# Apolipoprotein C3 and beta-cell dysfunction are linked in patients with systemic lupus erythematosus

C. Martín-González[1,2], C. Ferrer-Moure[3], J.C. Quevedo-Abeledo[4], M.Á. González-Gay[5,6,7], I. Ferraz-Amaro[2,8]

*[1]Division of Internal Medicine, Hospital Universitario de Canarias, Tenerife; [2]Department of Internal Medicine, University of La Laguna (ULL), Tenerife; [3]Division of Central Laboratory, Hospital Universitario de Canarias, Tenerife; [4]Division of Rheumatology, Hospital Doctor Negrín, Las Palmas de Gran Canaria; [5]Epidemiology, Genetics and Atherosclerosis Research Group on Systemic Inflammatory Diseases, [6]Division of Rheumatology, Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, Spain; [7]Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; [8]Division of Rheumatology, Hospital Universitario de Canarias, Tenerife, Spain.*

## Abstract

### Objective

*Systemic lupus erythematosus (SLE) has been associated with insulin resistance and beta-cell dysfunction. Apolipoprotein C3 (ApoC3) is a component of very low-density lipoproteins. Since ApoC3 has been linked to beta-cell impairment in the general population, in this study we aimed to discover if this lipoprotein is related to glucose homeostasis disturbance in patients with SLE.*

### Methods

*One hundred and forty non diabetic patients with SLE who had a glycaemia lower than 110 mg/dl were recruited. Insulin, C-peptide, and ApoC3 were assessed. Insulin resistance and beta-cell function were calculated using the Homeostasis Model Assessment (HOMA2) indices. A multivariable regression analysis was performed to study the relationship of ApoC3 to those molecules and indices adjusting for classical factors associated with insulin resistance that included glucocorticoids.*

### Results

*In the multivariable regression analysis that included prednisone intake, a significant relation of ApoC3 to C-peptide was found (beta coef. 0.27 [95%CI 0.03–0.51) ng/ml, p=0.030). Similarly, ApoCa3 was associated with higher degree of beta-cell dysfunction (HOMA2-%B) although in this case statistical significance was not achieved (beta coef. 8 [95%CI–1-18], p=0.086). This relationship was not found with serum insulin levels or IR indices. Furthermore, in the univariable analysis, but not after multivariable adjustment, the disease damage score was found to significantly mediate the effect of ApoC3 on circulating C-peptide. and HOMA2-%B.*

### Conclusion

*Beta-cell dysfunction and ApoC3 are linked in patients with SLE.*

**Key words**

systemic lupus erythematosus, apolipoprotein C3, Insulin resistance, beta-cell dysfunction

*Candelaria Martín-González, MD*
*Carmen Ferrer-Moure, MD*
*Juan Carlos Quevedo-Abeledo, MD*
*Miguel Á. González-Gay, MD, PhD**
*Iván Ferraz-Amaro, MD, PhD**

**These authors share senior authorship.*

*Please address correspondence to:*
*Iván Ferraz-Amaro,*
*Division of Rheumatology,*
*Hospital Universitario de Canarias,*
*38320 Santa Cruz de Tenerife, Spain.*
*E-mail: iferrazamaro@hotmail.com*

*Miguel Ángel González-Gay,*
*Division of Rheumatology,*
*Hospital Universitario Marqués de Valdecilla,*
*Universidad de Cantabria,*
*39008 Santander, Spain.*
*E-mail: miguelaggay@hotmail.com*

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## Introduction

Insulin resistance (IR) is a condition in which defects in the action of insulin are such that normal levels of insulin do not trigger the signal for glucose absorption. It is accompanied by a compensatory beta cell response of increased mass and insulin secretion. The clinical consequences of IR include hyperglycaemia-induced tissue damage, hypertension, dyslipidaemia, metabolic syndrome, and cardiovascular disease. Both IR (1) and beta-cell dysfunction (2) has been described in patients with systemic lupus erythematosus (SLE) (3). Although the exact mechanisms involved in SLE's IR are not well understood, the inflammation that accompanies the disease has been proposed as responsible (1, 3).

