Int J Clin Exp Med 2016;9(9):17012-17027
www.ijcem.com /ISSN:1940-5901/IJCEM0027646

Review Article

Conventional radiography in rheumatoid arthritis: new scientific insights and practical application

Fausto Salaffi[1], Marina Carotti[2], Marco Di Carlo[1]

[1]*Clinica Reumatologica, Università Politecnica Delle Marche, Ancona, Italy;* [2]*Dipartimento di Radiologia S.O.D. Radiologia Clinica, Università Politecnica delle Marche, Ancona, Italy*

Received March 7, 2016; Accepted June 5, 2016; Epub September 15, 2016; Published September 30, 2016

Abstract: Rheumatoid arthritis (RA) is a chronic systemic disease of unknown origin that predominantly involves synovial tissue. RA affects 0.5% of the global population, with a clear predilection for women. Conventional radiography (plain radiographs or X-rays) is the most widely used imaging technique for diagnosing and monitoring the progression of RA. Advanced imaging techniques (e.g. magnetic resonance imaging, computed tomography, ultrasound, and nuclear scintigraphy), that are better suited for detecting soft-tissue inflammation are available, but they are more costly and some of them may expose the patient to higher doses of radiation. Plain film radiographs are inexpensive, easy to generate, can be compared with baseline and prospective films, and provide a permanent, reproducible record. The plain radiographs of the hands and feet can detect the features that are specific to RA such as joint space narrowing or erosions, and serial radiography can be used as a objective marker for monitoring treatment response in clinical trials. This review discusses the use of conventional radiography for diagnosing and detecting early structural changes in joints and providing a historical overview of commonly used methods of scoring radiographs in RA.

Keywords: Rheumatoid arthritis, conventional radiography, scoring methods, joint space narrowing, erosions, disease progression

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune joint inflammatory disease that if not treated or poorly controlled by therapy can lead to anatomical lesions and deformation of the joint through erosive changes to the cartilage and the subchondral bone [1]. The prevalence of the disease in Italy is about of 0.5%, with a clear predilection for women (male/female ratio 1:3) [2]. In daily clinical practice and in studies, structural damage in RA is assessed by the presence of bone erosions on conventional radiography. Although nowadays various advanced diagnostic imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), ultrasound (US), and nuclear imaging are at the disposal of the physicians, conventional radiography remains the imaging modality of choice and, therefore, is essential in evaluating the efficacy of experimental treatments [3, 4].

The presence of radiographic bone erosions is fundamental for the classification of RA, according to both the American College of Rheumatology (ACR) 1987 [5] and the ACR/European League against Rheumatism (EULAR) 2010 classification criteria [6]. The definition of erosive disease ('typical erosions') to be applied to 2010 ACR/EULAR criteria is when erosions are seen at least in three separate joints at any of the following sites: the proximal interphalangeal (PIP) joints, the metacarpophalangeal (MCF) joints, the wrist (counted as one joint) or the metatarsophalangeal (MTP) joints on radiographs of both hands and feet [7].

Many researches have shown that, joint damage occurs within the first 2 years after symptoms appearence [8]. Other authors have demonstrated how early versus delayed treatment is associated with better clinical and structural outcomes, emphasizing the precocity of structural damage [9, 10]. With the increasing use of

