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# Proprotein convertase subtilisin/kexin type 9 is related to disease activity and damage in patients with systemic erythematosus lupus

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***Abstract***

**Background:** Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that regulates cholesterol metabolism through low-density lipoprotein receptor degradation and that has been linked to cardiovascular (CV) disease. The purpose of the present study was to examine whether PCSK9 levels are disrupted compared with controls in patients with systemic lupus erythematosus (SLE). We additionally sought to establish whether PCSK9 is related to both the abnormalities in the lipid profile and to the disease activity or damage of patients with SLE.

**Methods:** We performed a cross-sectional study that encompassed 366 individuals: 195 SLE patients and 171 age-, sex-, and statin intake-matched controls. PCSK9, lipoproteins serum concentrations, and lipid profiles were assessed in patients and controls. A multivariable analysis, adjusted for standard CV risk factors, was performed to evaluate the role of PCSK9 in SLE-related dyslipidemia.

**Results:** Most lipid related-molecules were decreased in patients with SLE compared with controls. This downregulation included PCSK9, with PCSK9 levels being lower in patients than controls in the full multivariable analysis, including the modifications in lipid profiles that the disease itself produces {beta coefficient −73 [95% confidence interval (CI) −91 to −54] ng/ml, $p \leqslant 0.001$}. Both SLICC and SLEDAI scores were independently and positively related to PCSK9. Patients currently on hydroxychloroquine exhibited decreased levels of PCSK9 compared with those that were not taking hydroxychloroquine [beta coefficient −30 (95% CI −54 to −6) ng/ml, $p = 0.015$].

**Conclusion:** PCSK9 is downregulated in SLE compared with controls, but SLE patients with higher disease activity and damage exhibited higher PSCK9 serum levels.

***Keywords:*** Systemic lupus erithematosus, dyslipidemia, PCSK9

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## Introduction

Proprotein convertase subtilisin kexin 9 (PCSK9) – a serine protease – plays an important role in low-density lipoprotein (LDL) metabolism. PCSK9, which is synthesized primarily in the liver, enters the circulation, where it binds to hepatic LDL receptors and targets them for degradation.[1] This process reduces the capacity of the liver to bind and remove LDL-cholesterol, and results in increased LDL-cholesterol levels. The reduced incidence of cardiovascular (CV) events in patients bearing PCSK9 loss-of-function mutations provided a strong rationale for the development of molecules capable of inhibiting PCSK9 function.[2] In this sense, blocking the interaction between PCSK9 and LDL receptors by the use of a fully human monoclonal antibody that binds PCSK9 has been found to lower LDL-cholesterol levels in patients with hypercholesterolemia, and to reduce the rate of CV events.[3]

Inflammation and PCSK9 have been previously linked.[4] Moreover, autoimmune inflammatory diseases like rheumatoid arthritis and systemic sclerosis are known to have lower serum levels of PCSK9. In this regard, rheumatoid arthritis



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patients exhibited lower PCSK9 serum concentrations than controls after adjustment for classic CV risk factors, lipid profiles, and statins.[5] Similarly, PCSK9 serum concentrations were found to be downregulated in systemic sclerosis patients compared with controls, and were associated directly with disease severity and carotid intima media wall thickness.[6]

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease caused by perturbations of the immune system. The clinical presentation is heterogeneous, largely because of the multiple genetic and environmental factors that contribute to disease initiation and progression.[7] Lipid profiles appear to be altered in SLE patients due to disease activity and inflammation.[8] However, there is little information about the role of PCSK9 in the modified lipid profiles that patients with SLE exhibit. For this reason, we conducted a study to assess whether PCSK9 serum levels are different in SLE patients compared with controls. We additionally aimed to determine whether PCSK9 is associated with the changes that inflammation and the disease exert over the lipid profiles of SLE patients.

## Materials and methods

### *Study participants*

This was a cross-sectional study that included 366 individuals, 195 patients with SLE and 171 controls. All SLE patients were 18 years old or older, had a clinical diagnosis of SLE and fulfilled at least four American College of Rheumatology (ACR) classification criteria for SLE.[9] They had been diagnosed by rheumatologists and were followed up periodically at rheumatology outpatient clinics. For the purpose of inclusion in the present study, SLE disease duration was required to be $\geqslant$1 year. Controls included in the current study were subjects without any known condition or drug treatment history that could influence lipids, and who were not taking any lipid-lowering medications other than statins. None of the controls was receiving glucocorticoids. However, since glucocorticoids are often used in the management of SLE, patients taking prednisone or an equivalent dose $\leqslant$10 mg/day were included. As previously mentioned, both patients and controls under statin treatment were allowed to participate in the study. The controls were community-based, and recruited by general practitioners in primary health centers. Patients and controls were excluded if they had a history of myocardial infarction, angina, stroke, a glomerular filtration rate $<$60 ml/min/1.73 m$^2$, a history of cancer, any other chronic disease, or evidence of active infection. Research was carried out in compliance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Committee at Hospital Universitario de Canarias and Hospital Doctor Negrín (both in Spain), and all subjects provided informed written consent (Approval Number 2015_84).