Apolipoprotein C3 (ApoC3) is a protein that in humans is synthesised by the *APOC3* gene and is a component of very low-density lipoproteins. ApoC3 has been described to play a role in the pathogenesis of beta-cell impairment, IR and diabetes in the general population (4). Studies in cell models have demonstrated that ApoC3 induces pancreatic beta-cell apoptosis (5). Besides, ApoC3 increases cytokine expression in cultured monocytes and endothelial cells, thereby elevating monocyte adhesion to endothelial cells (6). These mechanisms may link ApoC3 to inflammation, pancreatic beta-cell function, and IR. This has been further supported by the fact that cross-sectional (7, 8) and prospective cohort studies (9) have shown that high levels of ApoC3 were strongly associated with a risk of diabetes.

The role of ApoC3 in the IR and beta-cell dysfunction of patients with SLE has not been explored before. In this work, our objective was to study whether ApoC3 is related to IR in patients with SLE. If this were the case, ApoC3 would participate in the pathogenic mechanisms through which SLE leads to IR and beta-cell impairment.

## Material and methods

### *Study participants*

This was a cross-sectional study that included 140 patients with SLE. All SLE patients were 18 years old or older, had a clinical diagnosis of SLE, and fulfilled ≥4 American College of Rheumatology (ACR) classification criteria for SLE (10). They were periodically followed-up at rheumatology outpatient clinics and all had been diagnosed by rheumatologists. For the purpose of inclusion in the present study, SLE disease duration had to be ≥1 year. Patients with diabetes mellitus were excluded. Furthermore, all patients had a glycaemia <110 mg/dl, and none of them were on glucose-lowering drugs or insulin therapy. SLE patients taking prednisone at an equivalent dose ≤10 mg/day were allowed to participate in the study. None of the patients had previously had pancreatitis or any pancreatic disease. Moreover, patients 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, or any other chronic disease or evidence of active infection. The research was carried out in accordance 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 pattients provided informed written consent (approval no. 2015_84).

### *Data collection and laboratory assessments*

The patients included in the study completed a questionnaire on medication use and CV risk factors and underwent a physical examination. Weight, height, body-mass index, abdominal circumference, and systolic and diastolic blood pressure were assessed under standardised conditions. Information regarding smoking status (current smoker versus non-smoker) and hypertension treatment was obtained from the questionnaire. Medical records were reviewed to ascertain specific diagnoses and medications. SLE disease activity and damage were assessed using the Systemic Lupus Erythematosus Disease Activity Index -2000 (SLEDAI-2K) (11) and the SLICC/ACR Damage Index (SDI) (12), respectively. 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 (11–19), and very high activity (>20) as previously described (13). Disease severity was measured as well, using the Katz Index (14).

The homeostatic model assessment (HOMA) method was performed to determine IR. Briefly, the HOMA model enabled an estimate of insulin sensitivity (%S) and β-cell function (%B) from fasting plasma insulin, C peptide, and glucose concentrations. In this study we used HOMA2, the updated-computer HOMA model (15). This model can be used to assess insulin sensitivity and beta- cell function from paired fasting plasma glucose and specific insulin, or C peptide, concentrations across a range of 1–2,200 pmol/l for insulin and 1-25 mmol/l for glucose. C peptide better estimates β-cell function since it is a marker of secretion; and insulin data is preferable when calculating %S since HOMA-%S is derived from glucose disposal as a function of insulin concentration. In our study, IR and %S were calculated using insulin serum levels. Otherwise, %B was calculated using C-peptide serum levels. The computer model provided a value for insulin sensitivity expressed as HOMA2-%S (in which 100% is normal). HOMA2-IR (insulin resistance index) is simply the reciprocal of %S. For the detection of ApoC3 an ELISA kit was used (Elabscience, USA). No significant cross-reactivity or interference between human ApoC3 and analogues is observed with this kit. Both intra and inter-coefficients of variability are <10% for this assay. Cholesterol, triglycerides, and HDL-cholesterol were measured using the enzymatic colorimetric assay. LDL-cholesterol was calculated using the Friedewald formula.

*Statistical analysis*

Demographic and clinical characteristics in patients with SLE were described as mean (standard deviation) or percentages for categorical variables. For non-normally distributed continuous variables, data were expressed as median and interquartile range (IQR). ApoC3 relationships with glucose homeostasis molecules or IR indices were analysed by multivariable linear regression analysis.

