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Review

MUSCULOSKELETAL MANIFESTATIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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SUMMARY – Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that most commonly affects the young, working, female population. Musculoskeletal manifestations are one of the most prevalent and presenting features in SLE. Arthralgia, myalgia, non-erosive arthritis, myositis but also tenosynovitis and enthesitis are present in more than 90% of SLE patients. Although not considered very severe SLE manifestations, they significantly affect the patient's quality of life and daily functioning. Clinical assessment of joints, tendons, entheses, and muscles is still the gold diagnostic standard. There are many radiological imaging methods, i.e., classic radiograms, ultrasound, bone scintigraphy, and magnetic resonance imaging that provide morphological information regarding damage and activity of musculoskeletal diseases in SLE and other rheumatic diseases. Musculoskeletal ultrasound stands out as an accessible and affordable method. Recognizing musculoskeletal manifestations may help establish an early diagnosis of SLE and assess disease activity, thus leading to early initiation of treatment and preventing chronic and irreversible changes with a beneficial effect on the quality of life.

Key words: *Systemic lupus erythematosus; Musculoskeletal; Arthritis; Myositis; Ultrasound*

Introduction

Systemic lupus erythematosus (SLE) is a systemic connective tissue disease of complex autoimmune etiology that affects almost every organ system. Not all organ systems are affected with the same intensity. Disease severity can vary from a cosmetic problem to a life-threatening condition[1]. Musculoskeletal symptoms (most commonly arthralgia, arthritis, and myalgia) are among the most common and earliest SLE manifestations. According to various studies, musculoskeletal manifestations occur in 69%-95% of SLE patients, in 60% of patients during relapses, and as the initial symptom in as many as 50% of patients[2,3]. Despite not being the most severe SLE manifestations, the musculoskeletal system involvement significantly affects the patient's quality of life, seriously affects functioning in daily activities, and leads to an incapacity to work[4,5]. It is estimated that almost two-thirds of SLE patients have occasional or permanent inability to perform certain activities at home or work, mostly due to decreased muscle strength and pain caused by activity. In recent studies evaluating subgroups of SLE patients and mortality, the group with arthritis as the main symptom of the disease (in addition to using higher doses of glucocorticoids and immunosuppressants) was also associated with poorer outcomes[6,7]. Musculoskeletal damage, in addition to damage to the cardiovascular system, is also significantly associated with increased mortality in patients with SLE, and it is of great importance to prevent their development on time[6].

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In recent years, thanks to the availability of newer imaging techniques to assess tendon and joint changes, an approach to defining and characterizing these manifestations in SLE is changing. It is essential to accurately assess joint disease to make it easier for physicians to diagnose SLE earlier and open up space for treatment. Ozbek *et al*. showed that despite musculoskeletal symptoms being the most often presenting symptoms in SLE patients, an accurate diagnosis of SLE was made in the first three months of the disease in only 27% of patients who presented those symptoms[8]. In contrast, if the initial presentation was with other symptoms such as butterfly rash or pericarditis, the diagnosis was made much earlier. Delaying diagnosis may have further impact on patient morbidity and mortality[9].

Clinical Presentation

Musculoskeletal symptomatology in SLE includes arthralgia, arthritis, myalgia, and myositis. Joint involvement in SLE is clinically highly heterogeneous, with a variety of phenotypes, from inflammatory arthralgia to severe erosive arthritis[10]. The most common clinical manifestation of joint involvement in SLE is transient or migratory inflammatory arthralgia, usually of the small hand joints, wrist joints, and knees. It may be accompanied by morning stiffness[11]. The use of newer imaging techniques such as musculoskeletal ultrasound (MSUS) in a group of patients with arthralgia revealed a 'hidden' subclinical synovitis in some patients[12].

van Vugt *et al*. defined three main types of arthropathy in SLE depending on the evidence and degree of deformity and the presence or absence of erosive changes on classic radiographs. These are non-deforming, non-erosive arthritis, Jaccoud arthropathy, and rhupus syndrome, a rare coexistence of SLE and rheumatoid arthritis (RA)[13]. Lupus arthritis in most patients has mild and non-deforming course, is usually transient, migratory and, reversible. Typical presentation is symmetric, non-erosive polyarthritis of small hand joints, wrists, and knees with associated morning stiffness. Patients may also have significantly more severe arthropathy that can lead to functional disability. Jaccoud's arthropathy, which affects 3%-13% of patients, is associated with longer disease duration. It is a form of chronic deforming lupus arthritis that occurs due to the ligament and joint capsule weakening and subluxation of the joints, especially hands and feet[2,10]. Deformities can mimic those in RA; however, unlike RA, they can be corrected but often also cause functional limitations and affect the patient's quality of life[2]. The classic definition of Jaccoud's arthropathy includes the absence of bone erosions on classic radiograms. However, using more sensitive imaging methods, the presence of erosions can be verified in about 20% of patients with Jaccoud's arthropathy[14,15]. Predictors of the development of erosive arthritis in SLE are poorly understood to date. Less than 5% of patients can also develop erosive arthritis similar to RA. Patients who meet the classification criteria for both diseases, RA and SLE, have a rare overlap syndrome called rhupus, with a prevalence of 0.01%-2% of SLE patients[16] (Fig. 1).