### *Data collection*

Surveys of SLE patients and controls were performed to assess CV risk factors and medication. Subjects completed a questionnaire and underwent a physical examination to determine anthropometric measurements and blood pressure. Medical records were reviewed to ascertain specific diagnoses and medications. Hypertension was defined as a systolic or a diastolic blood pressure higher than 140 and 90 mmHg, respectively. SLE disease activity and damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) and the SLICC/ACR Damage Index (SDI), respectively.[10,11] For the propose of the present study, the SLEDAI-2k index was broken down into none (0 points), mild (1–5 points), moderate (6–10 points), high ($>$10 points), and very high ($>$20 points) activity as previously described[12] (SLEDAI category could not be calculated in 10 patients due to missing data). Disease severity was measured as well, using the Katz Index.[13]

### *Lipids and PCSK9 assessments*

Fasting serum samples were collected and frozen at −80°C until analysis of circulating lipids. Human PCSK9 was measured using an enzyme-linked immunosorbent (ELISA) kit (R&D Duoset, R&D Systems, Minneapolis, MN, USA). Intra- and inter-assay coefficients of variation were $<$5% and 6.3%, respectively. Cholesterol, triglycerides, and high-density lipoprotein (HDL)-cholesterol were measured using the enzymatic colorimetric assay (Roche). Cholesterol range of detection was from 0.08 to 20.7 mmol/l (intra-assay coefficient of variation 0.3%); triglycerides range from 4 to 1.000 mg/dl (intra-assay coefficient of variation 1.8%); and HDL-cholesterol range from 3 to 120 mg/dl (intra-assay variation coefficient 0.9%). LDL-cholesterol was calculated using the Friedewald formula. The atherogenic index was

calculated using the total cholesterol/HDL-C ratio according to Castelli's formula. Indirect immunofluorescence in Hep-2 cell line assay were used for the detection of antinuclear antibodies. Anti-DNA and extractable nuclear antigens (anti-ENA) were assessed through ELISA solid-phase assays. Additionally, standard techniques were used to measure C-reactive protein (CRP) and serum lipids.

### *Statistical analysis*

Demographic and clinical characteristics were compared between SLE patients and controls using $\chi^2$ tests for categorical variables or a Student's $t$ test for continuous variables [data expressed as mean ± standard deviation (SD)]. For non-normally variables, either a Mann–Whitney $U$ test was performed or a logarithmic transformation was made, and data were expressed as a median and interquartile range (IQR). Univariable linear regression, computing unstandardized coefficients, were performed to establish the relation of demographics, traditional CV risk factors, lipid profile, and SLE-related data with PCSK9. Differences between patients and controls in terms of their lipid profiles were adjusted for variables with a $p$ value less than 0.20 in the differences in demographics and CV risk factors between both populations. Additionally, to avoid collinearity, variables derived from a formula were excluded from the regression models (e.g. LDL: HDL ratio, atherogenic index, etc.). SLICC and SLEDAI regression analysis with PCSK9 was adjusted for those variables with a correlation less than 0.20 with both the independent and dependent variable. All analyses used a 5% two-sided significance level and were performed using SPSS software, version 24 (IBM, Chicago, IL, USA) and STATA software, version 13/SE (Stata Corp., College Station, TX, USA). A $p$ value $< 0.05$ was considered statistically significant.

## Results

### *Demographic, laboratory, and disease-related data*

A total of 366 participants, 195 patients with SLE and 171 controls, were included in this study. Demographic- and disease-related characteristics of the participants are shown in Table 1. Patients and controls showed no differences regarding age, sex, and statins use. Additionally, although the presence of diabetes was higher in controls than in patients with SLE (16% *versus* 5%, $p < 0.001$), and hypertension was higher in SLE patients (39% *versus* 30%, $p = 0.049$), no differences were found in body mass index (BMI), waist circumference or smoking.

Most SLE patients were in the no (40%) or mild (32%) activity categories as shown by the SLEDAI score. Disease duration was 17 ± 10 years. SLICC and Katz indexes were, respectively, 1 (IQR 1–3) and 2 (IQR 1–3); 74% of the patients had a SLICC/ACR DI score ⩾1, and 38% had a Katz index ⩾3. About half of the patients (51%) were taking prednisone [the median dose of those 99 patients on prednisone was 5 (IQR 5–7.5) mg/day at the time of the study]. When the study was performed, 98 (50%) patients were found to be positive for anti-DNA, and 34% were positive for ENA, with anti-Ro being the most frequently found antibody (32%). Disease-modifying antirheumatic drug (DMARD) use was reported in 78% of the patients, and 68% were taking hydroxychloroquine at the time the study was performed. Major organ involvement like seizures ($n = 1$), psychosis ($n = 1$), organic brain syndrome ($n = 0$), vasculitis ($n = 1$), pericarditis ($n = 0$), or myositis ($n = 0$) were uncommon (data not shown). Additional information regarding disease-related data is shown in Table 1.

