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Low values of creatine kinase in systemic lupus erythematosus. Clinical significance in 300 patients

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ABSTRACT

Objective. *To study creatine kinase (CK) activity in a large series of patients with systemic lupus erythematosus (SLE) and identify the clinical and immunological features related to reduced levels.*

Methods. *In a cross-sectional study, serum CK activity was measured in 300 consecutive patients with SLE (271 females and 29 males, with a mean age of 36 years). All patients fulfilled the 1982 revised criteria of the American College of Rheumatology.*

Results. *Low serum CK levels (< 33 IU/L) were detected in 118 (39%) of SLE patients. When compared to SLE patients with normal serum CK levels, those with SLE and low serum CK levels had a higher frequency of fever (53% vs. 34%, p =0.017), renal involvement (43% vs. 27%, p = 0.004), and hemolytic anemia (13% vs. 6%, p = 0.037). In addition, SLE patients with low CK values also presented lower values of hemoglobin, total proteins, albumin, cholesterol and triglycerides, higher values of ESR and low C3 (44% vs. 27%, p = 0.004), C4 (57% vs. 37%, p = 0.001) and CH50 levels (60% vs. 41%, p = 0.02). We analysed in 69 patients the correlation between CK and 24-hour proteinuria values, and found that those with a 24-hour proteinuria > 1500 mg/day showed lower CK values than those with proteinuria < 1500 (31.95 vs 63.84 IU/L, p=0.046).*

Conclusion. *We observed that serum CK levels were reduced in 39% of SLE patients. Reduced serum CK activity was significantly related to some clinical (fever, nephropathy), hematological (high ESR, hemolytic anemia) and immunological (hypocomplementemia) features, which relate to disease activity. This suggest that reduced CK activity might be inversely correlated to inflammatory activity in SLE.*

Introduction

Systemic lupus erythematosus (SLE) is the most clinically and serologically diverse of the autoimmune connective tissue diseases, since it may affect any organ of the body and display a broad spectrum of clinical and immunological manifestations. The clinical features include articular and mucocutaneous involvement, renal disease, hematological abnormalities and central nervous system disease (1). However, it is now thought that SLE may be divided into more homogeneous subsets of pathogenic, therapeutic and prognostic significance (2-5).

Creatine kinase (CK) is a transferase that catalyses phosphocreatine formation from ATP and creatine, allowing ATP energy storage. The highest concentrations are found in skeletal muscle, the brain and the heart. When there is damage to any of these organs,serum CK level increases, while in other conditions, such as infectious processes in intensive care patients or in renal-transplant recipients, the levels of serum CK decrease (6-8). Some studies have analysed the CK levels in autoimmune and rheumatic diseases and described low CK values in small series of patients with rheumatoid arthritis or systemic lupus erythematosus (9-12). The causes are not established, although there is evidence that inflammatory activity may play an important role.

The aim of this study was to investigate serum CK activity in a large series of patients with SLE in order to identify the clinical and immunological features related to reduced CK levels.

Patients and methods

Patients had been attending our Unit either as in- or outpatients between 1980 and 2000. All had documented medical histories and underwent a medical interview as well as a routine general physical examination. A serum sample from each patient was collected for the immunologic tests. Clinical and serologic characteristics of all patients were consecutively collected in a protocol form. Features included in the protocol were: 1) age at onset of the disease, defined as the initial manifestation clearly attributable to SLE; 2) age at diagnosis, defined as the age when the patient fulfilled 4 or more of the 1982 revised ACR criteria for the classification of SLE (13); 3) age at protocol, defined as the age when the patient entered the protocol study; 4)

clinical manifestations at onset; 5) cumulative clinical manifestations during the evolution of the disease (from the onset until the protocol study); 6) associated autoimmune diseases; and 7) laboratory features at protocol including serum CK (normal values: 33-144 IU/L). Analytical tests were consecutively collected when patients entered the protocol study, and information collected in protocol forms was transferred to a computerized database.