**Table I.** Characteristics of patients with SLE included in the study.

| | (n=140) |
|---|---|
| Age, years | 49 ± 11 |
| Women, n (%) | 134 (96) |
| Body mass index, kg/m$^2$ | 27 ± 5 |
| Abdominal circumference, cm | 91 ± 13 |
| Systolic blood pressure, mmHg | 129 ± 26 |
| Diastolic blood pressure, mmHg | 84 ± 60 |
| **Cardiovascular co-morbidity** | |
| Current smokers, n (%) | 32 (23) |
| Diabetes, n (%) | 0 (0) |
| Hypertension, n (%) | 44 (31) |
| Obesity, n (%) | 32 (23) |
| Statins, n (%) | 30 (21) |
| Aspirin, n (%) | 37 (26) |
| Antihypertensive therapy, n (%) | 42 (30) |
| **Glucose homeostasis molecules** | |
| Glucose, mg/dl | 91 ± 10 |
| Insulin, μU/ml | 6.2 (3.8-9.3) |
| C-peptide, ng/ml | 2.6 ± 1.6 |
| HOMA2-IR | 1.02 ± 0.80 |
| HOMA2-S% | 146 ± 87 |
| HOMA2-B%-C-peptide | 137 ± 63 |
| **Lipid profile** | |
| Cholesterol, mg/dl | 198 ± 35 |
| Triglycerides, mg/dl | 118 ± 72 |
| HDL-cholesterol, mg/dl | 62 ± 18 |
| LDL-cholesterol, mg/dl | 113 ± 27 |
| LDL:HDL-cholesterol ratio | 1.96 ± 0.75 |
| Non-HDL cholesterol, mg/dl | 196 ± 35 |
| Apolipoprotein A1, mg/dl | 175 ± 32 |
| Apolipoprotein B, mg/dl | 93 ± 22 |
| Apo B:A1 ratio | 0.55 ± 0.16 |
| Lipoprotein (a), mg/dl | 38 (13-120) |
| Atherogenic index | 3.4 ± 1.1 |
| Apolipoprotein C3, mg/dl | 1.70 (1.19-2.58) |
| **SLE related data** | |
| CRP, mg/dl | 1.5 (0.7-3.4) |
| Disease duration, years | 15 ± 9 |
| SLICC | 1 (0-2) |
| SLICC ≥1, n (%) | 98 (70) |
| Katz Index | 2 (1-3) |
| SLEDAI | 2 (0-5) |
| SLEDAI categories, n (%) | |
| No activity, n (%) | 55 (39) |
| Mild or Moderate, n (%) | 68 (49) |
| High or Very High, n (%) | 8 (6) |
| Auto-antibody profile | |
| Anti-DNA positive, n (%) | 65 (46) |
| ENA positive, n (%) | 59 (42) |
| Anti-Ro, n (%) | 50 (36) |
| Anti-La, n (%) | 24 (17) |
| Anti-RNP, n (%) | 32 (23) |
| Anti-Sm, n (%) | 13 (9) |
| Antiphospholipid autoantibodies, n (%) | |
| Lupus anticoagulant, n (%) | 26 (19) |
| ACA IgM, n (%) | 14 (10) |
| ACA IgG, n (%) | 22 (16) |
| Anti beta2 glycoprotein IgM, n (%) | 7 (5) |
| Anti beta2 glycoprotein IgG, n (%) | 19 (14) |
| C3, mg/dl | 91 ± 25 |
| C4, mg/dl | 16 ± 7 |
| Current prednisone intake, n (%) | 70 (50) |
| DMARDs, n (%) | 111 (79) |
| Hydroxychloroquine, n (%) | 96 (69) |
| Methotrexate, n (%) | 16 (11) |
| Mycophenolate mofetil, n (%) | 13 (9) |
| Azathioprine, n (%) | 20 (14) |
| Rituximab, n (%) | 4 (3) |
| Belimumab, n (%) | 2 (1) |

Data represent mean ± SD or median (interquartile range) when data were not normally distributed.
BMI: body mass index; C3 C4: complement; CRP: C reactive protein; LDL: low-density lipoprotein; DMARD: disease-modifying anti-rheumatic drug; ACA: anticardiolipin; HDL: high-density lipoprotein; ANA: antinuclear antibodies; ENA: extractible nuclear antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index. SLEDAI categories were defined as: 0, no activity; 1-5 mild; 6-10 moderate; >10 activity.
SLICC: Systemic Lupus International Collaborating Clinics/American Colleague of Rheumatology Damage Index. HOMA2-IR: Homeostatic Assessment Model for the assessment of insulin resistance using insulin and glucose serum levels. HOMA2-%B-C peptide: Homeostatic Assessment Model for the assessment of beta-cell function using C peptide and glucose serum levels.

