Doctoral Thesis

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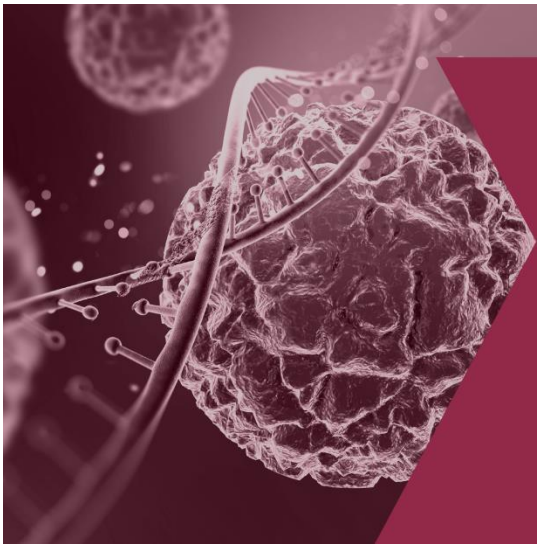
IMPACT OF PHYSICAL FITNESS ON MARKERS OF CARDIOMETABOLIC HEALTH IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS



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Impact of Physical Fitness on Markers of Cardiometabolic Health in Women with Systemic Lupus Erythematosus

Impacto de la condición física sobre marcadores de salud cardiometabólica en mujeres con lupus eritematoso sistémico

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CERTIFICA:

Que la Tesis Doctoral titulada “Impact of Physical Fitness on Markers of Cardiometabolic Health in Women with Systemic Lupus Erythematosus” que presenta D. Sergio Sola Rodríguez al superior juicio del Tribunal que designe la Universidad de Almería, ha sido realizada bajo mi dirección durante los años 2018-2021, siendo expresión de la capacidad técnica e interpretativa de su autor en condiciones tan aventajadas que lo hacen merecedor del Título de Doctor por la Universidad de Almería, siempre y cuando así lo considere el citado Tribunal.

A mis padres, Pedro y Mari Carmen
Y a mis hermanos, Iván y Pedro

Que han hecho posible
todo lo que he conseguido

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RESUMEN

El lupus eritematoso sistémico (LES) es una enfermedad autoinmune sistémica de etiología desconocida y multifactorial que afecta predominantemente a mujeres adultas jóvenes. Esta enfermedad crónica causa una amplia gama de síntomas que afectan a una gran variedad de órganos, incluida la piel, las articulaciones, los pulmones, los riñones y el cerebro. La identificación de factores asociados con una mejor sintomatología y una menor gravedad de la enfermedad es de gran interés clínico y de salud pública.

Los principales objetivos de la presente Tesis Doctoral fueron: estudiar la relación entre el nivel de los diferentes componentes de condición física con varios parámetros de la composición corporal, examinar la asociación entre la fuerza relative de prensión manual con varios marcadores de riesgo cardiometabólico y evaluar el papel de la condición física en la asociación de la masa corporal y la adiposidad con la inflamación en mujeres con LES.

Para abordar estos objetivos, se realizaron tres estudios en el contexto de un proyecto. En este proyecto, un total de 77 pacientes caucásicas con LES participaron en el proyecto EJERCITALES. Se llevaron a cabo medidas antropométricas, de condición física, medidas de fuerza relativa del agarre y factores de riesgo cardiometabólico, muestras de sangre y análisis bioquímicos junto a otras mediciones. Los principales hallazgos de esta Tesis Doctoral fueron: I) Que la condición física se asoció inversamente con el peso corporal y la composición corporal en mujeres con LES. Descubrimos que la capacidad aeróbica se asoció inversamente con el índice de masa corporal, el índice de masa grasa, el perímetro de cintura y el índice cintura-altura, aunque no con el índice cintura-cadera. Observamos diferencias en todos los resultados de composición corporal al dividir y comparar nuestra muestra en pacientes "fit" y "unfit" según las pruebas de capacidad aeróbica, como la prueba Siconolfi y la prueba de marcha de 6 minutos. II) Que una mayor fuerza relativa de agarre se asoció con una menor presión arterial sistólica, triglicéridos,

proteína C reactiva, velocidad de la onda de pulso e índice de riesgo cardiometabólico agrupado (puntaje z) en mujeres con LES. Además, la fuerza de agarre relativa podría ser una alternativa a la fuerza de agarre absoluta al evaluar el riesgo cardiometabólico. III) Que los niveles más altos de condición física podrían atenuar el impacto de una mayor masa corporal y adiposidad sobre la inflamación en mujeres con LES. En general, observamos que una mayor condición física se asoció con un menor aumento de algunos marcadores inflamatorios por cada unidad adicional de masa corporal o adiposidad. Los resultados de esta Tesis Doctoral mejoran nuestra comprensión sobre la condición física y la composición corporal en relación con la sintomatología y la gravedad de la enfermedad en mujeres con LES. Estos resultados conducirán a futuras investigaciones para comprender el valor preventivo y terapéutico de la condición física en esta población.

ABSTRACT

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown and multifactorial etiology that predominantly affects young adult women. This chronic disease causes a wide range of symptoms, affecting a wide variety of organs including skin, joints, lungs, kidneys, and brain. Identifying factors associated with better symptomatology and lower disease severity is of clinical and public health interest.

The major aims of the present Doctoral Thesis was to study the relationship between the level of different components of physical condition with various parameters of body composition, to examine the association between relative handgrip with various markers of cardiometabolic risk and to assess the role of physical fitness in the association of body mass and adiposity with inflammation in women with SLE.

To address these aims, three studies were conducted in the context of one project. In this project, a total of 77 Caucasian patients with SLE participated in the EJERCITALES project. Anthropometric, physical fitness measures, measurements of relative handgrip strength and cardiometabolic risk factors, blood samples and biochemical analyses and other measurements were carried out.

The main findings of this Doctoral Thesis were: I) That physical fitness was inversely associated with body weight and body composition composition in women with SLE. We found out that cardiorespiratory fitness was inversely associated with body mass index, fat mass index, waist circumference and waist-to-height ratio, although not with waist-to-hip. We observed differences in all the body composition outcomes when dividing comparing our sample in "fit" and "unfit" patients according to cardiorespiratory fitness tests, such as Siconolfi Test and 6-minute walk test. II) That a higher relative handgrip strength was associated with lower systolic blood pressure, triglycerides, high sensitivty C-reactive protein, pulse wave velocity, and clustered cardiometabolic risk index (z-

score) in women with SLE. Furthermore, relative handgrip strength could be an alternative to absolute handgrip strength when evaluating cardiometabolic risk. III) That that higher levels of physical fitness might attenuate the impact of higher body mass and adiposity on inflammation in women with SLE. Overall, we observed that higher fitness was associated with lower increase of some inflammatory markers for each additional unit of body mass or adiposity.

The results of this Doctoral Thesis enhance our understanding about physical fitness and body composition regarding SLE symptomatology and disease severity in women. These results will lead to future research to understand the preventive and therapeutic value of physical fitness in this population.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease of unknown and multifactorial etiology that predominantly affects young adult women [1]. This chronic disease causes a wide range of symptoms, affecting a wide variety of organs including skin, joints, lungs, kidneys, and brain [2].

Women with SLE face quite often comorbidities such as cardiometabolic disorders [3]. Furthermore, SLE prognosis has improved dramatically in the last decades because of the new diagnostic and therapeutic strategies. However, cardiovascular diseases of atherosclerotic origin are still one of the major causes of deaths in this population [4]. Cardiometabolic diseases in SLE are caused by both traditional risk factors including hypertension, diabetes, dyslipidemia, among others [5-6], and non-traditional risk factors including abdominal obesity, inflammation, or arterial stiffness [7-8]. As both traditional and non-traditional cardiometabolic risk factors are altered in SLE, addressing potential factors associated with a more cardiometabolic profile is of clinical interest.

A chronic low-grade inflammatory state is a common feature of SLE, which seems to be independent of the disease activity [1] and partially explains the high prevalence of cardiovascular disease observed in SLE. In the presence of obesity, including a high body mass index and/or adiposity (i.e., a less favorable body composition), this chronic inflammatory state becomes more pronounced because the adipose tissue has the capacity not only to recruit and activate mononuclear cells [9] but also to produce key inflammatory cytokines, such as IL-6, which stimulates the production of CRP and other acute phase proteins by the liver [10]. Consequently, obesity affects the SLE natural course by further promoting the chronic inflammatory state but also increases the disease-related activity, and the organ accrual damage [11-13]. Importantly, obesity promotes the development of atherosclerosis and cardiovascular disease [14] perhaps though increased inflammation. Women with SLE present a higher body mass index, waist-to-hip ratio,

and body fat percentage compared to the general population [15], and almost 50% of women with SLE have obesity [14]. Therefore, understanding potential factors associated to a more favorable body mass index and body composition is of research and clinical interest.

Physical fitness is a strong marker of cardiovascular health [16] that can be improved through exercise interventions. Several studies have shown that patients with SLE have significantly lower levels of both cardiorespiratory fitness [17-21] and muscular strength [22-23] compared to the general population, which is worrisome. In the general population, higher fitness significantly attenuates the detrimental effect that obesity has on cardiovascular health and cardiovascular mortality [24]. Similarly, lower physical fitness has also been related to higher levels of adiposity and higher BMI in the general population [25]. For instance, muscular strength has been inversely related to adiposity and cardiometabolic risk [26], and cardiorespiratory fitness has been negatively associated with BMI [27] and positively related to an increased fat-free mass in women [28]. However, the association of physical fitness with body composition in women with SLE is unknow and understanding their relationship would provide a framework to understand the potential interaction of these relevant health markers with both traditional and non-traditional cardiometabolic risk factors.

The association of body mass and adiposity with inflammation is well-described both in the general population [29-31] and in patients with SLE [32], but research analyzing the potential role of fitness in this association is limited and inconclusive. In SLE, physical fitness, in particular cardiorespiratory fitness, has also shown to attenuate the age-related arterial stiffness in women with SLE, thus contributing to the primary prevention of cardiovascular diseases [19]. Physical fitness has previously shown to attenuate the detrimental effect that obesity has on cardiovascular mortality in the general population

[24]. We might speculate that one of the mechanisms by which fitness attenuates this association is through attenuating the impact of obesity on inflammation. Therefore, the potential role of fitness in this association is of research and clinical relevance and requires further investigation, particularly in autoimmune diseases, because all the components of fitness can be enhanced through exercise programs.

The low levels of muscular strength observed in women with SLE [22-23] are also worrisome because low strength levels are associated with higher fatigue, worse quality of life [33], and higher risk of cardiovascular disease and mortality [34-35]. Handgrip strength is a simple and quick method to assess upper body muscular strength that is inversely associated with coronary heart disease [34,36], inflammation [37], and mortality risk [38] in the general population. In women with SLE, handgrip strength positively associated with quality of life [39]. Relative handgrip strength (rHGS), defined by the summation of both hands' strength divided by body mass index (BMI), is an easy instrument for measuring relative muscular strength in clinical practice and public health [40] and has been recommended in recent research to address the increased strength due to body mass [40–43]. Handgrip strength and BMI have both been linked to cardiometabolic disease risk in the general population [44-47], although the evidence regarding the association of rHGS with cardiometabolic risk in women is scarce [41]. Since rHGS is cost- and time-efficient, it is of clinical interest to understand the extent to which rHGS might be associated with cardiometabolic risk factors in SLE.

In autoimmune diseases including SLE [48] or rheumatoid arthritis [49], lower levels of cardiorespiratory fitness have shown to be associated with a less favorable cardiovascular profile and higher arterial stiffness.

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2. OBJETIVOS

El objetivo principal de la presente Tesis Doctoral fue proporcionar un análisis completo de la asociación entre la condición física y la composición corporal en mujeres con LES. Además, también se estudió la utilidad de la prensión manual relativa como herramienta para medir el riesgo cardiometabólico en esta población. El resultado de esta Tesis Doctoral se organiza en tres estudios, en función de los siguientes objetivos específicos:

I. Estudio I: El objetivo de este estudio fue evaluar la asociación de diferentes componentes de la condición física (capacidad aeróbica, fuerza muscular y flexibilidad) con la composición corporal (IMC, índice de masa grasa, perímetro de cintura, índice cintura-altura y el índice cintura-cadera) en mujeres con LES.

II. Estudio II: El objetivo de este estudio fue evaluar el papel de la condición física (capacidad aeróbica, fuerza muscular y flexibilidad) en la asociación de la masa corporal y la adiposidad con la inflamación (sensibilidad a proteina C reactiva, interleucina-6 y leptina) en mujeres con LES.

III. Estudio III: Este estudio tuvo como objetivo examinar la asociación de la prensión manual relativa con los factores de riesgo de enfermedad cardiometabólica, como la presión arterial, la glucosa en ayunas, la hemoglobina glicosilada, el colesterol, los triglicéridos, sensibilidad a proteina C reactiva, la velocidad de onda del pulso, la filtración glomerular y la microalbúmina en mujeres con LES.

3. AIMS

The major aim of the present Doctoral Thesis was to provide a comprehensive examination of the association of physical fitness and body composition in women with SLE. In addition, the utility of relative handgrip strength as a tool for measuring cardiometabolic risk was also studied. The outcome of this Doctoral Thesis is organized in three studies, based on the following specific aims:

IV. Study I: The aim of this study was to evaluate the association of different components of physical fitness (CRF, muscular strength, and flexibility) with body composition (BMI, fat mass index, waist circumference waist-to-height ratio, and waist-to-hip ratio) in women with SLE.

V. Study II: The aim of this study was to assess the role of physical fitness (CRF, muscular strength, and flexibility) in the association of body mass and adiposity with inflammation (hsCRP, interleukin-6, and leptin) in women with SLE.

VI. Study III: This study aimed to examine the association of relative handgrip strength with cardiometabolic disease risk factors, such as blood pressure, fasting glucose, glycosylated hemoglobin, cholesterol, triglycerides, hsCRP, pulse wave velocity, glomerular filtration and microalbumin in women with SLE.

4. METHODS

In this cross-sectional study, a total of 172 Caucasian patients with SLE were invited to participate in the study. Recruitment was performed through the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" University Hospital and the "San Cecilio" University Hospital in Granada.

Inclusion criteria were: Women aged between 18 and 60 years, with >4 SLE classification criteria provided by the American College of Rheumatology [1], a minimum follow-up of one year at our unit, and clinical stability (i.e., the absence of changes in the systemic lupus erythematosus disease activity index (SLEDAI) and/or treatment) during the previous 6 months. Exclusion criteria were: Not being able to read, understand, and/or sign the informed consent; cancer; history of clinical cardiovascular disease and/or lung disease in the last year, or receiving doses of biological treatment higher than 10 mg/d of prednisone (or equivalent) in the previous 6 months.

All participants received detailed information about the study aims and procedures and signed informed consent before being included in the study. The Research Ethics Committee of Granada reviewed and approved the study protocol on 31 October 2016 (reference number: 09/2016).

4.1 DESIGN AND PARTICIPANTS

This is a cross-sectional study in which 172 patients with SLE were recruited. Women, with a diagnosis of SLE, with a minimum medical follow-up of 1 year at our unit and both treatment and clinical stability (defined as no changes in the systemic lupus erythematosus disease activity index [SLEDAI]) during the previous 6 months of the study were included. Exclusion criteria were not being able to read, understand and/or sign the informed consent; personal history of clinical cardiovascular diseases in the

previous year, receiving a biological treatment or requiring doses of prednisone (or equivalent) greater than 10 mg/day during the previous 6 months of the study. Detailed information about the aims and study procedures was given to all the participants, who signed informed consent before being included in the study. The Research Ethics Committee reviewed and approved the study protocol.

4.2 PROCEDURES

Potentially eligible participants were invited by phone to a personal screening. Included participants attended the Hospital facilities on two different occasions. On day 1, socio-demographic and clinical information were collected, and anthropometric measures and physical fitness tests performed. On day 2 (i.e. between 2 and 4 days after day 1), 8-h fasting blood samples were collected between 8:00 am and 10:00 am.

4.3 ANTHROPOMETRIC MEASURES

Height (cm) was measured using a stadiometer (SECA 222, Hamburg, Germany) and weight, fat mass, and lean mass (kg) with a bioimpedance device (InBody R20, Biospace, Seoul, Korea). BMI (weight in kg/height in m2) and FMI (fat mass in kg/height in m2) were calculated. Waist perimeter and hip circumference (cm) were measured with an anthropometric tape (Harpenden, Holtain Ltd, Wales, United Kingdom). The waist-to-hip (waist circumference / hip perimeter) and waist-to-height (waist circumference / height) ratios were calculated.

