normal serum concentrations of SAP, whereas SAP-DNA complexes were decreased. Two-thirds of the SLE patients tested persistently SAP-DNA complex-negative. There was no relationship between the occurrence of SAP-DNA complexes and clinical manifestations. SAP-DNA-negative patients tended to have lower leukocyte counts and complement C3 levels, and higher erythrocyte sedimentation rates and C3d levels versus SAP-DNA-positive patients. There was an inverse association between the occurrence of anti-double-stranded DNA (anti-dsDNA) antibodies and SAP-DNA complexes. Co-occurrence of SAP-DNA complexes and anti-dsDNA antibodies was demonstrated in only one SLE patient, implying that 81/82 patients were discordant for the presence of anti-dsDNA antibodies and SAP-DNA complexes.

**Conclusion.** The decreased level of SAP-DNA complexes in SLE patients and the inverse relationship between these complexes and anti-dsDNA antibody supports the concept that SAP component is implicated in the clearance of cell nuclear debris. (First Release Feb 15 2008; *J Rheumatol* 2008;35:625–30)

*Key Indexing Terms:*

SYSTEMIC LUPUS ERYTHEMATOSUS  
SERUM AMYLOID P COMPONENT

IMMUNOLOGY  
ANTI-DOUBLE-STRANDED DNA COMPLEXES

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with a pleiomorphic phenotype involving multiple humoral and cellular effector mechanisms that may act singly or in concert<sup>1</sup>. A prominent feature of SLE is the presence of autoantibodies directed against cell nuclear constituents, DNA and histones in particular<sup>2</sup>. However, the immunogenic potential of these autoantigens in humans has been a matter of controversy due to their intracellular localization. The demonstration that nuclear autoantigens are clustered in 2 populations of surface structures on apoptotic

cells supports the concept that DNA/histone chromatin material of nucleosomes released from injured and apoptotic cells are the source of the abnormal immunogenic responses towards cell nuclear constituents in SLE<sup>3</sup>. In recent years evidence has emerged that in addition to altered surface expression of nuclear autoantigens on cells undergoing apoptosis, defective scavenging of apoptotic cells and nuclear debris may play significant roles in lupus pathogenesis<sup>3–5</sup>. Thus, it has been reported that immunization of mice with purified DNA leads to production of anti-double-stranded DNA (anti-dsDNA) and glomerulonephritis<sup>6</sup>. Similarly, deletion of the gene encoding for serum amyloid P (SAP) component, a phylogenetically well conserved plasma protein belonging to the pentraxin protein family that avidly binds to damaged cell membranes and chromatin, results in antinuclear autoimmunity and glomerulonephritis<sup>7,8</sup>. The same authors reported that chromatin binding to SAP leads to controlled and less aggressive degradation of chromatin, thereby probably decreasing its immunogenicity<sup>7</sup>. More recently, the significance of SAP for cellular waste disposal has been further emphasized by the demonstration that SAP binds to chromatin-containing blebs on late apoptotic cells, thereby facilitating their phago-

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cytosis by macrophages<sup>9,10</sup>. Further, SAP-chromatin complexes can activate the classical complement cascade via C1q and possibly also single complement factors leading to opsonization<sup>10,11</sup>.

In previous studies on human lupus the concentration of SAP in serum did not differ between patients and healthy control individuals<sup>7,12,13</sup>. By contrast, complexes of SAP-DNA in a sample of 25 SLE patients recruited from a Danish and a Hungarian lupus clinic were significantly decreased as compared with healthy control subjects<sup>12</sup>.

The aims of our investigation were (1) to extend our previous study by measuring SAP and SAP-DNA complexes in serum collected serially from an unselected, population-based SLE cohort (n = 82) of predominantly Caucasian origin; and (2) to study the correlation between SAP-DNA complexes and disease manifestations, including the occurrence of anti-dsDNA antibodies.

## MATERIALS AND METHODS

*Ethics.* The study was approved by the Local Ethics Committee.

A complete community-based cohort of patients with SLE was retrieved from 4 separate and independent sources as described<sup>14</sup>. Briefly, the patients were diagnosed according to Fries and Holman<sup>15</sup> and subsequently classified according to the American College of Rheumatology (ACR) classification criteria<sup>16,17</sup>. A total of 82 patients were included with a female:male ratio at 75:7. Mean age was 46 years (95% CI 42–49) and median disease duration 5 years (95% CI 4–10). Cumulative disease manifestations included nephropathy (44%), central nervous system disease (11%), lupus skin disease (82%), and arthralgia/arthritis (94%). All were antinuclear antibody-positive, 85% had anti-dsDNA, and 63% antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies). Patient characteristics are presented in Table 1.