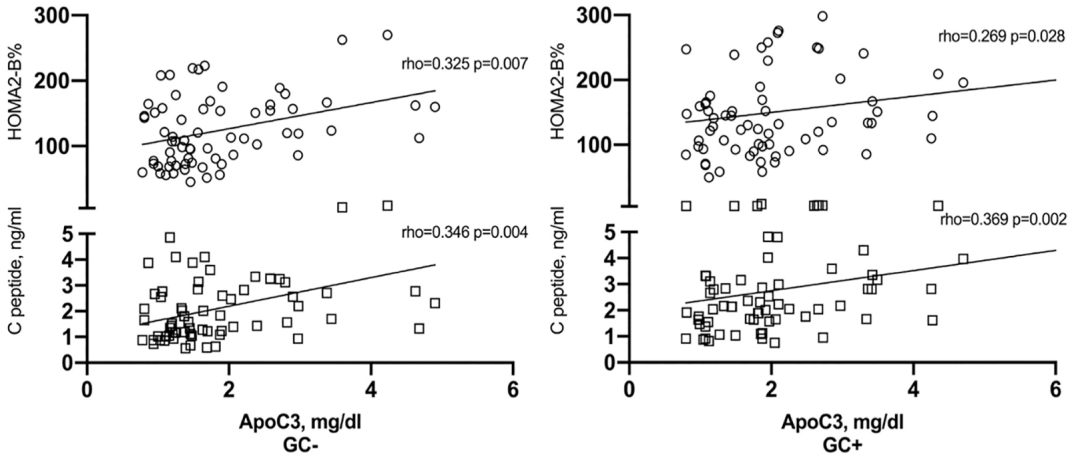


**Fig. 1**. Univariable correlation (Spearman's Rho) of Apo3 serum levels to circulating C-peptide and HOMA2-%B index in patients without (GC-) and with glucocorticoids (GC+).

Confounding factors were selected if they had a *p*-value less than 0.20 in their univariable relationship with ApoC3. Mediation analysis, as described elsewhere (16,17), was performed to test if the relationship of ApoC3 to beta-cell function was mediated by disease damage (SLICC). All the analyses used a 5% two-sided significance level and were performed using SPSS software, v. 26 (IBM, Armonk, NY, USA) and Stata software, v. 17/SE (StataCorp, College Station, TX, USA). *p*-values <0.05 were considered statistically significant.

## Results

### *Demographics and disease-related data of systemic lupus erythematosus patients*

A total of 140 patients with SLE were included in this study. Table I shows demographic and disease-related characteristics of the participants. Most of them (96%) were women (mean age ± SD: 49±11 years). Traditional cardiovascular risk factors were common. In this sense, 23% were current smokers, 31% had hypertension, and 23% were obese. Moreover, 21% were taking statins, and 26% and 30% were under aspirin or antihypertensive therapy, respectively.

While average glucose serum levels were 91±10 mg/dl, circulating insulin and C-peptide values were 6.2 (IQR 3.8–9.3) μU/ml and 2.6±1.6 ng/ml, respectively. IR and insulin sensitivity were HOMA2-IR 1.02±0.80 and HOMA2-%S 146±87, respectively. Beta-cell function through HOMA2-%B index showed a value of 137±63. Besides, the median ApoC3 was 1.70 (IQR 1.19–2.58) mg/dl. Additional data on lipid profile molecules of SLE patients are shown in Table I.

