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Visceral fat, cardiovascular risk factors and quality of life in lupus activity categorised via complement C3

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ABSTRACT

Background Patients with lupus face increased cardiovascular risk linked to their autoimmune status. This study assesses the relationships between cardiovascular risk factors, lifestyle and health-related quality of life (HRQoL) concerning SLE activity categorised by complement C3.

Methods 74 patients with SLE were recruited and stratified as active (C3 <90 mg/dL) or inactive (C3 >90 mg/dL), alongside 74 controls with obesity-related low-grade inflammation, at Hospital Universitario Puerta de Hierro Majadahonda. Anthropometric measurements, clinical and demographic data were recorded, and participants completed validated questionnaires on physical activity, dietary intake and HRQoL. Fasting blood samples were collected for metabolic determinations. Comparative analyses between SLE groups and controls, along with regression models adjusted for variables associated with disease activity, were performed.

Results The inactive SLE group exhibited a less healthy adiposity profile compared with the active group (36.7% vs 33.2% total fat mass; 8.5 AU vs 6.5 AU visceral fat mass) and showed a higher prevalence of cardiovascular risk factors, including markers of obesity, hypertension, dyslipidaemia and increased waist circumference, along with worse HRQoL outcomes. Notably, age, body mass index and insulin resistance were associated with SLE inactivity, while fibrinogen correlated with disease activity as assessed by complement C3 levels. Interestingly, household composition as a sociodemographic variable (alone, couple/children/elderly or other) also showed an independent association with SLE activity.

Conclusions Inactive patients with SLE exhibited more adverse cardiovascular risk markers compared with active patients categorised by complement C3, even when glucocorticoid administration was accounted for. Additionally, this research highlights the potential influence of fibrinogen as well as metabolic and sociodemographic factors on disease activity. These findings emphasise the need for personalised precision management strategies such as measurement of fibrinogen levels and insulin resistance and sociodemographic considerations that address both cardiovascular risk and overall lifestyle plus exposome in patients with SLE and may partly explain SLE activity evolution.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with lupus are known to have an increased cardiovascular risk associated with autoimmune disease status.

WHAT THIS STUDY ADDS

⇒ This study highlights that visceral fat mass and lifestyle factors are significant determinants associated with lupus activity, providing new concepts for early detection and management of SLE involving the exposome.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This research suggests that considering body fat composition and insulin resistance is relevant for the diagnosis, prognosis and management of SLE, which will enable the early detection and more precise lupus treatment.

INTRODUCTION

SLE is a complex autoimmune disease characterised by multiple organs and systems affectation.[1] SLE clinical manifestations include fever, fatigue, skin rashes and arthritis, and up to 40% of patients develop renal complications, whose evolution often follows a relapsing-remitting course, leading to disability and a reduced health-related quality of life (HRQoL).[2] The pathogenesis of SLE is multifactorial, involving genetic/epigenetic, microbiota environmental, lifestyle and neuroendocrine factors that trigger immune dysregulation.[3] Key features include autoreactive B cells producing autoantibodies and imbalances in immune cell populations, such as regulatory and cytotoxic T cells.[4] Genetic studies have identified susceptibility loci, especially in the major histocompatibility complex, interferon and complement pathways.[5] Although altered self-tolerance and autoantibody production are central to SLE, the precise mechanisms driving the disease remain unclear.[6]

Current research leverages artificial intelligence and machine learning to improve diagnostic accuracy, tailor treatments and develop individualised management for patients with SLE by integrating clinical data, including exposome information.[7] In this context, lifestyle is important both as a cause and a consequence of the SLE.[8] The exposome encompasses all non-genetic environmental factors influencing health and disease,[9] with diet and physical activity playing key roles in SLE onset and progression. Integrating environmental exposures with genetic/epigenetic data and omics information can help identify disease triggers, improve prevention strategies and enable personalised treatments for patients with SLE.[10]

The classification criteria for SLE established by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) include 10 domains (7 clinical and 3 immunological).[11] ANAs are relevant biomarkers and an entry criterion for SLE classification, although not exclusive to this condition.[12] Complement system components, such as C3 and C4, correlate with SLE disease activity, with low levels frequently associated with increased severity and immunoinflammatory phenomena and have been used as a criterion for SLE activity.[13]

SLE is related to an increased risk for early atherosclerosis and cardiovascular diseases (CVD) as described in recent guidelines.[14] The pathogenesis of SLE concerns endothelial dysfunction, accelerated atherosclerosis and lipid metabolism alterations, exacerbated by lifestyle factors, including physical inactivity and unbalanced diets.[15] CVD in SLE arises from both traditional risk factors—hypertension, dyslipidaemia, diabetes, obesity and smoking—and SLE-specific mechanisms such as chronic inflammation, oxidative stress, endothelial dysfunction, antiphospholipids, complement cascade, autoantibodies and glucocorticoid use.[16] These factors contribute to endothelial injury and proatherogenic dyslipidaemia,[17] highlighting the need for personalised cardiovascular management in SLE.[12]