Synovial effusion in SLE patients is usually transparent, with signs of mild inflammation, low levels of

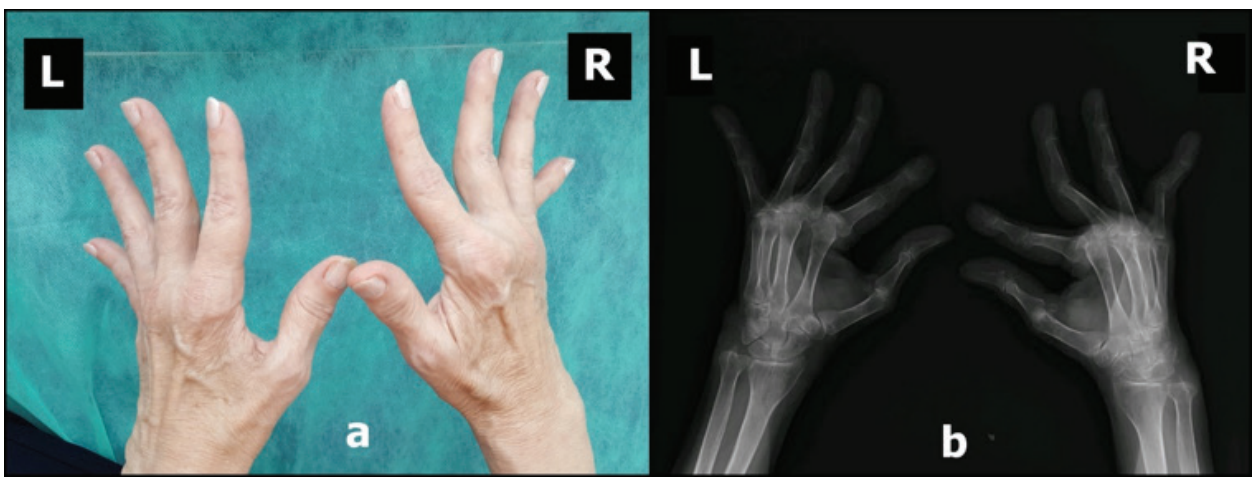

Fig. 1. Hands of the patient with rhupus: (a) typical hand arthritis; (b) x-rays.

protein, and leukocytes, similar to transudate[2]. Antinuclear antibodies (ANA) and lupus erythematosus (LE) cells can be found in the synovial fluid. Histopathologic changes of the synovium are nonspecific, with fibrin-like surface deposits and local or diffuse proliferation of synovial cells[2].

Periarticular structures can also be affected by inflammation, so tendinitis and tenosynovitis are described in patients with SLE, which can sometimes be the only cause of pain and instability in these patients. Thanks to newer diagnostic methods of MSUS and magnetic resonance imaging (MRI), it is evident that tendon and joint capsule involvement is significantly more common than previously thought[14]. Tenosynovitis was found mostly in finger flexor tendons and hand extensor tendons, even in clinically asymptomatic patients[17]. Recent ultrasound studies also showed the involvement of entheses, which have not traditionally been considered the site of inflammation in SLE patients[18]. In a study by Di Matteo *et al*., as many as 67% of patients had at least one pathologic change on lower extremity entheses, primarily changes suggestive of active enthesitis, significantly more than healthy controls[18].

Muscle pain (myalgia) or muscle weakness is frequent in patients with SLE, appearing in more than half of patients. In contrast, true myositis in SLE is relatively rare, with a published prevalence of 4%-16%[19]. Although it is not placed in either the American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) classification criteria, myositis in SLE can sometimes have a severe clinical course. Myositis activity usually correlates with disease activity and survival. To make a proper diagnosis of myositis, besides clinical picture and elevated serum creatine kinase, it is mandatory to have a histopathologic diagnosis. Perivascular and perifascicular infiltrates with mononuclears are found in muscle biopsy in 25% of patients. In addition to the underlying disease, muscle weakness can be drug-induced; both glucocorticoids and antimalarials can cause myopathy[20]. The prevalence of sarcopenia is increased in patients with SLE, which indicates a decrease in muscle mass and function[21]. The clinical importance of sarcopenia is that it affects mortality and causes patient disability.

In addition to musculoskeletal manifestations related to disease activity, there are also manifestations of long-term damage caused by prolonged glucocorticoid therapy, such as osteoporosis, osteoporotic bone fractures, and avascular bone necrosis. Osteoporotic fractures are common in SLE patients, leading to worsening morbidity and mortality and contributing to social and economic burden of the disease, especially hip fracture. The prevalence of osteoporotic fractures in SLE is high, as much as 29.2%[22]. According to the results of a recently published study, patients with SLE have a high risk of developing osteoporotic fractures even when their value of bone mineral density falls in the category of osteopenia[22]. Standard international calculator for assessing the risk of bone fractures, Fracture Risk Assessment Tool (FRAX), also underestimates the risk in SLE patients, even when adjusted for age and glucocorticoid treatment, which prevents timely application of preventive therapy in these patients.

The prevalence of symptomatic avascular necrosis in SLE patients is 9%, and of asymptomatic (verified by MRI) 29%, with femoral head being the most common localization[23]. According to a recently published meta-analysis, high-dose glucocorticoid therapy, pulse therapy, and the maximum and cumulative dose of glucocorticoids are associated with avascular necrosis development. In contrast, glucocorticoid therapy duration does not affect the occurrence of avascular bone necrosis[23].

Tendon ruptures are rare, and in SLE patients, most of them are associated with glucocorticoid therapy and trauma. The Achilles and patellar tendons are most often affected by tendon rupture[24].

Musculoskeletal System in Classification Criteria and Disease Activity Indices

Joint involvement was introduced into the classification criteria in 1971 and was retained in later versions[25,26]. In these classifications, musculoskeletal system involvement was defined as "non-erosive arthritis involving two or more peripheral joints, characterized by pain, swelling or effusion"[25,26]. Newer SLICC classification criteria from 2012 have expanded the definition of joint involvement to include also arthralgia with joint stiffness with a duration of more than 30 minutes[27]. The changes include arthritis, where the term "nonerosive" has been excluded, considering that lupus arthritis may also be an erosive disease. In the latest 2019 EULAR/ACR criteria, the definition of synovitis has not changed[28]. The musculoskeletal system involvement carries six additional points out of 10

total points required for disease classification. Different definitions of joint involvement in various disease classification criteria are shown in Table 1.

