

SHOULDER INVOLVEMENT IN DAILY PRACTICE – ULTRASONOGRAPHIC APPROACH

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Rezumat

Patologia umărului, de natură inflamatorie sau degenerativă este frecvent întâlnită în practica reumatologică. Pe fondul unei lipse de specificitate a simptomatologiei clinice, metodele imagistice au devenit un element indispensabil unui diagnostic de certitudine.

Scopul studiului a constat în evaluarea prezenței diferitelor modificări patologice la pacienții cu simptomatologie la nivelul umărului și în identificarea unei eventuale interrelații cu afecțiunea de bază și factorii de risc asociați.

Material și metodă. Am efectuat un studiu retrospectiv ce a inclus 40 de pacienți evaluați în ultimele 6 luni, pentru omalgie, în clinica de reumatologie a Spitalului Clinic Județean de Urgență Craiova. Toți pacienții au fost evaluați prin ultrasonografie musculoscheletală, conform recomandărilor EULAR.

Rezultate. Leziunile manșonului rotatorilor, cel mai frecvent asociate patologiei non-traumatice, au fost identificate în procente similare cu cele descrise în literatura de specialitate. În plus, anumite comorbidități, în special diabetul zaharat, au fost asociate mai frecvent cu modificări degenerative sau leziuni tendinoase.

Concluzii. Deși a inclus un număr relativ redus de subiecți, studiul nostru relevă date similare altor publicații și subliniază necesitatea unui algoritm de management al patologiei umărului, ce trebuie să includă obligatoriu și evaluarea ultrasonografică, în vederea diagnosticului de certitudine, aplicării terapiei individualizate și îmbunătățirii calității vieții pacienților.



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Cuvinte cheie: patologia umărului, ultrasonografie, comorbidități, tendon suprasinos, tendon suprascapular, bursa subacromio-subclaviculară.

Abstract

Shoulder involvement is one of the most frequent findings in rheumatology and many of the rheumatic diseases can determine inflammatory lesions, as well as degenerative ones. Due to the non-specificity of clinical symptoms, imaging methods are emerging into the daily practice in order to establish an accurate diagnosis.

Objectives. *The aim of the study was to determine the presence of different pathologic changes in patients with shoulder pain, depending on the concurrent disease and associated risk factors.*

Material and methods. *We included in our retrospective study 40 consecutive patients that presented with shoulder pain, during the past 6 months, in the Department of Rheumatology. All those patients underwent ultrasound evaluation according to EULAR Guidelines for musculoskeletal Ultrasound in Rheumatology.*

Results. *Rotator cuff lesions, which most commonly underlie non traumatic pain in adults, were detected with frequencies similar to the ones described by the literature. It seems that comorbidities, as the presence of diabetes, may influence tendon degeneration or rupture.*

Conclusions. *Although it included a relatively low number of subjects, our paper reveals data similar to the ones previously published and underlines the necessity of applying an algorithm for managing shoulder pathology, that should mandatory include ultrasonography examination, in order to obtain an accurate diagnosis and individualize each patient's therapeutic approach and improve their life quality.*

Keywords: *shoulder pathology, ultrasonography, comorbidities, supraspinatus tendon, subscapularis tendon, subacromial - subdeltoid bursa.*

Background

Shoulder involvement is one of the most frequent findings in rheumatology and many of the rheumatic diseases can determine inflammatory lesions, as well as degenerative ones⁽¹⁻⁵⁾. Inflammatory conditions are associated to tendons lesions or distension of joint capsule, bursitis, and consecutive changes in bone profile^(1, 2). On the other hand, shoulder pain, a common symptom in general population, can be found associated to mechanical trauma, with or without tears, or crystal deposits inside the tendons, as well as associated to osteoarthritis. Due to the non-specificity of clinical symptoms, along with the location of the pain that cannot always be attributed to certain lesions, imaging methods are emerging as mandatory in order to establish an accurate diagnosis^(1, 6, 7). Conventional radiography, extensively used for many decades, shows only late, major changes, into the bone structure or crystal deposits, without identifying early changes, such as synovitis, bursitis or even tendon tears. Arthrography or magnetic resonance imaging (MRI) represent techniques that offer valuable and precise information but are not always available and may be difficult to be approached in daily practice^(7, 8). The last progresses in ultrasound examination (US), with protocols specific to each anatomic area, has made this method the best diagnostic option for the shoulder involvement, being a reliable, low cost, and easily reproducible technique⁽⁸⁻¹⁰⁾.

Experimental part

The aim of the study was to determine the presence of different pathologic changes in patients with shoulder pain, depending on

the concurrent disease and associated risk factors.

Material and methods

We performed a retrospective, transversal study, including 40 consecutive patients with shoulder involvement evaluated in the Department of Rheumatology, Emergency County Hospital of Craiova, Romania, during the past 6 months.

The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova. All patients provided their written informed consent, after receiving a standard form, which mentioned that the results would be used for research purposes.

The exclusion criteria were recent severe trauma +/- fracture of shoulder bones. In the same manner, patients with comorbidities which might influence shoulder symptomatology, like cervical spine involvement, neuropathy of any cause or cardiac involvement that could mimic shoulder pain, were also excluded. All patients underwent clinical, biologic and ultrasonographic assessment.

Ultrasonography

The examination was performed by an experienced sonographer, blinded to the history, clinical findings, and biology of each patient, using an Esaote MyLab 25 machine, equipped with a high frequency linear probe (10-18MHz). The US was performed with the patients sitting and the examination of the different structures included bilateral, longitudinal, and transverse planes, followed by dynamic evaluation, according to EULAR Guidelines for musculoskeletal Ultrasound in Rheumatology (table 1)⁽¹¹⁾.