Adopting a healthy lifestyle, including a balanced diet, regular exercise and stress management, seems essential for reducing disease activity and enhancing HRQoL in patients with SLE.[18] A Mediterranean-style diet, rich in fruits, vegetables, whole grains, fish, olive oil and nuts, has been shown to reduce inflammation and alleviate symptoms in these patients. This dietary pattern provides key nutrients such as antioxidants, omega-3 fatty acids and polyphenols, which help combat oxidative stress/inflammation and support overall immune function.[19] While excess meat protein, saturated fatty acids, refined grains and added sugars have been associated as dietary proinflammatory components.[19]

Overweight exacerbates chronic inflammation and oxidative stress, leading to increased disease activity, worse outcomes and higher organ damage.[20] Hypocaloric or low-glycaemic index diets have shown benefits in reducing fatigue and improving weight management.[21] Exercise improves cardiovascular health, insulin sensitivity and alleviates fatigue, depression[22] and corticosteroid-induced weight gain and muscle weakness.[12]

Despite advances in pharmaceutical treatments, many patients with SLE continue suffering from organ damage, pain, fatigue and reduced HRQoL.[23] While cardiovascular risk in SLE is well-established, the roles of visceral fat, insulin resistance and fibrinogen in disease activity and HRQoL remain underexplored. Additionally, the influence of exposome-related factors, such as lifestyle and household composition, has received so far limited attention. This study addresses these gaps by investigating these associations in patients with SLE categorised by complement C3 levels.[2] We hypothesise that C3 levels may be associated with body composition, exposome factors and biochemical markers of cardiovascular risk, which could be considered for better precision management and treatment of people with SLE. This research aims to address this gap by evaluating lifestyle risk factors and HRQoL in relation to SLE activity and various cardiovascular risk factors, including fat mass, insulin resistance and fibrinogen as well as sociodemographic factors among SLE outpatients. By focusing on these factors, the research will contribute to the development of personalised, precision medicine strategies for managing autoimmune diseases, offering a novel approach to SLE treatment and care and integrating information related to cardiovascular risk.

METHODS

Participants

A population of adults (≥18 years) diagnosed with SLE (n=74) and a control group without SLE (n=74) were recruited from January 2022 to February 2024 at the Department of Internal Medicine, Hospital Universitario Puerta de Hierro Majadahonda, Madrid. These volunteers are involved in the METAINFLAMACIÓN-CM project (ref. Y2020/BIO-6600). All data collection procedures followed the approved ethical guidelines and validated hospital protocols. The RECORD guidelines were followed as appropriate for observational routinely collected health data. The inclusion of participants in the study was subject to their acceptance and the signing of the informed consent form. For the diagnosis of SLE, the classification criteria established by the EULAR/ACR[11] were applied. Additionally, patients with a stable SLE diagnosis (the disease is in a state where symptoms and clinical manifestations are well-controlled or show minimal to no activity with a SLE Disease Activity Index (SLEDAI) <4)[24] and under supervised medical treatment (prescribed, supervised and recorded by the specialists of the department according to European guidelines and clinical experience) were selected to minimise potential biases related to the effect of medical treatments. The study participants were undergoing various pharmacological treatments and were continuously monitored by medical professionals: 36.49% were prescribed

glucocorticoids, 79.73% received hydroxychloroquine (dolquine), 17.57% were treated with mycophenolate mofetil, 16.22% received belimumab, 6.76% were administered methotrexate, 6.76% were on azathioprine and 5.41% were treated with mepacrine. The prescription was similar in both C3 categorised groups, and no statistical differences were found in the pharmacological prescription of these therapeutic agents. SLE activity was determined by analysing complement C3 levels, stratifying the population into active (C3 <90 mg/dL) and inactive (C3 >90 mg/dL) groups.[25]

Patient and public involvement

Neither patients nor the public were involved in the design, conduct, reporting or dissemination plans of our research. However, the patients participated voluntarily and were provided with individualised reports on their clinical and metabolic status following their participation in the study.

Clinical, anthropometric and body composition measurements

SLEDAI-2K test was used to assess lupus activity. Systolic and diastolic blood pressures were measured using a sphygmomanometer by a trained dietitian, following standardised criteria and international guidelines for hypertension. Anthropometric measurements including body weight, height, waist and hip circumferences were collected at baseline by the same dietitian using appropriate equipment and validated methods. Height was measured with a stadiometer, and body weight and composition were assessed using bioimpedance equipment (TANITA SC-330; Tanita Corporation). Waist and hip circumferences were measured using a standard tape measure according to established protocols. Body mass index (BMI) was calculated as body weight divided by height squared (Kg/m^2) in accordance with official guidelines.