Blood samples were collected at regular intervals for 2 years. Disease activity was expressed as SLE Disease Activity Index (SLEDAI)<sup>18</sup> and tissue or organ damage as Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI)<sup>19,20</sup>. No patient had clinical signs of infection at the time of blood sampling.

*Healthy control subjects.* Ninety randomly selected healthy blood donors, mean age 42 years (95% CI 40–45), equally distributed between men and women, served as controls. None exhibited signs of current infection. Blood samples were assayed only once in the control group.

Patient and control sera were stored at –80°C.

*Biochemical analyses.* SAP and SAP-DNA complexes were measured in serum samples from SLE patients and controls. The study design included a cross-sectional analysis for comparison with the controls. In addition, serial measurements for up to 2 years were done in order to study temporal changes and possible associations with clinical and serological variables. Thus, 4 measurements were done in 61 (74%) patients, 3 in 7 (9%), 2 in 10 (12%), and 1 in 4 (5%).

SAP was measured by an ELISA as described<sup>21</sup>. Polysorb plates were coated with F(ab')<sub>2</sub> antibodies against amyloid P component, incubated overnight at 4°C, and washed 3 times with washing buffer. The wells were quenched with phosphate buffered saline (PBS), pH 7.4, including Tween 20 for 30 min. Samples were diluted in PBS, pH 7.4, added to the wells, and incubated for 2 h at room temperature. After 3 washes the wells were incubated with rabbit anti-amyloid P component IgG for 1 h at room temperature. p-nitrophenyl-phosphate in 9.7% diethanolamine, pH 9.6, was added and after 30 min in the dark optical density was read at 405 nm.

SAP-DNA complexes were measured by an ELISA as described<sup>12</sup>. Briefly, Polysorb ELISA plates were coated with F(ab')<sub>2</sub> anti-human SAP (Dako, Glostrup, Denmark). The wells were quenched and incubated with Ca<sup>2+</sup>-rich serum samples for 45–60 min and then washed. A monoclonal antibody against dsDNA, (Chemicon International, Temecula, CA, USA) was added for 60 min followed by incubation with alkaline phosphatase conjugated rabbit anti-mouse IgG (Dako). After washing, a substrate of para-nitrophenyl phosphate (Boehringer Mannheim, Mannheim, Germany) was added. Optical density at 405 nm was read after 30 min in the dark<sup>12</sup>. The lower detection limit of SAP-DNA complexes was 20 ng/ml. Interassay coefficient of variation was 9%. Anti-dsDNA antibodies did not block the epitope on DNA recognized by the monoclonal antibody used<sup>12</sup>.

Anti-dsDNA antibodies were quantified by ELISA (Dako).

Complement C3 and C4, complement C3 split product (C3d), hemoglobin, leukocyte and platelet counts, C-reactive protein, and erythrocyte sedimentation rate (ESR) were measured by standard laboratory techniques.

*Statistics.* Student's t test was applied for comparisons between normally distributed variables (the Kolmogorov-Smirnov test was used to verify nor-

Table 1. Inception cohort demographic, clinical, and serological profile (n = 82).

Characteristic	Data
Female:male	75:7
Age, yrs, mean (95% CI)	46 (42–49)
Disease duration, yrs, median (95% CI)	5 (4–10)
SLICC/ACR DI median (range)	2 (0–8)
SLEDAI median (range)	2 (0–12)
SAP, µg/ml, mean (95% CI)	46.1 (42.7–49.3)
Cumulative SLE manifestations and treatment, %	
Cutaneous manifestations (butterfly rash, discoid lupus, photosensitivity)	82
Arthralgia/arthritis	94
Renal disease (elevated serum creatinine or decreased creatinine clearance, protein > 0.5 g/l abnormal cellular casts)	44
Central nervous system disease (epilepsy, psychosis)	11
Anti-dsDNA antibodies	85
Thromboembolic events (transient ischemic attack, stroke, or venous thrombosis)	25
Antiphospholipid antibodies	63
Glucocorticoid treatment	83

SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI: SLE Disease Activity Index; SAP: serum amyloid P.

mal distribution). Nonparametric statistics, chi-squared test, and Mann-Whitney U test were used for additional comparisons. Correlations were calculated by means of Spearman's rho and one-way analysis of variance (ANOVA) was used for comparison of means.