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We used as landmarks, in order to facilitate probe positioning, the bicipital groove, the clavicle, the acromion and the coracoid process^(5,11-14).

The US examination searched for pathological findings in the tendons of the shoulder, such as the long head of the biceps (LHB), subscapularis (SSC), supraspinatus (SSP), infraspinatus (ISP) and teres minor (TM), but in the subacromial - subdeltoid bursa (SASD) and anterior/ posterior glenohumeral (GH) joint, also. LHB and SSC tendons were examined on the anterior aspect of the shoulder, in the seating position, with the arm held in neutral position, the elbow flexed to 90°, and the forearm in a supinated position on the thigh.

For the LHB tendon we searched for tendinitis or tenosynovitis, defined according to OMERACT definitions and for tendon rupture. SSP tendons were examined with slight laterally moved transducer, with the patient's arm behind the back and the hand on the back pocket (modified Crass position), with shoulder in internal rotation, both on long and short axis of the tendons.

These positions allowed us to visualize the maximal length of those tendons. For the examination of ISP tendon and the posterior GH joint, patients were asked to sit and to put the hand on their abdomen, with the arm in neutral position and to make moves of external/internal rotation, for the dynamic

evaluation. The joint effusion in the GHJ was noted when distance between joint capsule and inferior margin of ISP tendon was above 2 mm. SASD bursa is located deep to the deltoid muscle and extends beyond the attachment of the rotator cuff on the lateral, overlies the bicipital groove in the anterior part and the rotator cuff in the back, exceeding the margin of acromioclavicular joint on the medial side. SASD bursitis was noted, when the distension of the bursa was bigger than 2 mm^(11,15).

Statistical analysis was performed using GraphPad Prism 5.5. Results are presented as mean $\pm$ SD and data were analyzed using t-test and One-way ANOVA for comparing groups, and Pearson/Spearman's coefficient for evaluating correlations. We considered a level of $p < 0.05$ statistically significant.

Results

We included 40 consecutive patients, with a mean age of 59.42 ± 7.51 years. Their main characteristics are presented in table 2.

Twenty-seven patients had an inflammatory main disease, such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), crystal related arthropathy (CA) and 13 patients had degenerative involvement of the shoulder, main diagnosis being osteoarthritis (OA) or just presented for shoulder pain secondary to minor trauma (figure 1).

Aspect	Planes
Anterior	transverse scan in neutral position
	transverse scan in maximal internal rotation
	longitudinal scan
	longitudinal scan in maximal internal rotation
Lateral	longitudinal scan in neutral position
	longitudinal scan in maximal internal rotation
Posterior	transverse scan.
Axillary	longitudinal scan with raised arm
Acromioclavicular	joint scan

Table 1. US examination of the shoulder

Age (years)	59.42 $\pm$ 7.51
Sex (male/female)	32/8
Duration of shoulder pain (months)	10.9 $\pm$ 15
Involved site (N; %)	
Left	10
Right	14
Both	16
Type of disease (N; %)	
Inflammatory	15; 37.5
Non-inflammatory	25; 62.25
ESR (mm/h)	26.6 $\pm$ 24.66
CRP (mg/dl)	12.2 $\pm$ 3.96
Diabetes (N;%)	
Yes	12; 30
No	28; 70
Cholesterol (mg/dl)	212 $\pm$ 49.62
HDL cholesterol (mg/dl)	61.2 $\pm$ 45.2
LDL cholesterol (mg/dl)	172.3 $\pm$ 76.3
Triglycerides (mg/dl)	278 $\pm$ 59.23

Table 2. Baseline characteristics of the patients



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Shoulder involvement, defined as any of the shoulder structures pathology, according to EULAR standard procedures, was found for most of our patients (38/40). The most frequent US finding was SASD bursitis, for 19 out of 40 patients (47.5%), followed by SSP tendon involvement, in 15 out of 40 patients (33.3%) and LHB tendinitis for 11 patients (27.5%) (figure 2, 3, 4, 5, 6, table 2).

Between the 19 patients with SASD bursitis, most of them had inflammatory conditions (16) with the most frequent diagnosis RA (11 patients; 52.38%), followed by traumatic involvement of the shoulder (6 patients; 28.57%) (figure 7). In the same way, SSP tendon lesion was mainly found in RA patients (8; 57.14%), followed by traumatic involvement of the shoulder (4; 28.6%) (figure 8). Two of the patients with SSP rupture were previously treated with quinolones, which could explain tendon lesions (figure 5, 6).

Calcifications were found mainly in non-inflammatory diseases, being the second finding in this type of patients, after tendon lesions (figure 3).

Evaluating the influence of associated conditions, we identified that of the 12 patients with diabetes, 8 (66.66%) had calcifications either on the SSP, SSC, or both, compared to 11 (39.28%) of the ones without this associated pathology ($p=0.089$). Another important observation is the direct

relationship between the presence of dyslipidemia and rotator cuff lesions, with a significant correlation both for cholesterol levels ($r=0.525$, $p=0.0007$) and triglycerides ($r=0.327$, $p=0.042$). The mean values of dyslipidemia parameters are presented in table 2.

Discussions

Shoulder pain is a frequent symptom in adult primary care and one of the most important complaints in general population addressing to rheumatologists. Several disorders, of degenerative, post-traumatic and inflammatory types constitute common causes of shoulder pain. Compared to clinical examination and radiographic assessment, high resolution US is a fast, reproducible, and non-invasive diagnostic technique that enables the clinician an accurate diagnosis, identifying all the articular and periarticular lesions, that can involve several sites simultaneously⁽¹⁻⁵⁾.

