

DYSARMA II STUDY: UTILITY OF ULTRASOUND IN THE DETECTION OF CHANGES PREDICTIVE OF SEVERITY (PAIN AND DYSFUNCTION) IN WOMEN WITH HAND OSTEOARTHRITIS

ESTUDO DISARMA II: UTILIDADE DA ECOGRAFIA NA DETECÇÃO DE ALTERAÇÕES PREDITIVAS DE GRAVIDADE (DOR E DISFUNÇÃO) EM MULHERES COM OSTEOARTROSE DAS MÃOS

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**DYSARMA** STUDY: UTILITY OF ULTRASOUND IN THE DETECTION OF CHANGES PREDICTIVE OF SEVERITY (PAIN AND **DYSFUNCTION**) IN WOMEN WITH HAND OSTEO**ARTHRITIS**

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## **ABSTRACT**

**Introduction:** Hand osteoarthritis (HOA)... **Objective:** ...**Population and methods:** ..

**KEY-WORDS:** hand osteoarthritis; disability; erosive osteoarthritis; prognosis; severity; ultrasound; erosions; synovitis; power Doppler

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## RESUMO

**Introdução:** A osteoartrose (OA) das mãos ...**Objectivo:** ...**Participantes e métodos:**

...

**PALAVRAS-CHAVE:** Osteoartrose das mãos; disfunção; artrose erosiva; prognóstico; gravidade; erosões; ecografia; sinovite; power Doppler

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## **INTRODUCTION**

Osteoarthritis (OA), a heterogeneous group of conditions that lead to articular symptoms and signs associated to the deficient cartilage integrity and to subchondral bone changes (1), is the most frequent articular disease, affecting the whole joint components (2). Hands are a frequent OA localization (3,4). Hand OA (HOA) definition can be clinical, using the classification criteria of the American College of Rheumatology (ACR) (5), or radiographic, using the radiographic changes described by Kellgren and Lawrence (6). This limits the study of disease prevalence (7) and causes heterogeneity in the different studies. Other radiographic indexes have been proposed to HOA, such as the Kallman index (8) or the radiographic progression index of Verbruggen and Veys (9). There is a distinct pattern of HOA, called erosive OA (EOA) (10,11), defined by the radiographic appearance of central joint erosions and subchondral bone collapse at the interphalangeal (IF) joints (12,13). It is not clear if this is a different entity or a phase in the evolution of HOA (14). A study estimated the prevalence of EOA in the general population to be 2,8%, being 8% in the cases of extensive radiographic HOA and 8,5 to 10% in the cases of symptomatic HOA (7,15). EOA is associated with greater prevalence of pain, worse functional prognosis and worse quality of life (7,16-18). Nevertheless, at least in part this greater severity can be attributed to the coexistence of nodal OA (19).

Genetic factors are relevant to the initiation and progression of HOA (12-16), and some genes and genetic polymorphisms have been suggested to be associated to some HOA patterns (17-20). Other factors have been associated with HOA progression, namely obesity and profession (3). HOA predominates in women (21) and affects particularly distal interphalangeal (DIP), trapezo-metacarpal (TMC) - rizarthrosis and proximal interphalangeal (PIP) joints, that have different roles in the manual functions. Beginning in the peri-menopause, HOA causes articular pain, stiffness and swelling, in an additive pattern (22).

The prevalence of radiographic HOA was 56% in a Netherland population, in which 11% individuals were symptomatic (38). Auto-declared prevalence of HOA (including nodal and rizarthrosis) was 13,5%, according to a study in 2004 in 980 adults in Portugal, by telephonic inquiry (39). Framingham study showed a prevalence of radiographic HOA in 50% of women

and 48% of men, in general population, being progressive in more than 80% of individuals (40). Cohort studies show that almost 51% of women with more than 65 years have radiographic HOA (41) and, of these, in 20 to 40% HOA is symptomatic (38,42,43).