Organ involvement in SLE was defined according to previous studies (1, 5):

1) Malar rash: fixed flat or raised erythema, over the malar eminences, tending to spare the nasolabial folds.
2) Subacute cutaneous lesions: photosensitive, non-scarring dermatitis appearing as either papulosquamous or annular lesions.
3) Articular involvement: presence of nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion.
4) Renal involvement: a) persistent proteinuria > 0.5 g/day, b) cellular casts (red cell, hemoglobin, granular, tubular, or mixed), or c) otherwise unexplained elevation of serum creatinine > 0.75 mg/dL.
5) Neurologic involvement: seizures, psychosis, chorea or migraine, in the absence of drugs or known metabolic disturbances, e.g., uremia, ketoacidosis, or electrolyte imbalance.
6) Thrombosis: clinically-diagnosed venous and/or arterial thrombosis, confirmed by complementary tests.
7) Myositis: muscle weakness accompanied by elevation of muscle enzymes, with electromyography or biopsy findings characteristic of myositis.
8) Oral ulcers: oral or nasopharyngeal ulceration, usually painless.
9) Serositis: pleuritis (pleuritic pain or rub or evidence of pleural effusion) or pericarditis (documented by electrocardiogram, rub, or evidence of pericardial effusion).
10) Hemolytic anemia (decrease of ≥3 g/dL in blood hemoglobin, coincident with a rise in conjugated bilirubin and a reticulocyte count > 5% at the time of the hemolytic episode).
11) Fever: temperature of > 38°C or 100°F in the absence of infection
12) Raynaud phenomenon: blanching of the fingers, toes, ears, nose, tongue, induced by exposure to cold, stress, or both

Immunological tests included determination of antinuclear antibodies (ANA) by indirect immunofluorescence using mouse liver as substrate, antibodies to double-stranded DNA (anti-dsDNA) by Farr's technique (positive if > 7 units/ml), precipitating antibodies to the extractable nuclear antigens (U1RNP, Sm, Ro/SSA, La/SSB) by ELISA, and rheumatoid factor by latex fixation and Waller-Rose tests. Complement factors (C3 and C4) were estimated by nephelometry, and CH50 by Lachmann's haemolytic technique. The IgG and IgM anticardiolipin antibodies (aCL) were estimated by the ELISA technique. Finally, lupus anticoagulant was measured by coagulation assays following the recommendations of the Subcommittee on Lupus Anticoagulant of the Scientific and Standardisation Committee of the International Society of Thrombosis and Hemostasis.

Statistical methods

The chi-square and Fisher exact tests were used to analyse qualitative differences. For comparison of quantitative parameters, the Student t-test was used in large samples of similar variance, and the nonparametric Mann-Whitney U-test for small samples. Values of quantitative variables are expressed as mean ± standard error of the mean (SEM). A value of $p < 0.05$ indicates statistical significance. Statistical analysis was performed using the SPSS program.

Results

The cohort of SLE patients consisted of 271 (90.3%) women and 29 (9.7%) men (female:male ratio, 9:1). Mean age of onset of symptoms attributable to the disease was 31.1 ± 0.6 years (range, 5-84) and at the diagnosis of SLE was 32.7 ± 0.6 years (range, 8-85). Mean age at the entry in the protocol was 36.8 ± 0.7 years (range, 8-85). Evolution of the disease before entry in the protocol study ranged between 1 and 528 months (m CK levels (< 33 IU/L) were detected in 118 (39%) of SLE patients. Epidemiological and clinical features in SLE patients with low or normal serum CK levels are summarized in Table I. Compared with patients with normal CK levels, those with low levels presented a higher fre-

Table I. Clinical manifestations of SLE in patients with and without low serum CK levels.

	Low CK values (n = 118)	Normal CK values (n = 182)	p value	Bonferroni correction
Sex (female)	110 (93)	161 (89)	ns	-
Mean age (years)	35.1 ± 15.4	37.1 ± 15.2	ns	-
Evolution (months)	59.4 ± 73.8	68.9 ± 82.3	ns	-
Fever	63 (53%)	71 (34%)	0.017	0.196
Photosensitivity	46 (39%)	77 (42%)	ns	-
Malar rash	62 (53%)	87 (48%)	ns	-
Oral ulcers	35 (35%)	50 (28%)	ns	-
Arthritis	98 (83%)	144 (79%)	ns	-
Myositis	11 (9%)	10 (6%)	ns	-
Serositis	29 (25%)	44 (24%)	ns	-
Nephropathy	51 (43%)	49 (27%)	0.004	0.048
Neurological involvement	10 (9%)	17 (9%)	ns	-
Raynaud phenomenon	20 (17%)	40 (22%)	ns	-
Cutaneous vasculites	21 (18%)	25 (14%)	ns	-
Hemolytic anemia	15 (13%)	11 (6%)	0.037	0.518
Thrombosis	11 (9%)	8 (4%)	ns	-