Most SLE patients were in the no activity (39%) or mild-moderate activity (49%) categories as shown by the SLEDAI score. Disease duration was 15±9 years. SLICC and Katz indexes were 1 (IQR 0–2) and 2 (IQR 1–3), respectively. Seventy percent of the patients had a SLICC/ACR DI score equal to or higher than 1. Half of the patients were taking prednisone. At the time of recruitment, 46% patients were found to be positive for anti-DNA, and 42% were positive for ENA, being anti-Ro the most frequently found antibody (36%). More than two-thirds of the patients were taking hydroxychloroquine when the study was conducted. Other data also included in Table I.

### *Relationship of ApoC3 to glucose homeostasis molecules and HOMA indices*

ApoC3 showed a significant correlation with C peptide and HOMA2-%B in SLE patients with and without glucocorticoids (Fig. 1). However, this relationship was not found with other hydrocarbon metabolism molecules such as glucose and insulin, nor with the HOMA2-IR and HOMA2-%S indices (Table II).

**Table II.** Correlation and multivariable regression analysis of the relation of ApoC3 to glucose homeostasis molecules and HOMA indices.

| | ApoC3, mg/dl | | | | ApoC3, Beta coef. (95%CI), *p* | | | |
|---|---|---|---|---|---|---|---|---|
| | Not on GC | | On GC | | | | | |
| | Rho | *p* | Rho | *p* | Unadjusted | | Adjusted | |
| Glucose, mg/dl | -0.041 | 0.74 | 0.093 | 0.46 | 0.23 (-1.29-1.75) | 0.77 | 0.20 (-1.42-1.83) | 0.81 |
| Insulin, μU/ml | 0.194 | 0.12 | 0.176 | 0.16 | 0.55 (-0.42-1.53) | 0.26 | -0.07 (-1.12-0.98) | 0.90 |
| C-peptide, ng/ml | **0.346** | **0.004** | **0.369** | **0.002** | **0.48 (0.25-0.71)** | **0.000** | **0.27 (0.03-0.51)** | **0.030** |
| HOMA2-IR | 0.186 | 0.13 | 0.175 | 0.16 | 0.07 (-0.05-0.20) | 0.24 | -0.01 (-0.14-0.13) | 0.94 |
| HOMA2-S% | -0.186 | 0.13 | -0.175 | 0.16 | **-15 (-28- -2)** | **0.027** | -6 (-20-8) | 0.39 |
| HOMA2-B%-C-peptide | **0.325** | **0.007** | **0.269** | **0.028** | **17 (7-26)** | **0.001** | 8 (-1-18) | 0.086 |

ApoC3 is considered the independent variable. GC: Glucocorticoids. Rho: Spearman's rho correlation coefficient.
Multivariable regression analysis is adjusted for age, body mass index, systolic blood pressure and statins and prednisone intake.
HOMA2-IR: Homeostatic Assessment Model for the assessment of insulin resistance using insulin and glucose serum levels.
HOMA2-%B-C peptide: Homeostatic Assessment Model for the assessment of beta-cell function using C peptide and glucose serum levels.
Significant *p*-values are depicted in bold.

**Table III.** Mediation analysis of the relationship of ApoC3 to beta-cell dysfunction mediated by SLICC.

| | Beta coef. (95%CI), *p* | | | |
|---|---|---|---|---|
| | C-peptide serum levels | | | |
| | Univariable | | Multivariable | |
| ApoC3 | | | | |
| Direct effect | **0.36 (0.13-0.58)** | **0.011** | 0.24 (0.00-0.48) | 0.053 |
| Indirect effect | **0.12 (0.04-0.21)** | **0.002** | 0.03 (-0.03-0.10) | 0.31 |
| Total effect | **0.48 (0.25-0.71)** | **0.000** | **0.27 (0.03-0.51)** | **0.030** |
| | HOMA2-%B | | | |
| ApoC3 | | | | |
| Direct effect | **11 (2-20)** | **0.010** | 7 (-2-16) | 0.14 |
| Indirect effect | **5 (1-9)** | **0.017** | 1 (-1-4) | 0.31 |
| Total effect | **17 (7-26)** | **0.001** | 8 (-1-18) | 0.086 |

Apoc3 is the independent variable in this analysis. Mediation variable is SLICC score.
ApoC3: Apolipoprotein C3. Multivariable regression analysis is adjusted for age, body mass index, systolic blood pressure and statins and prednisone intake. HOMA2%B-C peptide: Homeostatic Assessment Model for the assessment of beta cell function using C peptide and glucose serum levels.
Significant *p*-values are depicted in bold.

