

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
PhD SCHOOL

PhD THESIS
ULTRASOUND EVALUATION OF JOINTS AND
ENTHESES IN SPONDYLOARTHRITIS

- ABSTRACT -

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CONTENTS

I. CURRENT STATE OF KNOWLEDGE	3
INTRODUCTION.....	3
I.1. CLASSIFICATION OF SPONDYLOARTHRITIS.....	3
I.2. IMAGING TECHNIQUES IN SPONDYLOARTHRITIS	3
I.3. ANKYLOSING SPONDYLITIS.....	3
I.4. PSORIATIC ARTHRITIS	4
I.5. REACTIVE ARTHRITIS	5
I.6. ENTEROPATHIC ARTHRITIS	6
II. PERSONAL CONTRIBUTION.....	6
II.1. PURPOSE AND OBJECTIVES OF THE PhD THESIS.....	6
II.2. MATERIAL AND METHODS.....	7
II.3. RESULTS.....	7
II.4. DISCUSSIONS	10
II.5. CONCLUSIONS	10
REFERENCES.....	11

I. CURRENT STATE OF KNOWLEDGE

INTRODUCTION

The spondyloarthritis group is an association of interrelated pathologies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis, enteropathic arthritis and undifferentiated spondyloarthritis.

Musculoskeletal ultrasound is an inexpensive, non-invasive and accessible method used in the case of patients with inflammatory pathologies. In addition to the ability to identify inflammatory structural damage of cortical bones, joints and periarticular structures such as erosions, synovitis, tenosynovitis, the technique is suitable for a dynamic, multi-planar evaluation of the treatment response and guidance of therapeutic maneuvers.

I.1. CLASSIFICATION OF SPONDYLOARTHRITIS

ASAS (Assessment of SpondyloArthritis International Society) classification criteria for axial SpA - In patients with back pain > 3 months and age at onset < 45 years

1. Sacroiliitis on imaging* plus 1 of the following SpA features

- Inflammatory back pain
- Arthritis
- Enthesitis (heel)
- Uveitis
- Dactylitis
- Psoriasis
- Crohn disease (CD) or ulcerative colitis (UC)
- Good response to NSAIDs
- Family history of SpA
- HLA-B27
- Elevated CRP

2. HLA-B27 plus 2 or more than 2 characteristic SpA features

* Sacroiliitis on imaging*: active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with SpA or definite radiographic sacroiliitis according to modified New York criteria.

I.2. IMAGING TECHNIQUES IN SPONDYLOARTHRITIS

Currently available imaging techniques play a key role in determining the diagnosis of musculoskeletal disorders and in particular of spondyloarthritis. For this purpose, radiography, ultrasonography, computed tomography, magnetic resonance imaging can be used [3].

I.3. ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a chronic inflammatory disease which is part of the spondyloarthritis group, characterized by involvement of the axial skeleton (spine, sacroiliac

joints), peripheral joints and entheses, in addition to extra-articular manifestations (eyes, heart, lungs) in the presence of HLA-B27 antigen [4].

Inflammatory pain of the lumbar spine is the most common symptom in AS patients and should be differentiated from the mechanical cause of pain.

The shoulder and hip joints are the most commonly involved, in 35% in AS patients. Hip damage through repeated coxitis episodes with the occurrence of secondary arthrosis may lead to an increase in patient disability. Rarely, asymmetric oligoarticular arthritis, predominantly of lower limbs can be highlighted [5].

Ultrasound evaluation of peripheral joints in grey scale or power Doppler involves the identification of synovial proliferation or joint effusion (quantified in degrees from 0 to 3, as defined by OMERACT - Outcome Measures in Rheumatology), tenosynovitis (on a scale from 0 to 3), the presence of erosions and bursitis [6].

In order to detect subclinical enthesitis and evaluate the response to treatment, ultrasound scores were developed for the assessment of entheses in AS:

- Glasgow Ultrasound Enthesitis Index (GUESS);
- D'Agostino;
- Spanish Sonographic Enthesitic Index (SEI);
- Madrid Sonographic Enthesitis Index (MASEI);
- Belgrade Ultrasound Enthesitis Score (BUSES) [7].

