

ULTRASOUND EVALUATION OF THE MUSCULAR STRUCTURAL PARAMETERS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Evaluación ecográfica de los parámetros estructurales del músculo en pacientes con lupus eritematoso sistémico

Karen Natalia Nieto Taborda¹
 Germán Enrique Galvis Ruiz²
 Rodolfo Alberto Mantilla Espinosa²
 Claudia Patricia Dávila²
 Diego Javier Martínez Lozano³

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Summary

Objective: To detect muscle structure alterations related to patients diagnosed with Systemic Lupus Erythematosus (SLE) and to describe their relationship with disease activity and time of treatment. **Methods:** patients > 18 years with diagnosis of SLE affiliated to Sanitas Health System and treated during the period from January 2016 to September 2018. The demographic, clinical and serological information were obtained from the patient's medical records, prior to ultrasound examination from the proximal pennate triceps and vastus lateralis muscles. The qualitative and quantitative variables of the muscular architecture were evaluated (muscle thickness, fascicle length, angle of pennation, echogenicity, atrophy and muscular edema). **Results:** 21 patients were included of which 18 were women (85.7%), 19 of them in the age range of 18-50 years (90.4%), 15 patients reported myalgia in the interview (71%) and 7 presented loss of their strength in the MRC scale (33%). The majority of patients received a steroid-based treatment (95%) plus a disease-modifying medication. Ten patients presented a mild to moderate disease activity index (81.2%). Regarding ultrasound measurements, we found a relationship between a pennation angle of less than 11.4 degrees and the presence of atrophy with a value of $p = 0.035$. **Conclusions:** Musculoskeletal ultrasound is a useful non-invasive method for detecting changes in the muscle architecture of the vastus lateralis muscle in patients diagnosed with SLE.

Resumen

Objetivo: Detectar las alteraciones estructurales de los músculos peniformes proximales en pacientes con diagnóstico de lupus eritematoso sistémico (LES) y

¹Resident of Radiology and Diagnostic Imaging, Fundación Universitaria Sanitas, Bogotá, Colombia.

²Radiologist, Department of Radiology, Clínica Colombia, Associate Professor, Fundación Universitaria Sanitas, Bogotá, Colombia.

³Internist specialist in Rheumatology, Clínica Universitaria Colombia.

describir su relación con la actividad de la enfermedad y tiempo de tratamiento. *Métodos:* Pacientes > 18 años con diagnóstico confirmado de LES atendidos durante el periodo comprendido entre enero de 2016 y septiembre de 2018. Se extrajeron de las historias clínicas datos demográficos, clínicos y serológicos previa realización de una ecografía musculoesquelética de los músculos peniformes proximales, tríceps y vasto lateral, para evaluar parámetros cualitativos y cuantitativos de la arquitectura muscular (grosor muscular, longitud del fascículo, ángulo de penación, ecogenicidad, atrofia y edema muscular). *Resultados:* Se incluyeron 21 pacientes de los cuales 18 eran mujeres (85,7 %), 19 de ellos en el rango de 18-50 años de edad (90,4 %), 15 refirieron mialgia en la entrevista (71 %) y 7 mostraron leve pérdida de la fuerza según la escala Medical Research Council (MRC) (33 %). La mayoría de pacientes recibió tratamiento a base de esteroides (95 %) más un medicamento modificador de la enfermedad. Diez pacientes tenían índice de actividad de la enfermedad leve a moderado (81,2 %). En cuanto a las medidas ecográficas, se encontró una relación significativa entre un ángulo de penación menor a 11,4 grados y atrofia muscular con valores de $p = 0,035$. *Conclusiones:* La ecografía musculoesquelética es un método no invasivo útil para la detección de cambios estructurales en la arquitectura muscular del músculo vasto lateral en pacientes con diagnóstico de LES.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, systemic disease. It has an incidence of 4.6 per 100,000 inhabitants with predominance in women and is characterized by autoantibodies that affect multiple organs and systems, of which the musculoskeletal is the most affected during the disease, with a frequency that reaches up to 95-97 % (1-3). Approximately 40 to 48 % of these patients suffer from myalgia in the proximal musculature of the extremities, of which the histopathological diagnosis of inflammatory myopathy by lupus is confirmed in only 5 to 10 % (4).