In the linear univariable regression analysis and assuming ApoC3 as the independent variable, ApoC3 was significantly related to C-peptide serum levels (beta coef. 0.48 [95%CI 0.25–0.71] ng/ml, $p$=0.000), and to HOMA2-%S (beta coef. -15 [95%CI -28 – -2), $p$=0.027) and HOMA2-%B (beta coef. 17 [95%CI 7–26] $p$=0.001) indices (Table II). When these relations were adjusted for confounders (age, body mass index, systolic blood pressure, and prednisone and statins intake), although the associations between ApoC3 and HOMA2-%S and HOMA2-%B were lost, the relation of ApoC3 to C-peptide was maintained (beta coef. 0.27 [95%CI 0.03–0.51) ng/ml, $p$=0.030) (Table II).

*Mediation of SLICC in the relationship of ApoC3 to C-peptide and beta-cell function*

Table III represents the analysis of the mediation of SLICC in the association between ApoC3 and beta-cell disruption. In this sense, indirect effects, that accounts for the amount of mediation, were significant in the univariable analysis. It was the case for SLICC that significantly mediated the effect of ApoC3 on circulating C-peptide and HOMA2-%B. However, when the mediation analysis was further adjusted for confounding factors, the significance of the mediation was lost, with only the total effect being significant (Table III).

SLEDAI score or hydroxychloroquine intake were not associated with ApoC3 or beta-cell function (data not shown). For this reason, the analysis of the mediation of disease activity in the relation of ApoC3 to beta-cell dysfunction did not apply.

## Discussion

ApoC3 has been proposed in general population as an important diabetogenic factor involved in the impairment of beta-cell function. This is supported by the fact that ApoC3 increases in diabetes and that *in vitro* studies revealed that healthy beta cells exposed to ApoC3 became apoptotic and that humans with higher levels of the apolipoprotein, due to mutations in the gene, are more susceptible to developing diabetes (18). According to our results, ApoC3 is related to the malfunction of beta-cell that is present in patients with SLE. According to our results, ApoC3 is associated with the dysfunction of beta cells that is present in patients with SLE. We therefore propose that the dysregulation of glucose homeostasis in patients with SLE may be related, to some extent, to ApoC3.

ApoC3 expression in SLE patients has only been preliminarily studied. With respect this, ApoC3 levels in lupus nephritis patients were significantly elevated compared to controls or non-renal SLE patients in a study of 17 healthy subjects and 33 patients (19). In another report that evaluated the association of ApoC3 with subclinical atherosclerosis in 58 patients with SLE, no cardioprotective or atherogenic effect of ApoC3 was found (20).

Unlike the studies described above, our study addressed for the first time the role of ApoC3 in the development of IR in patients with SLE. We observed that ApoC3 is related to serum levels of C-peptide but not to circulating insulin or IR indices in patients with SLE. With respect to this, it is known that the initial phase of glucose homeostasis disruption is characterised by peripheral tissue insulin resistance with a beta-cell compensatory response of increasing mass and insulin secretion. However, after prolonged hyperinsulinaemia, beta cells begin to fail, causing defects in insulin secretion and eventually increased beta cell apoptosis. Therefore, IR and beta cell dysfunction, although related, are not equivalent disease states. For this reason, we believe that it is feasible to find a relationship of ApoC3 with beta cell function, but not with IR.

In our study, a statistically significant mediation of SLICC was found in the univariate analysis. That is, SLICC appears to mediate the effect of ApoC3 on both serum C-peptide and HOMA2-% B levels. However, after multivariable adjustment, the significance of this mediation was lost. Regarding this, we believe that the fact that there is a significant mediation in the univariable analysis may indicate that there is an effect of ApoC3 on the function of beta cells, although it can be masked by other factors related to the disorder of the metabolism of the glucose.

We acknowledge the limitation that patients recruited in our study had a long-standing disease and that organ damage was frequent in our series. For this reason, we believe that our findings will have to be replicated in the future in SLE patients with a different clinical profile.

In conclusion, our results highlight for the first time the involvement of ApoC3 in the beta cell dysfunction observed in patients with SLE.

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