## RESULTS

Mean serum SAP was 46.1 (95% CI 42.7–49.3) in SLE patients versus 42.1  $\mu\text{g/ml}$  (95% CI 39.7–44.6) in controls (NS). No temporal changes were observed among SLE patients based on up to 3 additional measurements within the 2-year followup (mean SAP 41.7, 45.5, and 43.5  $\mu\text{g/ml}$ , respectively; one-way ANOVA,  $p = 0.1$ ). In addition, serum SAP did not exhibit age-related changes among SLE patients (Spearman's rho 0.151,  $p = 0.3$ ) or in controls (Spearman's rho 0.172,  $p = 0.1$ ).

SAP-DNA complexes were demonstrated in 5 of 82 (6%) SLE patients participating in the cross-sectional study as compared with 79 of 90 (88%) controls ( $p < 0.001$ ; Figure 1). In SLE patients the concentration of SAP-DNA complexes was independent of age (Spearman's rho 0.115,  $p = 0.3$ ). Also in controls the level of SAP-DNA complexes did not change with age (Spearman's rho 0.02,  $p = 0.6$ ) or between sexes (SAP-DNA complexes occurred in 82% of females and 93% of males;  $p = 0.1$ ).

In serially collected samples from SLE patients, 56 (68%) patients persistently tested negative for SAP-DNA complexes, as assessed from a total of 289 measurements, of which 244 (84%) tested negative. SAP-DNA complexes were demonstrated at least once in 26 (32%) of the patients. However, SAP-DNA complexes were only occasionally demonstrated more than once in the same patient: one patient 4 times, 3 patients 3 times, 10 patients 2 times, and 12 patients only once.

Co-occurrence of SAP-DNA complexes and anti-dsDNA in serum was observed in only one patient: a 21-year-old female with newly diagnosed active SLE (SLEDAI 10). However, only one measurement was done in this patient because she emigrated shortly after SLE diagnosis. Thus, 81/82 SLE patients were discordant for anti-dsDNA and SAP-DNA complexes.

Comparison of lupus patients with and without SAP-DNA complexes in the cross-sectional setting showed female preponderance in both groups (Table 2). Patients with SAP-DNA complexes were slightly older ( $p = 0.324$ ), had longer median disease duration ( $p = 0.342$ ), and had a higher median SLICC/ACR DI score ( $p = 0.188$ ) versus SAP-DNA-negative patients, albeit without reaching statistical significance. There was no difference between patients