HOA evolution occurs with clinical and radiographic deterioration (20) in almost half cases, related to the degree of initial pain and dysfunction (21). Clinically, the characteristic bone swellings come to evidence, named Heberden (in DIP) and Bouchard (in PIP) nodes, associated with relative frequency to lateral joint deviations, more pain and dysfunction (19). Radiographically, there is a growth of osteophytes and narrowing of joint space, but the radiographic lesions can be symptomatic or not (16).

Some comparative studies with patients with HOA and rheumatoid arthritis (RA) revealed that the dysfunction between the two groups can be similar (22-25), and quality of life is worse than in healthy population, for the two conditions, and can be similar between them (26,46,47).

EpiReumaPt is the first portuguese national survey about rheumatic diseases. Its primary aim is to determine the prevalence of rheumatic diseases in Portugal and its specific objectives are to estimate the prevalence of the different rheumatic diseases in Portugal, identify socio-demographic and clinical factors associated to each diagnosis and determine the impact of rheumatic diseases in the quality of life, function and work capacity. Over four years, 10.000 individuals (about 1% of total national population) will be interviewed and evaluated by rheumatologists in the field, in a huge project that began on September in 2011 (50).

Ultrasonography (US) is an imaging technique progressively more recognized to be useful in the evaluation of different articular diseases, such as rheumatoid arthritis. It has high resolution, does not have ionizing radiation, permits multi-planar joint imaging and a dynamic observation, is relatively inexpensive and so practical that it can be done inside the consultation room (27,28). Recent studies in inflammatory arthritis have demonstrated ultrasound to be more sensitive than radiography to the presence of cortical defects (29,30, 33, 35,48) and to have reasonable sensitivity compared with magnetic resonance imaging to the presence of synovitis and cortical defects (31,32).

Radiological scores of joint damage in OA rely mainly on joint space narrowing and on osteophytes, lesions that take some time to manifest, while synovial inflammation can appear more rapidly and be short lived (33). These characteristics and the higher sensitivity of US than conventional radiographs in detecting osteophytes and erosions make US a better tool to diagnose early HOA, particularly the features commonly associated with worse prognosis in radiographic assessment. It can be performed as a follow-up technique, allowing monitoring therapeutic response, as shown already by a recent trial (49), and progression to deformation and dysfunction. Ultrasound can visualize intra-articular and peri-articular changes, such as

synovitis, effusion, the presence of power Doppler signal, articular cartilage thickness, erosions and even osteophytes (27, 28,33-39).

In general, it is possible to state that US can detect and measure inflammation (synovitis, effusion, Doppler sign presence), and so be preferable to radiography in early HOA evaluation, but also in the detection of osteophytes and bone erosions (33,35,48). There is correlation between this inflammation parameters detected and measured by US and the clinical status of HOA (36,37,41). The detection of central erosions can be limited by the interposition of osteophytes, with narrowing of the acoustic window (27,28,34), which probably justifies why the studies diverge in US sensitivity compared to radiography in the detection of central erosions in HOA (34,35), but they are in line to state that US detects erosions better than radiographs. The evaluation of cartilage thinning is not standardized yet (27). A group of experts in the field of OA, US and novel tool development are preparing an US outcome scoring system for hand OA to be used in multicenter clinical trials, that includes as parameters synovitis, power Doppler and osteophytes (42).

## **RELEVANCE OF THE STUDY**

The relationship between the presence of radiographic changes, including erosions, and the more severe functional impairment in patients with RA is nowadays clearly established. In these patients, the aim of treatment is remission, to avoid dysfunction and consequent incapacity, with its associated personal, social and economic costs. In the case of HOA, patients may have radiographic erosions and severe joint deformities, even during professionally active age, with dysfunction, impairment and reduced quality of life identical to the ones in RA (46,47), which reinforces the need for a good follow-up and for new therapeutic strategies (43). Classical diagnosis of erosive OA relies and depends on hand radiography, that shows the typical inflammation consequences, such as erosions and collapse of the subchondral bone, but not the inflammation signs themselves.