Assessment of SLE disease activity is still a challenge for clinicians due to the wide range of manifestations, and adequate assessment of musculoskeletal system activity is no exception. In the validated indices for measuring disease activity (SLEDAI 2K, ECLAM, BILAG), joint involvement is measured differently, but all indices consider clinical assessment of arthritis[30-32]. Their main complaint is the inability to record changes in individual organ systems (including musculoskeletal) over time and to determine the severity of changes, as total points mask this. The only index that differentiates the severity of changes in a particular system is BILAG 2004. However, the study that initially validated the BILAG 2004 index showed that the index reliability in the musculoskeletal system was insufficient and that most differences among physicians were in scoring musculoskeletal system activity, especially the degree of arthritis present[32]. Different definitions of musculoskeletal involvement in different indices to assess disease activity are shown in Table 2.

Table 1. Definitions of joint involvement in different systemic lupus erythematosus classifications criteria

Classification criterion	Definition of joint involvement
ACR 1971	Arthritis without deformity (involving 1 or more peripheral joints)
ACR 1982	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
ACR 1997	Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
SLICC 2012	Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness
EULAR/ACR 2019	Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness

Adopted from:[25,26,28,29]
ACR = American College of Rheumatology; SLICC = Systemic Lupus International Collaborating Clinics; EULAR = European League Against Rheumatism

Table 2. Definitions of musculoskeletal involvement in the most commonly used indices of disease activity

Activity index	Definition of musculoskeletal involvement	Time (days)	Points
BILAG 2004	Arthritis (severe) Arthritis (moderate)/tendonitis/tenosynovitis Arthritis (mild)/arthralgia/myalgia	28	Improved, same, worse, new
SLEDAI 2K	Arthritis ≥2 joints with pain and signs of inflammation (tenderness, swelling, or effusion)	30/10	4
ECLAM	Any of the following: non-erosive arthritis involving at least 2 peripheral joints (wrist, metacarpophalangeal or proximal, interphalangeal joints); new onset or worsening of specific localized pain without objective symptoms in at least two peripheral joints	28	1

Adapted from:[30-32]
BILAG = British Isles Lupus Assessment Group; SLEDAI = Systemic Lupus Erythematosus Disease Activity; ECLAM = European Consensus Lupus Activity Measurement

Diagnostics

Radiological diagnostics in SLE has been evolving in recent years, especially newer imaging methods such as ultrasonography and MRI. Conventional radiological examination of the joints provides data on bone structure while giving very little data on the surrounding soft tissue (Fig. 2). Joint changes in a patient with SLE visible on conventional radiographs include juxta-articular osteopenia, periarticular soft tissue swelling, joint space narrowing, cysts, joint subluxations such as ulnar subluxation of metacarpophalangeal joints, and very rarely erosions[33].

Computed tomography is an excellent method for diagnosing and assessing bone changes. However, a large amount of radiation limits its routine use. Various imaging techniques including Doppler ultrasound, MRI, and scintigraphy can be used to detect increased flow in inflamed synovium tissue[34] (Fig. 3). The choice of an appropriate technique depends on several factors, the pathology we expect, examiner's experience, availability of techniques, and their specific advantages, disadvantages, and contraindications.

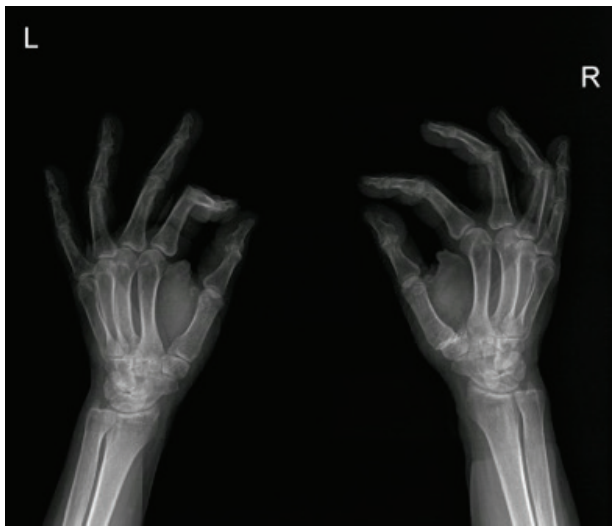

Fig. 2. Imaging technique: x-rays of the hands.

Magnetic resonance imaging is a multiplanar, non-ionizing, noninvasive, high-resolution imaging method. It can show both bone and soft tissue structures and is very sensitive in detecting joint changes, so it has become the reference method in assessing inflammatory joint disease[35]. It is the only imaging method showing bone marrow edema, a feature that is strongly associated with disease activity and progression[36]. MRI allows assessment of active inflammation of peripheral joints detecting effusions, synovitis, bone marrow edema, structural lesions such as joint surface damage, and cortical bone erosions[37]. It also allows assessment of tenosynovitis and enthesopathy, qualitative and quantitative measurements of active inflammation and chronic joint damage, and diagnosis of complications such as fractures and avascular bone necrosis[37]. Early inflammatory features of soft tissues (joints, tendon sheaths, bursae, muscles) that cannot be seen on radiographs or with ultrasound or their ultrasound assessment is limited (such as hip and glenohumeral joints) may be visible on MRI. The possible indications for the use of MRI in inflammatory rheumatic diseases include early diagnosis, confirmation of active inflammation and very early structural changes, monitoring of disease and response to therapy, and identification of disease complications, in particular avascular necrosis. False-positive findings are encoun-