NSAIDs are the first-line of treatment in AS. The first NSAIDs which have proven their efficacy in SA were phenylbutazone and indomethacin, with the subsequent addition of diclofenac, naproxen, ibuprofen, piroxicam, ketoprofen and selective cyclooxygenase-2 (COX-2) inhibitors such as etoricoxib and celecoxib.

Biological therapy (DMARDb) has proven its effectiveness in improving joint symptoms. The drugs used in AS are: TNF- α inhibitors such as infliximab, etanercept, adalimumab, golimumab and certolizumab pegol, and IL-17 inhibitors such as secukinumab [8].

I.4. PSORIATIC ARTHRITIS

Psoriatic arthritis (PsA) is an inflammatory joint disease that predominantly affects the peripheral joints, with or without the association of axial and enthesal involvement. The absence of the rheumatoid factor and the presence of cutaneous psoriasis are defining elements of this pathology [9].

Articular damage in PsA can vary considerably, from isolated monoarthritis to destructive, extensive arthritis and may involve both peripheral and axial joints. The most widely used descriptive classification is the one proposed by Moll and Wright, which identifies five major subtypes of PsA: distal interphalangeal joint involvement, asymmetric mono / oligoarticular disease, symmetrical polyarticular disease, mutilating arthritis and psoriatic spondyloarthritis [10].

Clinical scoring systems are used for the quantification of enthesal involvement such as:

- *Mander Enthesis Index (MEI)*;
- *Maastricht Ankylosing Spondylitis Enthesis (MASES)*;
- *MAJOR enthesitis index*;
- *Spondyloarthritis Research Consortium of Canada Enthesitis Index (SPARCC)*;
- *LEEDS enthesitis index (LEI)* [11].

Musculoskeletal ultrasound evaluation has proven its effectiveness in depicting the inflammatory changes in the joints in the early stages of the disease - the presence of synovitis and joint effusion in grey scale and power Doppler, in tendons – tenosynovitis or tendinitis, dactylitis and enthesitis aspects, but also in the assessment of cutaneous involvement and of the nail bed. Characteristic for PsA is the aspect of paratenonitis, described as tendinous and peritendinous inflammation accompanied by tendon thickening and hypoechogenicity, for tendons without synovial sheath, with or without the presence of power Doppler signal [12].

Ultrasound scoring systems are used for the quantification of enthesal involvement such as:

- *Glasgow Ultrasound Enthesitis Index (GUESS)*;
- *D'Agostino*;
- *Belgrade Ultrasound Enthesitis Score (BUSES)*;
- *PsASon22, PsASon 13*;
- *5 Targets Power Doppler for Psoriatic Disease (5TPD)* [13].

TREATMENT

- NSAIDs are useful in mild forms of PsA, being more effective in relieving joint pain for a short period of time;
- Glucocorticoids are recommended in severe forms of disease, in polyarticular forms, but after the treatment is interrupted, the psoriasis lesions are aggravated;
- DMARDcs (Methotrexate, Leflunomide, Sulfasalazine, Cyclosporine A);
- Biological therapy: TNF- α inhibitors (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol), IL-17 inhibitors such as secukinumab, inhibitors of the JAK STAT - signaling pathways - tofacitinib and baricitinib [14].

I.5. REACTIVE ARTHRITIS

Reactive arthritis (AR) is part of the spondyloarthritis group and usually occurs within 4 weeks, especially after an urogenital or enteral infection. The articular pattern is typically a sterile asymmetric mono / oligoarthritis that predominantly involves the joints of the lower limbs. Patients with RA are frequently HLA-B27-positive and have systemic symptoms with particular extra-articular manifestations in the eyes, skin and entheses [15].

Extra-articular infection may be the cause of acute joint symptoms in 9-18% of patients with inflammatory joint disease lasting less than 6 months. The clinical characteristics of RA are those of SpA, the arthritis being the most common articular manifestation [16].

The typical clinical feature of joint involvement is asymmetric mono / oligoarthritis, often in the lower limb joints, such as the knees, ankles or feet. Hip joint damage is rare. Also, forms with a polyarticular pattern involving hand joints (wrists, MCP, PIP, DIP) are described.