quency of fever (53% vs. 34%, p = 0.017), hemolytic anemia (13% vs. 6%, p = 0.037) and renal involvement (43% vs. 27%, p = 0.004), although only nephropathy reached statistical significance after Bonferroni's correction. Specifically, we analysed the mean CK values according to the WHO classification of renal biopsies, and found the lowest CK levels in classes IV (35.3 ± 19.1), III (36.0 ± 21.8) and V (44.7 ± 54.7), in comparison with classes I (50.7 ± 29,7) and II (63.5 ± 67.4). We also analysed the correlation between CK and 24-hour proteinuria values in 69 patients, and found that patients with 24-hour proteinuria > 1500 mg/day showed lower CK values than those with proteinuria < 1500 mg/day (31.95 vs 63.84 IU/L, p = 0.046).

Table II shows the mean values of the main biologic and hematologic parameters in patients with low and normal CK values. SLE patients with low CK levels showed lower mean values of total proteins and albumin and higher mean values of cholesterol and triglycerides. The hematologic profile of SLE patients with low CK showed a higher mean value of ESR and lower values of hemoglobin.

Immunologic features in SLE patients with low or normal serum CK levels are summarized in Table III. SLE patients with low CK values presented a higher frequency of low C3 (44% vs. 27%,p = 0.004), C4 (57% vs. 37%, p = 0.001) and CH50 (60% vs. 41%, p = 0.02). Finally, we analysed the different therapies used and found that SLE patients with low CK levels received high doses of corticoids (> 0.5 mg/Kg/day) more frequently (27% vs. 15%, p = 0.01).

Table II. Mean values of the main analytical parameters in patients with low and normal CK values.

	Normal CK	Low CK values	P value
ESR (mm/h)	28.3 ± 22.8	36.1 ± 25.0	0.007
Hemoglobin (g/dL)	12.2 ± 1.7	11.5 ± 2.0	0.003
Leukocyte count ($x10^9$/L)	5.9 ± 2.2	6.6 ± 2.9	-
Lymphocyte count ($x10^6$/L)	1376.2 ± 821.2	1345.6 ± 700.6	-
Platelet count ($x10^9$/L)	199.2 ± 81.8	191.6 ± 83.2	-
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.2	-
Total proteins (g/L)	70.6 ± 4.9	61.4 ± 10.9	0.0001
Albumin (g/L)	40.0 ± 7.9	37.7 ± 7.8	0.016
Cholesterol (mg/dL)	186.1 ± 39.5	218.6 ± 63.1	0.017
Tryglicerids (mg/dL)	100.8 ± 58.7	146.4 ± 103.9	0.031
LDH (IU/L)	332.2 ± 86.0	315.0 ± 86.5	-

Table III. Immunological features of SLE patients with and without low serum CK values.

Parameters	Low CK values (n = 118)	Normal CK values (n =182)	p value	Bonferroni correction
ANA	108/114 (85%)	172/179 (96%)	ns	-
Anti-dsDNA > 7 U/ml	83/111 (75%)	116/178 (65%)	ns	-
Anti-Ro/SSA antibodies	25/107 (23%)	39/172 (23%)	ns	-
Anti-La/SSB antibodies	10/106 (9%)	11/172 (6%)	ns	-
Anti-U1RNP antibodies	14/105 (13%)	26/172 (15%)	ns	-
Anti-Sm antibodies	12/106 (11%)	20/172 (12%)	ns	-
Rheumatoid factor	17/103 (17%)	21/171 (12%)	ns	-
IgG aCL antibodies	18/106 (17%)	23/169 (14%)	ns	-
IgM aCL antibodies	12/106 (11%)	16/169 (9%)	ns	-
Lupus anticoagulant	16/107 (15%)	28/170 (17%)	ns	-
Low C3 (< 0.82 g/L)	50/113 (44%)	49/179 (27%)	0.004	0.039
Low C4 (< 0.11 g/L)	64/113 (57%)	66/179 (37%)	0.001	0.012
Low CH50 (< 34 U/mL)	68/113 (60%)	74/179 (41%)	0.002	0.022