4.4 PHYSICAL FITNESS MEASURES

Cardiorespiratory fitness was assessed using the Siconolfi step test and the 6MWT. The Siconolfi step test [2] has been previously validated to estimate maximum oxygen consumption (VO2max) in patients with SLE [3]. The test was carried out as described in the original protocol [2], using a wooden box (25.4 cm high × 30.5 cm wide × 45.7 cm long). In stage 1, each patient was instructed to step up and down the box for 3 minutes at a rate of 17 times per minute, controlled by a metronome. Heart rate (HR) was continuously monitored with a HR monitor (Polar V800, OY, Finland). The test was finalized when the average HR during the last 30 seconds of stage 1 reached ≥65% of the estimated maximum HR (220 - age). Otherwise, the participant would perform a second stage of 3 minutes at a rate of 26 times per minute. In case the participant did not reach ≥65% of the maximum HR during the last 30 seconds of stage 2, a third stage was performed at a rate of 32 times per minute. The stage in which 65% of the maximum HR was reached was recorded and VO2max was estimated from the following formula [2]:

VO_{2max} = 0.302 × (stage multiplier × body weight/ 1,000) / (((0.667 × heart rate stage) – 42) / 100) - (0.019 × age) + 1.593

equation, where stage multiplier was 16.287 for stage 1, 24.910 for stage 2, and 35.533 for stage 3. Stage HR corresponds to average HR obtained during the last 30 seconds of the highest stage reached.

The 6MWT measures the maximum distance (in meters) that a person can walk during six minutes [4]. This test has been widely used in rheumatic diseases, including patients with SLE [5]. The test was performed along a 50 meters circuit, broken into 5-meter long sections by 10 cones. The total distance was calculated as the number of complete laps

plus the number of sections covered within the last lap in case of an incomplete final lap at the expiration of the allowed time.

Muscular strength was assessed through the 30-second chair stand test (lower body) and the handgrip strength test (upper body). The 30-second chair stand test [4,6] measures the number of times a person can get up completely from a chair, starting from a sitting position, with a straight back and feet flat on the floor in 30 seconds.

Upper body flexibility was assessed through the back-scratch test [4] that measures how close the hands can be brought together behind the back. In the standing position, the participant should place one hand (facing inwards, fingers extended) behind the head and back over the shoulder, and move down the back to reach as far as possible. The other hand should be placed behind the back (palm facing outward, fingers extended) and reach up as far as possible, trying to touch or overlap the middle fingers of both hands. The distance between the tips of the middle fingers of the hands was measured. If the fingers only touch, the score would be "zero", if they do not touch the score would be negative and if they overlap the score would be positive. The participants performed the test twice with each hand and the average of the best value from both hands was used.

4.5 MEASUREMENT OF RELATIVE HANDGRIP STRENGTH

Upper body muscular strength was assessed through the handgrip strength test. The handgrip strength test [7] was assessed using a digital dynamometer (Model T.K.K.540®; Takei Scientific Instruments Co., Ltd., Niigata, Japan) with a precision to the nearest 0.1 kg. Participants performed the trial in a standing position, with the elbow fully extended and the arm relaxed in a neutral position, and were encourage by the evaluators to exert to their maximal effort during aproximately 3 seconds, alternating between the two hands.

Participants performed the test twice with a one-minute break between the two attempts of each hand. Absolute handgrip strength was summed from the best score of each hand. Relative handgrip strength was defined as absolute handgrip strength divided by BMI [8].

4.6 MEASUREMENT OF CARDIOMETABOLIC RISK FACTORS

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and resting heart rate were measured using the Mobil-O-Graph® 24 h pulse wave analysis monitor (IEM GmbH, Stolberg, Germany) in a sitting position according to the European Society of Hypertension [9], after 5 min of rest.

Arterial stiffness was indirectly assessed through the pulse wave velocity (PWV) [10]. The test was performed in a sitting position after 5 min of rest, using the Mo-bil-O-Graph® 24 h pulse wave analysis monitor, the operation of which is based on oscillometry recorded by a blood pressure cuff placed on the brachial artery. This instrument is validated for clinical practice [10]. PWV was obtained from a single measurement. The coefficient of variation (CV) of the Mobil-O-Graph for consecutive PWV analyses is 3.4%, and its intraclass correlation coefficient is 0.98 (0.96–0.99) [11].

4.7 BLOOD SAMPLES AND BIOCHEMICAL ANALYSES

Venous fasting blood samples were collected in the morning with heparin as the anticoagulant. Blood was centrifuged at 3500 rpm for 15 min to separate the plasma, which was subsequently removed. Plasma triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total cholesterol, glucose, urea, albumin and creatinine concentrations were analyzed enzymatically with

an autoanalyzer (Olympus Diagnostic, Hamburg, Germany). Insulin was measured with an enzyme immunoassay kit, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated [(fasting insulin (μIU/mL) × fasting glucose (mg/dL))/405]. Apolipoproteins A and B and a highly sensitive C-reactive protein (hs-CRP) and glycosylated hemoglobin were determined by immunoturbidimetry (HORIBA-ABX Diagnostics, Japan) with an autoanalyzer (PENTRA-400, HORIBA-ABX Diagnostics, Japan). The albumin-creatinine ratio was measured from a first morning urine sample. Values above or equal to 30 mg/g in women were considered pathological. The estimated glomerular filtration rate was determined by the modification of diet in renal disease (MDRD) equation [12] (GFe (MDRD)):

$175 \times SCr - 1.154 \times age - 0.203 \times 0.742$

SCr: serum creatinine

Regarding inflammatory markers, serum high-sensitivity CRP and interleukin 6 (IL-6) were measured in serum. Serum were initially separated by centrifugation and stored at –70°C. CRP levels were assessed by an immunoturbidimetric method using the ARCHITECT cSystems; MULTIGENT CRP Vario assay. Bioserum concentration of IL-6 (pg/mL) was measured by immunoradiometric assay using commercial kits (MILLIPLEX MAP Kit Human High Sensitivity T Cell Magnetic Bead Panel [HSTMAG-28SK], Millipore) following the manufacturer's instructions. Quantitative data were obtained by using the Luminex-200 system (Luminex Corporation, Austin, TX), and data analysis was performed on XPonent 3.1 software. The detections limits for IL-6 were 0.73 pg/mL.

Leptin was measured by the enzyme-linked immunosorbent assay DBC Direct Kit (Diagnostic Biochem. Canada, Canada) with 0.5 ng/ml sensitivity. Intraassay coefficient of variation (CV) and interassay CV of the kit were 5.9 and 3.7%, respectively.

4.8 OTHER MEASUREMENTS

All participants filled out a sociodemographic and clinical data questionnaire to gather information, such as age, disease duration, presence of dyslipidemia, diabetes, hypertension, current medication (antidiabetic and corticosteroid), and tobacco consumption. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was included to assess disease activity [13]. SLEDAI considers the presence or absence of several clinical and analytical manifestations. The final score goes from 0 to 105, where a higher score shows a higher degree of disease activity. The degree of tissue damage from the onset of the disease was evaluated by the Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index (SDI) [14]. The score ranges from 0 to 40, where a higher score means greater damage produced by SLE.

Below is a table showing each measurement and in which study each measurement was used.

Parameter	Study
Body Mass Index	Study 1, Study 2, Study 3
Fat Mass Index	Study 1
Body Fat Percentage	Study 2
Waist Circumference	Study 1, Study 2, Study 3
Hip Circumference	Study 1
Waist-to-height ratio	Study 1, Study 2
Waist-to-hip ratio	Study 1
Back-Scratch Test	Study 1, Study 2
Handgrip Strength	Study 1, Study 2, Study 3
Chair Stand Test	Study 1
6-Minutes Walk Test	Study 1, Study 2
VO_{2max}	Study 1
Relative Handgrip Strength	Study 3
Systolic Blood Pressure	Study 3
Diastolic Blood Pressure	Study 3
Pulse Wave Velocity	Study 3
Fasting Glucose	Study 3
Glycosylated Hemoglobin	Study 3
High Density Lipoprotein Cholesterol	Study 3
Low Density Lipoprotein Cholesterol	Study 3
Total Cholesterol	Study 3
Triglycerides	Study 3
Homeostatic Model Assessment for insuline resistance	Study 3
hs-CRP	Study 2, Study 3
Glomerular Filtration Rate	Study 3
Microalbuminuria	Study 3
Leptin	Study 2
Interleukin-6	Study 2
Dyslipidemia	Study 2

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5. RESULTS AND DISCUSSION

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Physical Fitness and Body Composition in Women with Systemic Lupus Erythematosus

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Abstract: *Background and objectives:* Higher physical fitness is associated with a more favorable weight and body composition in the general population, although this association has not been studied in patients with systemic lupus erythematosus (SLE). The aim of the present study was to examine the association of different components of physical fitness with body composition in women with SLE with mild disease activity. *Materials and Methods:* This cross-sectional study included 77 women with SLE (43.2 ± 13.8 years old) and clinical stability during the previous 6 months. Body composition (including body mass index (BMI), fat mass index (FMI), waist circumference, waist-to-height ratio and waist-to-hip ratio) was assessed using a stadiometer, an anthropometric tape, and a bioimpedance device. Physical fitness included cardiorespiratory fitness (Siconolfi step test and 6 min walk test), muscular strength (handgrip strength test as upper body measure and 30 s chair stand as lower body measure), and flexibility (back-scratch test). Participants with a fitness level equal or above the median of the study sample were categorized as "fit" and those below the median were categorized as "unfit". Linear regression assessed the association of physical fitness with body composition parameters. *Results:* Cardiorespiratory fitness and upper body muscular strength were negatively associated with BMI, FMI, waist circumference, and waist-to-height ratio (all, $p < 0.05$). Lower body muscular strength and flexibility were negatively related to FMI, waist circumference, waist-to-height ratio, and waist-to-hip ratio (all, $p < 0.05$). These relationships were still significant after controlling for age, disease duration, accrual damage, and SLE activity. Overall, fit patients presented significantly lower values in all body composition parameters compared to unfit patients (all, $p < 0.05$). *Conclusions:* The main findings of the present study suggest that physical fitness is inversely associated with body composition in women with SLE. Given the cross-sectional nature of this study, future clinical trials should study the causal pathways underlying these relationships.

Keywords: physical fitness; flexibility; muscular strength; cardiorespiratory fitness; body composition; systemic lupus erythematosus; obesity

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease of unknown origin which affects approximately 20 of every 100,000 females [1]. It is characterized by an immune mediated damage that may affect the skin, joints, kidney, brain, and most systems and organs [2]. SLE is associated

with progressive and irreversible accrual organic damage, which has been shown to be a predictor of morbidity and early mortality [3]. However, the prognosis of the disease and patients' quality of life has improved in recent years as a result of better diagnostic methods and more effective treatments [4].

Cardiovascular diseases currently represent one of the main causes of mortality in this population [5]. Obesity, which increases the risk of cardiovascular disease and atherosclerosis, is present in nearly 50% of women with SLE [6]. In particular, body mass index (BMI; as a measure of excess of body weight), fat mass index [7,8] (FMI; as measure of excess of body fat), waist circumference, and waist-to-hip and waist-to-height ratios [9] (as measures of central fat) represent independent predictors of cardiovascular disease [10,11]. Ramírez et al. [12] observed that women with SLE present a higher BMI, waist-to-hip ratio, and FMI compared to the general population. Adiposity is intimately associated with a systemic low-grade chronic inflammatory state, thus contributing to cardiovascular disease risk in this population [13]. Therefore, identifying modifiable factors that can potentially be associated with a more favorable body weight and composition is of clinical interest.

Physical fitness is a powerful marker of present and future cardiovascular health [10] that can be modified through exercise. In the general population, higher fitness significantly attenuates the detrimental effect that obesity has on cardiovascular health and cardiovascular mortality [14]. Similarly, lower physical fitness has also been related to higher levels of adiposity and higher BMI in the general population [10]. For instance, muscular strength has been inversely related to adiposity and cardiometabolic risk [15], and cardiorespiratory fitness (CRF) has been negatively associated with BMI [16] and positively related to an increased fat-free mass in women [17].

Patients with SLE present a reduced CRF [18–22], functional capacity [23,24], and muscular strength [25,26], and these fitness components have been positively associated with health-related outcomes [19,20,23]. However, the association of physical fitness components with body weight and composition has not been studied in detail in this population. This information is relevant because it could lead to implementation of new studies focused at increasing fitness levels in this population with the aim of improving body composition and ultimately reducing cardiovascular risk.

The aim of the present study was to evaluate the association of different components of physical fitness (CRF, muscular strength, and flexibility) with body composition (BMI, FMI, waist circumference, waist-to-height ratio, and waist-to-hip ratio) in women with SLE.

2. Materials and Methods

2.1. Design and Participants

In this cross-sectional study, a total of 172 Caucasian patients with SLE were invited to participate in the study. Recruitment was performed through the Systemic Autoimmune Diseases Unit of the "Virgen de las Nieves" University Hospital and the "San Cecilio" University Hospital in Granada. Inclusion criteria were: Women aged between 18 and 60 years, with $\geq$4 SLE classification criteria provided by the American College of Rheumatology [27], a minimum follow-up of one year at our unit, and clinical stability (i.e., the absence of changes in the systematic lupus erythematosus disease activity index (SLEDAI) and/or treatment) during the previous 6 months. Exclusion criteria were: Not being able to read, understand, and/or sign the informed consent; cancer; history of clinical cardiovascular disease and/or lung disease in the last year, or receiving doses of biological treatment higher than 10 mg/d of prednisone (or equivalent) in the previous 6 months.

All participants received detailed information about the study aims and procedures and signed informed consent before being included in the study. The Research Ethics Committee of Granada reviewed and approved the study protocol on 31 October 2016 (reference number: 09/2016).

The flowchart of the participants included in this study is presented in Figure 1. From a total of 172 patients initially invited, 81 refused to participate (41 patients reported living very far from the hospital, 36 were not able to find time to perform the evaluations, and 4 were not interested), 12 patients did not present clinical stability during the 6 previous months, and 2 patients had cardiovascular

disease during the previous year. A total of 77 women with SLE (mean age 43.2, SD 13.8) met the inclusion criteria, agreed to participate, and were assessed in two waves (49 women in October 2016 and 28 women in February 2017). Both evaluations were identical, with the exception that the 6 min walk test (6MWT) and Siconolfi step test were not carried out (n = 28) in the wave of 2017 due to timing issues. One woman did not perform the handgrip strength test and the back-scratch test due to a wrist injury.

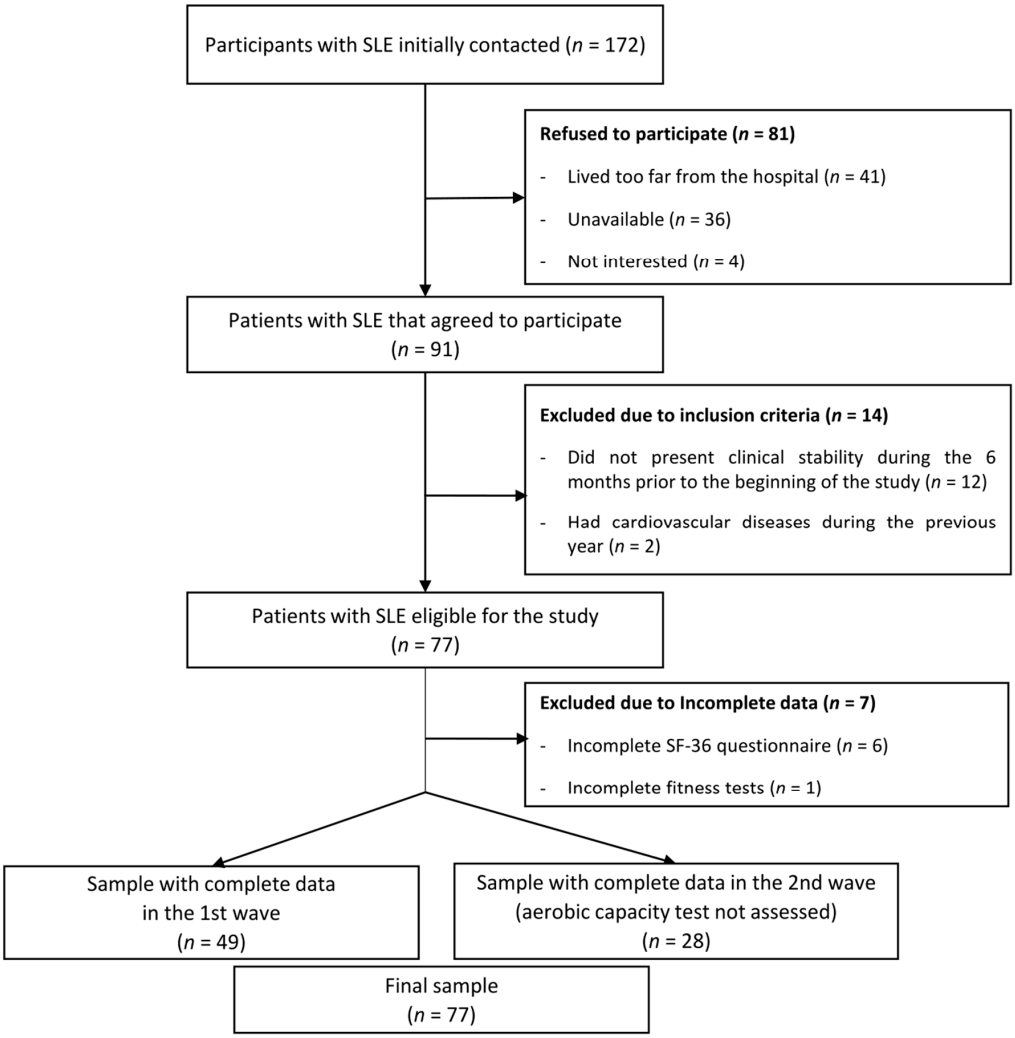

Figure 1. Flow diagram of the inclusion of women with systemic lupus erythematosus (SLE) for the present study.