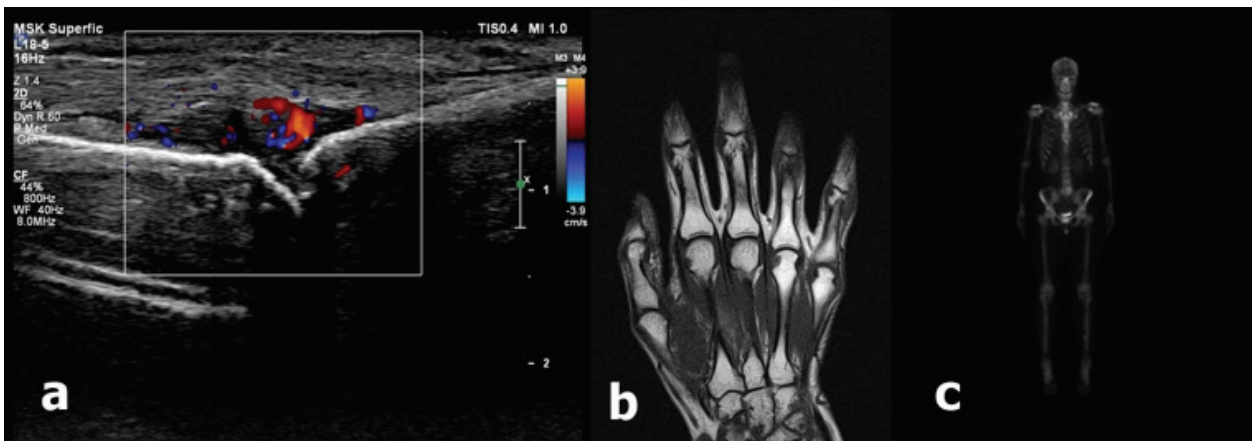

Fig. 3. Imaging techniques: (a) ultrasound + power Doppler; (b) magnetic resonance imaging; (c) scintigraphy.

tered in some cases[38]. MRI is not applicable in many patients due to the long duration of the examination, high cost, limited availability, the need to use contrast to increase the examination specificity, and contraindications in some patients[39].

High-resolution musculoskeletal ultrasound with power Doppler is a useful noninvasive diagnostic technique for assessing and monitoring pathologic changes in joints, tendons, and entheses, especially in assessing joint or tendon synovitis and cartilage and bone damage[40]. Several studies have shown that MSUS with power Doppler and MRI is more sensitive than clinical examination in detecting synovitis, especially in large joints such as the shoulder and knee[41-43]. A study comparing MSUS with MRI and radiographs of the hands and feet of patients with psoriatic arthritis and RA showed a good correlation between MSUS and MRI in the described bone changes and synovitis in RA and psoriatic arthritis patients[42]. Although ultrasound has been proven to be a useful diagnostic method in various inflammatory rheumatic diseases, it is still rarely used in everyday practice to evaluate patients with SLE[44,45]. Existing studies in SLE ultrasound indicate a high prevalence of joint and tendon inflammatory changes in lupus patients, even in patients with very mild symptoms on clinical examination[46]. Recent ultrasound studies have also shown the involvement of entheses, which have not traditionally been considered the site of inflammation in SLE patients[18]. Interestingly, bone erosions were verified by ultrasound in patients with SLE who do not have rhupus syndrome, e.g., in patients with non-deformable non-erosive arthropathy and Jaccuod's arthropathy, which were previously considered non-erosive diseases[46]. Recent MSUS studies in SLE suggest that clinical examination and laboratory testing are not sufficient for early diagnosis and follow-up of musculoskeletal involvement in SLE, considering a surprisingly high prevalence of subclinical synovitis and tendinitis[47,48]. So, the research supports the use of ultrasound as a more sensitive method for diagnosing and assessing the severity and prognosis of joint disease in order to classify patients better and avoid the risk of underestimating subclinical joint inflammation.

Treatment of Musculoskeletal Manifestations in Systemic Lupus Erythematosus

Treatment of musculoskeletal manifestations in SLE depends on the severity and type of manifestations. However, there are not enough high-quality data to guide therapeutic decisions. Controlled clinical trials in SLE have focused chiefly on lupus nephritis, usually without analyzing non-renal manifestations.

Antimalarials (chloroquine/hydroxychloroquine (HCQ)) are the most important drugs for treating SLE and inflammatory arthralgias, but patients with more severe arthritis often need additional medications. The recommended daily dose of HCQ should not exceed 5 mg/kg actual body weight, and periodic eye examination (baseline, after five years and yearly after that, in the absence of retinal findings) should be performed by one of the newer screening techniques recommended by the American Academy of Ophthalmology[49]. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be the drugs of choice for milder forms of arthritis, taken as needed or regularly in daily anti-inflammatory doses several days in a row. NSAIDs should be prescribed carefully, taking into account their known cardiovascular and renal side effects. Glucocorticoids can be administered locally intra-articular in case of mono- or oligoarthritis. Acute worsening of joint symptoms can be treated with short-term administration of oral or parenteral glucocorticoids. Prolonged treatment with high doses of glucocorticoids should be avoided to prevent long-term side effects such as diabetes mellitus, osteoporosis, iatrogenic Cushing's syndrome. More potent drugs should be included for persistent, severe forms of arthritis, especially where antimalarial therapy HCQ is insufficient or inadequate and requiring an unacceptable dose of prednisone.

Disease-modifying anti-rheumatic drugs (DMARDs) should be prescribed and combined with a previously given treatment. The DMARDs are slow-acting drugs, and their effect must be evaluated after two or three months of continuous taking. Methotrexate (MTX) is the drug of choice for severe arthritis, considering its effectiveness in treating rheumatoid arthritis and evidence for using MTX in non-renal SLE based on high-quality studies[50,51]. The experience with leflunomide in SLE arthritis is mainly based on case reports, with only one clinical trial with a small number of patients evaluating its efficacy in extra-renal manifestations (only four patients with arthritis in the leflunomide group)[52]. In cases of treatment failure or intolerance, mycophenolate mofetil (MMF), mycophenolate sodium (MPS), or azathioprine (AZA) may be considered as an alternative treatment in refractory to standard of care cases in non-renal manifestations in SLE, and steroid-sparing drugs[53-55]. A recent random-

ized study comparing MPS and AZA in patients with non-renal SLE, with a high percentage of patients with musculoskeletal lupus, showed that MPS was superior to AZA in achieving long-term clinical remission and preventing relapse in patients with active non-renal lupus disease[56]. Both study agents showed a similar profile of individual organ response. There is little evidence for using AZA in treating SLE arthritis because there are only a few clinical trials in non-renal SLE with a small number of patients included[50,57]. However, AZA may be a good and safe treatment option in pregnant women with SLE needing additional immunosuppressive treatment. There is a lack of evidence for using cyclosporine A and tacrolimus in non-renal SLE, and these drugs are usually taken for severe, organ-threatening disease manifestations but with caution because of frequent adverse events[50].