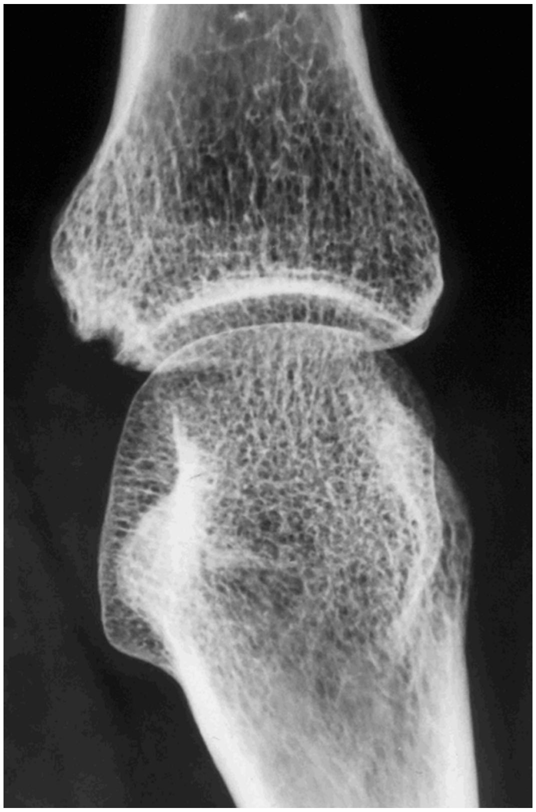

Figure 1. Marginal erosion in rheumatoid arthritis. The patient is a 37-year-old female with symptoms compatible with rheumatoid arthritis for six months. X-ray showing characteristics of erosive rheumatoid arthritis in its early stage: well-defined marginal erosion in the second metacarpophalangeal joint. The joint space is preserved, and neither deformity nor changes in bone alignment are observed.

disease-modifying antirheumatic drugs (DMARDs) and biological agents (bDMARDs), early diagnosis is now of paramount importance and disease progression has to be assessed regularly to monitor efficacy of the treatment [11, 15]. These points were outlined in European recommendations and models for management of early arthritis, and prognostic markers for persistent arthritis have been established [11, 16, 17].

Common radiographic features in RA

Radiographic lesions in RA include soft tissue swelling, juxta-articular osteopenia, bone erosions, joint space narrowing (indicative of loss of cartilage), cysts, joint subluxations, malalignment, and ankylosis [18].

The first radiographic changes observed in RA are soft tissue swelling and periarticular osteopenia. Bone density is reduced adjacent to the joint as a result of local synovial inflammation. Thus, the bone may appear less dense (a darker shade on the radiograph) around the articular surfaces. However periarticular osteopenia is not a specific radiographic sign of RA and can occur in other conditions [19].

Figure 2. Rheumatoid arthritis involving the wrist. The patient is a 56-year-old female with rheumatoid arthritis for 8 years. Plain radiograph, posteroanterior view of the right wrist showing gross erosions in the tip of the ulnar styloid process, marked osteoporosis in the neighboring medullary bone, and thickening of adjacent soft tissues.

The inflamed synovium slowly invades adjacent structures causing damage and destruction to the cartilage. This aggressive process leads to joint space narrowing and bone erosions that can be seen on radiographs. It is important to underline that X-ray imaging provides only limited information on soft tissue lesions. US or MRI are the modalities of choice to visualise these structures and provide useful and objective informations on pathological changes such as synovitis and tenosynovitis [4].

The joint space narrowing in RA tends to be uniform and concentric, reflecting the generalised nature of the synovial inflammation within the joint. This kind of damage may be the most important predictor of irreversible physical disability and work impairment [20].

The erosions in RA tend to be periarticular and are often described as marginal erosions as they are close to the joint and reflect the direct

Figure 3. Rheumatoid arthritis involving the metatarsophalangeal and interphalangeal joints. Radiograph of the both feet shows concentric joint space narrowing in all the metatarsophalangeal joints. Erosions are seen in the first, fourth and fifth metatarsophalangeal joints, which are deformed to some extent, and in the first interphalangeal joints.

mechanical action of the hypertrophied synovium and granulation tissue (**Figure 1**). Marginal erosions are the typical radiographic manifestation of the disease and are part of the classification criteria of RA [6]. These lesions primarily concern the "bare areas" in the periphery of joints and have to be searched for in both hands and feet. The hands are involved symmetrically. Usually, the second and third MCP and the third PIP are the first joints damaged. Distal interphalangeal (DIP) joints involvement without proximal involvement is rare.

The wrist joint is commonly affected in RA, has proved to be more sensitive to changes in bone erosions than other joint areas, and bone changes have been shown to possess a predictive value with respect to further radiographic erosive progression [21-23]. In a longitudinal study of wrist, radiographic erosions of the styloid ulnar were seen as a relatively early isolated finding in 25% of the patients. Moreover, the distal radioulnar joint showed a rapid increase of erosions and was involved in 78% of the patients with established disease [21] (**Figure 2**). In the feet, changes are most commonly seen in the MTP and PIP joints [24, 25]. Erosive damage in feet x-ray can appear before hand involvement becomes clear. All MTP joints could be involved and the fifth MTP joint has been recognized as an area of early joint damage [25-27] (**Figure 3**).