Rotator cuff lesions, which most commonly underlie non traumatic pain in general population, were detected with frequencies similar to the ones described by the literature. It has been stated that patient and pathology specific risk factors contribute to rotator cuff disorders and although there were several studies focusing on this pathology, the pathogenesis seems to be

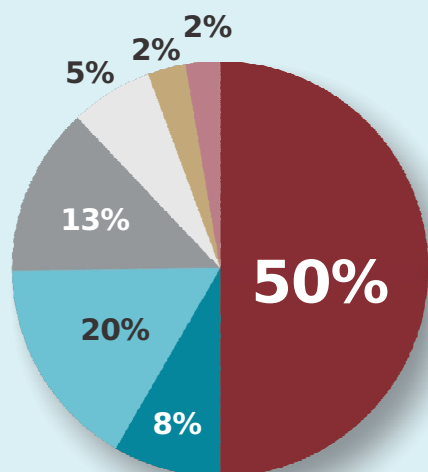


Figure 1. Main diagnosis of the patients
PsA-psoriatic arthritis; PM-polymyalgia
rheumatica; RA-rheumatoid arthritis, CA-
crystal related arthritis; PS-non specific
periarticular involvement; OA-
osteoarthritis

	N
LHB	
Tendinitis	9
Rupture	2
SASD bursitis	19
SSP	
Lesion	14
Calcification	5
IFP	
Lesion	1
Calcification	0
SSC	
Lesion	7
Calcification	6
TM lesion	1

Table 3. Main US findings

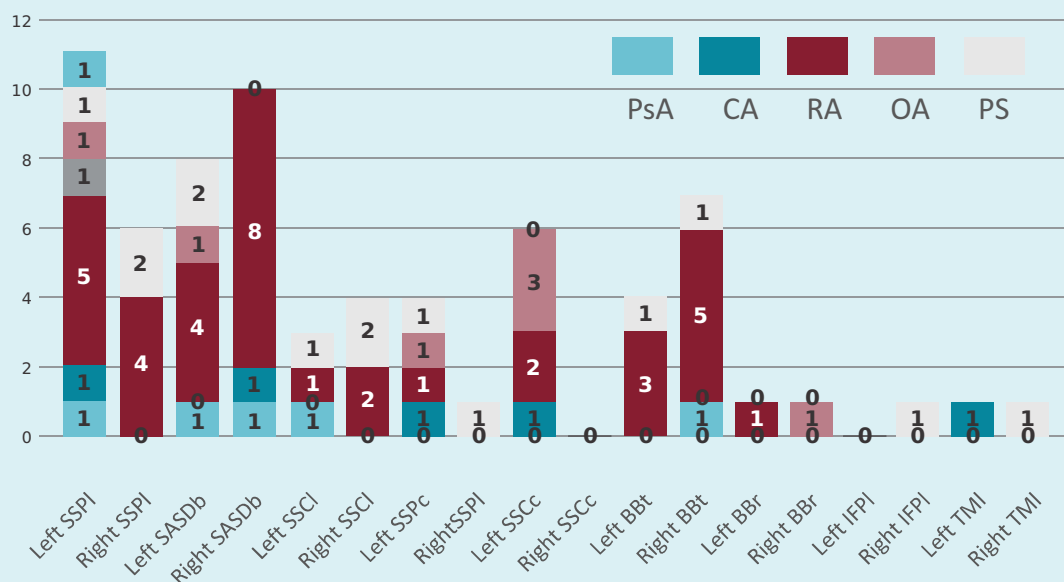


Figure 2. Main US findings.

SSPI - supraspinatus tendon lesion; SSPc - supraspinatus tendon calcification; SASD - subacromial - subdeltoid bursa; SSCl - subscapular tendon lesion, SSCc - subscapularis tendon calcification, BBt - biceps brahialis tendinitis; IFPl - infraspinatus tendon lesion; TMI-teres minor tendon lesion; PsA - psoriatic arthritis; CA - crystal related arthritis; RA - rheumatoid arthritis; OA - osteoarthritis; PS - non specific periarticular involvement



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multifactorial and the input of each variable is still not completely understood^(15,16).

It seems that comorbidities, as the presence of diabetes, may influence tendon degeneration or rupture. As previously concluded, a recent review, published by *Nichols et al*, in 2019, mentions that the presence of diabetes is associated to chronic tendinopathy, with a risk up to four times higher compared to non-diabetics, and to tendon rupture in a percentage five times higher⁽¹⁷⁾.

Diabetes determines both inflammatory and microvascular changes and the proper therapeutic management of these patients could slow down the progression of the lesions⁽¹⁸⁾. In consistency with these data, a recent meta-analysis that included 16 studies, published by *Leong et al*, concluded that age above 50 years and diabetes are associated to a high risk of rotator cuff tendinopathy in general population⁽¹⁹⁾. Although the number of studies is relatively small, and the population heterogeneity influences the results, other associated comorbidities, as cardiovascular diseases or osteoarthritis are also directly related to this shoulder pathology^(20,21).

Calcifications, second type of findings in our patients, without inflammatory conditions, were relatively frequent in patients with diabetes, compared to those without this associated pathology. Similar to our data,

calcific shoulder is often found by US examination and is found up to three times more often in patients of type II diabetes, compared to nondiabetic subjects^(22,23).

Regarding associated pathologies, dyslipidemia has represented a subject of emerging interest, multiple studies having the purpose of analyzing dyslipidemia-tendinopathy relation, with results that sustain specifically the effect on rotator cuff pathologies^(24, 25); in our study group, we noticed the direct positive correlation between both for cholesterol levels and triglycerides and shoulder tendon pathology. We also noted that two of the patients with SSP tendon rupture previously were treated with quinolones, which could explain tendon lesion.