### *Multivariable analysis of the differences in lipid profiles and PCSK9 between SLE patients and controls*

Many differences were found in the lipid profiles between patients and controls in the univariable analysis (Table 2). In this sense, HDL-cholesterol was found to be higher in SLE patients. In contrast, LDL-cholesterol, LDL:HDL cholesterol ratio, non-HDL cholesterol, apolipoprotein B, Apo A:Apo B ratio, and atherogenic index were downregulated in patients compared with controls. Mean PCSK9 serum levels were significantly lower in SLE patients compared with controls (252 ± 100 *versus* 181 ± 76 ng/ml, $p < 0.001$) when the univariable analysis was performed. In fully adjustment model (Model 1 in Table 2), most of these differences between the two populations were maintained, with the exception of total cholesterol, triglycerides, lipoprotein (a), and apolipoprotein A1. Remarkably, PCSK9 levels were still downregulated in SLE patients after the multivariable analysis [beta coefficient –77 (95% CI –96 to −58) ng/ml, $p \leqslant 0.001$].

**Table 1.** Characteristics of SLE patients and controls.

| | Controls (*n* = 171) | SLE patients (*n* = 195) | *p* |
|---|---|---|---|
| Age, years | 51 ± 17 | 51 ± 11 | 0.97 |
| Female, *n* (%) | 162 (95) | 185 (95) | 0.95 |
| BMI, kg/m$^2$ | 27 ± 6 | 27 ± 6 | 0.37 |
| Abdominal circumference, cm | 92 ± 9 | 92 ± 13 | 0.58 |
| Cardiovascular co-morbidity | | | |
| Smoking, *n* (%) | 31 (18) | 46 (24) | 0.20 |
| Diabetes, *n* (%) | 27 (16) | 9 (5) | <0.001 |
| Hypertension, *n* (%) | 51 (30) | 77 (39) | 0.049 |
| Statins, *n* (%) | 41 (24) | 52 (27) | 0.56 |
| SLE-related data | | | |
| CRP, mg/l | 2.2 (1.3–5.5) | 1.9 (0.9–4.9) | 0.31 |
| Disease duration, years | | 17 ± 10 | |
| SLICC | | 1 (1–3) | |
| SLICC ⩾1, *n* (%) | | 145 (74) | |
| Katz Index | | 2 (1–3) | |
| Katz Index ⩾3, *n* (%) | | 75 (38) | |
| SLEDAI | | 2 (0–5) | |
| SLEDAI activity categories, *n* (%) | | | |
| No activity, *n* (%) | | 78 (40) | |
| Mild, *n* (%) | | 63 (32) | |
| Moderate, *n* (%) | | 31 (16) | |
| High and very high, *n* (%) | | 13 (7) | |
| Auto-antibody profile | | | |
| Anti-DNA positive, *n* (%) | | 98 (50) | |
| ENA positive, *n* (%) | | 66 (34) | |
| Anti-Ro, *n* (%) | | 62 (32) | |
| Anti-La, *n* (%) | | 30 (15) | |
| Anti-RNP, *n* (%) | | 48 (25) | |
| Anti-Sm, *n* (%) | | 21 (11) | |
| Any antiphospholipid autoantibody, *n* (%) | | 71 (36) | |

*(Continued)*

**Table 1.** (Continued)

| | Controls (*n* = 171) | SLE patients (*n* = 195) | *p* |
|---|---|---|---|
| Lupus anticoagulant, *n* (%) | | 39 (20) | |
| ACA IgM, *n* (%) | | 20 (10) | |
| ACA IgG, *n* (%) | | 31 (16) | |
| Anti beta2 glycoprotein IgM, *n* (%) | | 13 (7) | |
| Anti beta2 glycoprotein IgG, *n* (%) | | 22 (11) | |
| C3, mg/dl | | 96 ± 27 | |
| C4, mg/dl | | 17 ± 7 | |
| Current prednisone, *n* (%) | | 99 (51) | |
| Prednisone, mg/day | | 5.0 (5.0–7.5) | |
| DMARDs, *n* (%) | | 152 (78) | |
| Hydroxychloroquine, *n* (%) | | 132 (68) | |
| Methotrexate, *n* (%) | | 23 (12) | |
| Mycophenolate mofetil, *n* (%) | | 15 (8) | |
| Azathioprine, *n* (%) | | 27 (14) | |
| Rituximab, *n* (%) | | 6 (3) | |
| Belimumab, *n* (%) | | 3 (2) | |
| Cyclophosphamide, *n* (%) | | 1 (1) | |
| Carotid intima media assessment | | | |
| Carotid plaque, *n* (%) | | 66 (34) | |
| Bilateral, *n* (%) | | 34 (17) | |
| cIMT, microns | | 627 ± 122 | |

Data represent means ± SD or median (IQR) when data were not normally distributed.
SLEDAI categories were defined as: 0, no activity; 1–5 mild; 6–10 moderate; >10 high; >20 very high.
ACA, anticardiolipin; ANA, antinuclear antibodies; BMI, body mass index; C3 C4, complement; cIMT, carotid intima-media thickness; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; ENA, extractible nuclear antibodies; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index.