Figure 4. Advanced rheumatoid arthritis. Radiograph of the hand shows severe joint space narrowing of the radiocarpal, intercarpal, carpometacarpal, metacarpophalangeal, and interphalangeal joints. There is also subluxation and deviation of the fingers.

Fusion or joint ankylosis characterize the later stages of RA. Fusion usually takes place in deformed or malaligned position (**Figure 4**). These alterations strongly reduce the functionality of hands and feet with a great impact on the activities of daily living. In the late stages, extensive erosions may be combined resulting in resorption and tapering of the ends of the bones.

The cervical spine is also a common target of RA, ranking only third after the hands and feet in the frequency of involvement [18, 28-30]. The proportion of RA patients who experience cervical spine involvement at some point of their disease has ranged from 14% to 88% [28, 29, 31, 32]. Inflammatory activity in the cervical spine begins early and progresses clinically and radiologically in tandem with the peripheral joint involvement. In fact, the severity of the peripheral erosive damage is strongly correlated with the degree of structural damage in the cervical spine. The atlas-axis - first and second cervical vertebrae (C1 and C2) - articulation is

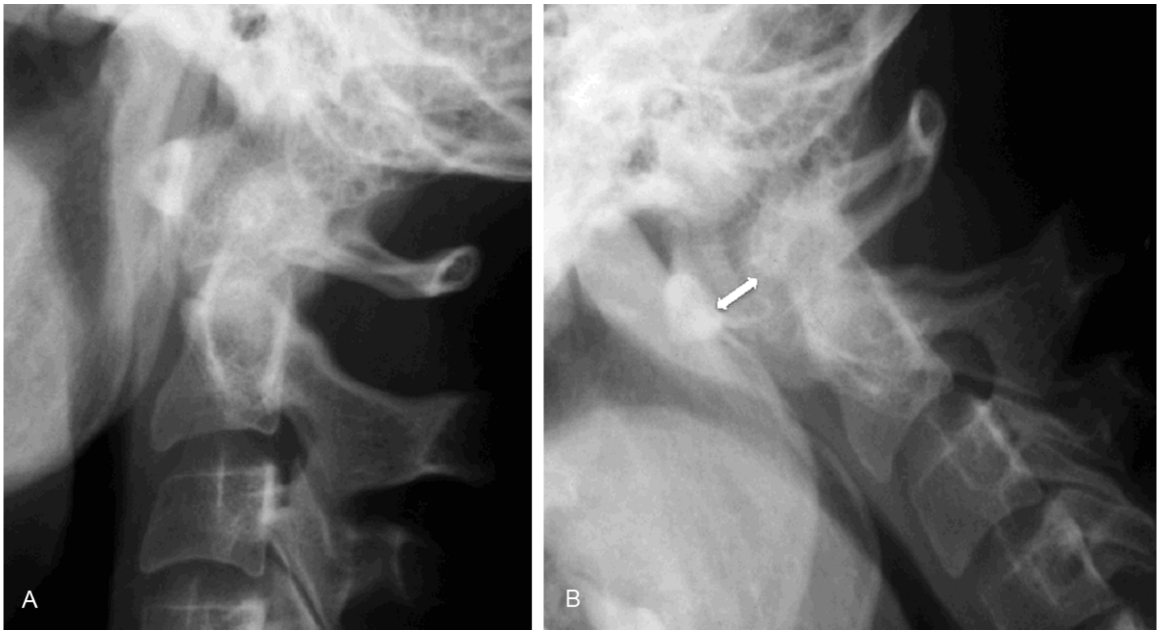

Figure 5. Anterior atlanto-axial subluxation (aAAS) in rheumatoid arthritis. The sensitivity of standard radiography for detecting aAAS can be improved by obtaining extension (A) and flexion (B) views. Anterior AAS is present on neck flexion as the anterior atlanto-dental interval (AADI) (arrow) measures 10 mm, suggestive of severe cervical spine involvement.