Fluoroquinolone antibiotics, broadly used to treat various infections, are known to be associated to tendon ruptures, though in relatively low percentages (less than 1 to 10000 patients), by a mechanism involving matrix metalloproteinases regulation^(26, 27). An important role is attributed to other risk factors, such as old age and metabolic factors (obesity, diabetes etc.)^(28,29).

Between patients with inflammatory conditions, RA is a relatively frequent cause of shoulder pain, over 90% of the patients having this symptom during evolution and almost half of them describing it in the first two years. US examination can reveal joint

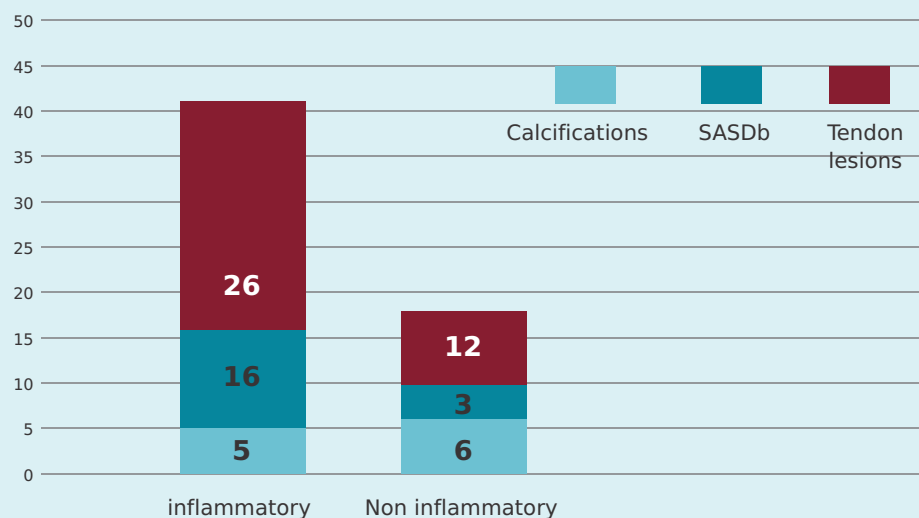


Figure 3. Main US findings depending on the type of disease

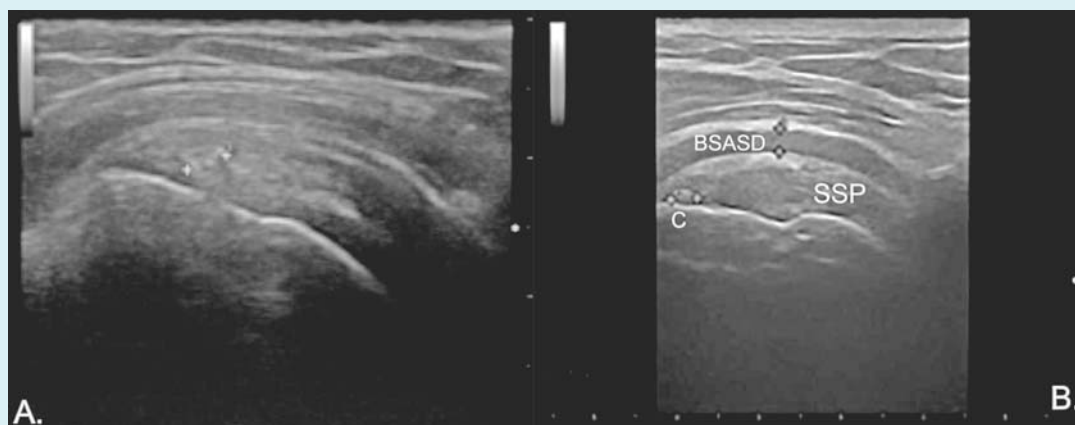


Figure 4. US image in long axis of SSP tendon showing: A. calcification, with accustic shadow inside tendon; B. SSP calcification (C) and SASD bursitis (BSASD). SSP - supraspinatus tendon

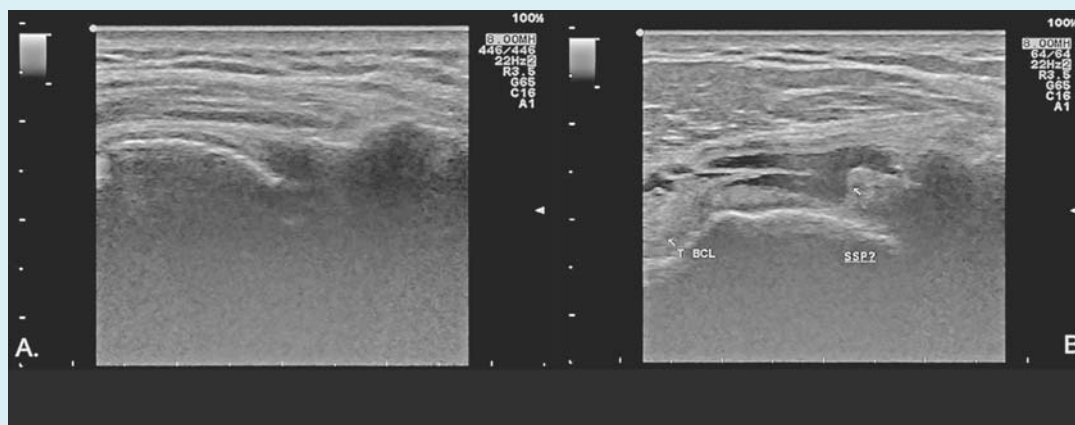


Figure 5. US images showing a full thickness SSP tendon rupture in: A. longitudinal view; B. transverse view. T BCL - long head of biceps tendon, SSP - supraspinatus remaining part



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effusion, rotator cuff lesions, bursitis, synovitis, or bone erosions and has a major impact, as it is highly sensitive and specific for several pathological abnormalities. In consistency with previous reports, our data shows variable percentages of SSC, SSP or ISP tendinopathy suggestive US changes in RA patients and OA ones⁽²⁶⁻²⁹⁾. Our study has certain limitations, since it was performed by a single ultrasound examiner, even if he was blinded to clinical findings, diagnosis, and biologic parameters. Further prospective studies, with more than one US examiner, to verify inter-rater reliability of the findings, and including more patients with variable pathologies, as well as a control group, without degenerative or inflammatory conditions, is required in order to add statistical significance to our data.