Biochemical data

Blood samples were obtained under fasting conditions through venipuncture. These samples underwent analysis for leucocytes, lymphocytes, neutrophils, platelets, haematocrit, erythrocyte sedimentation rate and erythrocyte distribution width using a Sysmex XN-20 automated haematology analyser (Roche, Basel, Switzerland).[26] The neutrophil/lymphocyte ratio was calculated directly from the measured values. Routine biochemical markers, including glucose, total cholesterol, glycosylated haemoglobin, uric acid, ferritin, high density lipoprotein, low density lipoprotein, triglycerides, alanine aminotransferase (ALT) and aspartate aminotransferase, were measured following standardised hospital protocols using a quality-controlled autoanalyser (Atellica Solution) as per established criteria. The homeostasis model assessment of insulin resistance (HOMA-IR) was estimated according to the following formula: HOMA-IR = (fasting insulin (mU/mL) × fasting glucose (mmol/L))/22.5. Prognosis-related variables, proinflammatory factors and markers such as C-reactive protein (CRP), fibrinogen, insulin, lactate dehydrogenase, D-dimer, interleukin-6 (IL-6), prothrombin activity, activated partial thromboplastin time, complement C3, complement C4, Anti-double-stranded DNA (dsDNA) and also followed standardised procedures (using duplicates), primarily employing ELISA kits (Sigma-Aldrich ELISA Kit) as outlined by the suppliers.[25]

Types of questionnaires

Patients completed several validated questionnaires,[27] covering sociodemographic information, family history, HRQoL (assessed with the 12-item Short Form Survey, SF-12) and lifestyle factors such as physical activity (evaluated using the International Physical Activity Questionnaire) and dietary patterns assessed using the 14-point Mediterranean Diet Adherence Screener (MEDAS-14) and a validated short food frequency questionnaire with 19 items, under the guidance of a trained dietitian.

Statistical analyses

As descriptive statistics, mean values and SD or medians and IQRs were used for continuous variables depending on the normality distribution, and frequencies with percentages for categorical variables. The normality of the variables was assessed using the Shapiro-Wilk test. Differences were statistically analysed using the t-test for comparing parametric continuous variables, the Mann-Whitney U test for non-parametric variables and the χ^2 test for categorical variables described as proportions.

To calculate the differences between the SLE groups and the control group, one-way analysis of variance was used to compare continuous variables, and the χ^2 test was used for categorical variables. Fisher's exact test was used when the expected frequencies in some cells of the contingency table were too low, which could affect the validity of the test results.

A multiple linear regression model was developed to predict the level of complement C3 as an indicator of SLE activity. The variables used in the regression models included fibrinogen, BMI, age, sex, household composition, HOMA-IR, occupation, CRP, Mediterranean diet adherence score and physical activity. Variance inflation factor analysis was conducted to test for collinearity among the independent variables, ensuring their independence. Additionally, sensitivity analyses were performed using linear regression models for each of the SLE activity groups (active and inactive).

RESULTS

Comparison of general, clinical, lifestyle, biochemical, anthropometrics and body composition outcomes according to complement C3 levels in patients with SLE

The main health, lifestyle and HRQoL characteristics of the cohort are summarised (table 1). Out of 74 patients, 93.2% were women and the average age was 52.1 years. Overall, 12.2% presented obesity, 5.4% diabetes, 17.6% hypertension and 21.6% dyslipidaemia, showing a greater

Table 1 Descriptive data on general health characteristics, lifestyle and HRQoL factors comparing active and inactive patients with SLE

	Overall	Complement 3		P value
		<90 mg/dL (active)	>90 mg/dL (inactive)	
n	74	28	46	
General and clinical characteristics				
Sex (%)				0.919
Men	6.8	40.0	60.0	
Women	93.2	37.7	62.3	
Age (years)	52.1 (12.5)	47.0 (11.4)	55.3 (12.4)	**0.005**
Household (%)				**0.018**
Alone	13.5	10.0	90.0	
Couple, children, elderly	81.1	40.0	60.0	
Other	5.4	75.0	25.0	
Occupation (%)				**0.035**
Paid work	51.4	50.0	50.0	
Unemployment	10.8	12.5	87.5	
Disability	10.8	25.0	75.0	
Retired	18.9	14.3	85.7	
Domestic worker	4.1	33.3	66.7	
Other	1.3	100.0	0.0	
Obesity (%)	12.2	22.2	77.8	0.306
Diabetes mellitus (%)	5.4	50.0	50.0	0.612
Hypertension (%)	17.6	30.8	69.2	0.565
Dyslipidaemia (%)	21.6	43.7	56.3	0.584
Systolic BP (mm Hg)	126.5 (18.2)	116.5 (110.0–126.0)	126.5 (118.0–142.0)	**0.005**
Diastolic BP (mm Hg)	74.4 (11.7)	71.6 (10.6)	76.1 (12.1)	0.109
SLEDAI-2K	2.7 (3.1)	3.5 (3.4)	2.2 (2.8)	**0.035**
Lifestyle and health-related quality of life (HRQoL)				
Sadness (%)	44.6	36.4	63.6	0.818
SRQ-20 (points)	5.7 (4.4)	4.5 (2.0–11.0)	5.0 (3.0–8.0)	0.599
FACIT-Fatigue Scale (points)	36.1 (11.1)	38.0 (22.0–47.0)	38.5 (29.0–47.0)	0.604
NPSQ9 (points)	21.34 (4.26)	21.32 (3.43)	21.35 (4.72)	0.980
MEDAS (points)	8.2 (1.8)	7.9 (2.0)	8.4 (1.7)	0.289
iPAQ (METs-min/week)	1203 (1191)	1020 (540–1800)	720 (320–1520)	0.687
Self-rated health (points)	2.30 (0.86)	2.50 (0.75)	2.17 (0.90)	0.112
PCS12 (points)	41.4 (12.8)	43.0 (35.3–54.8)	42.7 (26.2–52.4)	0.449
MCS12 (points)	42.5 (12.0)	46.6 (32.6–53.3)	45.7 (29.0–52.1)	0.490

