



Does non-erosive rheumatoid arthritis exist? A cross-sectional analysis and a systematic literature review



Jenny Amaya-Amaya^{a,b}, Omar-Javier Calixto^{a,b}, Sandra Saade-Lemus^a,
Enrique Calvo-Paramo^{a,c}, Ruben-Dario Mantilla^{a,b}, Adriana Rojas-Villarraga^{a,b},
Juan-Manuel Anaya^{a,b,*}

^a Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Carrera 24 No. 63C-69, 11001000 Bogotá, Colombia

^b Mederi, Hospital Universitario Mayor, Bogotá, Colombia

^c School of Medicine, Universidad Nacional de Colombia, Bogotá, Colombia

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ABSTRACT

Objective: To evaluate the prevalence and factors associated with non-erosive rheumatoid arthritis (RA).

Methods: First, a cross-sectional analytical study was performed. Non-erosive disease, defined as the absence of any erosion on X-rays after 5 years of RA, was evaluated in 500 patients. Further and additional evaluations including ultrasonography (US) and computed tomography (CT) were performed in those patients meeting the eligibility criteria. The Spearman correlation coefficient, kappa analysis, and Kendall's *W* test were used to analyze the data. Second, a systematic literature review (SLR) was performed following the PRISMA guidelines.

Results: Of a total of 40 patients meeting the eligibility criteria for non-erosive RA, eight patients were confirmed to have non-erosive RA by the three methods. A positive correlation between non-erosive RA and shorter disease duration, antinuclear antibodies positivity, lower rheumatoid factor (RF) and C-reactive protein titers, lower global visual analog scale values, toxic exposures, and lower disease activity-(RAPID3) was found. In addition, an inverse correlation with anticyclic citrullinated peptide antibodies (ACPA) positivity and medication use was observed. From the SLR, it was corroborated that factors associated with this subphenotype were shorter disease duration, younger disease onset, negative ACPA and RF titers, low cytokine levels, and some genetic markers.

Conclusion: Non-erosive RA is rare, occurring in less than 2% of cases. These findings improve on the understanding of RA patients who present without erosions and are likely to have less severe disease.

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Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthropathy worldwide. It is a chronic, multifactorial, and heterogeneous autoimmune disease (AD) characterized by the presence of long-standing inflammation of the diarthrodial joints, resulting in symmetric polyarthritis and systemic manifestations [1]. As with most ADs, it predominantly affects women, and its prevalence has been reported to be between 0.3% and 1.6% [2].

Chronic inflammation ultimately affects the joints, causing synovial membrane hypertrophy and bone and cartilage destruction. Erosion is the hallmark of the disease and is generally progressive and considered irreversible [1]. The presence of erosion at diagnosis is one of the factors most suggestive of a poor prognosis. Erosion reflects the cumulative history of the disease and correlates with deformity, disability (i.e., mainly in the hands [3] and the feet [4]), decreased functional work capacity, premature mortality, and reduced quality of life [5].

Radiographic assessment of joint damage is the most widely accepted standard tool for diagnosis, determination of disease extent, and RA follow-up. Despite demonstrating a high specificity in erosion detection, radiographs lack sensitivity in early disease [6]. Consequently, newer imaging techniques have been developed to improve diagnosis and follow-up of bone erosions [7].

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* Corresponding author at: Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Carrera 24 No. 63C-69, Bogotá 11001000, Colombia.

E-mail address: juan.anaya@urosario.edu.co (J.-M. Anaya).

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Even though erosions may occur within 2–3 years of onset of the disease, their progression does not correlate with the duration of RA. The factors associated with radiological progression have to be identified to aid in starting early, appropriate, and aggressive therapy before radiographic damage occurs [8,9]. However, few studies have evaluated the factors associated with erosion-free status [10]. Therefore, predictive factors for non-erosive disease cannot be considered as the simple converse of those associated with erosive disease. Moreover, the reported information about non-erosive RA is ambiguous. Thus, the purposes of this study were to evaluate the prevalence and factors associated with non-erosive RA by means of a cross-sectional study and systematic literature review (SLR) and to examine the sensitivity and specificity of different erosion assessment methods in patients with RA.

Material and methods

Study population

This was a cross-sectional analytical study in which 500 consecutive patients fulfilling the 1987 American College of Rheumatology (ACR) classification criteria for RA [11] were included. Other causes of polyarthritis (i.e., chondrocalcinosis, spondyloarthropathies, and other ADs) were excluded following the international classification criteria (as shown in [supplementary material](#)). The subjects were examined at the Center for Autoimmune Diseases Research (CREA) in Bogota, Colombia. This study was undertaken between February 1996 and April 2012 and was conducted in compliance with Act 008430/1993 of the Ministry of Health of the Republic of Colombia. The Institutional Review Board of the Universidad del Rosario approved the study design. Each patient was evaluated by a rheumatologist. The information on patient sociodemographic and cumulative clinical and laboratory data was obtained by interview, physical examination, and chart review, as previously reported [12].