one of the chief disease target. The erosive pannus formation at this site often leads to bony destruction and laxity in the surrounding ligamentous complex, especially the transverse. The subsequent loss or malfunction of anchoring structures results in atlantoaxial subluxation (AAS) [33] that is the most common abnormality at the cervical spine, with a prevalence of 5-75% [29, 34-36]. The subluxation can be anterior, posterior, lateral, and vertical. The anterior atlantoaxial subluxation (aAAS) is the most common subtype with a reported prevalence ranges from 10% to 55% [33, 35, 37-40]. A distance of the anterior odontoid peg (dens) from the anterior ring of atlas (anterior atlanto-dental interval-AADI) ranging from 2.5 mm to 5 mm has been considered pathological [41-43]. AADI values greater than 9 mm may indicate severe cervical spine involvement [36, 44]. Posterior AAS is less frequent and usually caused by fracture of the dens [44]. A posterior atlantodental interval smaller than 14 mm was used as a sensitive marker for spinal cord compression [45]. Lateral AAS has been reported in 10-20% of patients [46-48]. This kind of subluxation is considered when lateral masses of C1 are displaced laterally more than 2 mm in comparison with C2. They can lead to head tilt and rotational deformities [49]. Another form of subluxation is the vertical subluxation of the axis (VS), also known as altantoaxial impaction, cranial settling, superior migration of the odontoid, or psuedobasilar invagination. It is secondary to the destruction of occipitoatlantal and atlantoaxial joints and surrounding soft tissues [49]. The methods used to highlight vertical subluxation include McGregor's line, MacRae's line, Chamberlain's line, Ranawat's method, Redlunde Johnell's method, and Kauppie Sakaguchi's method [50-52].

Conventional radiography remains the first-line investigation of choice for detecting cervical spine subluxations. There is general agreement that dynamic views are extremely valuable, most notably for detecting aAAS, which may be present only when the neck is flexed [32, 53] (**Figure 5**). CT reconstructions in the coronal and sagittal planes supply a precise assessment of the C1-C2 complex, thereby ensuring the detection of lateral and vertical AAS [30]. MRI with a range of sections offers the most comprehensive evaluation of rheumatoid lesions. Furthermore, MRI is the only method capable of visualizing a clinically silent C1 e C2 pannus and of providing a detailed assessment of effects on neurological structures [29, 31, 54, 55].

Table 1. Major advantages and disadvantages of conventional radiography in rheumatoid arthritis

	Advantages	Disadvantages
Conventional radiography	Wide availability and easy access	Ionizing radiation
	Low cost	Relative insensitivity to early bone damage
	Images easilily understood by clinicians	Insufficient to assess soft tissues
	Standardization available	Pitfalls due to over-impression of three-dimensional structures on two-dimensional image
	Valid assessment methods	
	Good reproducibility	Technical variables (accurate joint placement, proper exposure, and reproducibility of films)
	High specificity for bone changes (differential diagnostic work-up)	Interpretational variables (reader training, inconsistencies in interpretation of radiographic change)
	American College of Rheumatology classification criteria of rheumatoid arthritis	Pathophysiological variables (lag time of radiographic change behind pathological change)

Table 3. A comparison of common radiographic scoring methods used in rheumatoid arthritis