Raw data. Variables are shown as mean (SD), median (IQR) or as proportion (%) according to their distribution. Continuous variables were compared using t-test or U Mann-Whitney. Categorical variables were compared using χ^2 test. Significant values are in bold font.
BP, blood pressure; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; iPAQ, International Physical Activity Questionnaire; MCS12, Mental Component Score; MEDAS, Mediterranean Diet Adherence Screener; METs, metabolic equivalent task; NPSQ9, Nutritional Perception Screening Questionnaire; PCS12, Physical Component Score; SLEDAI, SLE Disease Activity Index; SRQ-20, 20-item Self-Report Questionnaire.

tendency, though not statistically significant, in the inactive SLE group. Values of SLEDAI-2k as a marker of SLE status were inversely associated with C3 levels.

The comparison of general biochemical markers, inflammation and coagulation parameters, as well as anthropometric and body composition features between active and inactive SLE is presented in table 2, revealing significant differences in glutamic pyruvic transaminase/ALT, gamma-glutamyl transferase, complement C3, complement C4 and Anti-dsDNA. According to the C3 levels, a

Table 2 Descriptive data on general biochemical markers, inflammation and coagulation parameters and anthropometric and body composition determinants comparing active and inactive patients with SLE

		Complement 3		
	Hospital reference values women (men)	<90 mg/dL (active)	>90 mg/dL (inactive)	P value
n		28	46	
Biochemical markers				
Glucose (mg/dL)	60.0–100.0	87.0 (81.5–92.0)	90.0 (85.0–97.0)	**0.047**
Total cholesterol (mg/dL)	150.0–200.0	171.2 (29.7)	179.6 (40.8)	0.378
LDL-c (mg/dL)	70.0–160.0	96.7 (24.1)	100.8 (31.8)	0.588
HDL-c (mg/dL)	50.0–90.0 (35.0–75.0)	57.6 (16.7)	58.3 (15.3)	0.853
Triglycerides (mg/dL)	30.0–200.0	86.5 (55.5–109.0)	106.0 (67.0–129.0)	0.103
TyG index (mg/dL)	<8.7 (<8.8)	8.9 (0.6)	9.1 (0.5)	*0.088*
HbA1c (%)	4.5–6.4	5.4 (5.1–5.6)	5.5 (5.1–5.7)	0.537
Insulin (µIU/mL)	0.0–29.1	8.6 (3.9–11.6)	9.4 (5.8–11.5)	0.259
HOMA-IR	<1.96	1.80 (0.81–2.43)	2.16 (1.32–2.79)	0.128
GOT/AST (U/L)	6.0–40.0	20.0 (17.0–23.0)	21.0 (19.0–26.0)	0.171
GPT/ALT (U/L)	6.0–40.0	16.0 (14.0–18.5)	19.0 (15.0–27.0)	**0.031**
GGT (U/L)	6.0–36.0 (8.0–61.0)	13.5 (11.0–16.0)	19.0 (14.0–32.0)	**0.008**
CRP (mg/L)	0.1–10.0	0.9 (0.6–2.0)	1.3 (0.9–7.0)	*0.082*
IL-6 (pg/mL)	0.0–4.4	2.7 (2.6–3.2)	2.6 (2.6–3.5)	0.805
Leucocytes (10^3/µl)	4.0–11.5	5.2 (4.4–6.7)	5.0 (4.2–7.1)	0.953
Neutrophil/lymphocyte	–	2.18 (1.49–3.73)	2.09 (1.42–3.32)	0.661
Platelets (10^9/L)	150.0–400.0	207.0 (181.5–278.5)	229.5 (193.0–281.0)	0.612
Fibrinogen (mg/dL)	200.0–400.0	363.0 (286.0–394.0)	335.0 (295.0–404.0)	0.773
D-Dimer (ng/mL)	0.0–500.0	341.0 (212.5–628.0)	308.0 (220.0–468.0)	0.713
LDH (U/L)	120.0–246.0	188.5 (162.5–201.5)	189.0 (168.0–209.0)	0.729
RDW (%)	8.0–14.8	13.5 (12.7–14.8)	13.5 (13.0–14.4)	0.758
ESR (mm)	0.0–17.0 (0.0–11.0)	12.0 (3.5–17.5)	11.0 (5.0–21.0)	0.624
Complement 3 (mg/dL)	90.0–180.0	78.0 (65.6–84.0)	108.0 (101.0–121.0)	**<0.001**
Complement 4 (mg/dL)	10.0–40.0	12.7 (9.1–17.1)	20.6 (15.7–28.1)	**<0.001**
Anti-dsDNA (IU/mL)	<10	17.0 (5.1–53.0)	4.7 (1.7–17.0)	**0.034**
Anthropometric and body composition measurements				
Weight (kg)	72.0 (15.8)	66.6 (59.5–73.6)	71.4 (61.7–86.0)	0.229
BMI (kg/m^2)	27.7 (5.6)	25.5 (23.0–28.8)	28.4 (23.7–33.5)	0.127
Waist circumference (cm)	96.1 (14.0)	92.3 (11.4)	98.4 (14.9)	*0.066*
Muscle mass (kg)	43.3 (6.5)	41.7 (38.4–45.8)	43.2 (38.6–46.3)	0.507
Total fat mass (%)	35.3 (8.9)	33.2 (7.9)	36.7 (9.2)	*0.099*
Visceral fat (AU)	8.4 (4.3)	6.5 (4.0–8.8)	8.5 (6.0–13.0)	**0.013**
Bone mass (kg)	2.3 (0.3)	2.2 (2.1–2.4)	2.3 (2.1–2.5)	0.508
Body water (%)	46.9 (5.9)	48.6 (5.6)	45.9 (5.9)	*0.056*