Discussion

Low serum CK levels have been observed in various diseases in which the inflammatory process plays an important role, such as SLE (9-11), rheumatoid arthritis (9-12), ankylosing spondylitis (14), infected intensive care patients (6-7) and renal-transplant recipients (8). When comparing the same rheumatic disease with and without accompanying inflammatory features (e.g., ankylosing spondylitis with and without peripheral arthritis) there is a lower serum CK level in those with active clinical inflammation (10). This suggests that autoimmune features may participate in the lowering of the serum CK levels.

Delanghe *et al*. showed that molecular changes occur in the CK structure in infected intensive care patients (7). The authors incubated standard CK pool in normal serum at 37ºC, and then incubated normal serum with infected patients'serum. The second incubation showed a significant increase of activation energy of CK, indicating changes in the CK structure. This also occurred when they added liver and pancreatic tissue fragments, fibroblasts and isolated strains of bacteria. This suggests that modifying factors present in the patients'serum are able to alter the CK structure. High serum levels of interleukines, cytokines, prostaglandins, leukotrienes,neutrophils, macrophages and mastocytes, accompany inflammation. It seems possible that some of these molecules/cells may act as the modifying factor of the CK, thus facilitating its destruction.

Another mechanism that may contribute to the lowering of CK levels in some patients is an increased glomerular filtration rate. At first this seems highly unlikely, since human CK is metabolised mostly in the liver (15) and has a molecular mass of about 86 KDa, whereas the physiological threshold for glomerular filtration is about 65 KDa. In the nephrotic syndrome, however, there is a dysfunction of the size-selective barrier, which results in an increase in glomerular permeability for large proteins. This could result in increased clearance of CK through this pathway. In our study,

a significant association was found between low serum CK levels and nephropathy. This could be secondary to severe accompanying inflammation. We found a high number of patients with nephrotic syndrome and low serum CK levels. Furthermore, we found lower CK serum levels in nephropathies classes III, IV and V, in which glomerular membrane lesions may originate protein leakage, frequently in the nephrotic range. Lower CK serum levels were also associated with lower serum levels of albumin and higher mean values of cholesterol and tryglicerids, which usually are present in the nephrotic syndrome. Taken together, these data suggest that the hypothesis that at least some CK is cleared through this pathway cannot be ruled out.

Another contributive mechanism could be considered. Barnert and Bern demonstrated that physical inactivity is accompanied by reduced CK serum values (16). In the most severe SLE flares, rest is advised, which leads to physical inactivity. The role of steroids is still not well understood. As in other studies (10-11), we also found lower serum CK levels that correlated to higher doses of steroids. This could be the result of such a therapy, but could also be that the higher doses of steroids were needed because the disease was more active and therefore, more inflammation.

In our study, serum CK levels were significantly reduced in SLE patients. Reduced CK activity was related to some clinic laboratory variables of inflammatory activity, such as fever and a high ESR, suggesting that there might be an inverse correlation between inflammation and low CK values. This could be of major importance in a disease such as SLE, where muscle involvement is relatively frequent. Physicians should be aware that a normal serum CK value does not exclude the diagnosis of myositis, in SLE patients.

In conclusion, we observed that serum CK levels were reduced in 39% of SLE patients. Reduced serum CK activity was significantly related to some clinical (fever, nephropathy), hematological (high ESR, hemolytic anemia) and immunological (hypocomplementemia) features, which relate to disease activity. These facts suggest that reduced CK activity might be inversely correlated to inflammatory activity in SLE. The high rate of patients with nephrotic syndrome and low CK serum levels suggest that an increased glomerular filtration rate could also be a contributing factor to the lowering of the CK levels. A study in which the glomerular filtration rate is assessed could help clear up this issue.

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