2.2. Anthropometric Measures

Height (cm) was measured using a stadiometer (SECA 222, Hamburg, Germany) and weight, fat mass, and lean mass (kg) with a bioimpedance device (InBody R20, Biospace, Seoul, Korea). BMI (weight in kg/height in m^2) and FMI (fat mass in kg/height in m^2) were calculated. Waist perimeter and hip circumference (cm) were measured with an anthropometric tape (Harpenden, Holtain Ltd., Wales, UK). The waist-to-hip (waist circumference/hip perimeter) and waist-to-height (waist circumference/height) ratios were calculated.

2.3. Physical Fitness Measures

Cardiorespiratory fitness was assessed using the Siconolfi step test and the 6MWT. The Siconolfi step test [28] has been previously validated to estimate maximum oxygen consumption (VO_{2max}) in

patients with SLE [29]. The test was carried out as described in the original protocol [28], using a wooden box (25.4 cm high × 30.5 cm wide × 45.7 cm long). In stage 1, each patient was instructed to step up and down the box for 3 min at a rate of 17 times per min, controlled by a metronome. Heart rate (HR) was continuously monitored with an HR monitor (Polar V800, Osakeyhtiö, Kempele, Finland). The test was finalized when the average HR during the last 30 s of stage 1 reached ≥65% of the estimated maximum HR (220-age). Otherwise, the participant would perform a second stage of 3 min at a rate of 26 times per min. In case the participant did not reach ≥65% of the maximum HR during the last 30 s of stage 2, a third stage was performed at a rate of 32 times per min. The stage in which 65% of the maximum HR was reached was recorded and VO_{2max} was estimated from the following formula [28]:

$$\begin{aligned} VO2max = \; & 0.302 \times (stage\ multiplier \times body\ weight/1000)/(((0.667 \\ & \times heart\ rate\ stage) - 42)/100) - (0.019 \times age) + 1.593 \end{aligned} \quad (1)$$

where stage multiplier was 16.287 for stage 1, 24.910 for stage 2, and 35.533 for stage 3. Stage HR corresponds to average HR obtained during the last 30 s of the highest stage reached.

The 6MWT measures the maximum distance (in meters) that a person can walk in six min [30]. This test has been widely used in rheumatic diseases, including patients with SLE [24]. The test was performed along a 50 m circuit, broken into 5 m long sections by 10 cones. The total distance was calculated as the number of complete laps plus the number of sections covered within the last lap in case of an incomplete final lap at the expiration of the allowed time.

Muscular strength was assessed through the 30 s chair stand test (lower body) and the handgrip strength test (upper body). The 30 s chair stand test [30,31] measures the number of times a person can get up completely from a chair, starting from a sitting position, with a straight back and feet flat on the floor in 30 s. The handgrip strength test [32] was assessed using a digital dynamometer (Model T.K.K.540®; Takei Scientific Instruments Co., Ltd., Niigata, Japan). Alternating between the two hands, participants performed the test twice with a one-min break between the two attempts of each hand. The best score of each hand was used to compute an average of the two scores.

Upper body flexibility was assessed through the back-scratch test [30] that measures how close the hands can be brought together behind the back. In the standing position, the participant should place one hand (facing inwards, fingers extended) behind the head and back over the shoulder and move down the back to reach as far as possible. The other hand should be placed behind the back (palm facing outward, fingers extended) and reach up as far as possible, trying to touch or overlap the middle fingers of both hands. The distance between the tips of the middle fingers of the hands was measured. If the fingers only touch, the score would be "zero", if they do not touch the score would be negative and if they overlap the score would be positive. The participants performed the test twice with each hand and the average of the best value from both hands was used.

2.4. Other Measurements

All participants filled out a sociodemographic and clinical data questionnaire to gather information, such as age, disease duration, presence of dyslipidemia, diabetes, hypertension, current medication (including antidiabetics and corticosteroids), and tobacco consumption. The systemic lupus erythematosus disease activity index (SLEDAI) was included to assess disease activity [33]. SLEDAI considers the presence or absence of several clinical and analytical manifestations. The final score goes from 0–105, where a higher score shows a higher degree of disease activity. The degree of tissue damage from the onset of the disease was evaluated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) [34]. The score ranges from 0–40, where a higher score means greater damage produced by SLE.

2.5. Statistical Analysis

The descriptive characteristics of the study sample are presented as mean and standard deviation unless otherwise indicated. The physical fitness and body composition-related variables were assessed for normality through the Kolmogorov-Smirnov Test and Q–Q charts, and all showed an approximately normal distribution. Scatter plots and Pearson's bivariate correlations were used as preliminary analyses to understand the raw association of physical fitness (Siconolfi, 6MWT, handgrip, 30 s chair stand, and back-scratch tests) with body composition (BMI, FMI, waist circumference, waist-to-height ratio, and waist-to-hip ratio). Subsequently, linear regression models were built, including each parameter of body composition as dependent variables and each fitness test as independent variables in separate regression models along with age, SLEDAI, SDI, and disease duration as relevant factors that might confound the association of interest [35]. Additionally, participants were categorized as "fit" (i.e., equal or above the median in each fitness test) or "unfit" (below the median in each fitness test) and both groups (fit vs. unfit) were compared using analysis of covariance (ANCOVA) with the aforementioned covariables. Statistical analysis was performed with SPSS v.23 (IBM, New York, NY, USA). Statistical significance was established at $p < 0.05$ (all p-values were two-tailed).

3. Results

The descriptive characteristics of the study participants are presented in Table 1. The average BMI was 25.5 (SD 4.5) kg/m^2, the average waist circumference was 81.7 (SD 10.7) cm, and the average hip circumference was 98.1 (SD 9.9) cm. The average VO_{2max} assessed with the Siconolfi step test was 24.4 (SD 3.2) mL/kg/min and the average distance in the 6MWT was 570.8 (SD 71.7) meters. The average handgrip strength was 23.6 (SD 5.3) kg, the average score of the 30 s chair stand test was 14.9 (SD 3.1), and the average score of the back-scratch test was −0.8 (SD 9.6) cm.

Table 1. Descriptive characteristics of the study participants.

	N	Mean	SD
Age (years)	77	43.2	13.8
Weight (kg)	77	65.1	11.1
Height (cm)	77	160.1	6.8
BMI (kg/m^2)	77	25.5	4.5
FMI (kg/m^2)	77	9.23	3.87
Waist circumference (cm)	77	81.7	10.7
Hip circumference (cm)	77	98.1	9.9
Waist-to-height ratio (units)	77	0.51	0.07
Waist-to-hip ratio (units)	77	0.83	0.06
Back-Scratch test (cm)	76	−0.8	9.6
Handgrip strength (kg)	76	23.6	5.3
Chair stand test (rep)	77	14.9	3.1
6MWT (m)	49	570.8	71.7
VO_{2max} estimated (mL/kg/min)	49	24.4	3.2
SLEDAI (score)	77	0.68	1.5
SDI (score)	77	0.55	1.11
Duration of SLE (years)	77	13.9	10.1
Accumulated corticosteroid dose (last 3 years; mg)	77	2875	2677
Dyslipidemia (%)	77	18	
Diabetes (%)	77	1	
Arterial hypertension (%)	77	17	
Smokers (%)	77	53	
Statins intake (%)	77	18	
Antidiabetic drugs intake (%)	77	3	
Corticosteroid dose (%; mg/d)	77	65	

FMI: Fat mass index; BMI: Body mass index; SLEDAI: Systemic lupus erythematosus disease activity index; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; 6MWT: 6 min walk test; SLE: Systemic lupus erythematosus. All variables show mean and SD values except accumulated corticosteroid dose, dyslipidemia, diabetes, arterial hypertension, smokers, statins intake, antidiabetic drugs intake, and corticosteroid dose.

The raw association (without adjustment variables) between different components of physical fitness and BMI, FMI, waist circumference, waist-to-height ratio, and waist-to-hip ratio in women with SLE is presented in Figure 2. CRF was inversely associated with BMI, FMI, waist circumference, and waist-to-height and waist-to-hip ratios (r_{range} = from −0.74 to −0.43; all $p < 0.05$). Lower body muscular strength was inversely associated with waist circumference, and waist-to-height and waist-to-hip ratios (r_{range} = from −0.40 to −0.31; all $p < 0.05$). Flexibility was inversely associated with BMI, FMI, waist circumference, and waist-to-height and waist-to-hip ratios (r_{range} = from −0.52 to −0.38; all $p < 0.05$).

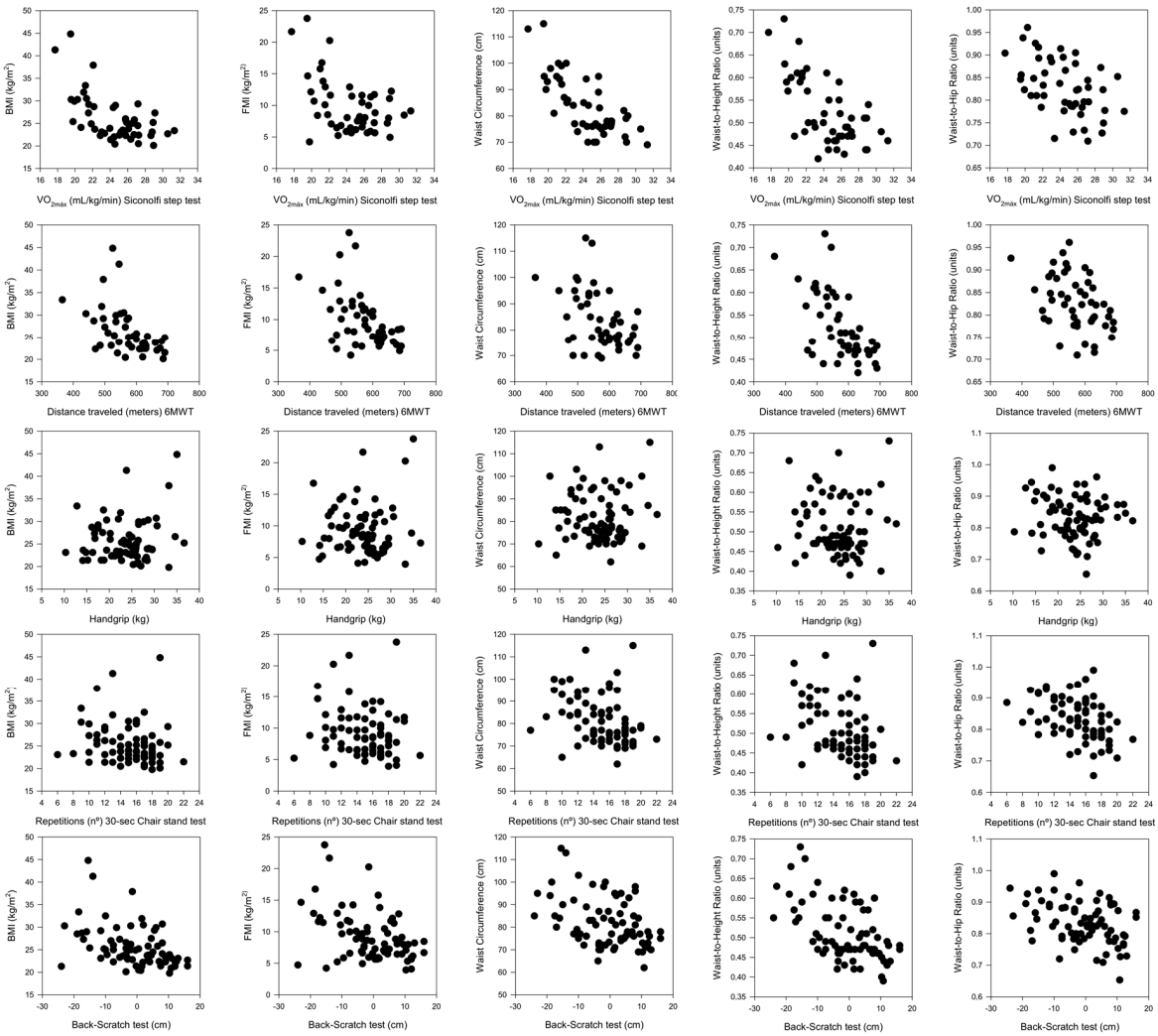

Figure 2. Graphic representation of the crude association between components of physical fitness and different components of body composition. 6MWT: 6-min walk test, BMI: Body mass index, FMI: Fat mass index.

The linear regression models evaluating the association between physical fitness levels and body composition in women with SLE are presented in Table 2. Both crude and adjusted analysis yielded virtually the same results. CRF, assessed through the Siconolfi step test, was inversely associated with BMI (unstandardized coefficient (B) = −1.83; 95% confidence interval (CI) −2.36 to −1.31; $p < 0.001$), FMI (B = −1.41; 95% CI −1.91 to −0.91; $p < 0.001$), waist circumference (B = −3.73; 95% CI −4.74 to −2.71; $p < 0.001$), and waist-to-height ratio (B = −0.02; 95% CI −0.03 to −0.01; $p < 0.001$). CRF, assessed through 6MWT, was inversely associated with BMI (B = −0.04; 95% CI −0.06 to −0.02; $p = 0.001$), FMI (B = −0.04; 95% CI −0.06 to −0.02; $p < 0.001$), waist circumference (B = −0.05; 95% CI

−0.10 to −0.01; $p = 0.029$), and waist-to-height ratio (B = −0.001; 95% CI −0.001 to 0.001; $p = 0.001$). The association of handgrip strength with the outcome variables was further adjusted for body weight, as some studies [36,37] have shown that obese people tend to perform best in the handgrip strength test. Muscular strength, as assessed through handgrip strength, was inversely associated with BMI (B = −0.14; 95% CI −0.24 to −0.04; $p = 0.006$), FMI (B = −0.21; 95% CI −0.31 to −0.11; $p < 0.001$), waist circumference (B = −0.40; 95% CI −0.70 to −0.11; $p = 0.007$), and waist-to-height ratio (B = −0.004; 95% CI −0.01 to −0.002; $p = 0.001$). Muscular strength, as assessed through the 30-s chair stand test, was inversely associated with waist circumference (B = −1.20; 95% CI −2.30 to −0.10; $p = 0.033$), the waist-to-height ratio (B = −0.01; 95% CI −0.01 to −0.001; $p = 0.03$), and the waist-to-hip ratio (B = −0.01; 95% CI −0.01 to −0.002; $p = 0.011$). Finally, flexibility, assessed through the back-scratch test, was inversely associated with BMI (B=-0.21; 95% CI −0.31 to −0.10; $p < 0.001$), FMI (B = −0.18; 95% CI −0.28 to −0.09; $p < 0.001$), waist circumference (B = −0.40; 95% CI −0.67 to −0.14; $p = 0.003$), waist-to-height ratio (B = −0.004; 95% CI −0.005 to −0.002; $p < 0.001$), and waist-to-hip ratio (B = −0.002; 95% CI −0.004 to −0.001; $p < 0.001$). Further adjustment for dyslipidemia, diabetes, arterial hypertension, smoking, and intake of statins and antidiabetics, or corticosteroids (and accumulated corticosteroid dose in the previous 3 years) as possible relevant confounders [34] did not change the results.

Table 2. Linear regression analysis evaluating the association between different components of physical fitness and body composition in women with systemic lupus erythematosus *.