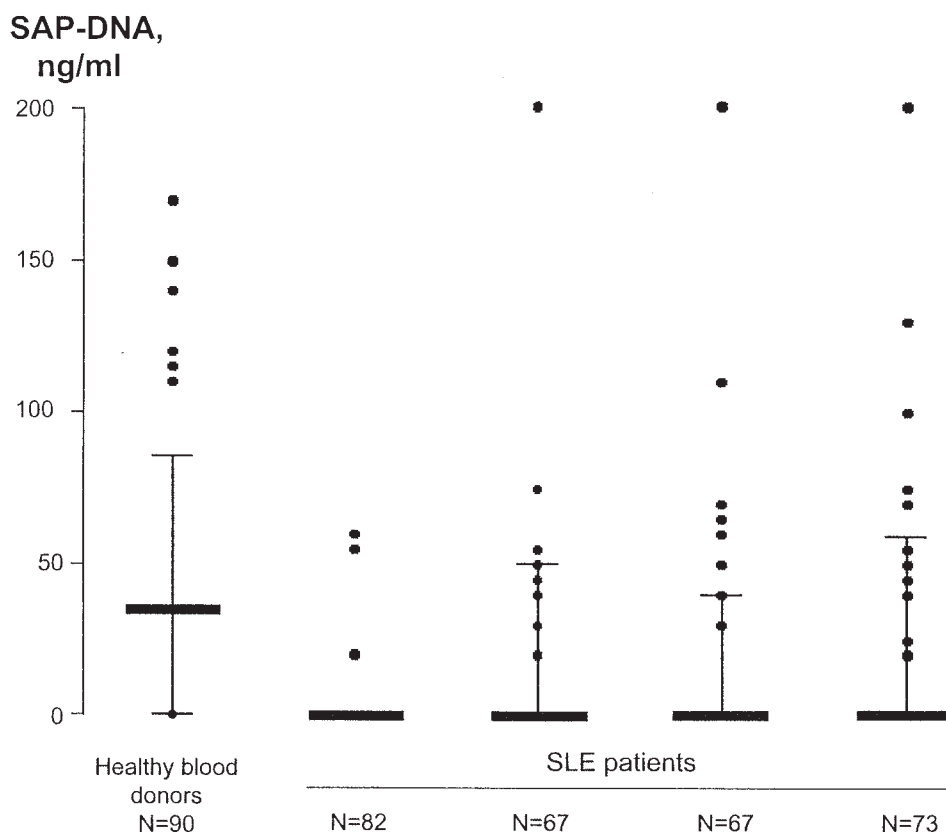


Figure 1. Distribution of serum SAP-DNA levels in healthy blood donor controls ( $n = 90$ ) and patients with SLE ( $n = 82$ ), median (bold lines) and 10–90 centiles (narrow lines). Serial measurements were done in most patients.

Table 2. Comparison between patients with and without SAP-DNA complexes (n = 82). Demographics, current SLE manifestations (%), SAP levels, current medical therapy (%), and serologic findings.

	SAP-DNA-negative, n = 77	SAP-DNA-positive, n = 5	p
Female %	91	100	> 0.5
Age, yrs, mean (95% CI)	45 (42–49)	38 (18–55)	0.324
Disease duration, yrs, median (range)	5 (0–33)	4 (0–12)	0.342
Current SLE manifestations (%), SAP level, therapy (%), and serologic findings			
SLICC/ACR-DI median (range)	1 (0–8)	2 (1–5)	0.188
SLEDAI median (range)	2 (0–12)	2 (0–4)	0.320
SAP, mean, µg/ml (95% CI)	46.0 (42–49)	45.5 (37–63)	> 0.5
Cutaneous manifestations*	12	0	> 0.5
Arthralgia/arthritis	66	40	0.480
Renal disease*	6	20	> 0.5
Constitutional symptoms	18	0	> 0.5
Anti-dsDNA	30	20	> 0.5
Thromboembolic events* (during followup)	12	0	> 0.5
Infections (during followup)	16	40	0.428
Glucocorticoid treatment	57	80	> 0.5
Antimalarial treatment	29	20	> 0.5
Azathioprine	14	0	> 0.5
Cyclophosphamide	4	0	> 0.5
C-reactive protein, mg/l	< 10	< 10	0.584
Erythrocyte sedimentation rate, mm/h	20	12	0.517
Hemoglobin, mmol/l	8.6	8.0	0.377
Leukocyte count, ×10 <sup>9</sup> /l	7.0	13.1	0.012
Platelet count, × 10 <sup>9</sup> /l	241	327	0.064
C3, g/l	0.89	1.09	0.278
C3d, mU/l	42	35	0.282
C4, g/l	0.16	0.16	0.267

\* As defined in Table 1. Reference levels: C3 0.9–1.8 g/l, C4 0.1–0.4 g/l. For definitions see Table 1.

with and without SAP-DNA with regard to disease activity expressed as SLEDAI scores on the day of blood sampling. Further, the distribution of current single disease manifestations did not differ between SAP-DNA positives and negatives (Table 2). Patients with and without SAP-DNA complexes had experienced equal numbers of infections demanding medical treatment and comparable numbers of thromboembolic events during followup. Drug treatment was equally distributed between SAP-DNA positives and negatives (Table 2).

The biochemical profile differed slightly between the 2 SLE subsets, albeit without reaching statistical significance. Thus, the ESR level tended to be higher, and leukocyte and platelet counts to be lower in patients without SAP-DNA complexes as compared with SAP-DNA-producing patients (Table 2). Moreover, complement C3 tended to be lower and C3d to be higher in patients who lacked SAP-DNA complexes.

In addition, patients testing SAP-DNA-positive ever (i.e., one or more positive SAP-DNA measurements, n = 26) were compared with those who were permanently negative (n = 56, Table 3). These subsets did not differ with respect to sex, age, disease duration, organ damage, and disease activity when serum samples were collected. However, ESR was

Table 3. Comparison between lupus patients testing SAP-DNA complex-positive at least once vs patients permanently negative for SAP-DNA during 2-year followup. Serologic findings at cross-sectional assessment. Values are median.