Ultrasonography is an imaging technique that is progressively more used, to characterize changes in different articular diseases. Recent studies demonstrated a better sensitivity compared to radiography in the detection of HOA osteophytes (35,39), and also a higher sensitivity to identify central erosions(35,48). Ultrasound can also detect other significant joint changes associated with severity in HOA, particularly some changes that radiography is not able to show, such as synovitis, so it can be a good (and probably better) tool to evaluate early HOA, identify joints at risk of higher deterioration and help to predict worse outcome. It would permit to detect in an early stage of disease which patients would benefit from a more intensive and specialized follow-up and would need more efficient treatment.

The investigators intend to conduct a study to answer the following **research questions**:

1. Are there clinical or imaging patterns of HOA and/or anthropometric, socio-demographic or psychosocial variables associated with clinical and functional severity and/or with worse clinical and functional outcomes?
2. Can ultrasound evaluate and predict, in an early symptomatic stage, worse clinical and functional HOA prognosis?
3. Is ultrasound performing at least as well, or maybe better than radiography in detecting early joint changes in patients with recent clinical HOA and in predicting a worse clinical and functional HOA outcome?

We will look for factors associated with severity (more elevated degrees of pain and dysfunction) of HOA, in a cohort of women from a community based population (EpiReumaPt), indicating the need for a more intensive treatment and a more regular and specialized follow-up, in order to modify HOA evolution. The choice of a community base population will capture an enlarged range of disease severity, avoiding a selection bias that would be likely to occur if they were chosen from the health system (for instance, in specialty consultations).

We will compare the performance of radiography (osteophytes and erosions) and of ultrasound (osteophytes, erosions, synovitis and power Doppler signal) in the evaluation of symptomatic early HOA. We will then relate the initial ultrasound and radiographic changes to the clinical and functional progression over two and four years. The principal aims of this study are: to investigate if some variables relate to worse clinical and functional outcomes in HOA; to investigate if more pronounced joint abnormalities in the evaluation with ultrasound of symptomatic early HOA are associated with worse clinical and functional outcomes. The secondary aims are to investigate if ultrasound performs better than radiography for the early detection of joint abnormalities and for the prediction of a worse outcome.

## **AIMS**

### **Primary:**

1. Identify anthropometric, socio-demographic and/or psychosocial variables or patterns of HOA that can be associated with a more elevated degree of pain or dysfunction and/or with worse clinical outcome
  - i. Hypothesis: elevated BMI, professions that suppose a greater manual effort, diagnosis of past or present depression, the existence of first degree family history of HOA, the presence of rizarthrosis or the presence of erosive arthrosis relate to a more elevated degree of pain and dysfunction and to worse clinical outcome

2. Investigate if more early joint changes evaluated with ultrasound relate to worse clinical and functional prognosis in early symptomatic HOA
  - i. Hypothesis: synovitis, erosions and Doppler signal detected by ultrasound in early clinical HOA predict worse clinical prognosis
3. Investigate if ultrasound is at least as valid as digital radiography in detecting early joint changes and in predicting worse clinical outcome in early symptomatic HOA
  - i. Hypothesis: ultrasound is more valid than digital radiography in detecting early joint changes and in predicting worse clinical outcome in early HOA

## **POPULATION AND METHODS**

### **POPULATION**

#### **INCLUSION CRITERIA**

1. Women censed in the population of EpiReumaPt, with clinical HOA defined by the ACR criteria and no more than two years of symptomatic evolution

#### **2. EXCLUSION CRITERIA**

1. History of rheumatoid arthritis, psoriatic arthritis, gout or other known arthritis, hemochromatosis or psoriasis
2. Traumatic deformations of one or both hands

### **METHODS**

This is a cohort follow-up study, with a baseline evaluation and subsequent evaluations at two and four years.