Conclusions

Although it included a relatively low number of subjects, it reveals data similar to the ones previously published and underline the necessity of applying a diagnostic algorithm in shoulder pathology, that should mandatory include US examination, in order to obtain an accurate diagnosis and individualize each patient's therapeutic approach and improve their life quality.

References:

1. Holmes RE, barfield wr, Woolf SK. Clinical evaluation of nonarthritic shoulder pain: Diagnosis and treatment, *Phys Sportsmed.*, 2015, 43 (3): 262-268.
2. Barbulescu AI, Ciurea P.L., Mitran, C., Chisalau, B.A., Parvanescu, C.D., Firulescu, S.C., Balasoii, M., Boldenau, M.V., Popoviciu, H., Vreju, F.A., High frequency ultrasonography of the hand versus anti-RA33 evaluation in early rheumatoid arthritis - a pilot study, *Med Ultrason*, 19, nr.2, 2017, p. 166-171.
3. Vreju, F.A., Ciurea, M.E., Popa, D., Popa, F., Parvanescu, C.D., Chisalau, B.A., Barbulescu, A.L., Parvanescu, V., Rosu, A., Ciurea, P.L., Ultrasonography in the diagnosis and management of noninflammatory conditions of the hand and wrist, *Med Ultrason*, 18, nr.1, 2016, p. 90-95.
4. Ciurea, M.E., Ciurea, R.N., Bărbulescu, A.L., Chisălău A.B., Pârvănescu, C.D., Firulescu, S.C., Covei Băncioiu, S., Ciurea, P.L., Vreju, A.F. Intramuscular hemangioma of the arm: ultrasonography and pathology features, *Rom J Morph Embryol*, 57, nr.2, 2016, p. 521-524.
5. Filippou, G., Scirè, C.A., Adinolfi, A., Damjanov, N.S., Carrara, G., Bruyn, G.A.W., Cazenave, T., D'agostino, M.A., Delle Sedie, A., Di Sabatino, V., Diaz Cortes, M.E., Filippucci, E., Gandjbakhch, F., Gutierrez, M., Maccarter, D.K., Micu, M., Möller Parera, I., Mouterde, G., Mortada, M.A., Naredo, E., Pineda, C., Porta, F., Reginato, A.M., Satulu, I., Schmidt, W.A., Serban, T., Terslev, L., Vlad, V., Vreju, F.A., Zufferey, P., Bozios, P., Toscano, C., Picerno, V., Iagnocco, A., Identification of calcium pyrophosphate deposition disease (CPPD) by ultrasound: reliability of the OMERACT definitions in an extended set of joints-an international multiobserver study by the OMERACT Calcium Pyrophosphate Deposition Disease Ultrasound Subtask Force, *Ann Rheum Dis*, 77, nr.8, 2018, p. 1195-1200.
6. Firulescu, S.C., Tudorașcu, D.R., Pârvănescu, C.D., Chisălău, A.B., Bastian, A.E., Efrem, I.C., Bărbulescu, A.L., Forțoiu, M.C., Criveanu, C., Ionescu, P., Dinescu, Ș.C., Tudorancea, A.D., Ciurea, P.L., Vreju, A.F., The role of skin and muscle biopsy in the diagnosis of main connective tissue diseases, *Rom J Morphol Embryol.*, 59, nr.1, 2018, p.55-64.
7. Mustafa, E.R., Firulescu, S.C., Parvanescu, C.D.,

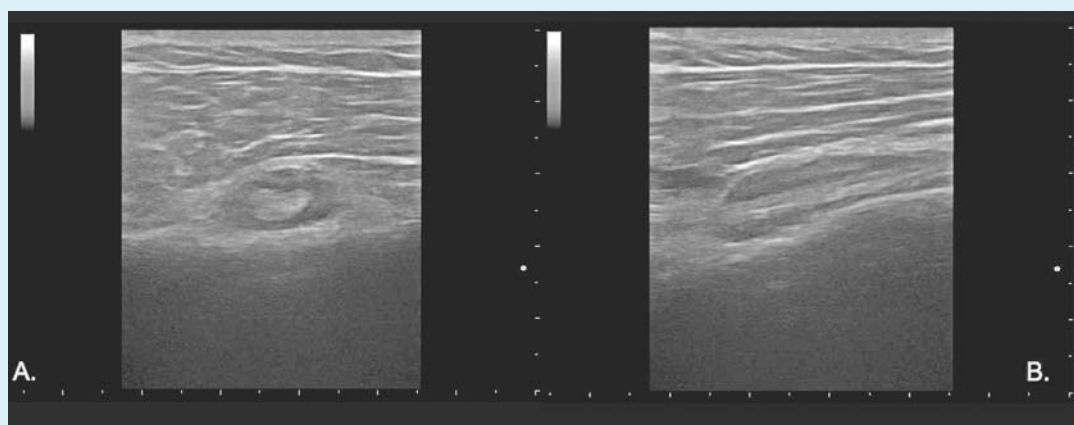


Figure 6. US image of the long head of the biceps tendon in: A. transverse view - notice hypoechoic halo suggestive of the fluid inside the tendon sheath, B. longitudinal view - notice hypoechoic areas superficial and deep to the tendon