Raw data. Variables are shown as mean (SD) or median (IQR) according to their distribution. Continuous variables were compared using t-test or U Mann-Whitney. Significant values are in bold font. A significance level of p<0.1 (italicised) indicates marginal significance (TyG index, CRP, waist circumference, total fat mass and body water).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AU, arbitrary units; BMI, body mass index; CRP, C-reactive protein; dsDNA, double-stranded DNA; ESR, erythrocyte sedimentation rate; GGT, gamma-glutamyl transferase; GOT, glutamyl oxaloacetic transaminase; GPT, glutamyl pyruvic transaminase; HbA1c, glycosylated haemoglobin; HDL-c, high density lipoprotein–cholesterol; HOMA-IR, homeostatic model assessment–insulin resistance; IL-6, interleukin 6; LDH, lactate dehydrogenase; LDL-c, low density lipoprotein–cholesterol; RDW, red cell distribution width; TyG, Triglycerides and Glucose Index.

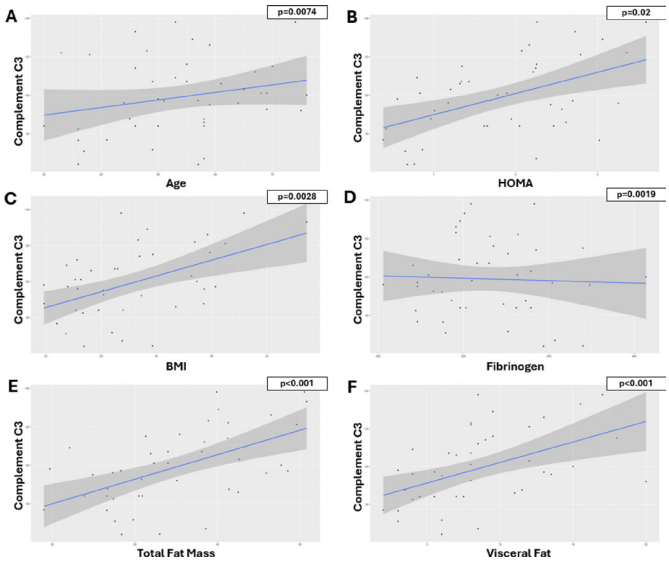

Figure 1 Linear regression graphs adjusted by age, sex, BMI, fibrinogen, HOMA, MEDAS, METs, household and occupation, between: (A) C3 and age; (B) C3 and HOMA; (C) C3 and BMI; (D) C3 and fibrinogen; (E) C3 and total fat mass; (F) C3 and visceral fat. BMI, body mass index; HOMA, homeostatic model assessment; MEDAS, Mediterranean Diet Adherence Screener; METs, metabolic equivalent tasks.

lower activity score was associated with increased visceral fat (p=0.013) and showed a marginal statistical relationship with a higher proportion of total fat mass (p=0.099), waist circumference (p=0.066) and less body water (p=0.056). No other clinically relevant differences were found.

Analysis of associations and the interplay between age, HOMA, BMI, fibrinogen, fat mass and visceral fat mass according to the complement C3 levels

Linear regression plots adjusted for age, sex, BMI, fibrinogen, HOMA, MEDAS, METs, household and occupation are shown in figure 1. The graphs show a significant positive association between complement C3 and age, HOMA, BMI, total fat mass and visceral fat. In contrast, complement C3 demonstrated a significant inverse relationship with fibrinogen.