Type of scoring method	Van der Heijde modification of the Sharp method	Genant modification of the Sharp method	Larsen method
	Detailed	Detailed	Global
Description of scoring system	Erosion is assessed in 16 joints for each hand and wrist, and six joints for each foot. One point is scored if erosions are discrete, rising to 2, 3, 4, or 5 depending on the amount of surface area affected. JSN is scored as follows: 0 = normal; 1 = focal or doubtful; 2 = generalised, less than 50% of the original joint space; 3 = generalised, more than 50% of the original joint space or subluxation; 4 = bony ankylosis or complete luxation.	Erosion is scored according to an eight point scale with 0.5 increments, where 0 = normal; 0+ = questionable or subtle change; 1 = mild; 1+ = mild worse; 2 = moderate; 2+ = moderate worse; 3 = severe; and 3+ = severe worse. JSN is scored according to a nine point scale with 0.5 increments, where 0 = normal; 0+ = questionable or subtle change; 1 = mild; 1+ = mild worse; 2 = moderate; 2+ = moderate worse; 3 = severe; 3+ = severe worse; and 4 = ankylosis or dislocation.	It differentiates six stages from 0 (normal) to 5, reflecting progressive deterioration, and provides an overall measure of joint damage. The grading scale ranges from 0 to 5: 0 = intact bony outlines and normal joint space; 1 = erosion less than 1 mm in diameter or JSN; 2 = one or several small erosions (diameter more than 1 mm); 3 = marked erosions; 4 = severe erosions (usually no joint space left and the original bony outlines are only partly preserved); and 5 = mutilating changes (the original bony outlines have been destroyed).
Advantages and disadvantages	Sensitive for detection of radiographic progression, but requires training and is time consuming to apply.	Sensitive, but presents difficulties in assessing progression of structural damage. Requires training to apply efficiently.	Semiquantitative global method, easier to learn and to use, less sensitive to changes than the modified Sharp methods.

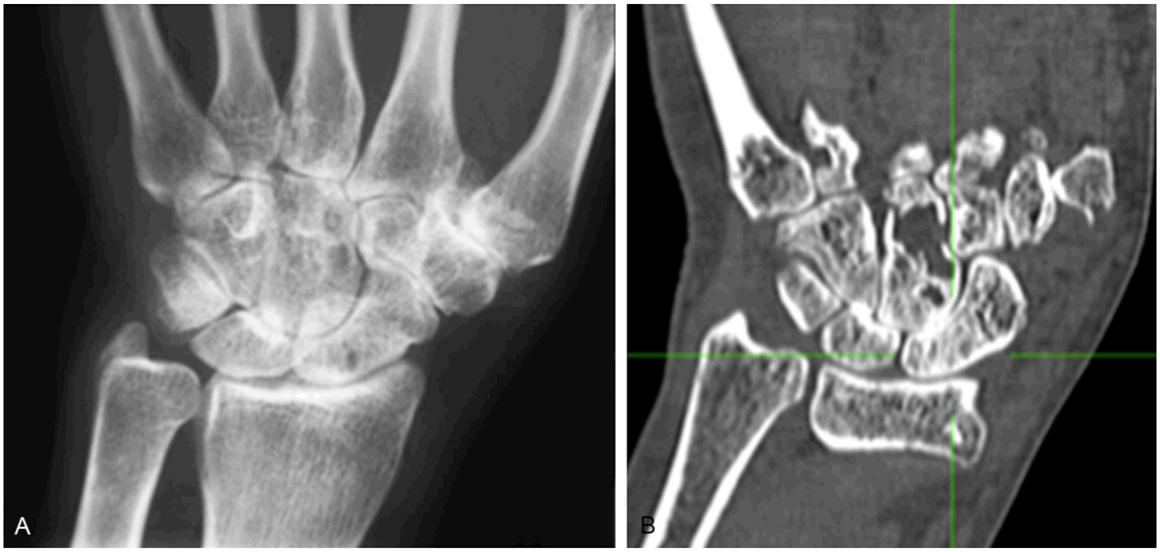

Figure 6. Rheumatoid arthritis involving the wrist. Wrist visualized by conventional radiograph (A) and by computed tomography (B). Bone erosion are clearly evident on computed tomography, but not on the corresponding radiograph.

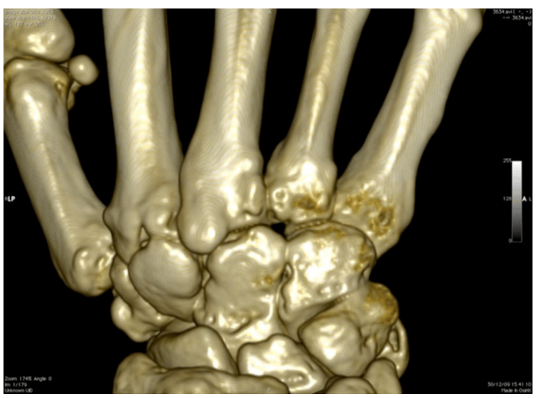

Figure 7. Early rheumatoid arthritis involving the wrist. Volume rendering technique obtained from computed tomography. The image shows a detailed 3D anatomical perspective.