For the most severe forms of arthritis and persistent active disease, biologic drugs could be considered after weighing up the individual benefit-risk ratio. A B-cell depleting drug belimumab or rituximab may be given after previous therapy failure[58-60]. Belimumab, a monoclonal antibody (mAb) that binds and neutralizes the B cell survival factor, is the first drug approved for SLE in over 50 years after successful clinical trials[61]. According to experts, it should be considered add-on treatment in patients with extra-renal manifestations of moderate severity and dependence on glucocorticoids despite standard treatment[62]. Safety data from extension studies of the BLISS trials up to 7 years suggest a good safety profile[58]. However, due to the high cost, its application is still quite limited in most countries. Rituximab (RTX), a chimeric monoclonal antibody to CD20, showed success in treating RA and antineutrophil cytoplasmic antibody-associated vasculitis. Although case series have shown the success of RTX in treating SLE, randomized clinical trials of RTX in SLE were unsuccessful and failed to reach primary clinical endpoints, so the use of RTX remains off-label[60]. Also, the efficacy of RTX has been reported amongst 136 patients in the French Autoimmunity and Rituximab Registry of patients with both renal and non-renal disease, with improvements in articular, cutaneous, renal, and hematologic manifestations[63].

Tocilizumab (a humanized monoclonal antibody to IL-6 receptor) was administered to 16 patients with SLE in an open-label, phase I clinical study[64]. Clinical improvement was observed predominantly in arthritis, with a decrease in the anti-dsDNA antibody titer. However, dose-dependent neutropenia was observed, and infection unrelated to neutropenia occurred in 11 patients. Tumor necrosis factor-alpha (TNF-α) inhibitors, the drugs used to treat RA, should be avoided[65]. TNF-α inhibitors can be associated with SLE worsening and may sometimes cause drug-induced lupus[66].

Advances in understanding the pathogenesis of the disease have led to several drugs currently under investigation in clinical trials for SLE. Novel therapeutic options already approved in other rheumatic diseases (RA, psoriatic arthritis, ankylosing spondylitis) are now under investigation in SLE. In a phase IIb clinical trial in patients with SLE, baricitinib, a Janus kinase (JAK) 1/2 inhibitor, was significantly more effective in relieving arthritis and skin manifestations than placebo and met the primary endpoint[67]. A multicenter phase II clinical trial is in progress. Evidence in murine lupus has shown that tofacitinib, another JAK inhibitor, can decrease the anti-double-stranded (ds) DNA and proteinuria, remit nephritis, and skin rash[68], but limited clinical data support those findings. Ustekinumab, an antibody against IL-12/ IL-23 (p 40), in a phase IIb clinical trial involving patients with highly active SLE despite standard therapy, showed significantly higher Systemic lupus erythematosus Responder Index (SRI-4) response rate, which was the primary endpoint, at week 24 in the ustekinumab group than in the placebo group. This effect was maintained for up to 1 year, with no significant adverse events detected[69]. An international phase III clinical trial is in progress. A phase III study of anifrolumab, a monoclonal antibody targeting type I interferon receptor, did not meet its primary endpoint despite a promising phase II study[70].

The selection of the drugs to treat musculoskeletal manifestations of SLE should be guided by several factors such as patient gender and age, comorbidities, patient preferences, and a wish to become pregnant. Treatment of severe arthritis in SLE is a clinical challenge, especially in cases with overlap with other autoimmune disorders and chronic regional pain syndrome or coexistence of fibromyalgia. The lack of recommendations and clinical research designed explicitly for articular manifestations makes it challenging to have a standardized treatment protocol for such patients. It is essential to regularly evaluate the patient musculoskeletal manifestations and avoid unnecessary escalation of therapy when the cause of joint pain is other than active inflammation. Rational usage of drugs and mostly minimal doses of glucocorticoids can prevent damage caused by long-term use of such therapy.

Conclusion

Even though arthritis is a frequent SLE manifestation, it has historically received very little attention in research. However, the significant reduction in patient mortality in recent decades has broadened the focus of treatment beyond survival to problems of accumulation of damage and issues related to patient quality of life, of which musculoskeletal involvement plays an important role[4,5]. Assessing the severity of arthritis, optimizing the treatment, and predicting progression to more severe forms continue to challenge rheumatologists taking care of SLE patients.