	β	B	SE	CI 95%		*p*
Siconolfi VO_{2max} *						
Body Mass Index	−1.14	−1.83	0.26	−2.35	−1.30	<0.001
Fat Mass Index	−1.05	−1.41	0.24	−1.91	−0.91	<0.001
Waist Circumference	−1.09	−3.73	0.50	−4.74	−2.71	<0.001
Waist-to-Height Ratio	−0.90	−0.02	0.00	−0.02	−0.01	<0.001
Waist-to-Hip Ratio	−0.30	−0.01	0.00	−0.01	0.00	0.151
6MWT *						
Body Mass Index	−0.57	−0.04	0.01	−0.06	−0.01	<0.001
Fat Mass Index	−0.65	−0.03	0.00	−0.05	−0.02	<0.001
Waist Circumference	−0.35	−0.05	0.02	−0.10	−0.00	0.029
Waist-to-Height Ratio	−0.53	−0.001	0.00	−0.001	<0.001	0.001
Waist-to-Hip Ratio	−0.22	<0.00	0.00	0.00	0.00	0.162
Handgrip						
Body Mass Index	−0.16	−0.14	0.05	−0.24	−0.04	0.006
Fat Mass Index	−0.29	−0.21	0.05	−0.31	−0.11	<0.001
Waist Circumference	−0.19	−0.40	0.14	−0.69	−0.11	0.007
Waist-to-Height Ratio	−0.29	−0.004	0.00	−0.01	−0.00	0.001
Waist-to-Hip Ratio	−0.15	−0.002	0.00	−0.00	0.00	0.246
Chair Stand Test						
Body Mass Index	−0.23	−0.33	0.24	−0.81	0.14	0.168
Fat Mass Index	−0.29	−0.36	0.20	−0.77	0.04	0.083
Waist Circumference	−0.35	−1.20	0.55	−2.30	−0.09	0.033
Waist-to-Height Ratio	−0.36	−0.01	0.00	−0.01	−0.00	0.030
Waist-to-Hip Ratio	−0.41	−0.01	0.00	−0.01	−0.00	0.011
Back-Scratch						
Body Mass Index	−0.43	−0.20	0.05	−0.31	−0.09	<0.001
Fat Mass Index	−0.44	−0.18	0.05	−0.28	−0.09	<0.001
Waist Circumference	−0.36	−0.40	0.13	−0.66	−0.14	0.003
Waist-to-Height Ratio	−0.48	−0.004	0.00	−0.01	−0.00	<0.001
Waist-to-Hip Ratio	−0.29	−0.002	0.00	−0.00	−0.00	<0.001

β, standardized coefficient; B, unstandardized coefficient indicating the expected unit change in the dependent variable for one unit change in the independent variable; SE, standard error; CI, confidence interval; * $n = 77$ except for models that include the Siconolfi step test and 6-min walk test (6MWT) ($n = 49$). All regression models were adjusted for age, SLEDAI, SDI, and disease duration. Handgrip was additionally adjusted for body weight.

Figure 3 shows the differences in body composition between patients categorized as "fit" and those categorized as "unfit" according to the median value for each fitness test. Regarding CRF, women categorized as "unfit" (using the Siconolfi step test) had a higher BMI (mean difference 5.44 kg/m^2; 95% CI 2.61–8.26; $p < 0.001$), FMI (mean difference 3.51 kg/m^2; 95% CI 0.99–6.03; $p = 0.007$), waist circumference (mean difference 14.18 cm; 95% CI 8.72—19.64; $p < 0.001$), waist-to-height ratio (mean difference 0.08 units; 95% CI 0.05–0.12; $p < 0.001$), and waist-to-hip ratio (mean difference 0.05 units; 95% CI 0.02–0.09; $p = 0.001$) than those categorized as "fit". Women categorized as "unfit" (using the 6MWT) had a higher BMI (mean difference 6.02 kg/m^2; 95% CI 3.24–8.81; $p < 0.001$), FMI (mean difference 4.46 kg/m^2; 95% CI 2.02–6.90; $p = 0.001$), waist circumference (mean difference 11.81 cm; 95% CI 5.70–17.96; $p < 0.001$), waist-to-height ratio (mean difference 0.09 units; 95% CI 0.05–0.12; $p < 0.001$), and waist-to-hip ratio (mean difference 0.05 units; 95% CI 0.01–0.08; $p < 0.008$) than those categorized as "fit". Regarding strength, women categorized as "unfit" (using the handgrip strength test) had a higher BMI (mean difference 1.08 kg/m^2; 95% CI 0.10–2.05; $p = 0.03$), FMI (mean difference 1.59 kg/m^2; 95% CI 0.58–2.59; $p = 0.002$), waist circumference (mean difference 3.34 cm; 95% CI 0.45–6.23; $p = 0.024$), and waist-to-height ratio (mean difference 0.03 units; 95% CI 0.008–0.05; $p = 0.008$) than those categorized as "fit". Women categorized as "unfit" (using the 30-sec chair stand test) had a higher waist-to-height ratio (mean difference 0.03 units; 95% CI 0.002–0.07; $p = 0.041$), and waist-to-hip ratio (mean difference 0.04 units; 95% CI 0.01–0.07; $p = 0.011$) than those categorized as "fit". Regarding flexibility, women categorized as "unfit" (using the back-scratch test) had a higher BMI (mean difference 3.21 kg/m^2; 95% CI 1.16–5.27; $p = 0.003$), FMI (mean difference 2.59 kg/m^2; 95% CI 0.82–4.36; $p = 0.005$), waist circumference (mean difference 5.08 cm; 95% CI 0.02–10.14; $p = 0.049$), waist-to-height ratio (mean difference 0.04 units; 95% CI 0.01–0.08; $p = 0.007$), and waist-to-hip ratio (mean difference 0.03 units; 95% CI 0.005–0.06; $p = 0.022$) than those categorized as "fit".

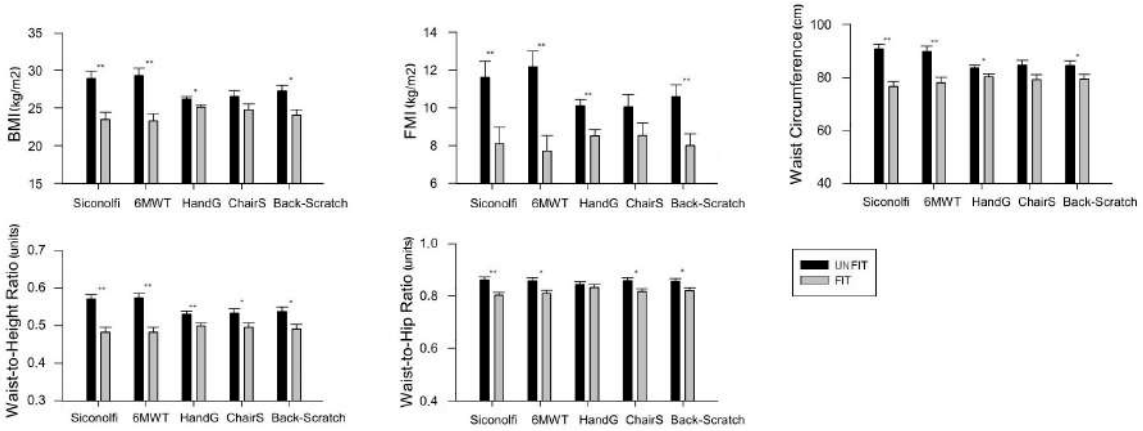

Figure 3. Means (95% confidence interval) of parameters of body composition in "fit" and "unfit" patients according to the median value for cardiorespiratory fitness (24.5 VO_{2max} in the Siconolfi step test; 575 m in the 6 min walk test (6MWT)), upper body strength (24.2 kg in handgrip strength test), lower body strength (15 repetitions in the 30 s chair stand test), and flexibility (1.35 cm in the back-scratch test). Differences between groups were studied using analysis of covariance (ANCOVA) with age, SLEDAI, SDI, and disease duration entered as covariates. * $p < 0.05$, ** $p < 0.01$. All analyses were adjusted for age, SLEDAI, SDI, and disease duration. Handgrip was additionally adjusted for body weight.

4. Discussion

The main findings of this study suggest that physical fitness is inversely associated with body weight and composition in women with SLE. These results were consistent regardless of the fitness component evaluated and despite the adjustment for multiple potential confounders.

In this study, CRF was inversely associated with BMI, FMI, waist circumference and waist-to-height ratio, although not with waist-to-hip. We observed differences in all the body composition outcomes when comparing "fit" and "unfit" patients according to the Siconolfi step and the 6MWT tests. Our results cannot be compared with other studies in SLE or similar conditions, as our objective has not been previously addressed in the literature. Our findings are, however, consistent with previous studies in the general population that showed an inverse association between CRF and body composition across all parameters. Dagan et al. [38] found negative associations of CRF with BMI and waist circumference in adult women. Other studies have also observed negative associations of CRF with total body fat [39] and central obesity (assessed by waist circumference [40], waist-to-hip ratio and waist-to-height ratio [41]). We hypothesized that an increase of CRF might be related to improvements in body composition-related parameters, since CRF substantially attenuates the obesity-related health risks through a reduction of abdominal adiposity [42] and total body fat [43]. It is worth noting that CRF is determined by genetic factors and physical activity, and it could be possible that CRF was an indirect measure of the physical activity performed, a recognized determinant of body composition in SLE [35]. On the other direction of the pathway between CRF and body composition, it is also plausible that greater fat mass leads to decreased VO_{2max} by reducing the amount of lean tissue (that extracts oxygen during the test) per kg of body weight. Importantly, CRF was the fitness component that presented the strongest inverse association with most body composition indicators assessed in the present study. The present results, along with the previous evidence relating positively CRF to different health outcomes in SLE [22,24], highlight that CRF is a relevant health marker in this particular population. Interventions aimed at increasing CRF in patients with SLE are warranted and have shown to be effective and safe for these patients [24]. For instance, Soriano-Maldonado et al. [24] recently showed that a 12-week aerobic exercise intervention combining continuous and interval sessions of progressing intensity improved the time to achieve the 85% of the maximal heart rate by an average of 2.3 min (i.e., corresponding to approximately 7.5 mL/kg/min of VO_{2max}).

A negative association between handgrip muscular strength and BMI, FMI, waist circumference and waist-to-height ratio was observed, but only when adding body weight [36,37] into the models. This finding suggests that a higher isometric muscular strength of the upper limb, relative to total body weight, might be an indicator of body composition. No previous studies have focused on the association between isometric muscular strength and body composition in SLE. Hayat et al. [44] found that grip strength was positively related to BMI, but after further adjustment for weight, as we did in our study, grip strength and BMI were inversely associated. Regarding fat mass percentage (FM%), another study found that absolute grip strength was inversely associated with fat mass in elderly people [45]. In terms of central adiposity, grip strength has been negatively related to waist circumference in older adults [46]. With reference to lower-body strength, we found no association between BMI, FMI, and the 30 s chair stand test, and no differences were observed between BMI, FMI, waist circumference and 30 s chair stand test either when comparing "fit" and "unfit" individuals. The differences found between the strength tests used could be due to the different features of strength assessed. While handgrip may be representative of the maximal isometric strength [47], the functional 30 s chair stand test may be representative of the maximum strength in older adults [31] but not necessarily in adults. Indeed, previous studies in postmenopausal women did not find an association between the 30 s chair stand test and waist circumference [48], whereas there was an association between the 30 s chair stand test and BMI in older women [49]. A higher muscular strength, and its maintenance, increases resting metabolic rate, increases high density lipoprotein cholesterol (HDL-c), decreases low density lipoprotein cholesterol (LDL-c), decreases triglycerides, and increases insulin resistance, thus contributing to a better body composition [50,51]. It is also possible that central obesity could reduce muscular strength through increasing subclinical inflammation and insulin resistance. Pro-inflammatory cytokines and adipokines are produced in adipose tissue, especially in visceral areas [52], leading to catabolism, and contributing to muscle mass and strength decline [53]. Moreover,

insulin resistance and a reduced anabolic action of insulin has been related to adiposity [54] and to loss of muscular strength [55]. Future prospective studies should elucidate whether muscular strength is able to counteract the effect of obesity in SLE, as it has been demonstrated in other populations [10,56].

We also found a negative relationship between flexibility and obesity in women with SLE. An inverse relationship between lower-body flexibility and BMI has been previously described in older men but not in women [57] or was not found in either gender [58]. Previous research linking fitness to cardiometabolic risk found higher values of waist circumference related to upper-body flexibility in perimenopausal women [59] and to lower-body flexibility in elderly people [60]. The low number of studies focused on assessing the benefits of flexibility in health, along with the heterogeneity of the populations and the methods used to assess it, constitute a limitation for the interpretation of the present results, which needs to be contrasted in future reports. The back-scratch test used in the present study assesses scapular mobility, and a reduced scapular motion has been previously linked to higher BMI by Gupta et al. [61]. Stretching has been shown to reduce inflammation [62] and improve vascular function [63], and it remains unknown whether these benefits could potentially be related to decreases in BMI. On the other hand, we speculate that a larger body size (especially greater arm mass) might limit the joint range of motion in this test. In line with our findings regarding FM%, the concentration of adipose tissue around the joints possibly increases the friction between the surfaces of the joints, which reduces the ability of stretching and may reduce, therefore, flexibility [64]. Due to the potential relevance of flexibility for health in SLE [65] and other populations [59,60,64], interventions and prospective studies are needed to clarify the role of this fitness component and the nature of the relationships found in this study.

This study has limitations that should be highlighted. The cross-sectional design of our study excludes establishment of causal relationships, and future prospective research should confirm or contrast these findings and attempt to evaluate the directionality of the association. The sample size was relatively small, excluding men and women with medium-to-high disease activity. Therefore, our results do not pretend to be generalizable to the whole SLE population.

5. Conclusions

In conclusion, the results of the present study suggest that lower physical fitness is associated with higher body weight and more unfavorable body composition (i.e., including measures of total and central adiposity) in women with SLE. More specifically, CRF, muscular strength, and flexibility components are inversely associated with BMI, FMI, waist circumference, and waist-to-height ratio. The relatively low levels of CRF and muscular strength, and the high prevalence of obesity consistently observed in this population underlie the need to take preventive actions to improve these health parameters. Due to the tight and bidirectional connection between physical fitness and body composition, further prospective and experimental research is needed to elucidate how their interaction affects the cardiovascular health of patients with SLE.

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Physical Fitness Attenuates the Impact of Higher Body Mass and Adiposity on Inflammation in Women With Systemic Lupus Erythematosus

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Aims: Higher body mass and adiposity represent independent contributors to the systemic low-grade inflammatory state often observed in patients with systemic lupus erythematosus (SLE). This study assessed the role of physical fitness in the association of body mass and adiposity with inflammation in women with SLE.

Methods: A total of 77 women with SLE were included in this cross-sectional study. We obtained body mass index, waist-to-height ratio, and body fat percentage as indicators of body mass and adiposity. Inflammation was assessed through Serum levels of C-reactive protein, interleukin 6, and leptin. Cardiorespiratory fitness was assessed with the 6-minute walk test, range of motion with the back-scratch test, and muscular strength with handgrip dynamometry.

Results: Cardiorespiratory fitness attenuated the association of both body mass index and body fat percentage with interleukin 6 (all, $P<0.05$). Range of motion attenuated the association of body mass index with interleukin 6 ($P<0.05$) and the association of body fat percentage with C-reactive protein ($P<0.05$). These interactions indicated that higher fitness was associated with a lower increase in inflammation per unit increase of body mass or adiposity. Muscular strength showed a non-significant trend to attenuate the

association of body fat percentage with interleukin 6 (P=0.057) but potentiated the association of body fat percentage with leptin (P<0.05).

Conclusion: These findings suggest that higher levels of cardiorespiratory fitness and range of motion might attenuate the impact of higher body mass and adiposity on inflammation in women with SLE. The role of muscular strength requires further investigation.

Keywords: obesity, systemic low-grade inflammation, cardiorespiratory fitness, range of motion, flexibility, autoimmune diseases, body mass index, body fat percentage (BF%)

1 INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a chronic low-grade inflammatory state that is independent of the disease activity (1). This inflammatory state, along with a higher prevalence of traditional cardiovascular risk factors, seems to contribute to the increased risk of atherosclerosis and premature cardiovascular diseases observed in this population (2, 3).

Higher body mass and adiposity represent have shown to be independent contributors to the systemic low-grade inflammatory state of patients with SLE (4, 5) that worsen the course of SLE (2) and are associated with higher disease activity and damage accrual (5). This is not surprising since adipose tissue is an active endocrine organ that secretes a variety of cytokines such as C-reactive protein (hsCRP), interleukin-6 (IL-6), and leptin, which are, in fact, involved in atherosclerosis not only in the general population (6) but also in patients with systemic autoimmune diseases (2, 7, 8). Among other relevant indicators, body mass index (BMI; a measure of body mass) (9), waist-to-height ratio (a measure of central adiposity) (10) and body fat percentage (a measure of total adiposity) (11), are independent predictors of cardiovascular diseases (2, 12).