To identify musculoskeletal involvement in SLE patients, diagnostic images, such as ultrasound and magnetic resonance imaging (MRI), are the non-invasive methods of choice as they show early structural changes ranging from oedema, increased thickness of muscle fibers and liquid collections in the acute phase to fat infiltration, atrophy and chronic calcifications (5,6).

Musculoskeletal ultrasound is considered the most cost-effective, widely available, reliable and highly accurate method for the detection of findings compatible with inflammatory myopathy, with a sensitivity of 82.9 %, specificity of 91.7 % and diagnostic accuracy of 91.3 % (7); it is also useful for the measurement of muscle structural parameters, such as muscle fiber thickness and length, pennation angle, echogenicity and muscle atrophy. These parameters are altered in lupus patients and are considered to be secondary to chronic corticosteroid use; However, so far, the only study carried out by Kaya and collaborators is not conclusive and its results are debated due to methodological weaknesses, such as its limited sample of patients, which do not allow an adequate analysis of the relationship between the alteration of the structural parameters of the muscle and the chronic consumption of drugs in patients with lupus, the recruitment of asymptomatic patients and the lack of ultrasound evaluation of the qualitative parameters of the muscle (8).

The detection of these structural changes of the muscle in patients with lupus is important, due to alterations catalogued as myositis leading to changes in the classification of the activity of their disease, according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (7,9) and to modifications in treatment, which finally affect

the prognosis and quality of life of these patients. The objective of this study was to describe the structural alterations of the proximal penile muscles in patients diagnosed with SLE and their relationship with their disease activity and treatment time.

2. Material and methods

Descriptive cross-sectional study of prospective data, conducted in patients over 18 years of age with a diagnosis confirmed by criteria of the American College of Rheumatology in 1997 (10) for systemic lupus erythematosus (SLE) treated at the institution between January 2016 and September 2018. We excluded patients who were pregnant, patients with incomplete laboratories or with a history of congenital or acquired myopathy, positive history of any inflammatory disease that may cause weakness or myalgia, history of trauma or intramuscular medication administration in the previous 12 weeks. After acceptance by the Research Ethics Committee (REC), participants were selected by reviewing the clinical histories of patients diagnosed with SLE, as well as those recruited from the Rheumatology outpatient clinic who met the inclusion criteria, informed consent was obtained from the selected patients who agreed to participate in the study. The following data were extracted from their clinical histories and supplemented with a pre-scan interview: demographic data (sex, age, weight, height, body mass index), clinical data (myalgia, strength scale According to the Medical Research Council) (11), disease activity index (SLEDAI) (9), disease duration time, current treatment, cumulative dose for chloroquine treatments, hydroxychloroquine and corticoids, duration of treatment and serological data (complement 3, complement 4, double chain DNA antibodies, C-reactive protein).

2.1. Imaging analysis

The ultrasounds were performed uniquely and intercalated by one of the two radiologists with 10 years of experience in musculoskeletal radiology selected as evaluators, who performed the examinations without knowledge of the patients' clinical history. General Electrics, Logic P8, with a linear probe of up to 15 MH were used. The definitions

of the findings were based on the EULAR (European League Against Rheumatism) (12) musculoskeletal ultrasound guidelines, and the measurement technique established by the guidelines and literature was previously socialized with the evaluating radiologists. Ultrasounds were performed on patients in supine position for the evaluation of the vast lateral muscle and in seating for the evaluation of the triceps, both in a state of no muscular contraction; the images were taken at a medium level of the distance between the palpable central point of the greater trochanter and the medial condyle of the femur for the vast lateral and the most prominent area for the triceps. This evaluation lasted approximately 10 to 15 minutes.

The structural parameters measured were: muscle thickness, taken as the perpendicular distance between the superficial and deep aponeurosis of a muscle at the thickest site (Figure 1); length of the muscle fascicle, distance from the origin of the muscle fiber closest to the insertion of the most distal fiber (Figure 2); pennation angle, angle between the orientation of the fascicle and its junction with the axis of the tendon (Figure 3); muscular edema, decrease of the echogenicity and increase of the volume of the muscular fibers; muscular atrophy, diffuse increase in the echogenicity and reduction in the volume of the muscular fibers and muscular echogenicity, measured in 4 degrees according to the capacity of the muscle fibers to generate reflection of the ultrasonic waves (Figure 4, Table 1).