References

1. Signorini V, Elefante E, Zucchi D, Trentin F, Bortoluzzi A, Tani C. One year in review 2020: systemic lupus erythematosus. Clin Exp Rheumatol. 2020;38(4):592-601. PMID: 32662410.
2. Grossman JM. Lupus arthritis. Best Pract Res Clin Rheumatol. 2009;23(4):495-506. doi: 10.1016/j.berh.2009.04.003
3. Petri M. Hopkins Lupus Cohort: 1999 Update. Rheum Dis Clin. 2000;26(2):199-213. doi: 10.1016/s0889-857x(05)70135-6.
4. Piga M, Congia M, Gabba A, Figus F, Floris A, Mathieu A, *et al*. Musculoskeletal manifestations as determinants of quality of life impairment in patients with systemic lupus erythematosus. Lupus. 2018;27(2):190-8. doi: 10.1177/0961203317716319.
5. Chiara T, Linda C, Andrea DS, Lucrezia R, Sabrina V, Rosaria T, *et al*. Impact of joint involvement on patients reported outcomes in systemic lupus erythematosus. Curr Rheumatol Rev. 2018;14(2):188-92. doi: 10.2174/1573397113666170314110022.
6. Pego-Reigosa JM, Lois-Iglesias A, Rúa-Figueroa Í, Galindo M, Calvo-Alén J, de Uña-Álvarez J, *et al*. Relationship between damage clustering and mortality in systemic lupus erythematosus in early and late stages of the disease: cluster analyses in a large cohort from the Spanish Society of Rheumatology Lupus Registry. Rheumatol Oxf Engl. 2016;55(7):1243-50. doi: 10.1093/rheumatology/kew049.
7. De Marchi G, Quartuccio L, Zuliani F, Bond M, De Vita S. The relevance of cluster analyses to stratify systemic lupus erythematosus: increased mortality with heavier treatment. Clin Exp Rheumatol. 2017;35(5):873-4. PMID: 28516870.
8. Ozbek S, Sert M, Paydas S, Soy M. Delay in the diagnosis of SLE: the importance of arthritis/arthralgia as the initial symptom. Acta Med Okayama. 2003;57(4):187-90. doi: 10.18926/AMO/32807.
9. Kernder A, Richter JG, Fischer-Betz R, Winkler-Rohlfing B, Brinks R, Aringer M, *et al*. Delayed diagnosis adversely affects outcome in systemic lupus erythematosus: cross sectional analysis of the LuLa cohort. Lupus. 2021;30(3):431-8. doi: 10.1177/0961203320983445.
10. Pipili C, Sfritzeri A, Cholongitas E. Deforming arthropathy in systemic lupus erythematosus. Eur J Intern Med. 2008;19(7):482-7. doi: 10.1016/j.ejim.2008.01.017.
11. Ball EMA, Bell AL. Lupus arthritis – do we have a clinically useful classification? Rheumatol Oxf Engl. 2012;51(5):771-9. doi: 10.1093/rheumatology/ker381.
12. Yoon H-S, Kim K-J, Baek I-W, Park Y-J, Kim W-U, Yoon C-H, *et al*. Ultrasonography is useful to detect subclinical synovitis in SLE patients without musculoskeletal involvement before symptoms appear. Clin Rheumatol. 2014;33(3):341-8. doi: 10.1007/s10067-014-2502-9.
13. van Vugt RM, Derksen RH, Kater L, Bijlsma JW. Deforming arthropathy or lupus and rhupus hands in systemic lupus erythematosus. Ann Rheum Dis. 1998;57(9):540-4. doi: 10.1136/ard.57.9.540.
14. Gabba A, Piga M, Vacca A, Porru G, Garau P, Cauli A, *et al*. Joint and tendon involvement in systemic lupus erythematosus: an ultrasound study of hands and wrists in 108 patients. Rheumatology. 2012;51(12):2278-85. doi: 10.1093/rheumatology/kes226.
15. Sá Ribeiro D, Galvão V, Luiz Fernandes J, de Araújo Neto C, D'Almeida F, Santiago M. Magnetic resonance imaging of Jaccoud's arthropathy in systemic lupus erythematosus. Jt Bone Spine Rev Rhum. 2010;77(3):241-5. doi: 10.1016/j.jbspin.2009.10.013.
16. Amezcua-Guerra LM, Márquez-Velasco R, Bojalil R. Erosive arthritis in systemic lupus erythematosus is associated with high serum C-reactive protein and anti-cyclic citrullinated peptide antibodies. Inflamm Res Off J Eur Histamine Res Soc Al. 2008;57(12):555-7. doi: 10.1007/s00011-008-8110-x.
17. Lins CF, Santiago MB. Ultrasound evaluation of joints in systemic lupus erythematosus: a systematic review. Eur Radiol. 2015;25(9):2688-92. doi: 10.1007/s00330-015-3670-y.
18. Di Matteo A, Filippucci E, Cipolletta E, Satulu I, Hurnakova J, Lato V, *et al*. Entheseal involvement in patients with systemic lupus erythematosus: an ultrasound study. Rheumatol Oxf Engl. 2018;57(10):1822-9. doi: 10.1093/rheumatology/key189.
19. Liang Y, Leng R-X, Pan H-F, Ye D-Q. Associated variables of myositis in systemic lupus erythematosus: a cross-sectional study. Med Sci Monit Int Med J Exp Clin Res. 2017;23:2543-9. doi: 10.12659/msm.902016.
20. Kanayama Y, Shiota K, Horiguchi T, Kato N, Ohe A, Inoue T. Correlation between steroid myopathy and serum lactic dehydrogenase in systemic lupus erythematosus. Arch Intern Med. 1981;141(9):1176-9. PMID: 7259378.
21. An HJ, Tizaoui K, Terrazzino S, Cargnin S, Lee KH, Nam SW, *et al*. Sarcopenia in autoimmune and rheumatic diseases: a comprehensive review. Int J Mol Sci. 2020; 7;21(16):5678. doi: 10.3390/ijms21165678.
22. Lai E-L, Huang W-N, Chen H-H, Hsu C-Y, Chen D-Y, Hsieh T-Y, *et al*. Ten-year fracture risk by FRAX and osteoporotic fractures in patients with systemic autoimmune diseases. Lupus. 2019;28(8):945-53. doi: 10.1177/0961203319855122.
23. Nevskaya T, Gamble MP, Pope JE. A meta-analysis of avascular necrosis in systemic lupus erythematosus: prevalence and risk factors. Clin Exp Rheumatol. 2017;35(4):700-10. PMID: 28240590.
24. Potasman I, Bassan HM. Multiple tendon rupture in systemic lupus erythematosus: case report and review of the literature. Ann Rheum Dis. 1984;43(2):347-9. doi: 10.1136/ard.43.2.347.
25. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. doi: 10.1002/art.1780400928.
26. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982;25(11):1271-7. doi: 10.1002/art.1780251101.