#### **1. Baseline evaluation**

After obtaining approval from an ethic commission, we will conduct this study in three phases: baseline evaluation, at two years and at four years. Data for baseline evaluation will be collected in the field, throughout the Portuguese continental territory only, excluding the islands, for practical reasons. We will have the records of 300 women censed in the national epidemiological wide study of EpiReumaPt, with diagnosis of HOA by ACR criteria with no more than two years of symptoms or signs duration.

EpiReumaPt is the first portuguese national survey about rheumatic diseases. Its primary aim is to determine the prevalence of rheumatic diseases in Portugal and its specific objectives are to estimate the prevalence of the different rheumatic diseases in Portugal, identify socio-demographic and clinical factors associated to each diagnosis and determine the

impact of rheumatic diseases in the quality of life, function and work capacity. Over four years, 10.000 individuals (about 1% of total national population) will be interviewed and evaluated by rheumatologists in the field, in a huge project that began on September in 2011. All the individuals evaluated in this study previously gave written informed consent to the use of collected clinical and radiographic data.

ACR classification criteria for HOA are: hand pain, aching or stiffness for most days of prior month AND at least three from the following criteria: 1. Hard tissue enlargement in at least 2 of 10 selected hand joints (second and third DIP, second and third PIP and TMC on both hands); 2. Bone swelling in at least two DIP; 3. Fewer than 3 swollen metacarpophalangeal (MCP) joints; 4. Deformity of at least 2 of 10 selected joints (5).

The records of women with HOA introduced in EpiReumaPt have the following data, to permit the baseline evaluation: age, learning degree, profession and working situation, leisure occupations, weight and height to calculate body mass index (BMI), age at menopause, hormonal substitution therapy and duration, first degree family history of HOA, past and present diseases, namely psoriasis, rheumatoid arthritis, psoriatic arthritis, arthritic gout or other arthritis, hemochromatosis, thyroid diseases, diabetes, hypertension, hypercholesterolemia, traumatic deformity of one or both hands, past or present depression, present medication, joint pain and/or stiffness in fingers, presence and localization of non-traumatic deformities of fingers. Women who have some exclusion criteria will not be included in the present study. The others will be included and proceed to clinical evaluation.

The clinical evaluation comprises the application of a 100 mm visual analogic scale (VAS) to assess digital joint pain during the past 48 hours, the number of tender joints on palpation, number of inflamed joints (defined as having erythema, recent flare in pain and/or soft periarticular swelling) (44), morning stiffness degree in 100 mm VAS and duration and the number of deformed joints (presence of Heberden (HN) or Bouchard nodes (BN), lateral or flexion deviation of DIP or PIP, TMC subluxation), in 20 joints (5 DIP, 4 PIP and 2 TMC, bilateral). This evaluation is done by different rheumatologists throughout continental Portugal. We will consider as significant pain a score of  $\geq 40$  mm on a VAS.

Functional disease evaluation will be performed by the Dreiser index (FIHOA) (45), which includes 10 questions about daily life activities and evaluates for each of them the degree of dysfunction between 0 and 3, with a maximal score of 30 (range 0-30). The choice of this HOA functional index relates to the fact that it was the first validated in HOA, it is simple and has good reproducibility. This index demonstrated a comparable association with grip strength and with radiographic severity. Will be considered as relevant a dysfunction a score of  $\geq 5$ .

After this clinical and functional evaluation, all women will do a bilateral postero-anterior hand radiograph, parallel on the same cassette, that will be stored in digital support and identified only with a number, for the blind reading by the investigators. Radiographs will permit to score the location and severity of radiographic HOA. The evaluation will be based on

osteophytes and erosions only, using the Verbruggen and Veys score. This HOA specific radiographic index evaluates a total of 22 joints (symmetrically 11 in each hand: 5 DIP (including first finger IP), 4 PIP, TMC and scaphotrapezial joint), with a graduation between 0 and 3 for osteophytes and joint space narrowing and 0 or 1 for the absence/presence of subchondral bone sclerosis, subchondral cysts, deformity (subluxation > 15 degrees) and bone erosion. Erosions are not scored for the thumb base joints. Osteophytes and deformation are not scored for scaphotrapezial joint. All radiographs will be blindly evaluated by two investigators, to graduate osteophytes and erosions in 20 joints, excluding the scaphotrapezial joints. For this study evaluation, the number of joints with erosions and the number of joints with osteophytes will be considered, in separated scores (from 0 to 18 and from 0 to 20, respectively).