Physical fitness is a strong modifiable health marker both in the general population (13) and in patients with rheumatological diseases (14, 15). Several studies have observed that patients with SLE present low levels of cardiorespiratory fitness (16, 17) and muscular strength (18), which are closely related to the functional status, fatigue and the quality of life of the patients (19). As low physical fitness, and particularly low cardiorespiratory fitness is a significant mortality predictor in the general population (20) that seems to be associated with higher age-related arterial stiffness (16) and a worse cardiovascular profile in patients with rheumatic conditions (14), we hypothesized that physical fitness could attenuate the impact of higher body mass and adiposity on inflammation in women with SLE. As fitness is modifiable through exercise interventions, investigating the extent to which fitness influences the association of body mass and adiposity with inflammation in patients with SLE is of clinical interest and may help to provide further insight into the potential role of exercise as an anti-inflammatory therapy in this population.

Therefore, the aim of this study was to assess the role of physical fitness in the association of body mass and adiposity with inflammation in women with SLE.

2 MATERIAL AND METHODS

2.1 Design and Participants

This is a cross-sectional study in which 172 patients with SLE were recruited. Women, with a diagnosis of SLE according to the ACR criteria (21), with a minimum medical follow-up of 1 year at our unit and both treatment and clinical stability (defined as no changes in the systemic lupus erythematosus disease activity index [SLEDAI]) during the previous 6 months of the study were included. Exclusion criteria were not being able to read, understand and/or sign the informed consent; personal history of clinical cardiovascular diseases in the previous year, receiving a biological treatment or requiring doses of prednisone (or equivalent) greater than 10 mg/day during the previous 6 months of the study. Detailed information about the aims and study procedures was given to all the participants, who signed informed consent before being included in the study. The Research Ethics Committee reviewed and approved the study protocol.

2.2 Sample Size Calculation

The sample size was calculated for a clinical trial (NCT03107442) about the effects of aerobic exercise on arterial stiffness (primary outcome), inflammation, fitness (secondary outcomes) and patient-reported outcomes that was published earlier (22, 23). A total of 58 women with SLE were recruited for the trial, although a larger sample (n=77) performed baseline evaluations for cross-sectional analyses. Therefore, the nature of this study can be considered exploratory.

2.3 Procedures

Potentially eligible participants were invited by phone to a personal screening. Included participants attended the Hospital facilities on two different occasions. On day 1, socio-demographic and clinical information were collected, and anthropometric measures and physical fitness tests performed. On day 2 (i.e. between 2 and 4 days after day 1), 8-h fasting blood samples were collected between 8:00 am and 10:00 am.

2.4 Outcome Measures

2.4.1 Body Mass and Adiposity Assessment

Height (cm) was measured using a height gauge, weight (kg) and body fat percentage with a bioimpedance device (InBody R20, Biospace, Seoul, Korea), and BMI was calculated (kg/m^2). Waist

circumference (cm) was measured with an anthropometric tape (Harpenden, Holtain Ltd., Wales, UK), and waist-to-height ratio (waist circumference/height) was calculated.

2.4.2 Blood Samples and Biochemical Analyses

Fasting blood specimens for biochemical and immunological tests were collected and routinely processed by the central laboratory of our hospital.

Regarding inflammatory markers, high-sensitivity CRP and interleukin 6 (IL-6) were measured in serum, which was initially separated by centrifugation and stored at –70°C. CRP levels were assessed by an immunoturbidimetric method using the ARCHITECT cSystems; MULTIGENT CRP Vario assay. Bioserum concentration of IL-6 (pg/mL) was measured by immunoradiometric assay using commercial kits (MILLIPLEX MAP Kit Human High Sensitivity T Cell Magnetic Bead Panel [HSTMAG-28SK], Millipore) following the manufacturer's instructions. Quantitative data were obtained by using the Luminex-200 system (Luminex Corporation, Austin, TX), and data analysis was performed on XPonent 3.1 software. The detections limits for IL-6 were 0.73 pg/mL.

Leptin was measured in serum by the enzyme-linked immunosorbent assay DBC Direct Kit (Diagnostic Biochem. Canada, Canada) with 0.5 ng/ml sensitivity. Intra assay coefficient of variation (CV) and interassay CV of the kit were 5.9 and 3.7%, respectively.

2.4.3 Physical Fitness

Cardiorespiratory fitness was assessed through the 6-minute walk test. The 6-minute walk test measures the maximum distance (in meters) a person is able to walk during six minutes (24). Previously, this test has been commonly used to investigate cardiorespiratory fitness in rheumatic diseases, including patients with SLE (25–27).

Upper-body range of motion, also referred to as flexibility, was assessed with the back-scratch test (24). This test measures how close the hands can be brought together behind the back. The distance between (or overlap of) the middle fingers behind the back was recorded twice for each arm, and the best scores from the right and left arms were averaged.

Muscular strength was assessed with the handgrip strength test as previously described (28). In this test, the subject holds a dynamometer in the hand, with the arm at right angles and the elbow by the side of the body. When ready, the subject squeezes the dynamometer with maximum isometric effort for about 5 seconds. The best result after two trials for each hand is recorded, with at least 30 seconds recovery between each effort, and best score of each hand was used to compute an average of the two hands.

2.4.4 Other Measurements

All participants filled out a socio-demographic and clinical data questionnaire, information that was completed consulting a computerized database of the patients that included age, educational level, occupational status, and SLE data (diagnostic criteria, year of diagnosis, time of evolution, and treatments). Disease activity was assessed through SLEDAI, which takes into account the presence/absence of several clinical and analytical manifestations; the final score ranges from 0 to 105, where a higher score indicates higher degree of disease activity (29). Blood pressure was measured with Mobil-O-Graph® (IEM GmbH, Stolberg, Germany) (30).

2.5 Statistical Analysis

The descriptive characteristics of the study participants are presented as median and interquartile range for continuous variables, and frequencies and percentages for categorical variables, unless otherwise indicated. Two inflammatory markers (i.e. IL-6 and hsCRP) were winsorized due to the presence of 1 and 3 outliers, respectively. The distribution of the main study variables assessed through histograms, Kolmogorov-Smirnov Test, and Q–Q charts, showed a non-normal distribution. Consequently, non-parametric tests were used. Quantile regression models were built, including each inflammatory marker as dependent variable in separate models and the body mass or adiposity indicator, fitness, and the body mass/adiposity×fitness interaction as independent variables. Age, SLEDAI, and corticosteroid intake were entered as potential confounders (31). Whenever the interaction was not significant, it was removed from the models and the results are presented without the interaction term.

The statistical analyses were performed with Stata v.14.0 (Stata Corp LP., Texas, USA. Statistical significance was set at $P<0.05$.

3 RESULTS

The flowchart of the study participants is presented in **Figure 1**. From a total of 172 patients initially invited, 81 refused to participate (41 patients reported living very far from the hospital, 36 were not able to find time to perform the evaluations, and 4 were not interested), 12 patients did not present clinical stability during the previous 6 months at the beginning of the study, and 2 patients had cardiovascular disease during the previous year. A total of 77 women with SLE (mean age 43.2, SD 13.8) fulfilled the inclusion criteria, agreed to participate, and were assessed in two waves (49 women in October 2016 and 28 women in February 2017). Both evaluations were identical, with the exception that 6-minute walk test, IL-6 and CRP were not carried out (n=28) in 2017 wave due to timing issues. One woman did not perform both handgrip strength test and back-scratch test due to a wrist injury.

The descriptive characteristics of the study participants are presented in **Table 1**. The median BMI was 24.0 (IQR 22.5 – 27.3) kg/m^2, the median waist-to-height ratio was 0.48 (IQR 0.47 – 0.55) cm and the median body fat percentage was 34.5 (IQR 28.9 – 40.5). Regarding inflammatory variables, the median hsCRP levels were 1.77 mg/L (IQR 0.7 – 3.12), the median IL-6 levels were 2.16 (IQR 1 – 4.23) pg/mL, and the median leptin levels were 28.8 ng/mL (IQR 19.15 – 52.55). For cardiorespiratory fitness, the median walking distance assessed with the 6-minute walk test was 575 (IQR 525 – 625) meters. For muscular strength, the median handgrip strength was 24.2 (IQR 20.2 – 26.5) kg. For range of

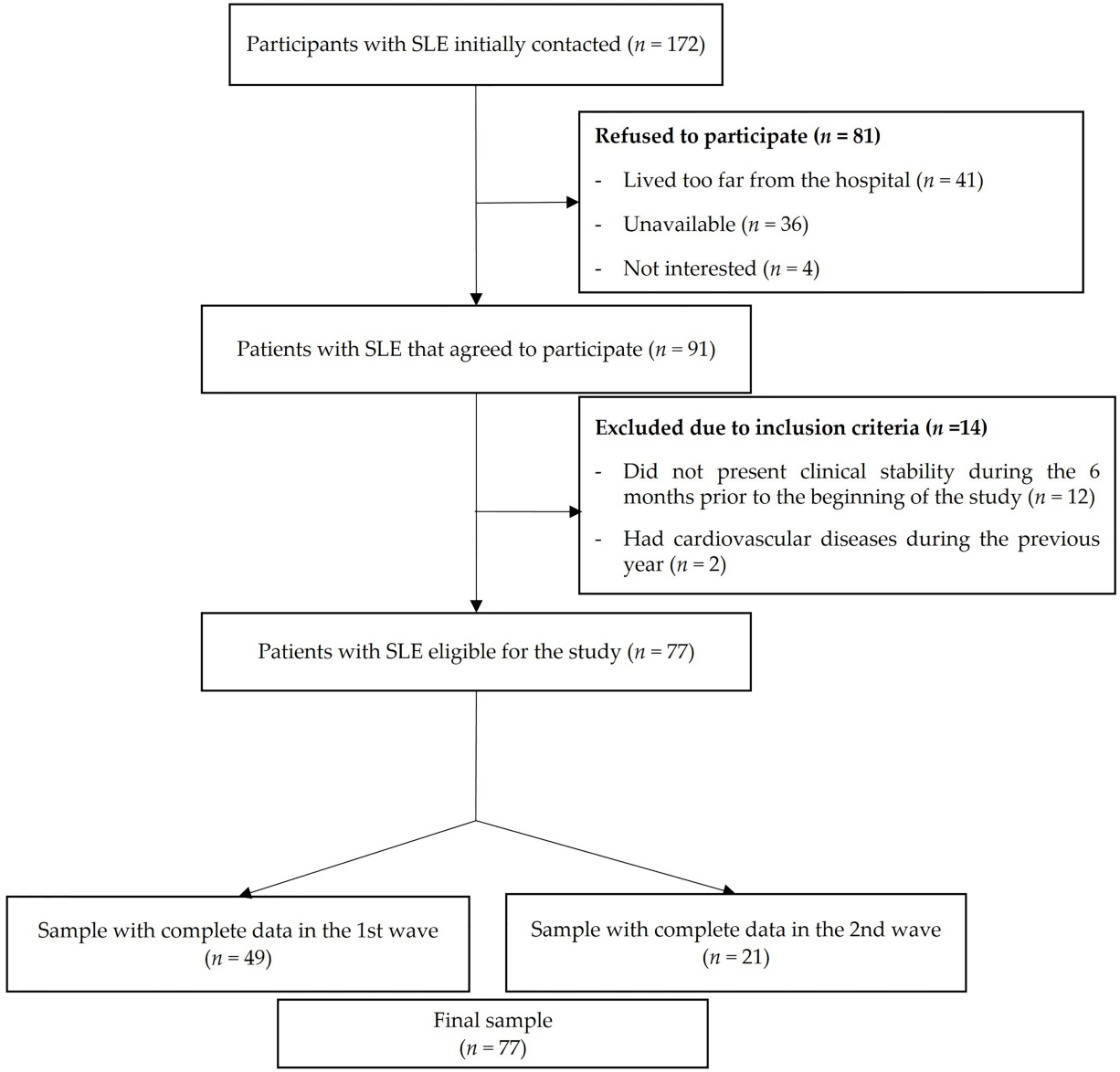

FIGURE 1 | Flow diagram of the study participants throughout the study.

TABLE 1 | Descriptive characteristics of the study participants.

	N	Median	IQR
Age (years)	77	42.7	32.6 – 53.88
Weight (kg)	77	62.7	57.9 – 69.0
Height (cm)	77	159.5	155 – 164
Body Mass Index (kg/m^2)	77	24.0	22.5 – 27.3
Waist-to-Height Ratio (cm)	77	0.48	0.465 – 0.552
Body Fat (%)	77	34.5	28.9 – 40.5
Waist circumference (cm)	77	78.0	73.4 – 87.0
6-Minute Walk Test (meters)	49	575	525 – 625
Back-scratch Test (cm)	76	0.125	-7.5 – 7.25
Dominant back-scratch Test (cm)	76	3.0	-4.5 – 8.25
Non dominant back-scratch Test (cm)	76	-2.75	-11.5 – 6.0
Handgrip Strength (kg)	76	24.2	20.2 – 26.5
Dominant Handgrip Strength (kg)	76	24.05	20.3 – 27.25
Non dominant Handgrip Strength (kg)	75	24.0	20.3 – 27.0
Interleukin 6 (pg/mL)	44	2.16	1.0 – 4.23
hsCRP (mg/L)	77	1.77	0.7 – 3.12
Leptin (ng/mL)	44	28.75	19.15 – 52.55
Dyslipidemia (n, %)	77	14 (18)	
Diabetes (n, %)	77	1 (1)	
Smokers (n, %)	77	45 (58)	
Duration of SLE (years)	77	12	6 – 21
SLEDAI*	77	0.68	1.5
SDI*	77	0.55	1.11
Cumulative Prednisone dose (mg)	77	2547.5	0 – 5056.25
Daily Prednisone dose (mg)	77	2.5	0 – 5
		n (%)	
Prednisone use (%)	77	50 (65)	
Immunosuppressants (%)	77	35 (45)	
Antimalarials (%)	77	69 (89)	
NSAIDs intake (%)	77	0 (0)	

*IQR, Interquartile range; hsCRP, High sensitivity C-reactive protein; SLEDAI, Systemic lupus erythematosus disease activity index; NSAIDs, Nonsteroidal anti-inflammatory drugs; SLE, Systemic lupus erythematosus. SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. All variables show mean and SD values except corticosteroid dose, immunosuppressants, dyslipidemia, diabetes, and smokers. *Mean and standard deviation.*

motion, the average score in the back-scratch test was 0.1 (IQR -7.5 – 7.25) cm.

Tables 2–**4** represent the association of body mass/adiposity and physical fitness (and their interaction) with inflammation after controlling for potential confounders. Regarding cardiorespiratory fitness, there was a significant interaction with BMI on IL-6 ($P<0.05$), indicating that higher cardiorespiratory fitness was associated with a lower increase in IL-6 per each additional BMI unit. For example, participants who were able to walk 380 meters in the 6-minute walk test presented an increase of 1.13 pg/mL in IL-6 for 1 incremental BMI unit, while those who were able to walk 560 meters presented an increase of 0.12 pg/mL in IL-6 for 1 incremental BMI unit. There was also a significant interaction of cardiorespiratory fitness with body fat percentage on IL-6 ($P<0.05$). Range of motion also interacted with BMI on IL-6 ($P<0.05$) so that, for example, a score of -20 cm in the back-scratch test was associated with an increase of 0.80 pg/mL in IL-6 for 1 incremental BMI unit, while a score of +1 cm was associated with an increase of 0.07 pg/mL in IL-6 for 1 incremental BMI unit. Furthermore, there was an interaction with body fat percentage on hsCRP ($P<0.05$). Finally, there was an interaction of muscular strength with body fat percentage on leptin ($P<0.05$). There were also non-significant interactions, such as interaction of range of motion with BMI on hsCRP ($P=0.056$), the interaction of cardiorespiratory fitness with waist-to-height ratio on IL-6 ($P=0.078$), and the interaction of muscular strength with body fat percentage on IL-6 ($P=0.057$). A graphical representation of the main study findings presenting the key interactions of body mass/adiposity with physical fitness on inflammatory markers is displayed in **Figure 2**.

4 DISCUSSION

The main findings of this study suggest that higher levels of physical fitness might attenuate the impact of higher body mass and adiposity on inflammation in women with SLE. Overall, we observed that higher fitness was associated with lower increase of some inflammatory markers for each additional unit of body mass/adiposity. These findings open a window of opportunity to understand the potential of fitness to counteract the effect of higher body mass and adiposity on inflammation in autoimmune diseases, although this needs to be corroborated in future and larger prospective studies.