Association between clinical and biochemical markers with complement C3 values

The associations between complement C3 values, clinical and serological biomarkers were calculated in a multivariate model (figure 2). The relationships between C3 levels and fibrinogen, BMI, age, household composition and HOMA resulted in statistically significant results ($p<0.05$), identifying the first one as the main contributing factor. An inverse (not statistically significant) correlation between C3 and anti-DNA levels was identified in this SLE group (data not shown). The comparative analysis of the different pharmacological treatments between the active and inactive groups revealed a homogeneous distribution between both groups and no statistically significant differences between the two groups (data not shown). A linear regression model was performed with the raw data, including glucocorticoid medication as a confounding variable (p=0.753), and no effect modification was observed (data not shown).

Comparisons of total fat mass and visceral fat mass according to the complement C3 levels

Differences in complement C3 levels between active and inactive patients with SLE, based on total fat mass and visceral fat, are represented in figure 3. Regarding fat mass, patients with inactive SLE exhibited higher total and visceral fat compared with the active SLE group. Furthermore, within the inactive SLE group, complement C3 levels were significantly higher in the presence of greater total fat and visceral fat.

Additional sensitivity analyses and comparisons with a reference population

A sensitivity analysis was performed (online supplemental table 1), showing a negative association between C3 levels and fibrinogen in the group with C3 <90 mg/dL, while a positive association was found between C3 levels and BMI in the group with C3 >90 mg/dL.

The comparison between patients with SLE and a reference population was included (online supplemental tables 2 and 3). Statistically significant differences

	Estimate (β)	p-value	Ordered Contribution Percentage
(Intercept)	89.600	0.006*	
Fibrinogen	**-0.164**	**0.003***	13.2%
BMI	**1.664**	**0.005***	11.9%
Age	**0.651**	**0.015***	8.6%
Household	**-13.450**	**0.019***	7.9%
HOMA-IR	**7.264**	**0.027***	6.9%
Occupation	-2.695	0.197	2.3%
CRP	1.032	0.335	1.2%
MEDAS	-0.646	0.648	0.3%
METs	0.001	0.702	0.2%
Sex	2.693	0.787	0.1%

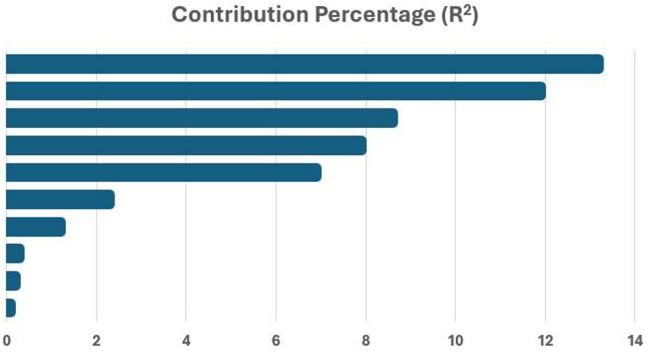

Figure 2 Complement C3 regression model: influence of demographic and biomarker variables. Significant values are in bold font. BMI, body mass index; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment-insulin resistance; MEDAS, Mediterranean Diet Adherence Screener; METs, metabolic equivalent task.

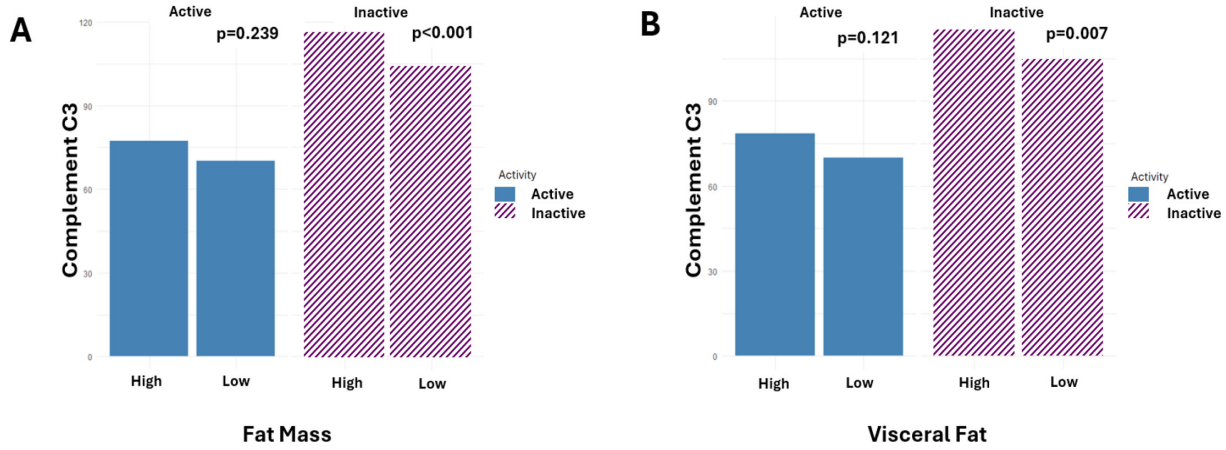

Figure 3 Differences in complement C3 between active (solid-coloured bars) and inactive (striped bars) patients with SLE depending on: (A) total fat mass; (B) visceral fat.

related to age and BMI were found. Concerning body composition measurements and classical cardiovascular risk factors, inactive SLE and controls presented similar total fat mass percentages and glucose/tension values, respectively. Nevertheless, the analysis revealed statistically significant differences in bone mass and body water among SLE groups and controls. In addition, lower serological cholesterol levels were found in both SLE groups.