Because lipid-related molecules are interrelated (they share metabolic pathways and it is not easy to separate the effect of one from the others), we performed a multivariable analysis adjusting for demographics and CV risk factors plus all the lipid-related molecules that were found to be different between patients and controls in the univariable analysis (Model 2 in Table 2). Because of collinearity, lipid molecules derived from a formula were excluded from the regression model (LDL-cholesterol, LDL:HDL ratio, non-HDL cholesterol, apoB:apoA, and atherogenic index). HDL-cholesterol [beta coefficient 7 (95% CI 3–11), $p = 0.001$] and apolipoprotein B [beta coefficient −8 (95% CI −14 to −3), $p = 0.004$] maintained their differences between patients and

**Table 2.** Multivariable analysis of the differences in the lipid profiles and PCSK9 serum levels of SLE patients and controls.

| | Controls | SLE patients | Univariable | Model #1 | Model #2 |
|---|---|---|---|---|---|
| | (*n* = 171) | (*n* = 195) | model | beta coefficient (95% CI) | |
| **Lipid profile** | | | | | |
| Cholesterol, mg/dl | 200 ± 46 | 200 ± 38 | 0.88 | −1 (−10 to 7), 0.77 | |
| Triglycerides, mg/dl | 139 ± 64 | 127 ± 80 | 0.14 | −13 (−28 to 3), 0.11 | 13 (−2 to 28), 0.085 |
| HDL cholesterol, mg/dl | 54 ± 15 | 63 ± 21 | <0.001 | 9 (5–13), <0.001 | 7 (3–11), 0.001 |
| LDL cholesterol, mg/dl | 118 ± 37 | 111 ± 29 | 0.037 | −8 (−15 to −1) 0.028 | – |
| LDL:HDL cholesterol ratio | 2.29 ± 0.86 | 1.91 ± 0.75 | <0.001 | −0.38 (−0.56 to −0.21), <0.001 | – |
| Non-HDL cholesterol, mg/dl | 146 ± 41 | 136 ± 33 | 0.016 | −11 (−19 to −3), 0.007 | – |
| Lipoprotein (a), mg/dl | 41 (13–106) | 38 (12–116) | 0.36 | 7 (−10 to 25), 0.39 | |
| Apolipoprotein A1, mg/dl | 181 ± 40 | 180 ± 37 | 0.75 | −1 (−9 to 7), 0.84 | |
| Apolipoprotein B, mg/dl | 103 ± 30 | 95 ± 24 | 0.009 | −8 (−14 to −2), 0.009 | −8 (−14 to −3), 0.004 |
| Apo B:Apo A1 ratio | 0.59 ± 0.18 | 0.55 ± 17 | 0.044 | −0.04 (−0.08 to −0.00), 0.043 | – |
| Atherogenic index | 3.85 ± 1.08 | 3.39 ± 1.08 | <0.001 | −0.48 (−0.71 to −0.24), <0.001 | – |
| PCSK9, ng/ml | 252 ± 100 | 181 ± 76 | <0.001 | −77 (−96 to −58), <0.001 | −73 (−91 to −54), <0.001 |

Data represent means ± SD or median (IQR) when data were not normally distributed.
Model #1: Adjusted for hypertension and diabetes (variables with a *p* value < 0.20 difference between patients and controls).
Model #2: Adjusted for model #1 + rest of lipid molecules (with a *p* value < 0.20 in Model #1) other than the one that is compared.
Because collinearity LDL cholesterol, LDL:HDL ratio, non-HDL cholesterol, apoB:apoA, and atherogenic index were excluded from the multivariable analyses included in Model 2.
HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PCSK9, Proprotein convertase subtilisin/kexin type 9; SD, standard deviation; SLE, systemic lupus erythematosus.

controls. Interestingly, PCSK9 serum levels [beta coefficient −73 (95% CI −91 to −54) % mg/dl, $p \leq 0.001$] remained downregulated in SLE patients after adjusting for other lipid profile-related molecules.

### *Relation of demographics, lipid profile, and disease-related data with PCSK9 serum levels in SLE patients and controls*

The presence of hypertension and the use of statins and CRP serum levels were significantly and positively related to PCSK9 serum levels in patients and controls. Additionally, age in controls, as well as BMI and waist circumference in patients, were also positively related to PCSK9. Regarding lipid profiles, PCSK9 was positively related to triglycerides in patients and controls. Some other associations were found, mostly in SLE patients. For example, while HDL-cholesterol and apolipoprotein A1 were associated negatively with PSCK9, the atherogenic index was positively related to PCSK9 in SLE patients. No associations between PCSK9 and total cholesterol, LDL-cholesterol, and lipoprotein (a) were found in patients nor controls (Table 3).

Regarding disease-related data, disease duration was positively associated with PCSK9 serum levels [beta coefficient 1 (95% CI 0–2), $p = 0.020$]. SLICC score, both in a continuous [beta coefficient 10 (4–15), $p \leq 0.001$] and dichotomic fashion (SLICC ⩾ 1) [beta coefficient 40 (15–65), $p = 0.002$], was associated with PCSK9. Moreover, patients in the high or very high disease activity SLEDAI category showed higher serum levels of

PCSK9 compared with those in remission [beta coefficient 70 (24–117), $p=0.003$]. Concerning SLE therapies, while patients on prednisone showed higher levels of PCSK9 [beta coefficient 35 (14–57), $p=0.001$], those currently on hydroxychloroquine exhibited a downregulation in PCSK9 [beta coefficient –34 (57 to –11), $p=0.003$] (Table 3).