The training of the two raters will be realized after they familiarize with the Verbruggen and Veys scoring and discuss it first, in a session with 10 random hand radiographies (20 hands, 400 joints). The inter-reader reliability will be determined. To determine the intra-reader reliability, the rating will be repeated by both investigators, one month later, with the same random radiographies.

Radiographies that reveal changes due to other rheumatic diseases, namely arthritis, findings of hemochromatosis or crystal deposition arthropaties, will lead to exclusion of those women. Doubtfull cases will be analyzed by the two investigators, to decide the exclusion or not.

After that, all women will be evaluated with ultrasound (US) by two investigators that are unaware of the radiography findings, in a General Electrics apparatus, model Logiq 9, with a linear probe using a 9-12 MHz frequency in mode B and power Doppler. For the Doppler evaluation, parameters will be: lowest PRF (0,5 to 1 KHz), appropriate colour gain (below level causing noise artifacts), medium wall filter and the focus in the area of interest, including the upper part of the image, to avoid reverberation artifacts. The US joint examination will be performed using light pressure and a large quantity of visible scanning gel between the transducer and the skin and as multi-planar, longitudinal and transversal, continuous to see from ulnar to radial sides, volar and dorsal sides in full joint extension and dorsal side also in flexion (to find erosions), in the defined 20 joints. The parameters to evaluate will be osteophytes, erosions, synovitis and power Doppler signal, defined as present or absent. For this study evaluation, the number of joints with erosions, the number of joints with osteophytes, the number of joints with synovitis and the number of joints with Doppler signal will be considered, in separated scores (from 0 to 20, in each one except for erosions, from 0 to 18).

There are OMERACT US definitions for synovial hypertrophy (abnormal hypoechoic – relative to subdermal fat, but sometimes may be isoechoic or hypoechoic – intra-articular tissue that is nondisplaceable and poorly compressible and which may exhibit Doppler signal), synovial fluid (abnormal hypoechoic or anechoic intra-articular material that is displaceable and

compressible, but does not exhibit Doppler signal) and erosions (an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes), in the context of RA (40), but the authors consider that they can be applied to HOA as well (27,28, 42). There are no OMERACT definitions for osteophytes, but the definition by Keen – cortical protrusions of the joint margin, seen in two planes and visualized as either proximal or distal to the joint (39) can be used (27,28). The articular cartilage changes, namely thinning, can be appreciated (27,33,36,38,39), but there is as yet no consensus about it.

The two investigators will perform a previous session to familiarize with the apparatus settings and with the definitions. Then, in a session they will rate 20 hands (400 joints) from 10 patients and the inter-reader reliability will be determined.

## **2. Evaluation at two years**

After two years, all women will be again evaluated. The same clinical parameters will be recorded (pain score on VAS, number of tender and inflamed joints, morning stiffness), as well as the functional status, with FIHOA. Radiography will be performed again, to evaluate as dichotomous variables the presence of osteophytes and erosions. Ultrasound will be performed as well, to search for osteophytes, erosions, synovitis and power Doppler signal. The aim is to compare the initial evaluations with the subsequent ones, to analyze HOA structural progression and to relate it with functional status at the beginning. The performance of ultrasound and of radiography will also be compared, as to the association with worse prognosis.

## **3. Evaluation at four years**

After four years, all women will be again evaluated. The same clinical parameters will be recorded (pain score on VAS, number of tender and inflamed joints, morning stiffness), as well as the functional status, with FIHOA. Radiography will be performed again, to evaluate as dichotomous variables the presence of osteophytes and erosions. Ultrasound will be performed as well, to search for osteophytes, erosions, synovitis and power Doppler signal. The aim is to compare the initial evaluations with the subsequent ones, to analyze HOA structural progression and to relate it with functional status at the beginning. The performance of ultrasound and of radiography will also be compared, as to the association with worse prognosis.