Radiological assessment

As there is no agreement about the time lag interval for lack of erosions in RA, and there is no universally accepted definition for non-erosive RA, a zero score through an evaluation by two blinded researchers, a musculoskeletal radiologist (E.C.P.) and a rheumatologist (A.R.V.), according to a modified Sharp-van der Heijde (SvHD) method [13] in the last follow-up radiographs of the hand and the feet (posteroanterior view) in patients with a disease duration of more than 5 years of RA was considered as the eligibility criteria for such a condition. Last follow-up radiographs must meet the criteria of being taken in the last year of the disease. Eligible patients were invited for reassessment, which included new X-rays, ultrasound (US) imaging, and computed tomography (CT).

For qualified patients, radiography was conducted using an IEC Explorer Direct Capture, 1600 (Toshiba, Otawara, Japan). Posteroanterior radiographic projection of the hands and the feet was obtained. For CT examinations, a Toshiba Aquilion 64 CXL multi-detector unit (Toshiba, Otawara, Japan) was used. Patients were examined, including their wrist, metacarpophalangeal (MCP), proximal interphalangeal (PIP) joints in the hands and the metatarsophalangeal (MTP) joints in the feet. Images with an in-plane resolution of 0.4 mm × 0.4 mm and slice thickness of 0.5 mm were obtained, and Quantum Denoising Software for multiplanar reconstruction created 3D reconstructions with a slice thickness of 0.5 mm, and these were used for image evaluation. To assess the inter-observer agreement, CT and X-ray images were evaluated

independently by two blinded researchers (A.R.V. and E.C.P.). Prior to the evaluation, it was decided that E.C.P.'s scoring would be used for comparison with the results of the other imaging modalities.

US analyses were performed by a musculoskeletal radiologist (E.C.P.) with experience in the US of RA joints. The General Electric LOGIQ® E unit (General Electric Healthcare Medical Systems, Milwaukee, WI, USA), with a linear array transducer of 7–12 MHz, was used for all examinations. The dorsal and palmar aspects of the second and third MCP and IFP joints and second and fifth MTP joints were evaluated for synovitis, joint effusion, and inflammation. On the wrist, the dorsal, palmar, ulnar, and radial aspects were examined for the same parameters. Erosions were assessed on all joints (i.e., first to fifth MCP, PIP, MTF, and wrist).

All imaging modalities were evaluated with investigators blinded to clinical and other imaging data. On the X-rays, each joint quadrant was scored for the presence or absence of erosions following the SvHD method [13]. Erosions on CT were defined as a sharply demarcated area of focal bone loss observed in two planes, with a cortical break (loss of cortex) observed in at least one plane. These images were evaluated by using the rheumatoid arthritis magnetic resonance scoring system (RAMRIS) method [14]. US erosions were defined as irregularities of the bone surface of the area adjacent to the joint and observed in two planes, as suggested by the outcome measures in rheumatology (OMERACT) [15] (Fig. 1).

Statistical analysis

The Kendall's tau-*b* correlation coefficient was used in order to evaluate the categorical variables, while the Spearman's correlation test was used to analyze quantitative variables vs. categorical variable (i.e., non-erosive state). The inter-observer and intra-observer agreement between the two readers of the CT and X-ray images were calculated by agreement statistic (Kappa). Statistical significance was considered at 0.05. With CT as the standard reference method, the sensitivity and specificity of X-ray and US were calculated. Statistical analysis was performed in IBM SPSS Statistics 21.

Search strategy of systematic literature review

The SLR of articles on non-erosive RA was conducted using the following databases: PubMed, Scopus, SciELO, and Virtual Health Library (VHL), which includes BIREME, LILACS, and many others LA sources (Fig. 2). The SLR included articles published between January 1971 and February 2014. Three reviewers did the search independently (J.A.A., O.J.C., and S.S.L.) while applying the same selection criteria described below. The search results were compared and disagreements were resolved by consensus. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed in data extraction, analysis, and reporting [16].

The search was performed in PubMed and Scopus, using the following medical subject headings (MeSH terms): “Arthritis, rheumatoid,” and “ultrasonography,” or “tomography, X-ray computed,” or “positron-emission tomography and computed tomography,” or “multidetector computed tomography,” or “radiography,” or “X-Rays,” or “magnetic resonance imaging.” Each term was cross-referenced with the following key words: “Non erosive,” or “without erosions,” or “no erosive.” No limits regarding language, period of publication, or publication type were used. A similar strategy was followed for the other databases. Each MeSH term was translated into DeCS (Health Sciences Descriptors) to explore sources of information in Portuguese, Spanish, and English from the SciELO and VHL databases. The following terms were selected: Artritis reumatoide or artrite reumatóide and ecografia, or ultrasonografia, or tomografia, or tomografia computarizada, or tomografia computarizada por emisión de positrones, or radiografia, or rayos X, or

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