**Table 3.** Relation of demographics, lipid profile, and disease-related data with PCSK9 serum levels in SLE patients and controls.

| | **PCSK9 ng/ml, beta coefficient (CI95%), *p*** | |
|---|---|---|
| | **Controls** | **SLE** |
| Age, years | 1 (0–2), 0.007 | 0.58 (–0.37 to 1.53), 0.23 |
| Female | 43 (–24 to 110), 0.21 | 42 (–7 to 90), 0.091 |
| Body mass index, kg/m$^2$ | 2 (–1 to 4), 0.26 | 2 (0–4), 0.027 |
| Abdominal circumference, cm | –0.20 (–1.97 to 1.56), 0.82 | 1 (0–2), 0.004 |
| Cardiovascular co-morbidity | | |
| Smoking | 0.46 (–39.43 to 40.35), 0.98 | 16 (–10 to 41), 0.22 |
| Diabetes | 5 (–37 to 47), 0.81 | 27 (–24 to 78), 0.30 |
| Hypertension | 51 (18–83), 0.003 | 35 (14–57), 0.001 |
| Statins | 79 (45–113), <0.001 | 63 (40–86), <0.001 |
| Analytical and lipid profile | | |
| CRP, mg/dl | 4 (1–6), 0.004 | 1 (0–2), 0.001 |
| Cholesterol, mg/dl | –0.15 (–0.49 to 0.18), 0.37 | –0.25 (–0.53 to 0.04), 0.088 |
| Triglycerides, mg/dl | 0.37 (0.14–0.61), 0.002 | 0.16 (0.02–0.29), 0.022 |
| HDL cholesterol, mg/dl | –0.92 (–1.93 to 0.09), 0.074 | –0.69 (–1.21 to –0.18), 0.009 |
| LDL cholesterol, mg/dl | –0.30 (–0.71 to 0.11), 0.15 | –0.30 (–0.67 to 0.07), 0.11 |
| LDL:HDL cholesterol ratio | –3 (–21 to 14), 0.70 | 19 (5–34), 0.008 |
| Non-HDL cholesterol, mg/dl | –0.06 (–0.43 to 0.31), 0.74 | –0.26 (–0.54 to 0.03), 0.077 |
| Lipoprotein (a), mg/dl | 0.12 (–0.09 to 0.33), 0.26 | 0.03 (–0.09 to 0.16), 0.58 |
| Apolipoprotein A1, mg/dl | –0.16 (–0.54 to 0.23), 0.42 | –0.31 (–0.60 to –0.02), 0.034 |
| Apolipoprotein B, mg/dl | –0.06 (–0.56 to 0.45), 0.83 | –0.08 (–0.54 to 0.38), 0.74 |
| Apo B:Apo A1 ratio | –0.53 (–83.80 to 82.73), 0.99 | 78 (14–142), 0.017 |
| Atherogenic index | 4 (–10 to 18), 0.56 | 17 (7–27), 0.001 |
| SLE-related data | | |
| Disease duration, years | | 1 (0–2), 0.020 |
| SLICC ⩾ 1 | | 40 (15–65), 0.002 |
| *log* SLICC | | 37 (20–54), <0.001 |
| Katz Index | | 5 (–1 to 10), 0.11 |
| Katz Index ⩾ 3 | | 19 (–3 to 42), 0.085 |
| SLEDAI | | 2 (–1 to 4), 0.19 |
| SLEDAI > 0 | | 8 (–15 to 31), 0.49 |

*(Continued)*

**Table 3.** (Continued)

| | PCSK9 ng/ml, beta coefficient (CI95%), *p* | |
|---|---|---|
| | **Controls** | **SLE** |
| SLEDAI activity categories | | |
| No activity | | - |
| Mild | | 0.69 (–24.53 to 25.91), 0.96 |
| Moderate | | 0.46 (–31.18 to 32.10), 0.98 |
| High and Very High | | 70 (24–117), 0.003 |
| Auto-antibodies profile | | |
| Anti-DNA positive | | –12 (–41 to 17), 0.40 |
| ENA positive | | 5 (–30 to 41), 0.76 |
| Anti-Ro | | –10 (–33 to 14), 0.41 |
| Anti-La | | –16 (–45 to 13), 0.28 |
| Anti-RNP | | 14 (–13 to 40), 0.30 |
| Anti-Sm | | 3 (–32 to 39), 0.85 |
| Any antiphospholipid auto-antibody | | 3 (–30 to 37), 0.84 |
| Lupus anticoagulant | | 13 (–14 to 41), 0.34 |
| ACA IgM | | 7 (–28 to 43), 0.69 |
| ACA IgG | | 13 (–17 to 43), 0.38 |
| Anti beta2 glycoprotein IgM | | 36 (–8 to 79), 0.11 |
| Anti beta2 glycoprotein IgG | | –19 (–54 to 16), 0.28 |
| C3, mg/dl | | –0.19 (–0.63 to 0.26), 0.41 |
| C4, mg/dl | | –0.03 (–1.66 to 1.60), 0.97 |
| Current prednisone, *n* (%) | | 35 (14–57), 0.001 |
| Prednisone, mg/day | | –2 (–8 to 4), 0.53 |
| Current DMARDs | | –21 (–47 to 5), 0.11 |
| Hydroxychloroquine | | –34 (–57 to –11), 0.003 |
| Methotrexate | | 16 (–17 to 50), 0.34 |
| Mycophenolate mofetil | | 9 (–31 to 50), 0.66 |
| Azathioprine | | 8 (–23 to 39), 0.61 |
| Rituximab | | –28 (–91 to 34), 0.37 |
| Belimumab | | 11 (–76 to 99), 0.80 |
| Cyclophosphamide | | 107 (–43 to 257), 0.16 |

Beta coefficients higher than 1 are shown without decimals.
Demographics, lipid profile, and disease-related data are considered the independent variables, and PCSK9 is the dependent variable, in this analysis.
SLEDAI categories were defined as: 0, no activity; 1–5 mild; 6–10 moderate; >10 >10 high; >20 very high.
ACA, anticardiolipin; ANA, antinuclear antibodies; BMI, body mass index; C3 C4, complement; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drug; ENA, extractible nuclear antibodies; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index.