27. Urowitz MB, Gladman DD, Ibañez D, Sanchez-Guerrero J, Romero-Diaz J, Gordon C, *et al*. American College of Rheumatology criteria at inception, and accrual over 5 years in the SLICC inception cohort. J Rheumatol. 2014;41(5):875-80. doi: 10.3899/jrheum.130704.
28. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, *et al*. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019;78(9):1151-9. doi: 10.1136/annrheumdis-2018-214819.
29. Petri M, Orbai A-M, Alarcón GS, Gordon C, Merrill JT, Fortin PR, *et al*. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012 Aug;64(8):2677-86. doi: 10.1002/art.34473.
30. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29(2):288-91. PMID: 11838846.
31. Mosca M, Bencivelli W, Vitali C, Carrai P, Neri R, Bombardieri S. The validity of the ECLAM index for the retrospective evaluation of disease activity in systemic lupus erythematosus. Lupus. 2000;9(6):445-50. doi: 10.1191/096120300678828640.
32. Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, *et al*. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatol Oxf Engl. 2005;44(7):902-6. doi: 10.1093/rheumatology/keh624.
33. Goh YP, Naidoo P, Ngian G-S. Imaging of systemic lupus erythematosus. Part II: Gastrointestinal, renal, and musculoskeletal manifestations. Clin Radiol. 2013;68(2):192-202. doi: 10.1016/j.crad.2012.06.109.
34. Grassi W, Filippucci E, Carotti M, Salaffi F. Imaging modalities for identifying the origin of regional musculoskeletal pain. Best Pract Res Clin Rheumatol. 2003;17(1):17-32. doi: 10.1016/s1521-6942(02)00099-2.
35. Sugimoto H, Takeda A, Hyodoh K. Early-stage rheumatoid arthritis: prospective study of the effectiveness of MR imaging for diagnosis. Radiology. 2000;216(2):569-75. doi: 10.1148/radiology.216.2.r00au20569.
36. van Steenbergen HW, van Nies JAB, Huizinga TWJ, Reijnierse M, van der Helm-van Mil AHM. Subclinical inflammation on MRI of hand and foot of anticitrullinated peptide antibody-negative arthralgia patients at risk for rheumatoid arthritis. Arthritis Res Ther. 2014;16(2):R92. doi: 10.1186/ar4536.
37. Sudoł-Szopińska I, Schueller-Weidekamm C, Plagou A, Teh J. Ultrasound in arthritis. Radiol Clin North Am. 2017;55(5):985-96. doi: 10.1016/j.rcl.2017.04.005.
38. Ejbjerg B, Narvestad E, Rostrup E, Szkudlarek M, Jacobsen S, Thomsen HS, *et al*. Magnetic resonance imaging of wrist and finger joints in healthy subjects occasionally shows changes resembling erosions and synovitis as seen in rheumatoid arthritis. Arthritis Rheum. 2004;50(4):1097-106. doi: 10.1002/art.20135.
39. Dill T. Contraindications to magnetic resonance imaging. Heart. 2008;94(7):943-8. doi: 10.1136/hrt.2007.125039.
40. Joshua F, Lassere M, Bruyn GA, Szkudlarek M, Naredo E, Schmidt WA, *et al*. Summary findings of a systematic review of the ultrasound assessment of synovitis. J Rheumatol. 2007;34(4):839-47. PMID: 17407235.
41. Szkudlarek M, Narvestad E, Klarlund M, Court-Payen M, Thomsen HS, Østergaard M. Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. Arthritis Rheum. 2004;50(7):2103-12. doi: 10.1002/art.20333.
42. Wiell C, Szkudlarek M, Hasselquist M, Møller JM, Vestergaard A, Nørregaard J, *et al*. Ultrasonography, magnetic resonance imaging, radiography, and clinical assessment of inflammatory and destructive changes in fingers and toes of patients with psoriatic arthritis. Arthritis Res Ther. 2007;9(6):R119. doi: 10.1186/ar2327.
43. Naredo E, Aguado P, De Miguel E, Uson J, Mayordomo L, Gijon-Baños J, *et al*. Painful shoulder: comparison of physical examination and ultrasonographic findings. Ann Rheum Dis. 2002;61(2):132-6. doi: 10.1136/ard.61.2.132.
44. Riente L, Delle Sedie A, Filippucci E, Iagnocco A, Meenagh G, Grassi W, *et al*. Ultrasound imaging for the rheumatologist IX. Ultrasound imaging in spondyloarthritis. Clin Exp Rheumatol. 2007;25(3):349-53. PMID: 17631728.
45. D'Agostino M-A, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, *et al*. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce. Part 1: Definition and development of a standardised, consensus-based scoring system. RMD Open. 2017;3(1):e000428. doi: 10.1136/rmdopen-2016-000428.
46. Lins CF, Santiago MB. Reply to Letter to the Editor Re: Ultrasound findings on hands and wrists of patients with systemic lupus erythematosus: relationship with physical examination. Ultrasound Med Biol. 2017;43(12):2959-60. doi: 10.1016/j.ultrasmedbio.2017.08.003.
47. Iagnocco A, Ceccarelli F, Rizzo C, Truglia S, Massaro L, Spinelli FR, *et al*. Ultrasound evaluation of hand, wrist and foot joint synovitis in systemic lupus erythematosus. Rheumatology. 2014;53(3):465-72. doi: 10.1093/rheumatology/ket376.
48. Ruano CA, Malheiro R, Oliveira JF, Pinheiro S, Vieira LS, Moraes-Fontes MF. Ultrasound detects subclinical joint inflammation in the hands and wrists of patients with systemic lupus erythematosus without musculoskeletal symptoms. Lupus Sci Med. 2017;4(1):e000184. doi: 10.1136/lupus-2016-000184.
49. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). Ophthalmology. 2016;123(6):1386-94. doi: 10.1016/j.ophtha.2016.01.058.
50. Pego-Reigosa JM, Cobo-Ibáñez T, Calvo-Alén J, Loza-Santamaría E, Rahman A, Muñoz-Fernández S, *et al*. Efficacy and safety of nonbiologic immunosuppressants in the treatment of nonrenal systemic lupus erythematosus: a systematic review. Arthritis Care Res. 2013;65(11):1775-85. doi: 10.1002/acr.22035.
51. Fortin PR, Abrahamowicz M, Ferland D, Lacaille D, Smith CD, Zummer M, *et al*. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2008;59(12):1796-804. doi: 10.1002/art.24068.
52. Tam L-S, Li EK, Wong C-K, Lam CWK, Szeto C-C. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. Lupus. 2004;13(8):601-4. doi: 10.1191/0961203304lu1067sr.
53. Rahman P, Humphrey-Murto S, Gladman DD, Urowitz MB. Efficacy and tolerability of methotrexate in antimalarial resistant lupus arthritis. J Rheumatol. 1998;25(2):243-6. PMID: 9489814.