To the best of our knowledge, this is the first study evaluating how the association of body mass and adiposity with relevant inflammatory markers might be dependent of physical fitness in

TABLE 2 | Quantile regression analyses assessing the interaction of body mass/adiposity with cardiorespiratory fitness on inflammatory markers.

	hsCRP					
	B	**SE**	**95% CI**			**p**
BMI	0.209	0.063	0.082	,	0.336	**0.002**
CRF	0.01	0.005	-0.001	,	0.02	0.065
BMI×CRF						NS*
WHtR	4.661	5.193	-5.811	,	15.133	0.374
CRF	0.005	0.005	-0.006	,	0.016	0.371
WHtR×CRF						NS*
BF%	0.048	0.038	-0.028	,	0.124	0.213
CRF	0.006	0.005	-0.048	,	0.017	0.268
BF%×CRF						NS*
	IL-6					
	B	**SE**	**95% CI**			**p**
BMI	5.504	1.478	2.509	,	8.5	**0.001**
CRF	0.229	0.071	0.085	,	0.372	**0.003**
BMI×CRF	-0.009	0.003	-0.015	,	-0.004	**0.002**
WHtR	142.8	71.72	-2.522	,	288.1	0.054
CRF	0.122	0.069	-0.019	,	0.263	0.088
WHtR×CRF	-0.245	0.135	-0.519	,	0.029	0.078
BF%	1.351	0.537	0.264	,	2.438	**0.016**
CRF	0.076	0.035	0.004	,	0.148	**0.039**
BF%×CRF	-0.002	0.001	-0.004	,	0	**0.026**
	Leptin					
	B	**SE**	**95% CI**			**p**
BMI	3.188	0.568	2.038	,	4.338	**<0.001**
CRF	0.016	0.047	-0.079	,	0.111	0.741
BMI×CRF	NS*					
WHtR	-356.93	295.76	-956.21	,	242.33	0.235
CRF	-0.587	0.283	-1.16	,	-0.013	**0.045**
WHtR×CRF	NS*					
BF%	2.442	0.346	1.742	,	3.142	**<0.001**
CRF	0	0.048	-0.097	,	0.097	0.997
BF%×CRF						NS*

The markers of inflammation were high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6) and leptin. The markers of body mass/adiposity were body mass index (BMI), waist-to-height ratio (WHtR) and body fat percentage (BF%); CRF, cardiorespiratory fitness.

B, unstandardized regression coefficient indicating the expected unit change in the dependent variable for one-unit change in the independent variable; SE, standard error NS, non-significant.

Quantile regression models were built including each inflammatory marker as dependent variable in separate models and the body mass or adiposity indicator, CRF, and the body mass/adiposity×CRF interaction as independent variables. All the analyses were adjusted for age, SLEDAI, and accumulated corticosteroid intake. When the interaction was not significant, the interaction term was removed from the regression model and the results are presented without interaction (i.e., the independent association of body mass/adiposity and CRF with the inflammatory marker).

women with SLE. Although the association of body mass and adiposity with inflammation is well-described both in the general population (32–34) and in SLE (4), research analyzing the potential role of fitness in this association is limited and inconclusive. While Park etal. (35) found an interaction effect of cardiorespiratory fitness with waist circumference on IL-6 in young adults, Bergens, Nilsson and Kadi (36) did not found an interaction effect when considering cardiorespiratory fitness and adiposity with pro and anti-inflammatory biomarkers in a sample of older women.

In this study, higher cardiorespiratory fitness was associated with lower increase in IL-6 per additional unit of either BMI, body fat percentage and, to a lesser extent, of waist-to-height ratio. These findings suggest that the association of body mass and adiposity with inflammation in SLE could depend on the level of cardiorespiratory fitness and that SLE patients with lower cardiorespiratory fitness levels could have higher risk of obesity-related low-grade inflammation. Cardiorespiratory fitness is a relevant health-related parameter that strongly predicts mortality risk in the general population (13) and is associated with a more favorable body composition (37) and higher health-related quality of life in SLE (38). These results extend the potential beneficial roles of cardiorespiratory fitness in women with SLE.

We also observed that higher levels of upper-body range of motion were associated with lower increase in IL-6 per unit of

TABLE 3 | Quantile regression analyses assessing the interaction of body mass/adiposity with range of motion on inflammatory markers.

hsCRP						
	B	**SE**	**95% CI**			**p**
BMI	-0.014	0.067	-0.148	,	0.12	0.835
ROM	0.203	0.135	-0.066	,	0.473	0.137
BMI×ROM	-0.01	0.005	-0.021	,	0.0003	0.056
WHtR	3.359	4.472	-5.561	,	12.281	0.455
ROM	-0.054	0.034	-0.123	,	0.139	0.116
WHtR×ROM						NS*
BF%	-0.02	0.03	-0.08	,	0.04	0.496
ROM	0.222	0.087	0.048	,	0.397	**0.013**
BF%×ROM	-0.008	0.002	-0.013	,	-0.003	**0.001**
IL-6						
	B	**SE**	**95% CI**			**p**
BMI	0.109	0.203	-0.302	,	0.52	0.594
ROM	0.932	0.443	0.035	,	1.829	**0.042**
BMI×ROM	-0.035	0.017	-0.068	,	-0.001	**0.045**
WHtR	1.845	10.924	-20.27	,	23.96	0.867
ROM	0.06	0.074	-0.089	,	0.21	0.417
WHtR ×ROM						NS*
BF%	0.135	0.08	-0.028	,	0.298	0.102
ROM	0.07	0.073	-0.078	,	0.218	0.34
BF%×ROM						NS*
Leptin						
	B	**SE**	**95% CI**			**p**
BMI	3.636	0.558	2.507	,	4.766	<0.001
ROM	0.433	0.323	-0.221	,	1.086	0.188
BMI×ROM						NS*
WHtR	253.53	52.62	147.01	,	360.06	**<0.001**
ROM	0.17	0.4	-0.639	,	0.98	0.673
WHtR×ROM						NS*
BF%	2.374	0.402	1.56	,	3.189	**<0.001**
ROM	-0.064	0.392	-0.859	,	0.73	0.871
BF%×ROM						NS*

The markers of inflammation were high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6) and leptin. The markers of body mass/adiposity were body mass index (BMI), waist-to-height ratio (WHtR) and body fat percentage (BF%); ROM, range of motion (ROM).

B, unstandardized regression coefficient indicating the expected unit change in the dependent variable for one-unit change in the independent variable; SE, standard error; NS, non-significant.

Quantile regression models were built including each inflammatory marker as dependent variable in separate models and the body mass or adiposity indicator, ROM, and the body mass/adiposity×ROM interaction as independent variables. All the analyses were adjusted for age, SLEDAI, and accumulated corticosteroid intake. When the interaction was not significant, the interaction term was removed from the regression model and the results are presented without interaction (i.e., the independent association of body mass/adiposity and ROM with the inflammatory marker).

both BMI, and with lower increase in hsCRP per additional unit of body fat percentage. Evidence regarding the role of range of motion on health in patients with SLE is scarce, although its potential has recently gained attention in other populations (39–41). For instance, greater range of motion has been related with lower cardiometabolic risk (42) and a more favorable cardiovascular profile (43) in perimenopausal women, and with lower risk of metabolic syndrome in older adults (44). Further research on the association of range of motion with health-related parameters in autoimmune diseases is needed. Taken together, these findings suggest that the low-grade inflammatory profile associated with higher body mass and adiposity in SLE could be attenuated in people with higher range of motion, which also needs to be confirmed or contrasted.

Our results corroborated prior research underlining that higher body mass and adiposity is associated with higher leptin concentrations (45, 46). However, we failed to observe that fitness attenuated the association of body mass and adiposity with leptin. In fact, higher muscular strength was surprisingly related to higher increase in leptin per additional unit of body fat percentage. This particular result is difficult to explain and further research is needed to understand the rationale behind

TABLE 4 | Quantile regression analyses assessing the interaction of body mass/adiposity with muscular strength on inflammatory markers.

hsCRP						
	B	**SE**	**95% CI**			**p**
BMI	0.181	0.056	0.069	,	0.293	**0.002**
HGS	-0.05	0.052	-0.154	,	0.054	0.342
BMI×HGS						NS*
WHtR	5.574	4.352	-3.109	,	14.258	0.205
HGS	-0.038	0.062	-0.162	,	0.085	0.539
WHtR×HGS						NS*
BF%	0.054	0.033	-0.011	,	0.121	0.103
HGS	-0.026	0.057	-0.141	,	0.089	0.653
BF%×HGS						NS*
IL-6						
	B	**SE**	**95% CI**			**p**
BMI	0.067	0.187	-0.312	,	0.446	0.723
HGS	-0.013	0.163	-0.342	,	0.317	0.939
BMI×HGS						NS*
WHtR	0.407	9.671	-19.17	,	19.98	0.967
HGS	0.002	0.114	-0.228	,	0.233	0.983
WHtR ×HGS						NS*
BF%	0.571	0.276	0.012	,	1.129	**0.046**
HGS	0.751	0.429	-0.118	,	0.354	0.989
BF%×HGS	-0.021	0.107	-0.043	,	0	0.057
Leptin						
	B	**SE**	**95% CI**			**p**
BMI	3.193	0.526	2.128	,	4.259	**<0.001**
HGS	-0.282	0.564	-1.424	,	0.859	0.619
BMI×HGS						NS*
WHtR	264.53	35.574	192.52	,	336.55	**<0.001**
HGS	0.543	0.5	-0.47	,	1.557	0.285
WHtR×HGS						NS*
BF%	-0.231	1.094	-2.448	,	1.985	0.834
HGS	-3.095	1.735	-6.611	,	0.42	0.083
BF%×HGS	0.106	0.043	0.019	,	0.194	**0.018**

The markers of inflammation were high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6) and leptin. The markers of body mass/adiposity were body mass index (BMI), waist-to-height ratio (WHtR) and body fat percentage (BF%); HGS, handgrip strength (HGS).

B, unstandardized regression coefficient indicating the expected unit change in the dependent variable for one-unit change in the independent variable; SE, standard error NS, non-significant.

Quantile regression models were built including each inflammatory marker as dependent variable in separate models and the body mass or adiposity indicator, HGS, and the body mass/adiposity×HGS interaction as independent variables. All the analyses were adjusted for age, SLEDAI, and accumulated corticosteroid intake. When the interaction was not significant, the interaction term was removed from the regression model and the results are presented without interaction (i.e., the independent association of body mass/adiposity and HGS with the inflammatory marker).

it. In fact, previous research showed that resistance training decreases plasma leptin levels in elderly women (47), which to some extent contrasts this observation.

Physical fitness has previously shown to attenuate the detrimental effect that obesity has on cardiovascular mortality in the general population (48). We might speculate that one of the mechanisms by which fitness attenuates this association is through attenuating the impact of obesity on inflammation. Obesity is present in almost 50% of women with SLE (8) and adipose tissue has the capacity not only to recruit and activate mononuclear cells (49) but also to produce key inflammatory cytokines, such as IL-6, which stimulates the production of CRP and other acute phase proteins by the liver (50). Therefore, the potential role of fitness in this association is of research and clinical relevance and requires further investigation, particularly in autoimmune diseases, because all the components of fitness can be enhanced through exercise programs.

This study has limitations. The cross-sectional design precludes establishment of causal relationships; therefore, we do not know whether increasing fitness through exercise programs will have an impact on the obesity-inflammation relationship. The sample size was relatively small, particularly for the leptin and IL-6 analyses, and thus they need to be confirmed or contrasted in future prospective and experimental research with larger sample sizes.

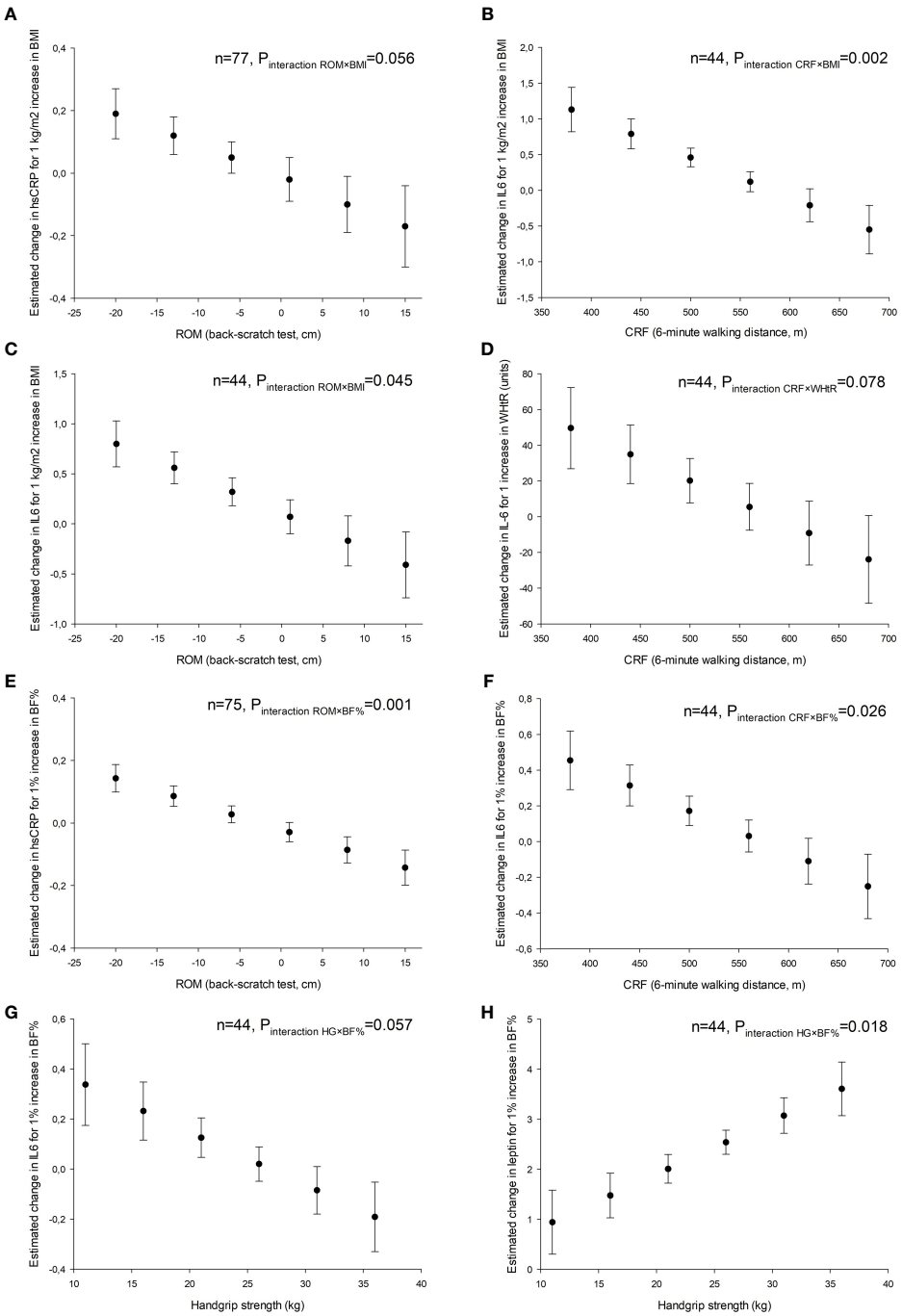

FIGURE 2 | Graphical representation of the interaction of body mass and adiposity with physical fitness on inflammation in women with systemic lupus erythematosus. **(A, C, E)** ROM, upper-body range of motion assessed by the back-scratch test. **(B, D, F)** CRF, cardiorespiratory fitness assessed by the distance walked in the 6-minute walk test. **(G, H)** Muscular strength assessed with handgrip dynamometry. BMI, body mass index; BF%, body fat percentage; WHtR, waist-to-height ratio; hsCRP, high sensitivity C-reactive protein; IL6, interleukin6.

Finally, the study was performed only in women with SLE with low or inactive disease; thus, we do not know whether these results apply to men or to women with higher disease activity.

In conclusion, the findings of the present study suggest that higher levels of physical fitness, particularly cardiorespiratory fitness and range of motion, might attenuate the association of higher body mass and adiposity with inflammation in women with SLE. These results underline a potential mechanism by which fitness might mitigate the effect of obesity on cardiovascular disease, although they must be corroborated in future prospective and experimental research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committee of Granada. The participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, SS-R, JV-H, and AS-M. Data curation, JVH and AS-M. Formal analysis, SS-R, BG-C, and AS-M. Funding acquisition, JVH, JS, and AS-M. Investigation, SS-R, JVH, BG-C, AR-C, RR-F, JM, and AS-M. Methodology, BG-C, JV-H, and AS-M. Project administration, JV-H. Resources, AR-C, RR-F, JM, and AS-M. Supervision JV-H and AS-M. Visualization, AR-C. Writing—Original draft, SS-R, JVH, and AS-M. Writing—Review & editing, SS-R, JV-H, BG-C, AR-C, RR-F, JS, and AS-M. All authors contributed to the article and approved the submitted version.