**Table 4.** Multivariable regression analysis of SLICC and SLEDAI scores in relation to lipid profiles and PCSK9 serum levels.

| | *log* SLICC | | | High and very high SLEDAI categories* | |
|---|---|---|---|---|---|
| | Pearson *r. p* | | Beta coefficient (95% CI), *p* | Beta coefficient (95% CI), *p* | Beta coefficient (95% CI), *p* |
| Cholesterol, mg/dl | −0.002 | 0.98 | | −12 (−34 to 11), 0.30 | |
| Triglycerides, mg/dl | 0.058 | 0.42 | | −4 (−53 to 45), 0.87 | |
| HDL cholesterol, mg/dl | 0.024 | 0.74 | | −4 (−17 to 9), 0.56 | |
| LDL cholesterol, mg/dl | −0.052 | 0.47 | | −7 (−25 to 10), 0.42 | |
| LDL:HDL cholesterol ratio | 0.013 | 0.86 | | −0.06 (−0.52 to 0.40), 0.79 | |
| Non-HDL cholesterol, mg/dl | −0.002 | 0.98 | | −12 (−34 to 11), 0.31 | |
| Lipoprotein (a), mg/dl | −0.021 | 0.78 | | 1 (−53 to 56), 0.97 | |
| Apolipoprotein A1, mg/dl | 0.048 | 0.51 | | 0 (−23 to 24), 0.98 | |
| Apolipoprotein B, mg/dl | −0.074 | 0.31 | | −6 (−20 to 8), 0.41 | |
| Apo B:Apo A1 ratio | −0.066 | 0.37 | | −0.01 (−0.11 to 0.09), 0.83 | |
| Atherogenic index | 0.045 | 0.53 | | −0.11 (−0.78 to 0.55), 0.74 | |
| PCSK9, ng/ml | 0.305 | <0.001 | 18 (0–35), 0.047 | 70 (24–117), <0.001 | 48 (1–96), 0.047 |

For *log* SLICC beta coefficient are adjusted for hypertension, statins, BMI, abdominal circumference and C-reactive protein.
For SLEDAI beta coefficient are adjusted for BMI, abdominal circumference and C-reactive protein.
*log* SLICC and SLEDAI scores are considered the independent variable in this regression analysis.
*Beta coefficient in this SLEDAI analyses refer to the size effect of high and very high SLEDAI categories *versus* remission.
CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index.

### *Multivariable regression analysis of the relation between SLICC and SLEDAI scores and hydroxychloroquine with lipid profiles and PCSK9 serum levels*

Lipid profile molecules were not associated with SLICC and SLEDAI scores (Table 4). In this sense, none of them, with the exception of PCSK9, yield a *p* value less than 0.20 in the univariable regression analysis. However, *log* SLICC and SLEDAI (as independent variables) were positively associated with PCKS9 in the univariable analyses. When this analysis was performed adjusting for confounders, these relations were maintained for both *log* SLICC [beta coefficient 18 (95% CI 0–35), $p=0.047$] and SLEDAI [beta coefficient 48 (95% CI 1–96), $p=0.047$] scores (Table 4). Moreover, when SLICC was split into its different items, those related to pulmonary, CV, musculoskeletal manifestations and premature gonadal failure were the items that individually were significantly related to PCSK9 serum levels (data not shown).

Use of hydroxychloroquine in SLE patients on hydroxychloroquine compared with those not taking hydroxychloroquine was associated with a significant decrease in PCSK9 serum levels [beta coefficient −30 (95% CI −54 to −6), $p=0.015$]. This finding remained significant after fully multivariable analysis, including hypertension, diabetes, prednisone intake and other lipid profile-related molecules (Table 5).

## Discussion

PCSK9 is now recognized as an important and major player in hypercholesterolemia and atherosclerosis pathophysiology. According to our results, although PCSK9 is globally downregulated in SLE patients compared with controls, the damage and inflammatory activity that the disease produces is positively related to PCSK9.