Advantages and disadvantages of plain radiography

The main utilities of plain radiographs include low costs, wide availability, standardization of validated assessment methods, and good reproducibility [56]. Moreover, thanks to its high specificity, conventional radiography is advantageous for differential diagnosis, easily revealing the features that are specific for each disorder.

By contrast, the disadvantages are well recognized, involving exposure to ionized radiation and insufficient assessment of the synovium or other soft-tissue structures, which can be critical in making diagnostic or therapeutic decisions (**Table 1**).

Some studies have reported that plain radiography has poor sensitivity in detecting bone erosions compared with MRI [23, 57-59]. We also found that plain radiography has very poor sensitivity (22%) in detecting bone erosions in RA wrist joints, compared with CT [60]. The wrist is one of the most difficult joint of the body to assess radiographically [61]. Difficulties of conventional radiography for a detailed evaluation of wrist are due to several factors, such as the complex anatomy of the wrist, the irregularities of the bone margins (e.g. at level of ligaments attachment) and the presence of nutritive foramina that can appear like erosions. These aspects make arduous the discrimination between the normal anatomy and the erosions [61]. For that reason, CT can be considered the standard reference method for the detection of erosive bone destructions in early stage of the disease [62, 63] (**Figure 6**). Current generation of ultrafast CTs allow to acquire high resolution volumetric data in few seconds and providing detailed anatomical informations. Moreover, 3D volume rendering techniques make feasible to generate high quality images, offering a realistic anatomical view from tomographic data (**Figure 7**).

Table 2. Features of rheumatoid arthritis included in the different radiographic scoring methods

Method	Erosion	Joint space narrowing	Osteoporosis	Soft tissue swelling	(Sub) luxation	Ankylosis	Cyst
Steinbrocker (1949)	+	+	+	-	-	+	-
Kellgren (1956)	+	+	+	-	-	-	-
Sharp (1971)	+	+	-	-	-	+	+
Larsen (1977)	+	+	+	+	-	-	-
Sharp (1985)	+	+	-	-	-	+	-
Genant (1998)	+	+	-	-	+	+	-
van der Heijde/Sharp (1989)	+	+	-	-	+	+	-
Larsen (1995)	+	+	-	-	-	-	-
Rau/Larsen (1995)	+	+	+	+	-	-	-
Ratingen (1998)	+	+	-	-	-	-	-
SENS (1999)	+	+	-	-	+	+	-
SES (2000)	+	+	-	-	-	-	-

SENS = Simple Erosion Narrowing Score; SES = Short Erosion Scale; + Included in the scoring system; - Not included in the scoring system.

Additional limitations of conventional radiography are the following: (a) technical variables, (b) interpretational variables, and (c) pathophysiological variables (**Table 1**).

Radiographic progression as an outcome measure in RA

Progression of structural damage to joints is commonly used as an outcome measure in RA and in observational studies. Reasons are that radiographs of hands and feet can be easily performed, that valid scoring methods are available, that inflammatory activity in the joints leads to radiographic progression, and that radiographic damage correlates with physical function [64]. Inflammation of the joints may fluctuate over time in individual patients, and radiographic damage may be considered a reflection of joint inflammation over time [65].

Numerous studies have documented the course and prognostic factors associated with progression of radiographic joint damage in RA [66-70]. These studies clearly show that the rate of progression of joint damage correlates strongly with disease duration and disease activity. In a cohort of active early RA patients, Knijff-Dutmer et al [71] found a linear relationship between time integrated disease activity parameters and progression of radiographic damage. Similar results were reported by Molenaar et al [72] and Welsing et al [73]. Our prospective analysis has confirmed that higher cumulative disease activity is associated with a higher radiological progression in early RA [65].

The hypothesis that chronic inflammation and joint destruction are closely linked is further supported by data from imaging studies. Some works demonstrated that, in early RA, bone damage occurs proportionately to the degree of synovitis, but not in its absence [72, 74, 75].