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Article

Relative Handgrip Strength as Marker of Cardiometabolic Risk in Women with Systemic Lupus Erythematosus

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Abstract: This study aimed to examine the association of relative handgrip strength (rHGS) with cardiometabolic disease risk factors in women with systemic lupus erythematosus (SLE). Methods: Seventy-seven women with SLE (mean age 43.2, SD 13.8) and clinical stability during the previous six months were included. Handgrip strength was assessed with a digital dynamometer and rHGS was defined as absolute handgrip strength (aHGS) divided by body mass index (BMI). We measured blood pressure, markers of lipid and glucose metabolism, inflammation (high sensitivity C-reactive protein [hs-CRP]), arterial stiffness (pulse wave velocity [PWV]), and renal function. A clustered cardiometabolic risk index (z-score) was computed. Results: Pearson's bivariate correlations revealed that higher rHGS was associated with lower systolic blood pressure (SBP), triglycerides, hs-CRP, PWV, and lower clustered cardiometabolic risk (r_{range} = from −0.43 to −0.23; all $p < 0.05$). Multivariable linear regression analyses adjusted for age, disease activity (SLEDAI), and accrual damage (SDI) confirmed these results (all $p < 0.05$) except for triglycerides. Conclusions: The findings suggest that higher rHGS is significantly associated with lower cardiometabolic risk in women with SLE.

Keywords: autoimmune disease; cardiovascular risk; muscle strength; body mass index; metabolism; cardiovascular disease; lupus; risk factors

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease marked with a wide variety of organ system dysfunctions, such as damage to joints, lungs, heart, kidneys, brain, blood vessels or skin [1,2]. The SLE prevalence rates are 20 of every 100,000 women [3], and it affects women at a rate of 10:1 more than men [4]. Due to improved diagnostic methods and treatments [5], mortality in SLE patients continues to improve. However, cardiovascular and metabolic diseases are still one of the biggest causes of mortality in SLE [6], and common risk factors cannot fully explain the increased cardiometabolic risk in this population [7].

Traditional cardiometabolic risk factors including hypertension, diabetes, dyslipidemia, and smoking [8,9], and non-traditional cardiometabolic risk factors including abdominal obesity, insulin resistance, lipid profile, arterial stiffness, renal markers, and high-sensitivity C-reactive protein (hs-CRP; as a marker of inflammation [10,11]) levels [8,12,13] are both expensive and difficult to measure outside a clinical environment [14].

Furthermore, patients with SLE are usually treated with corticosteroids, which at high doses interfere with lipid and glycemic metabolism [15].

Muscular strength is reduced in women with SLE [16,17], and low strength levels are associated with higher fatigue, worse quality of life [18], and higher risk of cardiovascular disease and mortality [19,20]. Handgrip strength, a simple and quick method to assess upper body muscular strength, is inversely associated with coronary heart disease [19,21], inflammation (which appears very often in SLE) [22], and mortality risk [23] in the general population. In women with SLE, handgrip strength is negatively related to obesity [13,17,19], and positively associated with quality of life [24].

Relative handgrip strength (rHGS), defined by the summation of both hands' strength divided by body mass index (BMI), is an easy instrument for measuring relative muscular strength in clinical practice and public health [25] and has been recommended in recent research to address the increased strength due to body mass [25–28]. Handgrip strength and BMI have both been linked to cardiometabolic disease risk in the general population [29–32], although the evidence regarding the association of rHGS with cardiometabolic risk in women is scarce [26]. Since rHGS is cost- and time-efficient, it is of clinical interest to understand the extent to which it might be associated with cardiometabolic risk factors in a population at high risk of cardiometabolic diseases, such as women with SLE.

The primary purpose of the current study was to examine the association of rHGS with biomarkers of cardiometabolic disease risk in women with SLE.

2. Materials and Methods

2.1. Design and Participants

In this cross-sectional study, a total of 172 Caucasian patients with SLE were invited to participate. Inclusion criteria were: (i) women aged between 18 and 60 years with (ii) >4 SLE classification criteria provided by the American College of Rheumatology [33]; (iii) a minimum follow-up of one year at our unit; and (iv) clinical stability (i.e., the absence of changes in the systemic lupus erythematosus disease activity index (SLEDAI) and/or treatment) during the previous 6 months. Exclusion criteria were: (i) not being able to read, understand, and/or sign the informed consent; (ii) having cancer; (iii) history of clinical cardiovascular disease and/or lung disease in the last year; and (iv) receiving doses of biological treatment higher than 10 mg/d of prednisone (or equivalent) in the previous 6 months. All participants received detailed information about the study aims and procedures and signed informed consent before being included in the study.

2.2. Measurement of Relative Handgrip Strength

Muscular strength was assessed through the handgrip strength test. The handgrip strength test [34] was assessed using a digital dynamometer (Model T.K.K.540®; Takei Scientific Instruments Co., Ltd., Niigata, Japan) with a precision to the nearest 0.1 kg. Participants performed the trial in a standing position, with the elbow fully extended and the arm relaxed in a neutral position and were encouraged by the evaluators to exert to their maximal effort during a couple of seconds, alternating between the two hands. Participants performed the test twice with a one-minute break between the two attempts of each hand. The aHGS was summed from the best score of each hand. The rHGS was defined as aHGS divided by BMI [25]. Height (cm) was measured using a stadiometer (SECA 222, Hamburg, Germany) and weight (kg) with a bioimpedance device (InBody R20, Biospace, Seoul, Korea). BMI was calculated as weight (kg) divided by height squared (m^2).

2.3. Measurement of Cardiometabolic Risk Factors

Systolic blood pressure (SBP), diastolic blood pressure (DBP), and resting heart rate were measured using the Mobil-O-Graph® 24 h pulse wave analysis monitor (IEM GmbH, Stolberg, Germany) in a sitting position according to the European Society of Hypertension [35], after 5 min of rest.

Arterial stiffness was indirectly assessed through the pulse wave velocity (PWV) [36]. The test was performed in a sitting position after 5 min of rest, using the Mobil-O-Graph® 24 h pulse wave analysis monitor, the operation of which is based on oscillometry recorded by a blood pressure cuff placed on the brachial artery. This instrument is validated for clinical practice [36]. PWV was obtained from a single measurement. The coefficient of variation (CV) of the Mobil-O-Graph for consecutive PWV analyses is 3.4%, and its intraclass correlation coefficient is 0.98 (0.96–0.99) [37].

Venous fasting blood samples were collected in the morning with heparin as the anticoagulant. Blood was centrifuged at 3500 rpm for 15 min to separate the plasma, which was subsequently removed. Plasma triglycerides, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total cholesterol, glucose, urea, albumin and creatinine concentrations were analyzed enzymatically with an autoanalyzer (Olympus Diagnostic, Hamburg, Germany). Insulin was measured with an enzyme immunoassay kit, and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated [(fasting insulin (μIU/mL) × fasting glucose (mg/dL))/405]. Apolipoproteins A and B, hs-CRP, and glycosylated hemoglobin were determined by immunoturbidimetry (HORIBA-ABX Diagnostics, Japan) with an autoanalyzer (PENTRA-400, HORIBA-ABX Diagnostics, Japan). The albumin-creatinine ratio was measured from a first-morning urine sample. Values above or equal to 30 mg/g in women were considered pathological. The estimated glomerular filtration rate was determined by the modification of diet in renal disease (MDRD) equation [38]: (GFe (MDRD)):

$$175 \times \text{SCr} - 1.154 \times \text{age} - 0.203 \times 0.742$$

SCr: serum creatinine

2.4. Other Measurements

All participants filled out a sociodemographic and clinical data questionnaire to gather information, such as age, disease duration, current medication (including antidiabetics and corticosteroids), and tobacco consumption. The systemic lupus erythematosus disease activity index (SLEDAI) was included to assess disease activity [39], considering the presence or absence of several clinical and analytical manifestations in the preceding 10 days. The final score ranges from 0 to 105, where a higher score indicates a higher degree of disease activity. The degree of tissue damage from the onset of the disease was evaluated by the International Collaborating Clinics/American College of Rheumatology's systemic lupus damage index (SLICC-SDI) [40]. The score ranges from 0 to 40, where a higher score indicates greater damage produced by SLE in the last 6 months.

2.5. Sample Size

The sample size was calculated for a clinical trial evaluating the effects of aerobic exercise on arterial stiffness, inflammation, and fitness, which was published earlier [41]. We recruited 58 participants for that trial, although a larger sample (n = 77) was used to perform baseline evaluations for cross-sectional analyses.

2.6. Statistical Analysis

The descriptive characteristics of the study participants are presented as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables, unless otherwise indicated in Table 1. Due to the presence of outliers, hs-CRP was winsorized. Normality was assessed through histograms, the Kolmogorov–Smirnov Test, and Q–Q plots, with muscular strength and cardiometabolic risk factors showing a normal distribution. Pearson's bivariate correlations were used to explore the raw association between rHGS and cardiometabolic risk factors, and we additionally assessed the crude association of aHGS and BMI with cardiometabolic risk factors. Regression models were built including each cardiometabolic risk factor as dependent variables in separate models. rHGS, age, SLEDAI, and SDI were entered as independent variables

in all models (enter method). Age, SLEDAI, and SDI were entered as covariables due to their potential role as confounders [42]. Menopause, statins or corticosteroids were initially included, but they did not alter the coefficients, and thus they were not included in final models to avoid overfitting [43].

Table 1. Descriptive characteristics of the study participants (n = 77).

	Mean	SD
Age (years)	43.2	1.57
Weight (kg)	65.1	1.27
Height (cm)	160.1	0.77
Body Mass Index (kg/m^2)	25.5	0.51
Absolute Handgrip Strength (kg)	47.2	1.24
Relative Handgrip Strength (kg/BMI)	1.89	0.05
SLEDAI	0.6	0.17
Duration of SLE (years)	13.9	1.15
Systolic Blood Pressure (mmHg)	118	1.29
Diastolic Blood Pressure (mmHg)	76.5	1.18
Pulse Wave Velocity (m/s)	6.47	0.17
Fasting Glucose (mg/dL)	76.3	2.17
Glycosylated Hemoglobin (%)	5.31	
High Density Lipoprotein (mg/dL)	57.8	1.57
Low Density Lipoprotein (mg/dL)	100.7	2.88
Total Cholesterol (mg/dL)	177.5	3.56
Triglycerides (mg/dL)	93.6	4.85
Homeostatic Model Assessment	1.45	0.09
hs-CRP (mg/L)	2.73	0.17
Glomerular Filtration (mL/min/1.73 m^2)	92.6	3.33
Microalbuminuria (%)	28	
Cumulative Prednisone dose (mg)	2875	2677
Daily Prednisone dose (mg)	3.99	0.57
Prednisone use (%)	65	
Immunosuppressants (%)	45	
Antimalarials (%)	89	

For absolute and relative handgrip strength the total sample size was n = 75 due to missing data. SLEDAI: systemic lupus erythematosus disease activity index; hs-CRP: high-sensitivity C-reactive protein.

A clustered cardiometabolic risk index (z-score) [12] was created using the mean of the standardized scores [(value-mean)/standard deviation] for SBP, fasting glucose, triglycerides, HOMA-IR, total cholesterol/HDL-c, and hs-CRP. Statistical significance was set at $p < 0.05$.

3. Results

The flowchart of the study participants is presented in Figure 1. From a total of 172 patients initially invited, 81 refused to participate (41 patients reported living very far from the hospital, 36 were not able to find time to perform the evaluations, and 4 were not interested), 12 patients did not present clinical stability during the previous 6 months to the beginning of the study, and 2 patients had cardiovascular disease during the previous year. A total of 77 women with SLE (mean age 43.2, SD 13.8) complied with the inclusion criteria, agreed to participate, and were assessed in two waves (49 women in October 2016 and 28 women in February 2017). Both evaluations were identical. Two women did not perform the handgrip strength test due to a wrist injury.

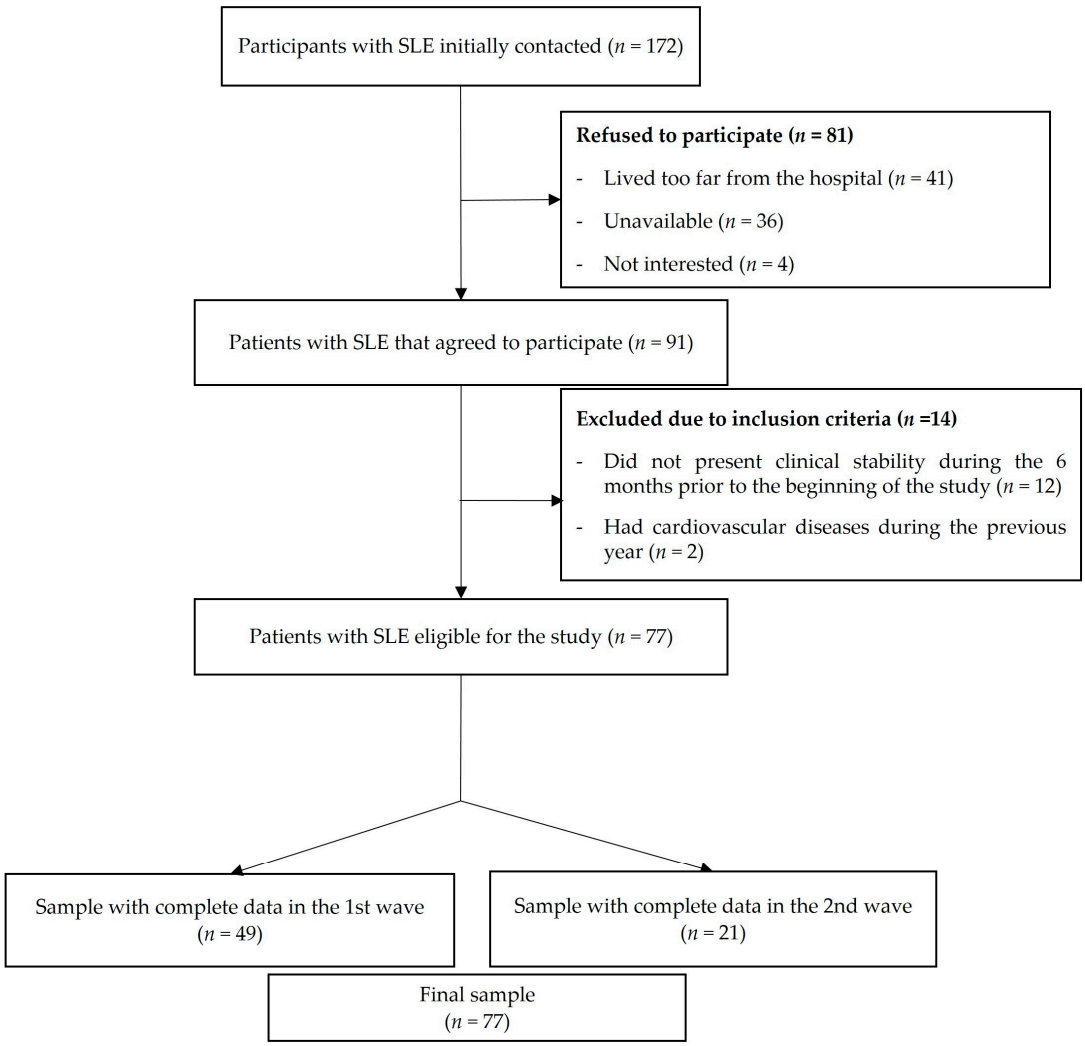

Figure 1. Flow diagram of the inclusion of women with systemic lupus erythematosus (SLE) for the present study.

The descriptive characteristics of the study participants are presented in Table 1. The average BMI was 25.5 (SD 0.51) kg/m^2. The average aHGS was 47.2 (SD 1.24) kg and for rHGS was 1.89 (SD 0.05) units. Regarding cardiometabolic risk variables, the average SBP was 118 (SD 1.29) mmHg, the average DBP was 76.5 (SD 1.18) mmHg, and the average fasting glucose levels were 76.3 (SD 2.17) mg/dL. Average total cholesterol was 177.5 (SD 3.56) mg/dL, the average hs-CRP levels were 2.73 (SD 0.35) mg/L and the average PWV was 6.47 (SD 0.17) m/s.