	SAP-DNA-negative, n = 56	SAP-DNA-positive, n = 26	p
C-reactive protein, mg/l	< 10	< 10	0.715
Erythrocyte sedimentation rate, mm/H	24	13	0.009
Hemoglobin, mmol/l	8.2	9.1	0.002
Leukocyte count, × 10 <sup>9</sup> /l	6.4	8.45	0.001
Platelet count, × 10 <sup>9</sup> /l	246	241	0.571
C3, g/l	0.88	0.94	0.638
C3d, mU/l	47	39	0.004

lower and hemoglobin and white blood cell count higher in SAP-DNA-positive patients compared with those testing negative. In addition, complement C3 tended to be higher and C3d lower in patients capable of producing SAP-DNA complexes. Platelet counts did not differ in the 2 subsets.

## DISCUSSION

Our study is the first to demonstrate that SLE patients have

persistently decreased levels of SAP-DNA complexes in the circulation despite normal serum levels of SAP component.

A growing body of evidence has emerged within recent years that defective processing of nuclear waste from apoptotic or necrotic cells may contribute to the development of SLE. This concept has gained support from both animal experiments and studies on human SLE patients. Thus, Bickerstaff, *et al*<sup>7</sup> reported that SAP-knockout mouse strains spontaneously produce high amounts of autoantibodies directed against chromatin DNA and histones. In addition, a high proportion of female SAP-deficient mice developed proliferative glomerulonephritis with immune complex deposition. Further, these authors demonstrated that chromatin degradation by leukocytes *in vitro* is decreased if SAP is added, and chromatin degradation in SAP deficient mice is accelerated, suggesting that complex formation between chromatin and SAP reduces the immunogenicity of chromatin constituents<sup>7</sup>. The additional observation that DNase1-deficient mice produce autoantibodies against chromatin, glomerulonephritis, and a spontaneous lupus-like syndrome adds to the evidence that chromatin excess and diminished clearance of cellular debris is involved in SLE pathogenesis<sup>22</sup>. Further evidence suggesting a link between abnormal cellular waste disposal and SLE has emerged from clinical studies demonstrating increased plasma levels of nucleosomes in SLE patients<sup>23</sup> and inappropriate handling of apoptotic cells by germinal center macrophages in some SLE patients<sup>24</sup>.

Our study was performed on an unselected population of SLE patients with generally low disease activity (SLEDAI 0–12). In accordance with 2 previous studies<sup>13,25</sup> we found no difference in the serum concentration of SAP between patients with SLE and healthy blood donors. Earlier investigations on the structure and function of SAP have not revealed qualitative differences between SLE patients and healthy subjects<sup>13</sup>.

Based on these observations, the low prevalence of SAP-DNA complexes in our lupus cohort was surprising. This study shows that SAP-DNA complexes could not be demonstrated in 70%–80% of SLE patients followed prospectively for up to 2 years. Although no association was found between disease activity or individual disease manifestations, there was a highly significant negative correlation between the occurrence of SAP-DNA complexes and anti-dsDNA antibodies. SAP-DNA complexes and anti-dsDNA were detected concomitantly in only one patient with newly diagnosed and very active disease. By contrast, traditional inflammatory markers such as ESR and complement C3 and C3d showed proinflammatory changes, particularly in persistently SAP-DNA-negative patients.

Most likely the negative association between SAP-DNA complexes and anti-dsDNA reflects competitive binding of DNA by SAP or by antibodies towards dsDNA. However, anti-SAP antibodies should also be considered as a source of

interference in chromatin binding to SAP in the SLE patients. Thus, Zandman-Goddard, *et al* recently demonstrated elevated anti-SAP antibody titers in SLE patients and a positive correlation with SLEDAI scores<sup>26</sup>.

Our study's limitations: first, the study comprised a low proportion of patients with very active disease, implying that possible temporal changes in the relationship between SAP-DNA complexes and anti-dsDNA antibodies cannot be determined. Second, consecutive serum samples were not available for all 82 SLE patients included in the cross-sectional study. Third, blood sampling was done at predetermined intervals and was unrelated to changes in disease manifestations. Future studies are warranted to study the dynamics of SAP-DNA complex formation in newly diagnosed active disease or during disease flares.

Our study demonstrates that SAP-DNA complex formation is decreased in an unselected SLE population. Permanent absence of SAP-DNA complexes occurs in two-thirds of these SLE patients of predominantly Scandinavian ancestry. In addition, an inverse relationship between the occurrence of anti-dsDNA and SAP-DNA complex formation was observed, adding further support to the concept that SAP is important for clearance of cell nuclear debris.

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