Enthesitis is encountered in 30% of patients, either as a single manifestation of the disease or in combination with arthritis. The most common involved tendons are: Achilles tendon, plantar fascia, posterior tibialis tendon and peroneus tendons [17].

MSUS is useful in highlighting synovial proliferation and joint effusion, as well as enthesitis, tenosynovitis and dactylitis.

In most patients (> 50%), symptom remission usually occurs within 2-6 months after the onset of the disease, but it can take up to 1 year for complete resolution of the symptoms.

Patients with recurrent arthritis (30-35%) or persistent symptoms (15-20%) despite appropriate NSAID treatment may require DMARDs. Sulfasalazine (2-3 g / day) is the preferred drug for refractory RA. Other DMARDs, such as methotrexate and leflunomide, have also been used with variable success rates. TNF- α inhibitor therapy presents limited evidence, but favorable results in the treatment of RA [18].

I.6. ENTEROPATHIC ARTHRITIS

Enteropathic arthritis is a subgroup of SpA with peripheral joint but also axial involvement such as spondylitis and sacroiliitis associated with intestinal inflammatory diseases (Crohn's disease and ulcerative colitis) [19].

Peripheral joint damage occurs in 10-15% of patients with CD and in 5-10% of patients with UC. Sacroiliitis is described in both CD and UC in 15% of patients.

- Type I (joint involvement is often parallel to IBD activity): occurs in 4-6% of patients with IBD and affects men and women equally. Arthritis is usually acute at onset (80%), asymmetric (80%) and pauciarticular (usually involving less than five joints, the knees and ankles being the most commonly affected).

- Type II (arthritis is independent of IBD activity): less common - 3-4% of patients with IBD. Arthritis tends to be symmetrical (80%), polyarticular, involving the joints of the hands more frequently, and does not correlate with extra-articular manifestations (except uveitis) [20].

MSUS has shown its utility in assessing peripheral joints with evidence of synovial proliferation, effusion and enthesitis [21].

TREATMENT

- NSAIDs are effective both in alleviating peripheral and axial symptoms;
- Corticosteroids are useful both in systemic and intra-articular administration, with beneficial effects on intestinal involvement but also on peripheral joint symptoms;
- DMARDs – Sulfasalazine, Mesalazine, Azathioprine;
- TNF- α inhibitors (infliximab, adalimumab) [22].

II. PERSONAL CONTRIBUTION

II.1. PURPOSE AND OBJECTIVES OF THE PhD THESIS

In the PhD thesis, my aim was to evaluate the types of peripheral joint damage in a group of patients with spondyloarthritis, as well as to identify enthesitis / entesopathy, both clinically and by ultrasound and to establish associations between clinical, ultrasonographic and biologic inflammatory syndrome markers, namely C reactive protein and the erythrocyte sedimentation rate.

II.2. MATERIAL AND METHODS

I included in the study 82 patients diagnosed with one of the disorders of the spondyloarthritis group: ankylosing spondylitis, psoriatic arthritis, reactive arthritis and enteropathic arthritis. I performed a prospective and retrospective longitudinal observational study on a group of patients admitted to the Department of Rheumatology of the Craiova County Emergency Clinical Hospital between 01.01.2016 and 01.01.2019.

The inclusion protocol consisted of anamnestic, clinical, ultrasonographic assessment of patients, but also laboratory investigations, also taking into account the therapy the patients were undergoing.

STATISTICAL PROCESSING OF THE OBTAINED DATA

In order to statistically process the data obtained from the patients included in the study group, we used the Microsoft Excel 2016 application and the SPSS Statistics version 20 application.

II.3. RESULTS

The initial group of 82 patients with SpA was divided according to the etiology of inflammatory pathology in 4 groups:

- The group with ankylosing spondylitis - 30 patients;
- The group with psoriatic arthritis - 36 patients;
- The group with reactive arthritis - 10 patients;
- The group with enteropathic arthritis - 6 patients.

THE GROUP OF PATIENTS WITH ANKYLOSING SPONDYLITIS

The study group included 30 patients, 23 men and 7 women, with minimum age of 17, maximum age of 57 years and the average age of 38.36 years.