54. Carneiro JR, Sato EI. Double blind, randomized, placebo controlled clinical trial of methotrexate in systemic lupus erythematosus. J Rheumatol. 1999;26(6):1275-9. PMID: 10381042.
55. Tselios K, Gladman DD, Su J, Urowitz MB. Mycophenolate mofetil in nonrenal manifestations of systemic lupus erythematosus: an observational cohort study. J Rheumatol. 2016;43(3):552-8. doi: 10.3899/jrheum.150779.
56. Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, Vidal X, Mitjavila F, Castro Salomó A, *et al*. Enteric-coated mycophenolate sodium *versus* azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. Ann Rheum Dis. 2017;76(9):1575-82. doi: 10.1136/annrheumdis-2016-210882.
57. Griffiths B, Emery P, Ryan V, Isenberg D, Akil M, Thompson R, *et al*. The BILAG multi-centre open randomized controlled trial comparing ciclosporin *vs* azathioprine in patients with severe SLE. Rheumatol Oxf Engl. 2010;49(4):723-32. doi: 10.1093/rheumatology/kep396.
58. Hahn BH. Belimumab for systemic lupus erythematosus. N Engl J Med. 2013;368(16):1528-35. doi: 10.1056/NEJMct1207259.
59. Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, *et al*. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet Lond Engl. 2011;377(9767):721-31. doi: 10.1016/S0140-6736(10)61354-2.
60. Merrill JT, Neuwelt CM, Wallace DJ, Shanahan JC, Latinis KM, Oates JC, *et al*. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. Arthritis Rheum. 2010;62(1):222-33. doi: 10.1002/art.27233.
61. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, *et al*. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63(12):3918-30. doi: 10.1002/art.30613.
62. Fanouriakis A, Bertsias G. Changing paradigms in the treatment of systemic lupus erythematosus. Lupus Sci Med. 2019;6(1):e000310. doi: 10.1136/lupus-2018-000310.
63. Terrier B, Amoura Z, Ravaud P, Hachulla E, Jouenne R, Combe B, *et al*. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. Arthritis Rheum. 2010;62(8):2458-66. doi: 10.1002/art.27541.
64. Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, *et al*. Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis Rheum. 2010;62(2):542-52. doi: 10.1002/art.27221.
65. Sršen S, Marušić E, Metličić V, Stričević L, Frković M, Jelušić M. How to treat patients after serious adverse effects caused by TNF inhibitors? Acta Clin Croat. 2020;59.(1.):161-5.
66. Soforo E, Baumgartner M, Francis L, Allam F, Phillips PE, Perl A. Induction of systemic lupus erythematosus with tumor necrosis factor blockers. J Rheumatol. 2010;37(1):204-5. doi: 10.3899/jrheum.081312.
67. Wallace DJ, Furie RA, Tanaka Y, Kalunian KC, Mosca M, Petri MA, *et al*. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet. 2018;392(10143):222-31. doi: 10.1016/S0140-6736(18)31363-1.
68. Furumoto Y, Smith CK, Blanco L, Zhao W, Brooks SR, Thacker SG, *et al*. Tofacitinib ameliorates murine lupus and its associated vascular dysfunction. Arthritis Rheumatol. 2017;69(1):148-60. doi: 10.1002/art.39818.
69. van Vollenhoven RF, Hahn BH, Tsokos GC, Lipsky P, Fei K, Gordon RM, *et al*. Maintenance of efficacy and safety of ustekinumab through one year in a phase II multicenter, prospective, randomized, double-blind, placebo-controlled crossover trial of patients with active systemic lupus erythematosus. Arthritis Rheumatol. 2020;72(5):761-8. doi: 10.1002/art.41179.
70. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, *et al*. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382(3):211-21. doi: 10.1056/NEJMoa1912196.

Sažetak

MIŠIĆNO-KOŠTANE MANIFESTACIJE SUSTAVNOG ERITEMSKOG LUPUSA

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Sistemski eritemski lupus (SLE) je multisistemska autoimuna bolest koja većinom zahvaća mladu, radno sposobnu žensku populaciju. Muskuloskeletne manifestacije su među najčešćim, a često i prezentirajućim karakteristikama SLE. Artralgije, mijalgije, ne-erozivni artritis, miozitis, ali također tenosinovitis i entezitis su prisutni u više od 90% bolesnika sa SLE. Iako se ne smatraju vrlo teškim manifestacijama SLE, značajno utječu na kvalitetu života i funkcioniranje u svakodnevnim aktivnostima oboljelih od SLE. Klinička procjena zglobova, tetiva i enteza i dalje je zlatni dijagnostički standard. Postoje brojne radiološke slikovne metode, tj. klasični radiogrami, ultrazvuk, scintigrafija i magnetska rezonanca, koje pružaju morfološke informacije o oštećenjima i aktivnosti muskuloskeletne bolesti u SLE kao i u drugim reumatskim bolestima. Muskuloskeletni ultrazvuk se ističe kao dostupna i cjenovno pristupačna metoda. Prepoznavanje muskuloskeletnih manifestacija može pomoći u postavljanju rane dijagnoze SLE, kao i u procjeni aktivnosti bolesti, što otvara prostor za rano uvođenje odgovarajuće terapije, sprječavajući tako razvoj kroničnih i ireverzibilnih promjena, te time pozitivno djeluje na kvalitetu života oboljelih od SLE.

Ključne riječi: *Sistemski eritemski lupus; Muskuloskeletni; Artritis; Miozitis; Ultrazvuk*