Table 1. Degrees of evaluation of muscular echogenicity

Grade	Characteristic
I	Normal echogenicity of muscle with an intense bone echo
II	Increased echogenicity, but with a distinguishable bone echo
III	Increased muscle echogenicity, but reduced to the ability to identify the adjacent bone echo
IV	Increased echogenicity, which reduces the ability to identify the adjacent bone echo

Source Heckmatt and others (13).

2.2 Statistical analysis

Univariate and bivariate data analysis was performed using STATA® version 14. Wilcoxon's nonparametric tests were used to compare differences between quantitative variables, and Fisher's test was chosen to compare some qualitative parameters; both in small samples of similar variance. Bivariate analysis was performed between the classification of activity according to disease activity index (SLEDAI), (9) and muscle structural parameters. Contingency tables were constructed to evaluate the relationship between myalgia and loss of strength according to the MRC scale (11), as well as for alterations in the MRC scale (11) and a cut-off point of 58 months of disease treatment according to our median treatment in months. The variables of muscular atrophy and pennation angle less than 11.4 degrees were also evaluated in contingency tables, taking their mean in our population as the cut-off point. The findings were expressed by

median and interquartile ranges. The value of $p < 0.05$ was considered statistically significant.

3. Results

21 patients diagnosed with SLE were ultrasonographically evaluated, 18 of them women (85 %) with a female:male ratio of 6:1; the median age was 33 years with a range of ages from 20 to 70 years; of all patients evaluated, 15 (71 %) referred a history of myalgia in the interview with the examiners, of which 7 (33.3 %) showed a discrete loss of strength according to the MRC (Medical Research Council) scale (11). The duration of the disease had a median of 58 months (minimum of 12 and maximum of 408 months) and the duration of the treatment, a median of 36 months with a minimum of 6 months and maximum of 264 months. Contingency tables were used to evaluate the relationship between myalgia and loss of strength according to the MRC scale, as well as for alterations in the MRC scale and a cut-off point of 58 months of disease treatment according to our median treatment in months, but in neither case was a statistically significant difference found. For most patients, treatment was based on corticosteroids (20 patients), exposed or not to different disease-modifying medications, such as hydroxychloroquine (12 patients), mycophenolate mofetil (6 patients), chloroquine (4 patients), methotrexate (4 patients), azathioprine (2 patients), leflunomide (1 patient), and cyclophosphamide (1 patient); Due to treatment variability and lack of specific clinical data on doses administered to most patients, cumulative doses were not calculated, nor were patients classified according to the different medications administered (Table 2).

Table 2. Analysis of demographic variables

Variable	Value (median, proportion)	Ranges (min.-max.)
Age (years)		
Sex (male/female)	34	20-70
Weight (kg)	3 men (14.3 %)/18 women (85.7 %)	
Size (cm)	61.4	42.1-90.7
Body mass index (kg/m ²)	159	145-183
Myalgia	26	17.3-33
MRC Force scale < 5	15 patients (71.4 %)	
Duration of illness (months)	7 (33.3 %)	
Duration of treatment (months)	58	12-408
SLEDAI Index	36	6-264
	No activity 3/13 (23.1 %)	
	Mild to moderate Activity 10/13 (76.9 %)	

Of the 21 patients collected, 13 (61.2 %) had their disease activity index recorded in the clinical history (SLEDAI) (9): 3 patients (23.1 %) showed no disease activity, 10 patients (76.9 %), a mild to moderate activity index and no severe activity. As for serological parameters: 11 patients (55 %) showed consumption of complement 3 with values lower than 0.9 g/l, 7 patients (35 %), consumption of complement 4 with values below 0.1 g/l; antibodies for double-stranded DNA were found in 6 patients (30 %) with titres higher than 1/10 and elevation of quantitative and ultrasensitive C-reactive protein with values higher than 5 mg/l in 7 patients (35 %); all reference parameters were extracted from “Parameters. Reference Manual” used by the laboratories of the Sanitas organization (14) and applied to all patients assigned to the Sanitas health service (Table 3).