The enthesal involvement assessed by the SPARCC score was distributed according to sensitivity at palpation of the tendon insertion as follows:

- Medial epicondyles - 6 tendons;
- Lateral epicondyles - 7 tendons;
- Greater humeral tuberosity - 7 tendons;
- The greater femoral trochanter - 23 tendons;
- Upper patellar pole - 20 tendons;
- Inferior patellar pole - 9 tendons;
- Achilles tendon - 42 tendons;
- Plantar fascia - 36 tendons.

After MSUS evaluation, out of the 60 Achilles tendons examined, 42 enthesal sites showed inflammatory changes as follows:

- Thickening - 38 tendons;
- Hypoechogenicity - 38 tendons;
- Loss of fibrillar pattern - 38 tendons;

- Entesophytes - 32 tendons;
- Calcifications - 28 tendons;
- Erosions - 28 bone corticals;
- PD signal - 12 tendons;
- Retrocalcaneal bursitis - 12 bursae;
- Retroachillean bursitis - 10 bursae.

Clinically and ultrasonographically, 240 hip, elbow, knee and ankle joints were assessed. Sensitivity at palpation of the joint and clinical signs of inflammation were highlighted in 13/60 knee joints, 11 ankle joints, 4 elbow joints, 2 shoulder joints.

Inflammatory changes (effusion, synovial proliferation, power Doppler signal) detected by ultrasound were distributed as follows:

- Knee joint - 18/60 with inflammatory changes;
- Ankle joint - 15/60 with inflammatory changes;
- Elbow joint- 7/60 with inflammatory changes;
- Shoulder joint - 3/60 with inflammatory changes.

ESR values did not show a statistically significant association with the SPARCC clinical score ($p = 0.619$) and the BUSES echographic score ($p = 0.200$). CRP values did not have a statistically significant association with the SPARCC clinical score ($p = 0.137$) and the BUSES echographic score ($p = 0.102$).

Regarding the BUSES ultrasound score and disease activity calculated using ASDAS, they did not show a statistically significant association ($p = 0.738$). BUSES also did not have a statistically significant association with disease activity quantified by the BASDAI score ($p = 0.094$).

The SPARCC clinical score was not significantly associated statistically with ASDAS ($p = 0.434$) and with BASDAI ($p = 0.130$).

The SPARCC clinical score and BUSES echographic score were significantly associated statistically with a $p = 0.018$ value.

THE GROUP OF PATIENTS WITH PSORIATIC ARTHRITIS

From the initial group of 36 patients diagnosed with PsA, two groups were formed:

- Group I - patients with peripheral joint disease (28 patients);
- Group II - patients with enthesitis (28 patients).

GROUP I OF PATIENTS WITH PSORIATIC ARTHRITIS

Within group I, 28 patients were enrolled, 20 of which were women and 8 were men. The minimum age was 25 years, the maximum age was 68 years, and the mean age was 52.5 years.

Altogether, 840 wrists, MCP, PIP, DIP joints were examined in 28 patients. From the clinical point of view, of the 840 joints, 32 were swollen and 59 had pain at palpation.

MSUS revealed the presence of synovial proliferation 108/840 examined joints, quantifying the synovitis as follows:

- Grade 1 - 4 joints;
- Grade 2 - 94 joints;
- Grade 3 - 10 joints.

The most affected joints were the second and third MCP joints. PD signal was highlighted in 29 of 840 joints and 32.14% of patients, respectively.

For evaluation of tenosynovitis, the flexor tendons of the fingers, the extensor compartment, as well as the flexor compartment of the wrist were examined.

The severity of tenosynovitis in SG was quantified as follows:

- Grade 1 - 0 tendons;
- Grade 2 - 40 tendons;
- Grade 3 - 8 tendons.

The most commonly affected tendons were the tendons of the flexors of the fingers (38 of the 48 tendons with inflammatory changes), followed by the extensor carpi ulnaris tendon and the flexor carpi radialis tendon. PD signal was detected in 20.83% of tendons with structural abnormalities.