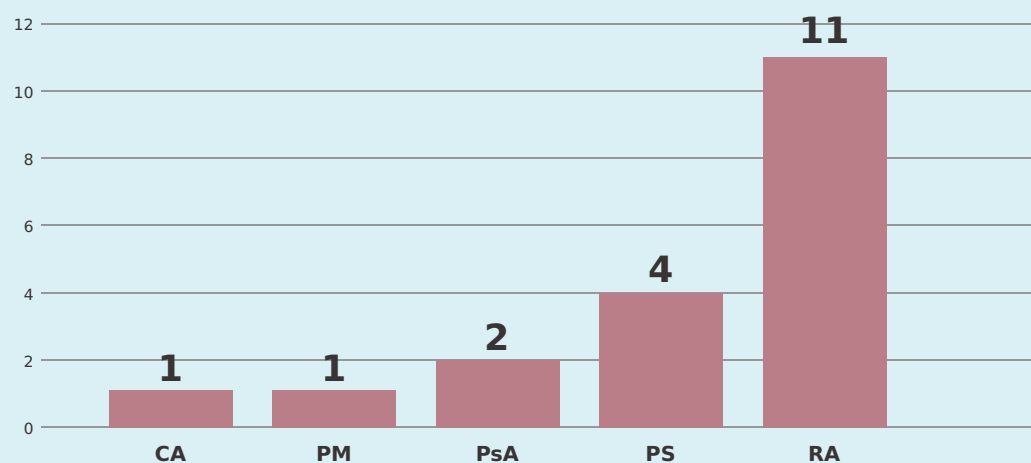


Figure 7. SASD bursitis depending on the disease

CA - crystal related arthritis; PM - polymyalgia rheumatica; PS - non specific periarticular involvement; PsA - psoriatic arthritis; RA - rheumatoid arthritis

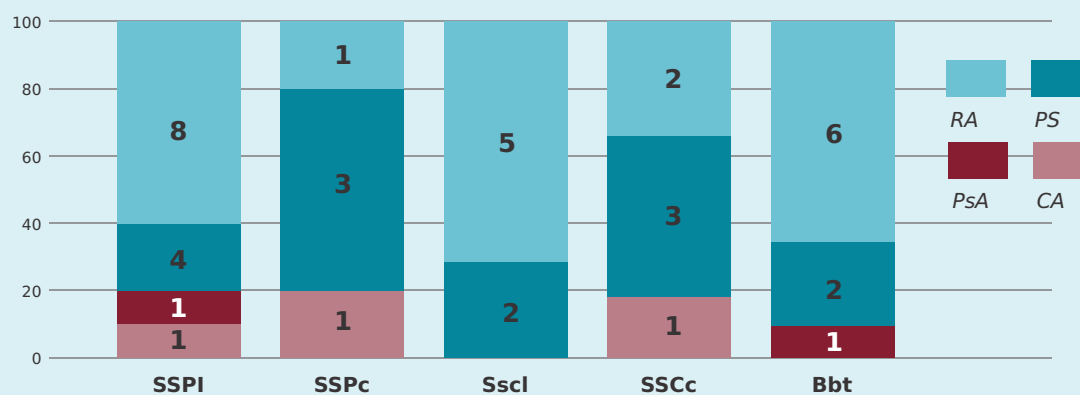


Figure 8. Tendon lesions depending on diagnosis

RA - rheumatoid arthritis; PM - polymyalgia rheumatica; PS - non specific periarticular involvement; PsA - psoriatic arthritis; CA - crystal related arthritis; SSPI - supraspinatus tendon lesion; SSPc - supraspinatus tendon calcification; Sscl - subscapular tendon lesion, SSCc - subscapularis tendon calcification, Bbt - biceps brahialis tendinitis



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Original Papers

Chisalau, B.A., Tarteia, G.C., Efrem, I.C., Barbulescu, A.L., Dinescu, S.C., Ciurea, P.L., Radu, L, Triple valve endocarditis-a late diagnosis, *Journal of Mind and Medical Sciences*, 5, nr.1, 2018, p.141-144.

8. Barbulescu, A.L., Sandu, R.E., Boldeanu, M.V., Vreju, A.F., Mihailovici, R.A., Boldeanu, L., Popoviciu, H.V., Ionescu, R.A., Catalin, B., Stoian, A.C., Florescu, O.A., Albu, C.V., Cognitive Dysfunction, Depression and Anxiety in a Cohort of Systemic Lupus Erythematosus Patients, *Revista de chimie*, 70, nr. 7, p. 2584-2589.

9. Stoian, A.C., Dumitrescu F., Sandu, R.E., Barbulescu, A.L., Vreju, A.F., Florescu, O.A., Catalin, B., Burada, E., Musatescu, A.E., Albu, C.V., The Role of Colistin in Urinary Tract Infections in the Neurologic Patient, *Revista de Chimie*, 70, nr. 8, p. 2831-2834.

10. Parvanescu, C.D., Barbulescu, A.L., Ciurea, P.L., Chisalau, B.A., Firulescu, S.C., Turcu Stiolica, A., Dinescu, S.C., Sandu, R.E., Albu, C.V., Popoviciu, H.V., Ionescu, R.A., Vreju, F.A., Gout - Risks, Comorbidities and Associations, *Revista de Chimie*, 70, nr.8, p.2948-2952.

11. Albu, C.V., Sandu, R.E., Barbulescu, A.L., Tarteia, E.A., Burada, E., Taisescu, O., Vreju, A.F., Boldeanu, M.V., Boldeanu, L., Enescu, A., Pascoveanu, D., Stoian, C.C., Catalin, B., The Relationship between the Acute Confusing State and the Comorbidities of the Elderly Patient, *Revista de Chimie*, 70, nr. 7, p. 2415-2419.