The lipid profile differences between patients and controls found in our report are in accordance

**Table 5.** Multivariable regression linear analysis of the effect of hydroxychloroquine on lipid profile and PCSK9 between patients with SLE with and without hydroxychloroquine.

| | **SLE patients on *versus* not on hydroxychloroquine.** | | |
|---|---|---|---|
| | **Beta coefficient (95% CI), *p*** | | |
| **Lipid profile** | | **Model #1** | **Model #2** |
| Cholesterol, mg/dl | −10 (−22 to 1), 0.064 | −12 (−24 to 0), 0.049 | −7 (−16 to 1), 0.098 |
| Triglycerides, mg/dl | −8 (−32 to 16), 0.50 | −13 (−39 to 14), 0.34 | |
| HDL cholesterol, mg/dl | −1 (−7 to 5), 0.71 | −1 (−7 to 6), 0.86 | |
| LDL cholesterol, mg/dl | −8 (−17 to 1), 0.078 | −9 (−18 to 1), 0.065 | – |
| LDL:HDL cholesterol ratio | −0.16 (−0.39 to 0.06), 0.15 | −0.17 (−0.41 to 0.08), 0.17 | – |
| Non-HDL cholesterol, mg/dl | −10 (−20 to 0), 0.062 | −11 (−22 to −1), 0.034 | – |
| Lipoprotein (a), mg/dl | −25 (−51 to 2), 0.068 | −33 (−62 to −4), 0.024 | −31 (−61 to −1), 0.042 |
| Apolipoprotein A1, mg/dl | −2 (−14 to 9), 0.67 | −2 (−14 to 11), 0.80 | |
| Apolipoprotein B, mg/dl | −5 (−12 to 2), 0.14 | −6 (−14 to 1), 0.093 | 0 (−5 to 6), 0.88 |
| Apo B:Apo A ratio | −0.03 (−0.08 to 0.02), 0.19 | −0.04 (−0.09 to 0.01), 0.15 | – |
| Atherogenic index | −0.26 (−0.58 to 0.07), 0.12 | −0.29 (−0.64 to 0.07), 0.11 | – |
| PCSK9, ng/ml | −34 (−57 to −11), 0.003 | −26 (−50 to −2), 0.036 | −30 (−54 to −6), 0.015 |

Hydroxychloroquine is considered the independent variable in this analysis.
Model #1: Adjusted for disease duration, SLICC and SLEDAI scores and prednisone intake.
Model #2: Adjusted for model #1 + rest of lipid molecules (with a $p$ value $< 0.20$ in Model #1) other than the one that is compared.
CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; SLE, systemic lupus erythematosus.

with the "lipid paradox" described in other inflammatory diseases such as rheumatoid arthritis.[14] This means that individuals with untreated inflammatory diseases, or those with these conditions who have high disease activity, exhibit lower levels of total cholesterol and LDL-cholesterol, and it is believed that this may be due to the lipid-lowering effects of systemic inflammation. Accordingly, in our study, most lipid molecules, with the exception of HDL-cholesterol, were lower in patients with SLE compared with controls. The large sample size assessed in the present study allowed us to perform a multivariable analysis. For this reason, we believe that our findings regarding lipid profile modifications in SLE may be attributable to the disease itself and not to confounding factors.

PCSK9 in SLE has been poorly studied in the literature.[15,16] In a study that included 90 SLE patients and 50 healthy controls, contrary to those in our own work, SLE patients had significantly elevated serum PCSK9 levels compared with controls.[15] This was especially true for the subgroup of SLE patients with accelerated atherosclerosis (higher ratio of carotid intima media thickening) or those with lupus nephritis. However, these differences were not assessed through multivariable analysis adjusting for possible confounders. For this reason, and because our sample size was higher and patients and controls were strictly matched for age, sex, and statins use, we believe that our design and applied methodology is adequate in terms of dealing with confounders or achieving statistical power. Similarly to our findings, CRP was positively correlated with PCSK9 and patients on hydroxychloroquine had lower levels of PCSK9.[15] In another study,[16] PCSK9 levels were non-significantly different among SLE patients compared with controls but significantly associated with SLE disease activity, as determined by the SLEDAI. This study also lacked full lipid profiles assessment and multivariable adjustment.

The fact that CRP levels were related to higher serum levels of PCSK9 in both patients and controls highlights the belief that inflammation can have a positive effect on PCSK9 in the general population.[17] Nevertheless, the overall effect of the disease itself, as occurs in rheumatoid arthritis and other inflammatory diseases, may have the overriding effect of lowering the lipid profile, including PCSK9. This is supported by the fact that, although trials with PCSK9 inhibitors have not shown any alterations in plasma CRP levels, there is growing evidence that decreased inflammatory response in the arterial wall may attenuate the development of atherosclerotic plaque beyond the established LDL-reducing effect of PCSK9 inhibition.[4]

In our study, hydroxychloroquine showed a negative association with PCSK9 after fully multivariable analysis. This result may be of potential interest since this effect has been previously described in the aforementioned report.[15] In this study, monotherapy with hydroxychloroquine, in a subgroup of 15 SLE patients followed-up for 3 months, significantly reduced PCSK9. In keeping with that, similar results were found in our study. Hydroxychloroquine has been shown to have cardioprotective properties and beneficial effects on lipid profiles.[18] The mechanism of cholesterol-lowering by antimalarials remains unclear, but it may involve an overall reduction in hepatic cholesterol synthesis, explained by the inhibition of lysosomal function, which leads to an accumulation of LDL in the lysosome. Moreover, it has been demonstrated *in vivo* that plasma LDL removal by LDL receptor was increased in SLE patients taking hydroxychloroquine with a consequent beneficial decrease in LDL levels.[19] We believe our study opens a new line of research to establish whether the downregulation of PCSK9 produced by hydroxychloroquine is responsible for these beneficial effects.