GROUP II OF PATIENTS WITH PSORIATIC ARTHRITIS

Study group II included 28 patients (18 women and 10 men) with an average age of 51.28 (± 2.22) years.

The clinical examination assessed swelling or pain at palpation of the entheses included in the LEI score as follows:

- Achilles tendon - 20 patients;
- Femoral medial condyles - 6 patients;
- Humeral lateral epicondyles - 11 patients.

MSUS in GS and PD revealed structural changes at the following examined sites:

- Achilles tendon - 21 patients;
- Plantar fascia - 12 patients;
- Proximal patellar tendon - 5 patients;
- Distal patellar tendon - 4 patients;
- Quadriceps tendon - 8 patients;
- Common extensor tendons in the lateral humeral epicondyles - 13 patients.

The scores for enthesal involvement, LEI and BUSES, showed a statistically significant association, $p = 0.001$.

THE GROUP OF PATIENTS WITH REACTIVE ARTHRITIS

The study group included 10 patients (6 males, 4 females) with a minimum age of 17 years, a maximum age of 54 years, and an average age of 34.5 years.

Inflammatory changes such as effusion / synovial proliferation were detected by ultrasound in 75% of patients. In terms of tendon pathology, tenosynovitis / tendinitis / enthesitis changes were noted in 65% of patients, most commonly in the Achilles tendon (35%), followed by the posterior tibialis tendon (30%) and the peroneus tendons (25 %).

MSUS highlighted the following changes in Achilles tendon:

- Thickening - 6 tendons;
- Hypoechoogenicity - 7 tendons;
- Loss of fibrillar pattern - 7 tendons;
- Entesophytes - 3 tendons;
- Erosions - 1 bone cortex;

- Presence of PD signal - 4 tendons.

THE GROUP OF PATIENTS WITH ENTEROPATHIC ARTHRITIS

The group included 6 patients with IBD, either ulcerative colitis, Crohn's disease and peripheral articular disease, diagnosed with enteropathic arthritis, aged 20-42 years, the mean age being 26.75 years.

Ultrasound examination of the hip, knee, ankle, wrist, MCP, PIP and DIP joints were performed. The ultrasonographic findings were distributed as follows:

- Synovial proliferation - 10 joints;
- Joint effusion - 2 joints.

The enthesitis / enthesopathy type changes were examined in the Achilles, patellar, quadriceps and plantar fascia tendons, with MSUS showing thickened tendons, hypoechogenicity with loss of fibrillar pattern and / or enthesophytes in 4 tendons.

II.4. DISCUSSIONS

Musculoskeletal ultrasound evaluation has demonstrated a high potential for identifying inflammation in early stages, determining groups of patients with low prognosis and monitoring the effects of conventional or biological disease modifying drugs on disease progression.

Numerous studies in the literature confirm the utility of musculoskeletal ultrasound in rheumatology as well as the echographic changes highlighted in my study. Also, the significant statistical association between clinical and ultrasound scores is supported in several recent studies.

II.5. CONCLUSIONS

- In the group of patients with PsA, we have shown that the wrist joint and MCP joints are most frequently affected. In addition, the presence of synovial proliferation was more frequently encountered in the second and third MCP joint.
 - In terms of highlighting tenosynovitis in PsA patients, MSUS has proven useful in detecting more affected tendons than those revealed by clinical examination. We also demonstrated that the most frequently affected tendons in the hands were flexor tendons in the fingers.
 - Enthesal changes were mainly observed in the Achilles tendon and plantar fascia in patients with APs.
 - The BUSES echographic score presented a statistically significant association with the LEI clinical score ($p = 0.001$).
 - The most frequent ultrasonographic changes at Achilles tendon level were increased tendon thickness, hypoechogenicity and loss of fibrillar pattern (over 90%).
 - The SPARCC clinical score and the BUSES echographic score had a statistically significant association, $p = 0.018$.
 - The pattern of joint involvement was of the monoarthritic type in 30% of the patients, and oligoarthritic and polyarthritic in 50% and 20% of patients diagnosed with RA, respectively.

- Regarding the type of joint involvement, the CD patients included in the study had involvement of the small joints of the hand, in contrast with UC patients which presented an oligoarticular pattern of the disease.

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