12. Sandu, R.E.; Balseanu, A.; Bogdan, C.; Slevin, M.; Petcu, E.; Popa-Wagner, A. Stem cell therapies in preclinical models of stroke. Is the aged brain microenvironment refractory to cell therapy, *Experimental Gerontology*, 94, 2017, p. 73-77.

13. Sandu, R.E., Uzoni, A., Ciobanu, O., Moldovan, M., Anghel, A., Radu, E., Coogan, A., Popa-Wagner A. Post-stroke gaseous hypothermia increases vascular density but not neurogenesis in the ischemic penumbra of aged rats. *Restor Neurol Neurosci.*, 34, nr. 3, 2016, p. 401-14.

14. Buga, A.M., Vintilescu, R., Pop, O.T., Popa-Wagner A. Brain Aging and Regeneration after Injuries: an Organismal approach, *Aging Dis*, 2, nr.1, 2011, p. 64-79.

15. Fîlfan, M., Sandu, R.E., Zăvăleanu, A., Greșită, A., Glăvan D, Olaru, D.G., Popa-Wagner, A., Autophagy in aging and disease. *Rom J Morphol Embryol.*, 58, nr.1, 2017, p. 27-31.

16. Popa-Wagner, A., Glavan, D.G., Olaru, A., Olaru, D.G., Margaritescu, O., Tica, O., Surugiu, R., Sandu, R.E., Present

Status and Future Challenges of New Therapeutic Targets in Preclinical Models of Stroke in Aged Animals with/without Comorbidities, *Int J Mol Sci.*, 19, nr.2, 2018.

17. Sandu, R.E., Uzoni, A., Coman, C., Popa-Wagner, A., Cerebral ischemia in the aged. Limited anti-inflammatory efficacy of the indomethacin treatment. *Rom J Morphol Embryol.*, 56, nr. 3, 2015, p. 1111-7.

18. Tudora^{cu}, D.R., Pirici, D., Târtea, E., Mustafa, E.R., Florescu, C., Vere, C.C., Balea, A.M., Puiu, I., Târtea, G.C., Albu, V.C., Synaptophysin expression as prognostic factor for survival in colorectal carcinomas. *Rom J Morphol Embryol.*, 58, nr.4, 2017, p. 1409-1415.

19. Mihailovici, A.R., Padureanu, V., Albu, C.V. Et Al, Myocardial Noncompaction. *Revista De Chimie*, 69, nr.8, 2018, p. 2209-2212.

20. Albulescu, Dm, Ionovici, N, Moldovan Hr, Demetrian Ad, Bălă Vs, Constantin C, Bumbea, Am, Pănu^o, C, Albu, V.C., Muscle metastases from cervical carcinoma - case report. *Rom J Morphol Embryol.*, 58, nr.2, 2017, p. 545-551.

21. Cătălin B., Mitran S., Ciorbagiu M., Osiac E, Bălșeanu T.A., Mogoantă L, Dinescu Sn, Albu C.V., Mirea Cs, Vilcea I.D., Iancău M., Sfredel V. Microglial voltage-gated sodium channels modulate cellular response in Alzheimer's disease - a new perspective on an old problem. *Rom J Morphol Embryol.*, 56, nr.1, 2015, p. 21-5.

22. Taisescu, Ci, Biciusca, V, Sas, L, Camen, G, Sas, T, Albu, C, Taisescu, O. Changes of Visual Evoked Potentials in Patients with Thyroid Dysfunction, *Revista de Chimie*, 10, nr.2, 2019, p. 961-968

23. Kim, H.A., Kim, S.H., Seo, Y., Ultrasonographic Findings of the Shoulder in patients with rheumatoid arthritis and Comparison with Physical Examination, *J Korean Med Sci*, 22, 2007, p.660-6.

24. Bruyn Ga, Naredo E, Möller I, Moragues C, Garrido J, De Bock Gh, D'agostino Ma, Filippucci E, Iagnocco A, Backhaus M, Swen Wa, Balint P, Pineda C, Milutinovic S, Kane D, Kaeley G, Narvaez Fj, Wakefield Rj, Narvaez Ja, De Augustin J, Schmidt Wa, Reliability of ultrasonography in detecting shoulder disease in patients with rheumatoid arthritis, *Ann Rheum Dis*, 68, nr.3, 2009, p. 357-361.

25. Hermann, K.G., Backhaus, M., Schneider, U., Labs, K., Loreck, D., Zühlsdorf, S., Schink, T., Fischer, T., Hamm, B., Bollow, M., Rheumatoid arthritis of the shoulder joint: comparison of conventional radiography, ultrasound, and