Table 3. Analysis of serological variables

Serological variables	n (%)	CI 95 %
C3 Complement	11 (55)	31-73
C4 Complement (0.1 g/l)	7 (35)	13-53
C-reactive protein (> 5 mg/l)	7 (35)	13-53
Autoantibody titers	6 (30)	9-47

The results of the ultrasound evaluation of the quantitative parameters of the proximal triceps and vast lateral muscles are recorded in Table 4, as for the evaluation of the qualitative parameters of the triceps muscle was found alteration in its echogenicity in 9 patients (42 %) specifically, all in grade 2, defined as the increase of the muscular echogenicity, but with a distinguishable bone echo; also was found muscular edema in 1 patient (4.7 %) and muscular atrophy in 4 patients (19 %). Ultrasound evaluation of qualitative parameters in the vast lateral muscle also found alterations: increase in echogenicity in 8 patients (38 %), of which there were 5 with grade 2 (62.5 %) already defined and 3 with grade 3 (37.5 %) defined as the increase in muscle echogenicity that reduces the ability to identify the adjacent bone echo. Muscle edema was also found in 1 patient (4.7 %) and muscle atrophy in 4 (19 %) (Table 4).

Table 4. Analysis of ultrasound variables

Variables	Triceps muscle	95 % CI	Vast lateral muscle	95 % CI
Muscle thickness (mm)	10.8 mm +/- 3.8 mm	9-12.5	13.4 mm +/- 3.6 mm	11.7-15
Fascicle length (mm)	15.2 mm +/- 4.1 mm	13.3-17	23.7 mm +/- 4.4 mm	21.7-25.7
Pennation angle (°)	10.8° +/- 2.3	9.7-11.8	11.4 +/- 3.1 mm	10-12.8
Muscle edema	1 (4.7 %)	4.3-13.9 %	1 (4.7 %)	4.3-13.9 %
Muscular atrophy	4 (19 %)	2-35 %	4 (19 %)	2-35 %
Muscular echogenicity (I-IV)	9/21 (42 %) II (100 %)	21-64 %	8/21 (38 %) II (62.5 %) III (37.5 %)	17.3-59 % 4-71 %

An exploratory analysis was carried out comparing the clinical, serological and ultrasound variables with the level of activity of the disease without finding a significant difference; however, when comparing the variables of muscular atrophy and angle of pennation less than 11.4 degrees, taking as cut-off point their mean in our population, a statistically significant relationship was evidenced between these two variables with a value of p = 0.035.

4. Discussion

This study sought a relationship between the structural changes of proximal penile muscles in patients with SLE and the time of evolution of their disease, as well as the activity of the same. According to the results, the diagnosis of SLE is more frequent in women compared to men, with a statistically significant difference, a finding consistent with that reported in the literature (15,16). Regarding the age of presentation of the disease, it was found that 28.5 % of patients are older than 50 years; however, subtracting the duration of the disease, only 2 of them are classified as late onset lupus (9.5 %), percentage consistent with what is reported in literature (6-18 %) (15,17).

Muscular compromise in patients with lupus has been considered an important manifestation of the disease, ranging from pain (myalgia) to an inflammatory muscle process, the latter evidenced by histopathological study. In the results of this study, myalgia in patients with lupus reaches 71 %, a finding consistent with the literature and described by Zoma (40-80 %) (2); no relationship was found between myalgia and loss of strength in patients, a finding that could be explained because the loss of strength corresponds to muscle fatigue resulting from chronic consumption of corticosteroids rather than a muscular inflammatory process (18-20), data supported by multiple studies showing myositis in only 3-8 % of symptomatic patients with SLE (18-21), data supported by multiple studies showing myositis in only 3-8 % of symptomatic patients with SLE (18-21).

Musculoskeletal ultrasound is now considered a cost-effective method for evaluating quantitative and qualitative structural parameters of muscle, especially proximal muscles if patients are diagnosed with SLE. In this study, a statistically significant relationship was found in the vast lateral muscle between muscular atrophy and a pennation angle of less than 11.4 degrees, taking as a cut point the mean pennation angle in patients, consistent with the mean of angles reported in a systemic review of the literature by Kwan et al (22).

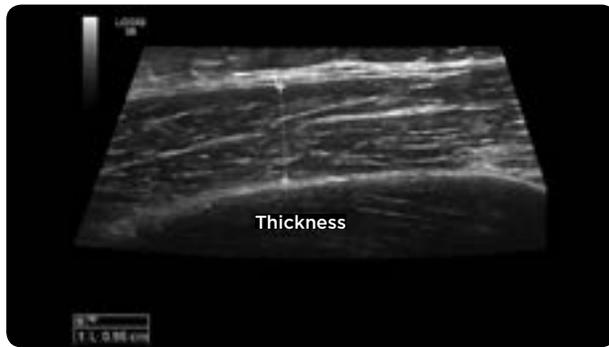


Figure 1. Muscular thickness: perpendicular distance between the superficial and deep aponeurosis of a muscle (taken at the thickest site).