## **STATISTIC ANALYSIS**

The distribution of continuous variables will be described by the respective mean and standard deviation (in case of normal distributions) or the median and interquartile interval (in case of distribution other than normal). Categorical variables distribution will be described by proportions.

The proportions will be compared between groups by Chi-square or Fisher tests, as appropriate. To compare continuous variables distribution between two or more groups the t-Student and ANOVA tests will be used (to normal distributions) or Mann-Whitney or Kruskal-Wallis tests (to distributions other than normal). The linear relationship between two continuous variables will be quantified by the correlation Pearson or Spearman coefficients, as appropriate.

The associations between the exposures in the study and the outcomes characterized by continuous variables (pain, dysfunction) will be quantified using simple linear regression coefficients and respective confidence intervals to 95%, to estimation of raw coefficients, or multiple linear regression, to estimate coefficients adjusted to potential confounders. The associations with outcomes defined by categorical variables will be estimated by the respective coefficients and confidence intervals to 95%, obtained by logistic regression binomial or multinomial, raw or adjusted. The outcomes pain and dysfunction will be analyzed as continuous and as categorical variables.

Using the above described methods, we will estimate:

**A. Baseline determinants and longitudinal predictors of clinical severity of HOA**

- a. Association between baseline BMI and degree of pain and dysfunction (BMI vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)
- b. Association between profession and degree of pain and dysfunction (profession vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)
- c. Association between past or present depression and degree of pain and dysfunction (depression vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)
- d. Association between family first degree history of HOA and degree of pain and dysfunction (mother or father or siblings and how many with HOA vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)
- e. Association between family first degree history of HOA and erosive arthrosis (mother or father or siblings and how many with HOA vs radiographic erosive arthrosis in  $\geq 2$  joints)
- f. Association between family first degree history of HOA and rizarthrosis (mother or father or siblings and how many with HOA vs radiographic rizarthrosis)
- g. Association between baseline number of deformed IP joints and degree of pain and dysfunction (number of IP deformed joints vs VAS and number of

tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)

- h. Association between baseline degree of pain and degree of dysfunction (VAS and number of tender and inflamed joints vs FIHOA score at baseline, 2 and 4 years evaluation)
- i. Association between baseline radiographic rizarthrosis and degree of pain and dysfunction (radiographic rizarthrosis vs VAS and number of tender and inflamed joints and vs FIHOA score, with or without HOA of IP, at baseline, 2 and 4 years evaluation)
- j. Association between baseline radiographic erosive HOA and degree of pain and dysfunction (radiographic erosive HOA vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)

**B. Compared performance of ultrasound and of radiography in the detection of early HOA changes and association with clinical and functional status (baseline imaging vs clinical parameters in a cross-sectional analysis)**

- a. Association between baseline radiographic findings and degree of pain and dysfunction (number of joints with radiographic erosions and osteophytes vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)
- b. Association between number of baseline sonographic findings and degree of pain and dysfunction (number of joints with ecographic erosions, osteophytes, synovitis and Doppler signal above 50% synovitis area vs VAS and number of tender and inflamed joints and vs FIHOA score, at baseline, 2 and 4 years evaluation)
- c. Number of joints with erosions detected with radiograph and comparison with number of joints with erosions detected by ultrasound, at baseline, 2 and 4 years evaluation
- d. Number of joints with osteophytes detected with radiograph and comparison with number of joints with osteophytes detected by ultrasound, at baseline, 2 and 4 years evaluation

**SIZE OF COHORT**

The cohort size was calculated assuming a participation proportion of 60%, including in the non participants women not possible to contact or who don't accept to participate. Between participants, we estimate that 60 to 70% refer symptoms. The resulting cohort size (n=120) will allow the calculation of prevalence of 50%, with a 3% precision, a statistical power of 80% to a significance level of 0,05.

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