Destructive joint damage judged on conventional radiography occurs within the first years of RA [76, 77] and early detection of erosions is closely related to a poor long-term clinical outcome [78-80]. Radiological outcome studies have shown that 70-75% of patients with recent-onset RA develop bony erosions within the first 2-3 years [8, 81]. Furthermore, we showed that within 3 months of disease onset, 34.9% of 481 patients have erosions evident on X-ray [82]. Similarly, in the ESPOIR cohort study (a French cohort of early arthritis), 20% of 813 patients with a mean disease duration of 107 days had hand or foot erosions [83].

The joint damage at baseline is a significant predictor of progression [65, 78, 84-86]. Two long-term studies [87, 88] found that the independent predictive variable of radiographic damage was baseline radiographic score.

Joint damage increases slowly over the course of RA [77], and disability decreases during the first years with disease control and worsens with disease duration [17, 81, 89]. In early RA, functional impairment is believed to be particularly due to inflammatory processes as measured by disease activity [65]. In long-term established RA, disability may be mainly related to joint damage [80, 90]. A significant correlation between the changes in x-ray scores and the subsequent disability status has been confirmed [64]. Thus, as recommended by EULAR [11], the changes in X-ray scores/progression should be evaluated in clinical practice to better monitor individual patients with early RA so that decisions to change therapeutic strategies and prevent further disease progression can be taken as early as possible.

Radiographic scoring methods

There are numerous radiographic methods to evaluate progressive joint damage in RA that continue to be an important end-point in trials assessing medication efficacy and in following response to treatment. Some give a global assessment for the whole patient [91, 92], whereas others score specific joint abnormalities [93, 94] (**Table 2**). Radiographic scores, such as the Sharp scores and their modifications [95, 96], are the standard methods for determining joint damage and its progression [65, 97].

The first attempt to standardize the assessment of radiographic damage in RA was made with the Steinbrocker method [91]. In this method, global damage score in the hands and wrists was graded as follows: stage I-osteoporosis may exist, no erosions; stage II-osteoporosis, slight cartilage or subchondral bone destruction may be present; stage III-osteoporosis, cartilage and bone destruction; and stage IV-same as III, with bony ankylosis. This method had several limitations and is no longer used.

The Kellgren scoring method was similar to the Steinbrocker method: a global grade was given as the summation of abnormalities for all the joints in both the hands and wrists [92]. Osteoporosis and erosions were recorded separately and graded as follows: none (0), doubtful (1), slight (2), moderate (3), and severe (4). The atlas of standard reference included films of the hands, wrists, forefoot, and cervical spine [94].

In 1971, Sharp et al proposed a scoring method for the hands and wrists that includes two scores, one for erosions and the other for joint space narrowing (JSN) [98]. Twenty nine areas in each hand and wrist are scored for erosions, and 27 for JSN. Counts for erosion range from 0 to 5, to give an erosion score between 0 and 290. Counts for JSN range from 0 to 4, to give a score between 0 and 216. The number and selection of joints in the Sharp score evolved in the years, and a modification proposed in 1985 of the Sharp method [99] is now considered the standard for the method. It considers 17 areas for erosion: five PIP joints, five MCP joints, 1st metacarpal base (MCB), multangular as one unit, navicular, lunate, triquetrum (and pisiform), radius, ulnar bone for each hand and wrist; and 18 areas for JSN: five PIP, five MCP, carpometacarpal (CMC) 3 to 5, multangular-navicular, lunate-triquetrum, capitate-navicular-lunate, radiocarpal, radioulnar joints for each hand and wrist. Each erosion scores one point, with a maximum of five points for each area. Erosion scores range from 0 to 170. One point is scored for focal joint narrowing, two points for diffuse narrowing of less than 50% of the original space, and three points if the reduction is more than half of the original joint space. Ankylosis is scored as four. The score for JSN ranges from 0 to 144. Another modification was devised by Genant et al [100]. The Genant modification of the Sharp method focuses on 14 sites for erosions and 13 sites for joint space narrowing (JSN): erosion is scored according to an eight point scale with 0.5 increments, where 0 = normal; 0+ = questionable or subtle change; 1 = mild; 1+ = mild worse; 2 = moderate; 2+ = moderate worse; 3 = severe; and 3+ = severe worse. In each hand, IP of the thumb, PIP, MCP, 1st CMC, scaphoid, ulna, and radius are included. The score for erosion for both hands ranges from 0 to 98. JSN is scored according to a nine point scale with 0.5 increments, where 0 = normal; 0+ = questionable or subtle change; 1 = mild; 1+ = mild worse; 2 = moderate; 2+ = moderate worse; 3 = severe; 3+ = severe worse; and 4 = ankylosis or dislocation. In each hand, IP of the thumb, PIP, MCP, CMC 3 to 5, capitate-scaphoid-lunate, and the radiocarpal joint are included (**Table 3**). The score for JSN for both hands ranges from 0 to 104. The total erosion score and the total joint score are each normalised based on a maximum score of 100, and these two normalised scores are added to give a joint total score in which erosions and JSN are evenly weighted.