Regarding HRQoL, a comparison of the SF-12 responses between the SLE and control groups revealed significant differences, particularly in the domains of physical role (questions 4 and 5), body pain (question 8) and vitality/energy (question 10) (online supplemental table 4).

A comparison of the Nutritional Perception Screening Questionnaire response frequencies and total score, stratified by group, was performed. The results showed a trend ($p<0.1$) between the SLE and control groups, but no significant differences among the SLE subgroups (online supplemental table 5).

DISCUSSION

Data from SLE outpatients were analysed, being categorised into two groups based on C3 cut-offs for disease activity[13] and compared with a control group with overweight, with a special focus on body composition, CVD risk factors and exposome determinants such as household composition, occupation and lifestyle factors.

Overweight is linked to a proinflammatory state and affects about one-third of patients with SLE, negatively impacting their functional capacity.[28] Obese patients with SLE show elevated levels of inflammatory markers such as CRP, IL-6 and TNF-α,[29] and are more prone to metabolic syndrome, which raises cardiovascular risk.[30] Inflammation has been related to visceral fat, fibrinogen and insulin resistance,[1 31] but data about SLE activity associated with cardiovascular risk through these factors are scarce.

In this context, available data suggest that body fat distribution is a better predictor of CVD risk than BMI alone.[31] Visceral fat, despite accounting for only 5–20% of total body fat, is associated with a higher CVD risk compared with subcutaneous fat due to enhanced influence on atherogenic gene expression[32] and a recognised correlation with elevated glucose, triglycerides and cardiovascular events.[33] Notably, this study found that the inactive SLE group exhibited a less healthy body composition, with higher visceral fat and abdominal circumference compared with the active SLE group, apparently due to older age, disease chronicity and long-term corticosteroid treatment,[34] which, combined with reduced physical activity, may increase predisposition to body fat accumulation and coronary heart events.

Visceral adipose tissue accumulates more M1 macrophages, which produce inflammatory cytokines such as TNF-α and IL-6, exacerbating inflammation.[35] In contrast, subcutaneous fat tends to contain anti-inflammatory M2 macrophages.[36] Thus, the balance between visceral and subcutaneous fat may be a key factor in the secretion of proinflammatory factors that contribute to CVD pathogenesis.[31] Thus, Seguro *et al* found correlations between visceral adipose tissue and traditional risk factors for cardiovascular events, describing a prognostic role in patients with SLE.[37] In addition, body composition has been closely related to disease duration and chronicity, similarly to other diseases and cirrhosis.[38]

Patients with SLE also exhibited a decreased muscle and bone mass proportion, probably due to previous therapies.[39] The majority of patients with SLE are treated with a combination of antimalarials, glucocorticoids and immunosuppressants, which have been associated with an elevated risk of lower bone mineral density, anaemia, elevated plasma homocysteine levels and other CVD risk determinants.[34] Data on treatments received, among others, was collected, revealing no significant pharmacotherapeutic differences between the groups. Furthermore, a regression analysis incorporating glucocorticoid administration as an independent variable demonstrated no impact of this medication on C3 levels, which were used as a dependent variable to assess disease activity in this population. The adverse effects of steroid therapy

are diverse and begin at the start of treatment, increasing with dosage and duration.[34] Patients with long-term SLE commonly experience musculoskeletal complications such as osteoporosis, avascular necrosis and myopathy.[34] Santos *et al* described that the sarcopenic obesity phenotype, defined as the coexistence of overfat with sarcopenia, was significantly associated with autoimmune pathologies such as rheumatoid arthritis and SLE.[40] This association is partially explained by the chronic inflammatory status in coexistence with the effects of pharmacological treatments and ageing, since corticosteroid administration has been reported as a predictor of fat mass.[41]

Data concerning the association between C3 and SLEDAI align with findings in patients with lupus nephritis.[42] SLE exhibits clinical heterogeneity, with a polygenic and multifactorial nature, where both genetic predisposition and environmental factors trigger the disease.[43] Innovative research on SLE should consider lifestyle factors (physical activity and diet) and the exposome (household, occupation…) in autoimmunity and chronic inflammation. Diet, particularly the Mediterranean diet, can help improve SLE outcomes. The inactive SLE group exhibited a higher BMI; however, there were no significant differences in adherence to the Mediterranean diet or in total physical activity compared with the active SLE group. Interestingly, patients with SLE may adhere more to healthy dietary habits, which positively affect disease activity and cardiovascular risk.[19]

Household composition, as part of the exposome, emerged as a relevant factor associated with SLE activity. These results suggest that living conditions could considerably influence health-related behaviours and outcomes.