Table 2 represents the raw association of rHGS, aHGS, and BMI with cardiometabolic risk factors. rHGS was negatively associated with SBP, triglycerides, hs-CRP, PWV, and z-score (r_{range} = from –0.43 to −0.23; all $p < 0.05$). aHGS was negatively associated with triglycerides and PWV (r_{range} = from −0.34 to −0.23; all $p < 0.05$). Finally, BMI was positively associated with SBP, DBP, fasting glucose, HOMA-IR, PWV, and z-score (r_{range} = from 0.23 to 0.44; all $p < 0.05$). A graphic representation of the crude association of rHGS and cardiometabolic risk factors is presented in Figure 2. The linear regression models evaluating the association of rHGS and cardiometabolic risk factors are presented in Table 3. rHGS was inversely associated with SBP (unstandardized coefficient (B) = −6.58; 95% confidence interval (CI) −11.91 to −1.26; $p = 0.016$), hs-CRP (B = −1.67; 95% CI −3.11 to −0.23; $p = 0.023$), PWV (B = −0.34; 95% CI −0.58 to −0.09; $p = 0.007$) and z-score (B = −0.30; 95% CI −0.54 to −0.06; $p = 0.014$). These results were consistent even when statins and corticosteroids were included as covariates.

Table 2. Pearson's bivariate correlations analysis evaluating the raw association between relative handgrip strength, absolute handgrip strength and body mass index with cardiometabolic risk components in women with systemic lupus erythematosus.

	rHGS (n = 75)	aHGS (n = 75)	BMI
SBP	−0.34 **	−0.15	0.40 **
DBP	−0.13	0.01	0.32 **
Fasting Glucose	−0.06	0.08	0.23 *
Glycosylated Hemoglobin	−0.13	−0.07	0.11
HDL	0.04	0.08	0.04
LDL	0.04	0.04	−0.00
Total Cholesterol	0.01	0.03	0.04
Triglycerides	−0.28 *	−0.23 *	0.15
HOMA-IR	−0.15	0.11	0.43 **
hs-CRP	−0.23 *	−0.15	0.17
PWV	−0.43 **	−0.34 **	0.24 *
Glomerular Filtration	0.11	0.08	−0.10
Microalbumin	0.05	−0.04	−0.15
z−score	−0.32 **	−0.09	0.44 **

SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; PWV: pulse wave velocity. Notes: * $p < 0.05$; ** $p < 0.01$.

Table 3. Multivariable linear regression analysis evaluating the association of relative handgrip strength with cardiometabolic risk components in women with systemic lupus erythematosus (n = 75).

	Beta	B	Std Error	95% CI		p	R^2
SBP	−0.29	−6.58	2.67	−11.91	−1.26	**0.016**	0.20
DBP	−0.10	−2.02	2.63	−7.27	3.23	0.445	0.03
Fasting Glucose	−0.09	−3.58	5.00	−13.55	6.39	0.476	0.01
Glycosylated Hemoglobin	−0.02	−0.02	0.11	−0.25	0.20	0.846	0.10
HDL	0.10	2.77	3.56	−4.33	9.89	0.438	0.02
LDL	0.16	8.06	6.08	−4.06	20.20	0.189	0.14
Total Cholesterol	0.15	9.03	7.25	−5.44	23.50	0.218	0.18
Triglycerides	−0.23	−19.41	10.50	−40.35	1.52	0.069	0.12
HOMA-IR	−0.19	−0.34	0.22	−0.79	0.10	0.127	0.03
hs-CRP	−0.29	−1.67	0.72	−3.11	−0.23	**0.023**	0.09
PWV	−0.11	−0.34	0.12	−0.58	−0.09	**0.007**	0.91
Glomerular Filtration	−0.14	−7.68	5.75	−19.16	3.80	0.187	0.37
Microalbumin	−0.11	−0.01	0.11	−0.23	0.21	0.925	0.10
z-score	−0.30	−0.30	0.12	−0.54	−0.06	**0.014**	0.15

B: unstandardized coefficient; SBP: systolic blood pressure DBP: diastolic blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostatic model assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein; PWV: pulse wave velocity. All regression models were adjusted for age, SLEDAI, and SDI. Regression models were built including each cardiometabolic risk factor as dependent variables in separate models. Relative handgrip strength was entered as the independent variable in all models (enter method) where age, SLEDAI, and SDI were entered as confounders in order to adjust the independent variable. Statistically significant associations ($p < 0.05$) are highlighted in bold.

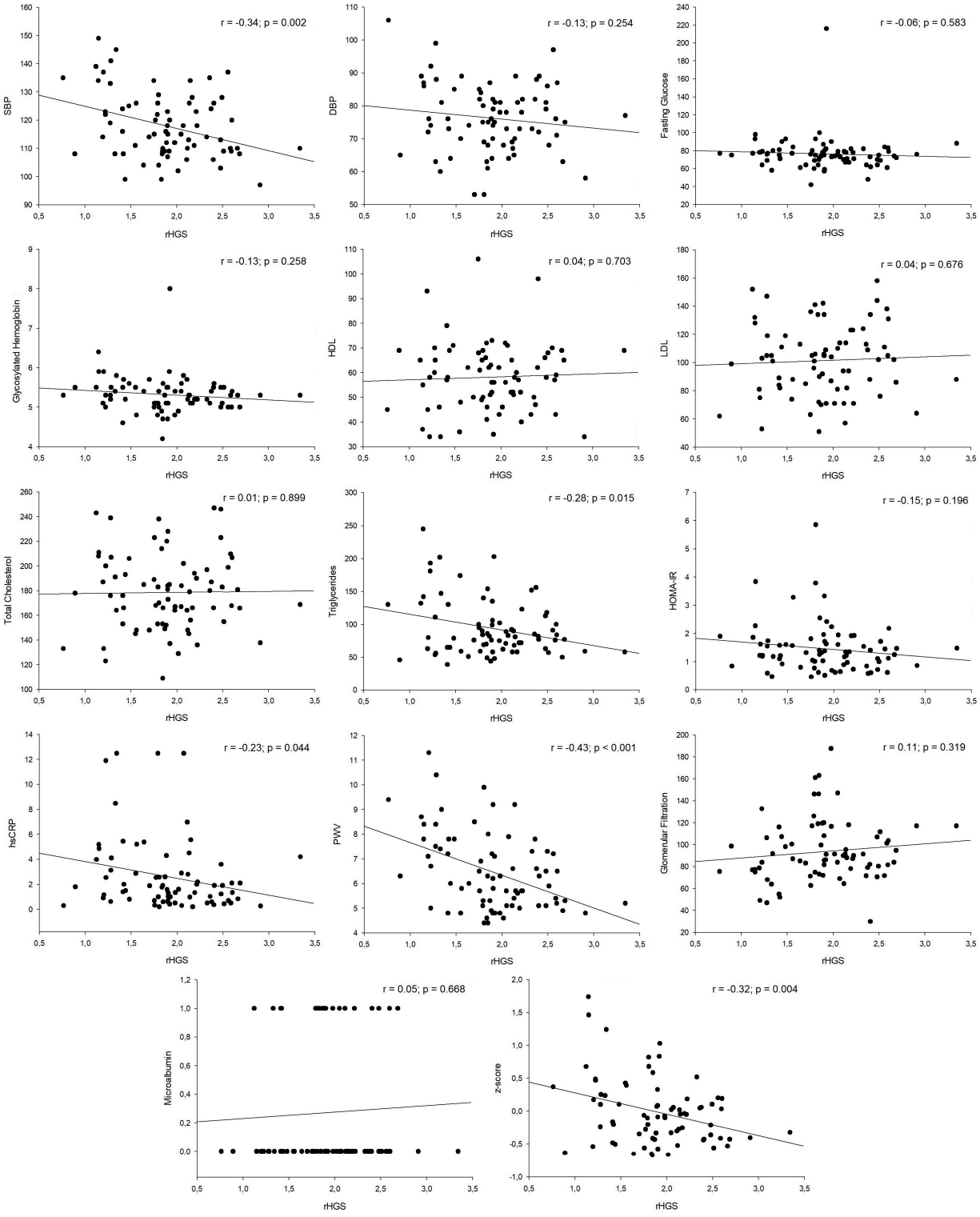

Figure 2. Graphic representation of the crude association of rHGS and cardiometabolic risk factors.

4. Discussion

The main finding of this study is that a higher rHGS was associated with lower SBP, triglycerides, hs-CRP, PWV, and clustered cardiometabolic risk index (z-score) in women with SLE. Furthermore, rHGS could be an alternative to aHGS when evaluating cardiometabolic risk. Our results were consistent despite adjusting for multiple potential confounders such as age, SLEDAI, SDI, statins, menopause, smoking or corticosteroids.

The association of aHGS and cardiometabolic risk has been previously studied in the general population. Lee et al. [27] found that a higher aHGS was associated with lower cardiovascular risk in older Korean adults. Similar findings were described by Leong et al. [21], who found that aHGS was inversely associated with all-cause death in a prospective cohort study with 140,000 men and women. However, Gregorio-Arenas et al. [44] found no association of aHGS with cardiometabolic risk in a sample of 228 perimenopausal women. In line with this, Gubelmann, Vollenweider and Marques-Vidal [45] observed no association between aHGS and cardiovascular risk in healthy adults. Regarding rHGS, previous studies have assessed its association with cardiometabolic risk, although not in rheumatological or autoimmune populations. Choquette et al. found that rHGS could be an indicator of cardiometabolic risk in 1793 community-dwelling men and women [25]. Moreover, Lawman et al. [28] found that higher rHGS was significantly associated with lower SBP, triglycerides, glucose, and higher HDL in both healthy men and women. Finally, Campa et al. [46] demonstrated that resistance training is effective in improving both cardiometabolic risk factors and rHGS in obese women, but improvements regarding rHGS are only achieved if training frequency is high and prolonged over time [47]. Our results are overall in line with these findings derived from other populations and extend current knowledge on potential indicators of cardiometabolic risk in SLE, as well as agreeing with recent literature.

The novel approach of this study is the concurrent analysis of the association of rHGS, aHGS and BMI itself with cardiometabolic risk factors. Although no statistical test can compare the strength of their independent association with the outcomes, these analyses provide the opportunity to determine which of these markers of risk is more worthwhile in clinical practice. Overall, rHGS and BMI were clearly better indicators of cardiometabolic risk than aHGS. However, when comparing BMI with rHGS, the results were less clear. While BMI was associated with markers of insulin resistance and the association with the clustered cardiometabolic risk score was stronger than with rHGS, rHGS was more strongly associated with arterial stiffness and, more importantly, with hs-CRP. As inflammation is a hallmark of autoimmune diseases including SLE, these results should not be taken into consideration when deciding whether to include the assessment of handgrip strength in clinical practice. The relatively low sample size precludes making strong arguments either in favor of or against this, although further research on this topic seems warranted. In practical terms, it is obvious that BMI is the simplest way to obtain a strong marker of cardiometabolic risk. However, it must be considered that adding a handgrip strength assessment takes approximately 2 min (including double assessment of both hands), which, depending on the context, might be feasible or not.

This study has potential limitations. Although other widely used tools to measure CV risk have been proposed, these tools could underestimate CV risk in patients with SLE. Our study provides a greater knowledge of CV risk using individual factors and a cluster score. The cross-sectional design precludes the establishment of causal relationships; therefore, our results must be corroborated in future prospective and experimental research. The sample size was relatively small, and we do not know whether these results apply to men or to women with medium or high disease activity, as only women with mild disease activity were included.

5. Conclusions

The findings suggest that higher rHGS is significantly associated with lower cardiometabolic risk in women with SLE. Although assessing rHGS might add relevant information regarding the potential cardiometabolic risk of SLE patients, BMI alone is a rather good indicator of cardiometabolic risk that might be preferred under time-constrained situations.

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6. CONCLUSIONES

Los resultados de la presente Tesis Doctoral sugieren que:

I. Una menor condición física se asocia con un mayor peso corporal y una composición corporal más desfavorable (es decir, incluidas las medidas de adiposidad total y central) en mujeres con LES. Más específicamente, los componentes de capacidad aeróbica, fuerza muscular y flexibilidad están inversamente asociados con el IMC, índice de masa grasa, perímetro de cintura y el índice cintura-altura. Los niveles relativamente bajos capacidad aeróbica y fuerza muscular, y la alta prevalencia de obesidad observada de manera constante en esta población, subyacen a la necesidad de tomar acciones preventivas para mejorar estos parámetros de salud. Debido a la estrecha y bidireccional conexión entre la condición física y la composición corporal, se necesitan más investigaciones prospectivas y experimentales para dilucidar cómo su interacción afecta la salud cardiovascular de los pacientes con LES.

II. Los niveles más altos de condición física, en particular la capacidad aeróbica y la amplitud de movimiento, podrían atenuar la asociación de una mayor masa corporal y adiposidad con la inflamación en mujeres con LES. Estos resultados subrayan un potencial mecanismo por el cual la condición física podría mitigar el efecto de la obesidad sobre la enfermedad cardiovascular, aunque deben ser corroborados en futuras investigaciones prospectivas y experimentales.

III. Una fuerza de prensión manual relativa más alta se asocia significativamente con un menor riesgo cardiometabólico en mujeres con LES. En particular, una mayor fuerza de prensión manual relativa se asoció con una menor presión arterial sistólica, triglicéridos, proteina C reactiva, velocidad onda-pulso e índice de riesgo cardiometabólico agrupado (puntaje z). Los resultados fueron consistentes a pesar de ajustar por múltiples factores potenciales de confusión como la edad, SLEDAI, SDI, estatinas, menopausia, tabaquismo o corticosteroides. Aunque la evaluación de la fuerza de prensión manual relativa podría agregar información relevante con respecto al riesgo cardiometabólico potencial de los pacientes con LES, el IMC por sí solo es un indicador bastante bueno del riesgo cardiometabólico que podría ser preferido en situaciones de tiempo limitado.

7. CONCLUSIONS

The results of the present Doctoral Thesis suggest that:

I. Lower physical fitness is associated with higher body weight and more unfavorable body composition (i.e., including measures of total and central adiposity) in women with SLE. More specifically, CRF, muscular strength, and flexibility components are inversely associated with BMI, FMI, waist circumference, and waist-to-height ratio. The relatively low levels of CRF and muscular strength, and the high prevalence of obesity consistently observed in this population underlie the need to take preventive actions to improve these health parameters. Due to the tight and bidirectional connection between physical fitness and body composition, further prospective and experimental research is needed to elucidate how their interaction affects the cardiovascular health of patients with SLE.

II. Higher levels of physical fitness, particularly cardiorespiratory fitness and range of motion might attenuate the association of higher body mass and adiposity with inflammation in women with SLE. These results underline a potential mechanism by which fitness might mitigate the effect of obesity on cardiovascular disease, although they must be corroborated in future prospective and experimental research.

III. Higher rHGS is significantly associated with lower cardiometabolic risk in women with SLE. In particular, higher rHGS was associated with lower SBP, triglycerides, hs-CRP, PWV, and clustered cardiometabolic risk index (z-score). The results were consistent despite adjusting for multiple potential confounders such as age, SLEDAI, SDI, statins, menopause, smoking or corticosteroids. Although assessing rHGS might add relevant information regarding the potential cardiometabolic risk of SLE patients, BMI alone is a rather good indicator of cardiometabolic risk that might be preferred under time-constrained situations.

8. FUTURE RESEARCH DIRECTIONS

The results of the first study suggest that lower physical fitness is associated with higher body weight and more unfavorable body composition in women with SLE. Low levels of CRF and muscular strength, and the high prevalence of obesity consistently observed in this population underlie the need to take preventive actions to improve these health parameters. Due to the tight and bidirectional connection between physical fitness and body composition, further prospective and experimental research is needed to elucidate how their interaction affects the cardiovascular health of patients with SLE.

The findings of the second study suggest that higher levels of physical fitness (cardiorespiratory fitness and range of motion) could attenuate the association of higher body mass and adiposity with inflammation in women with SLE. These results underline a potential mechanism by which fitness might mitigate the effect of obesity on cardiovascular disease, although they must be corroborated in future prospective and experimental research.

The findings of third study suggest that higher rHGS is significantly associated with lower cardiometabolic risk in women with SLE.Although assessing rHGS might add relevant information regarding the potential cardiometabolic risk of SLE patients.

Another interesting finding of this thesis is that higher muscular strength was surprisingly related to higher increase in leptin per additional unit of body fat percentage. This particular result is difficult to explain and further research is needed to understand the rationale behind it. In fact, previous research showed that resistance training decreases plasma leptin levels in elderly women, which to some extent contrasts this observation.

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No quiero hacer este apartado muy extenso, pero no me quiero olvidar de esa gente que no está vinculada al mundo académico pero que de una manera u otra me ha ayudado a que esta tesis doctoral sea una realidad. Juanma, Juanjo, Ricardo y Paquito, cuantas noches nos hemos quedado jugando o simplemente hablando, muchas gracias por aguantar mis enfados cuando las cosas no nos salían como debían.

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