Although, in our study, PCSK9 was downregulated in SLE patients, it correlated positively with some disease-specific factors such as CRP, disease duration and SLEDAI and SLICC scores. We believe that although PCSK9 may be reduced due to the presence of a chronic inflammatory state, the absolute levels of this molecule indicate an increased risk of CV disease in the subgroup of patients with more severe disease. Interestingly, these two scores, SLEDAI and SLICC, were not related to other lipid molecules but were associated with PSCK9 after conducting multivariable analysis. For this reason, the positive relation of these scores with PCSK9 cannot be attributed to the alterations that disease activity or damage might exert over LDL cholesterol or full lipid profile.

To the best of our knowledge, the effect of glucocorticoids on PCSK9 has not previously been explored in SLE. In our study, we found that PCSK9 was related to prednisone intake, proving higher in patients treated with glucocorticoids. Therefore, we cannot exclude the possibility that some deleterious effects of glucocorticoids on CV disease and dyslipidemia might be mediated by this molecule. Moreover, in our series, statin use was associated with higher PCSK9 serum levels in patients and controls. This upregulation effect has been previously described in a recent meta-analysis in which statin therapy was shown to increase plasma PCSK9 concentrations – an effect that has been correlated with the magnitude of reduction that statins exert over plasma LDL-cholesterol.[20]

In our study, PCSK9 in SLE patients was correlated negatively with HDL-cholesterol and apolipoprotein A1, and associated positively with LDL:HDL and ApoB:Apo A1 ratios and atherogenic index. Nevertheless, patients with SLE showed higher levels of HDL-cholesterol, and lower LDL-cholesterol, LDL:HDL ratios, non-HDL, and Apo A1 and Apo B compared with controls. This means that PCSK9 may not account for the differences observed in the lipid profiles of patients and controls. However, we do not have an exact explanation for this finding. We believe that the interconnections between lipid-related molecules are globally disrupted in SLE patients; thus, they cannot be explained solely by the downregulation of PCSK9 serum levels generated by the disease. Consequently, at the present time, we cannot determine whether PCSK9 disruption is a consequence or cause of the disturbance in the lipid profile.

Moreover, PCSK9 serum levels were not correlated with LDL in either patients or controls. This may be surprising in a way; however, several groups have recently reported that the correlation between circulating PCSK9 concentration and LDL level is less significant than expected, with several factors potentially associated with this observation. First, the serum PCSK9 level does not reflect total hepatic PCSK9 secretion, as the high levels of PCSK9 are cleared from circulation

by binding to hepatic LDL receptors. Second, circulating PCSK9 is present not only in its free form, but is also as a complex with apo B-containing lipoproteins. Furthermore, PCSK9 directly increases hepatic production of apo B-containing lipoproteins. Third, PCSK9 concentrations are reduced with fasting but LDL do not. This means that, while wide fluctuations in plasma PCSK9 concentrations over the course of a day may be observed, little diurnal variation in plasma LDL levels has been reported. For all the aforementioned concepts, many factors may contribute to the relationship between circulating PCSK9 and LDL-C levels.[21] When we performed the same analysis in the subgroup of patients and controls not taking statins, this lack of association between LDL and PCSK9 was maintained.

The first studies on the role of PCSK9 in CV disease came from the fact that, whereas gain of function mutations of PCSK9 are associated with increased levels of LDL and early onset of atherosclerosis, loss-of-function mutations, on the other hand, were linked to a lower LDL and a subsequent decrease in CV risk.[22] These initial findings were confirmed when circulating PCSK9 levels were shown to correlate with coronary artery calcification and with risk of CV events. In this sense, in a prospective cohort study of 4232 men and women, serum PCSK9 concentration was associated with future risk of CV disease even after adjustments for established CV disease risk factors.[23] The exact mechanism that links PCSK9 and CV disease is not completely understood. However, it is believed that PCSK9 has immunological effects in relation to activation and maturation of dendritic cells and plaque T cells by oxidized LDL, independent of LDL-lowering.[24] We understand that our finding of PCSK9 disruption in SLE patients, although preliminary, may open a new space of investigation in which PCSK9 could be a target in the treatment of CV disease in SLE.[25]

We acknowledge the limitations that diabetes patients were included in our study. Diabetes may modify lipid profile. However, we think that, since all analyses were adjusted for this variable, this confounding effect, if it exists, has been neutralized. Additionally, patients were matched for the use of statins. Nevertheless, we did not record the doses of statins. For this reason, some patients may have had a higher effect of statins than others. However, we understand that matching by statins intake probably capture and correct this limitation. Furthermore, we recognize that our study is clinical and descriptive and, therefore, in the future it will be necessary to elucidate the biological mechanisms of how PCSK9 is negatively regulated in SLE.

In conclusion, SLE patients exhibited disrupted lipid profiles in which most lipid-related molecules were downregulated. This downregulation includes PCSK9 serum levels. Disease activity and damage are associated positively with PCSK9. Since PCSK9 is associated with CV disease, our results indicate that the increased CV risk of SLE patients with greater damage and activity may be influenced by PCSK9. Nevertheless, further studies are needed to assess whether PCSK9 plays a pivotal role in the dyslipidemia and accelerated atherogenesis of patients with SLE.

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## Conflict of interest statement

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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