Sensitivity analyses revealed a distinctive impact of fibrinogen and adiposity depending on the activity status, which reinforces the notion that both fat mass and CVD risk factors need to be specifically assessed in SLE subjects, where age and chronicity are two variables to be carefully examined. Traditional cardiovascular risk factors include advanced age, male sex, hypertension and dyslipidaemia, among others.[44] Our analyses indicated a worse cardiovascular risk profile in older patients. Specific risk factors for SLE included prolonged disease duration, high disease activity, organ damage, glucocorticoid use and antiphospholipid antibodies,[44] which were more prominent in the inactive group, reflecting greater chronicity and long-term treatment.

Current research also revealed a close association between fibrinogen and cardiometabolic risk factors, such as HOMA and obesity, in patients with inactive SLE. Thus, fibrinogen plays a key role in predicting CVD and has been linked to coagulation disturbances in patients with SLE.[45] Indeed, fibrinogen may serve as a mechanism through which cardiovascular risk factors exert their final effects and consequences. Some authors have suggested including it in future cardiovascular assessment guidelines.[45] Fibrinogen measurement is minimally invasive, accessible and cost-effective, offering valuable insights into inflammation, coagulation issues and cardiovascular risks. Also, insulin resistance, assessed by HOMA, was clinically relevant in this autoimmune population despite the effect of age and sex being normalised in the analyses.[1]

In this context, HRQoL has become a key tool for assessing the perceived health and overall well-being.[46] While the mental component (MCS12) was similar between groups, both self-perceived health and the physical component (PCS12) were lower in the SLE group, reflecting the physical limitations and comorbidities of the disease.[23] Among patients with SLE, the PCS12 was lower in those with inactive SLE, possibly due to older age and disease chronicity, where long-term treatments and comorbidities impact health perception despite a stable clinical profile.[23] The 20-item Self-Report Questionnaire indicated a low likelihood of emotional disorders, but the Functional Assessment of Chronic Illness Therapy-Fatigue scale revealed a non-significant trend towards worse scores in patients with SLE, with mean scores falling within the moderate fatigue range.[47]

Lupus activity has been categorised by C3 levels, although other scales such as SLEDAI or criteria based on lupus low-disease activity state (LLDAS) or complete remission (CR) are suitable.[48] In any case, data on inverse correlation between C3 and anti-DNAs was found in this SLE group (data not shown).

On the other hand, in addition to the screened cardiovascular risk factors, other factors such as Systemic Lupus International Collaborative Clinics (SLICC) criteria, presence of antiphospholipid, evolution time and drug administration would need to be accounted for to better interpret current data.[49]

Indeed, ageing attenuates lupus activity as occurred in this group, but the ascertained independent involvement of visceral fat, fibrinogen and insulin resistance provides specific value for precision management of these patients which can be importantly affected by severe infections.[50]

This study suggests that C3 levels are influenced by age and disease background, exhibiting greater control with disease chronicity. Additionally, fibrinogen is identified as a marker of cardiovascular risk; our analysis indicates that it increases slightly and significantly with lower C3 levels after adjusting for various variables. Cardiovascular-related mortality has been rising among patients with SLE.[17] Consequently, accurate methods and new tools are required for early detection and management by considering the exposome with potential prognostic improvements. This research highlights that factors such as age, lifestyle, fibrinogen levels, HOMA index and adipose tissue mass are linked to complement C3, suggesting that chronic inflammation and long-term treatment may be discriminative between active acute and stable chronic SLE outpatients. Further studies are needed to compare and validate these findings. Summing up, our analyses emphasise that disease activity and duration, as well as age, are important to interpret current results and SLE features, and that the consideration of some variables and risk factors such as fat mass, fibrinogen and insulin resistance, in addition to lifestyle and exposome, need to be

accounted for personalised precision medicine and care in patients with SLE.

Limitations and strengths

Some limitations cannot be denied. A sample size of 74 SLE subjects may not be representative of the general population, and findings need to be validated by future studies. Some comparisons may lack statistical significance due to the small sample size. Moreover, the method used to analyse body composition is not considered the gold standard, such as Dual-energy X-ray absorptiometry (DXA) and magnetic imaging, which are more accurate but not commonly used in clinical practice due to their complexity and cost. Additionally, the distribution of patients with SLE concerning age and sex needs to be considered to carefully interpret current data, as type I and type II error cannot be discarded. Another limitation is the reliance on complement C3 levels as a sole marker of SLE activity, which may not capture the full range of disease variability.[13] Future research should adopt a more comprehensive approach to assessing SLE activity.

On the other hand, the study's strengths include the sample's homogeneity, a consistent protocol and the analysis of novel cardiovascular biomarkers, which have not been extensively studied in SLE. The research employed updated validated laboratory techniques and appropriate bioimpedance methods. Whereas suitable supervised and stepwise statistical methods were used, including univariate and multivariate models adjusted for known confounding variables, to explore the relationships between SLE activity, fat mass, lifestyle and cardiovascular risk factors.

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