Figure 2. Length of muscle fascicle: the distance from the origin of the nearest muscle fibre to the insertion of the most distal fibre.



Figure 3. Pennation angle: angle between the orientation of the fascicle and its junction with the axis of the tendon.



Figure 4. Muscular echogenicity: property of the muscle to generate reflection of ultrasonic waves, its alteration is evaluated in relation to the bone echo.

This structural change of muscular atrophy suggests a process of chronic evolution, and its relation with the decrease of the angle of pennation has been previously described (23,24), as well as the relation of the angle of pennation and the generation of force in the muscle, bearing in mind that the mechanisms generating force in the muscle are strongly influenced by factors of the muscular architecture, which could explain the weakness in the proximal musculature of these patients (25). Atrophy in patients with SLE has also been described by means of histopathological studies, as mentioned by Jakati and collaborators, who evaluated the findings found in 15 muscle biopsies performed on patients with SLE diagnosis and muscle symptoms, with predominant characteristic of atrophy type II in 13 of 15 patients (86.6%), defined as the type of muscle atrophy in the absence of inflammatory changes (18).

In a previous study carried out by Kaya and collaborators (8) the quantitative structural parameters of the vast lateral and gastrocnemius muscles were evaluated by means of musculoskeletal ultrasound while isokinetic tests were performed at 60 and 180 degrees/s in 31 healthy patients and 31 patients with SLE diagnosis, according to 1982 criteria of the American College of Rheumatology. An increase in muscle thickness and pennation angle of the vast lateral muscle was found in patients with SLE compared to the healthy control group, a finding that can be found in relation to an acute inflammatory process secondary to the consumption of high doses of corticoids during a short period of time, as well as the presence of mixed or superimposed rheumatologic pathologies, this last finding described in patients with pathologies of the connective system. Kaya's study also describes important secondary limitations to the small size of his sample, to the recruitment of asymp-

tomatic patients and to the lack of evaluation of qualitative parameters, especially of muscular echogenicity.

Our study also presents some limitations, such as the number of patients evaluated, the loss of data in clinical histories and the lack of assignment of a diagnosis according to the ICD-10 code by the treating physician; a problem that has also been described in the scenario of different hospitals and that, therefore, requires a prompt solution due to the fact that this limitation and the loss of data not only affects patients but also the progress of clinical studies and research projects (26,27). In addition to the limitations described above and in comparison with the Kaya study, this study carried out a quantitative and qualitative evaluation of the structural parameters of the muscle and the results are consistent with the time of evolution of the disease, especially those that together reflect a process of chronic evolution, in which, although there is no relationship with the time of treatment administration or the duration of the disease, we believe that most of these changes may correspond to a process of chronic consumption of corticosteroids and antimalarials, data supported in the relationship described in the literature of the appearance of myopathy in patients with chronic consumption of these drugs (28-30).

Therefore, future studies with a significant cohort of patients are necessary to confirm the differences found in this study, due to the relevance of the diagnosis of myopathy in patients with lupus, a process that will be easier with the development of automatic methods for measuring muscle structural parameters and tools for recording data that provide quality clinical histories (31,32).

5. Conclusions

The detection of structural changes in muscle architecture in patients with SLE diagnosis is possible through non-invasive diagnostic methods, such as musculoskeletal ultrasound, which becomes a useful tool for monitoring and muscle evaluation in these patients. In this study, a possible relationship was found between muscular atrophy and the reduction of the angle of pennation of less than 11.4 degrees in the vast lateral muscle, a finding that suggests a process of chronic evolution that could correspond to the chronic consumption of corticoids and antimalarials; However, this last relationship was not confirmed, therefore future studies are required with a larger cohort of patients and with complete and sufficient clinical histories to quantify the cumulative dose of these drugs in order to confirm the relationship between muscle atrophy and consumption of corticoids and / or antimalarials

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Correspondence

Germán Enrique Galvis Ruiz
 Coordinador académico posgrado de Radiología e Imágenes
 Diagnósticas
 Clínica Colombia
 Bogotá, Colombia
 gegrmd@gmail.com
 coordinacionradiologiasanitas@gmail.com,

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