- dynamic contrast-enhanced magnetic resonance imaging, 48, nr.12, *Arthritis Rheum*, 2003, p. 3338-49.
26. Wang, M.Y., Wang, X.B., Sun, X.H., Liu, F.L., Huang, S.C., Diagnostic value of high-frequency ultrasound and magnetic resonance imaging in early rheumatoid arthritis, *Exp Ther Med.*, 12, nr.5, 2016, p. 3035-3040.
 27. Abdelzaher, M.G., Tharwat, S., Abdelkhalek, A., Abdelsalam, A., Ultrasound versus magnetic resonance imaging in the evaluation of shoulder joint pathologies in a cohort of rheumatoid arthritis patients. *Int J Rheum Dis*, 2019, Oct 31. doi: 10.1111/1756-185X.13728. (Epub ahead of print)
 28. Backhaus, M., Burmester, G.R., Gerber T, Grassi, W., Machold, K.P., Swen, W.A., Wakefield, R.J., Manger. B., Working Group for Musculoskeletal Ultrasound in the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials.. Guidelines for musculoskeletal ultrasound in rheumatology, *Ann Rheum Dis*, 60, nr.7, 2001, p. 641-649.
 29. Iagnocco, A, Porta, F, Cuomo, G, Delle Sedie, A, Filippucci, E, Grassi, W, Sakellariou, G, Epis, O, Adinolfi, A, Ceccarelli, F, De Lucia, O, Di Geso, L, Di Sabatino, V, Gabba, A, Gattamelata, A, Gutierrez, M, Massaro, L, Massarotti, M, Perricone, C, Picerno, V, Ravagnani, V, Riente, L, Scioscia, C, Naredo, E, Filippou, G, Musculoskeletal Ultrasound Study Group of the Italian Society of Rheumatology The Italian MSUS Study Group recommendations for the format and content of the report and documentation in musculoskeletal ultrasonography in rheumatology. *Rheumatology (Oxford)*, 53, 2014, p. 367373,
 30. Kane, D, Balint, P, Sturrock, R, Grassi, W., Musculoskeletal ultrasound a state of the art review in rheumatology. Part 1: current controversies and issues in the development of musculoskeletal ultrasound in rheumatology. *Rheumatology Oxford*, 43, 2004, p. 823828.
 31. Petranova, T., Vlad, V., Porta, F., Radunovic, G., Micu, Nestorova, R., Iagnocco, A., Ultrasound of the shoulder, *Medical Ultrason.*, 14, nr.2, 2012, p. 133-140.
 32. Plachel, F., Moroder, P., Gehwolf, R., Tempfer, H., Wagner, A., Auffarth, A., Matis, N., Pauly, S., Tauber, M., Traweger, A., Risk Factors for Rotator Cuff Disease: An Experimental Study on Intact Human Subscapularis Tendons, *J Orthop Res*, 2019, doi: 10.1002/jor.24385. (Epub ahead of print).
 33. Schoenfeldt, T.L., Trenhaile, S., Olson, R., Glenohumeral osteoarthritis: frequency of underlying diagnoses and the role of arm dominance-a retrospective analysis in a community-based musculoskeletal practice, *Rheumatol Int.*, 38, nr.6, 2018, p. 1023-1029.
 34. Nichols, A.E.C., Oh, I., Loiselle, A.E., Effects of Type II Diabetes Mellitus on Tendon Homeostasis and Healing, *J Orthop Res.*, 2019 Jun 5. doi: 10.1002/jor.24388. (Epub ahead of print).
 35. Lui, P. P. Y., Tendinopathy in diabetes mellitus patients- Epidemiology, pathogenesis, and management, *Scandinavian Journal of Medicine & Science in Sports*, 27, nr. 8, 2017, p. 776787
 36. Leong, H.T., Fu, S.C., He, X., Oh, J.H., Yamamoto, N., Hang, S., Risk factors for rotator cuff tendinopathy: A systematic review and meta-analysis, *J Rehabil Med*, 51, nr. 9, 2019, p. 627-637.
 37. Northover, J.R., Lunn, P., Clark, D.I., Phillipson, M., Risk factors for the development of rotator cuff disease. *Int J Shoulder Surg*, 1, nr.3, 2007, p. 8286.
 38. Applegate, K.A., Thiese, M.S., Merryweather, A.S., Kapellusch, J., Drury, D.L., Wood, E., Kendall, R., Foster, J., Garg, A., Hegmann, K.T., Association between cardiovascular disease risk factors and rotator cuff tendinopathy: a cross-sectional study, *J Occup Environ Med*, 59, nr.2, 2017, p. 154160.
 39. Zakaria, M.H., Davis, W.A., Davis, T.M., Incidence and predictors of hospitalization for tendon rupture in type 2 diabetes: the Fremantle Diabetes Study, *Diabet Med.*, 31, nr. 4, 2014, p. 425430.
 40. Franceschi, F., Papalia, R., Paciotti, M., Francheschetti, E., Di Martino, A., Maffulli, N., Denaro, V., Obesity as a risk factor for tendinopathy: a systematic review. *Int J Endocrinol.*, 2014, ArticleID: 670262.
 41. Park, H.B., Gwark, J.Y., Jung, J., What Serum Lipid Abnormalities Are Associated with Adhesive Capsulitis Accompanied by Diabetes?, *Clin Orthop Relat Res.*, 476, nr.11, 2018, p.2231-2237.
 42. Sung, C.M., Jung, T.S., Park, H.B., Are serum lipids involved in primary frozen shoulder? A case- control study., *J Bone Joint Surg Am.*, 96, nr.21, 2014, p. 1828-33.
 43. Khaliq, Y., Zhanel, G.G., Fluoroquinolone-associated tendinopathy: a critical review of the literature, *Clin Infect Dis.*, 36, nr.11, 2003, p. 1404-10.
 44. Tsai, W.C., Hsu, C.C., Chen, C.P., Chang, H.N., Wong, A.M., Lin, M.S., Pang, J.H., Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen, *J Orthop Res.*, 29, nr.1, 2011, p. 67-73
 45. Spoendlin, J., Meier, C., Jick, S.S., Meier, C.R., Achilles or biceps tendon rupture in women and men with type 2 diabetes: A population-based case-control study, *J Diabetes Complications*. 30, nr.5, 2016, p. 903-9.
 46. Sanja, M.R., Mirjana, Z.S., Ultrasonographic study of the painful shoulder in patients with rheumatoid arthritis and patients with degenerative shoulder disease, *Acta Reumatol Port.*, 35, nr.1, 2010, p. 50-8.