In the final van der Heijde modification of the Sharp method [101], erosions are assessed in 16 joints (five MCP, four PIP, IP of the thumbs, 1st MCB, radius and ulna bones, trapezium and trapezoid as one unit (multangular), navicular, lunate) for each hand and wrist, and six joints (five MTP, IP) for each foot. One point is scored if erosions are discrete, rising to 2, 3, 4, or 5 depending on the amount of surface area affected (complete collapse of the bone is scored as 5). The score for erosion ranges from 0 to 160 in the hands and from 0 to 120 in the feet (the maximum erosion score for a joint in the foot is 10). JSN is evaluated in 15 joints (five MCP, four PIP, CMC 3 to 5, multangular navicular-lunate, radiocarpal) for each hand and wrist, and six joints (five MTP, IP) for each foot. JSN is combined with a score for (sub)luxation and scored as follows: 0 = normal; 1 = focal or doubtful; 2 = generalised, less than 50% of the original joint space; 3 = generalised, more than 50% of the original joint space or subluxation; 4 = bony ankylosis or complete luxation. The score for JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet. Therefore, the total van der Heijde radiographic score ranges from 0 to 448 [96] (**Table 3**).

In 1974, Larsen developed a method based on a set of standard films. It differentiates six stages from 0 (normal) to 5, reflecting progressive deterioration, and provides an overall measure of joint damage. The Larsen original method has also been modified several times by the author. In the 1977 version [102, 103], the six stages are the following: grade 0 = normal; grade 1 = slight abnormalities (periarticular soft tissue swelling and periarticular osteoporosis and slight JSN); grade 2 = definite early abnormalities; grade 3 = medium destructive abnormalities; grade 4 = severe definite abnormalities; and grade 5 = mutilating abnormalities. The wrist is considered as one unit and the score is multiplied by five. Joints assessed include five DIP, four PIP, five MCP, the wrist as one unit for each hand and wrist, and 10 MTP, two IP for the feet. The score ranges from 0 to 250 (**Table 2**). In 1995, Larsen revised a method to evaluate radiographs in long term studies [104]. The main differences from the original are deletion of scores for the thumbs and 1st MTP; subdivision of the wrist into four quadrants (the joints considered are PIP 2 to 5 and MCP 2 to 5 in each hand, four quadrants in the wrist, and MTP 2 to 5 in each foot); deletion of soft tissue swelling and osteoporosis; distinction between erosions of different sizes. The grading scale ranges from 0 to 5: 0 = intact bony outlines and normal joint space; 1 = erosion less than 1 mm in diameter or JSN; 2 = one or several small erosions (diameter more than 1 mm); 3 = marked erosions; 4 = severe erosions (usually no joint space left and the original bony outlines are only partly preserved); and 5 = mutilating changes (the original bony outlines have been destroyed) (**Table 3**). The score ranges from 0 to 160.

In 1995, Rau and Herborn proposed a modification of the Larsen method [105]. Thirty two joints are evaluated: eight PIP, two IP of the thumbs, 10 MCP, two wrists, and 10 MTP. The six stages are defined as follows: 0 = normal; 1 = soft tissue swelling and/or joint space narrowing/subchondral osteoporosis; 2 = erosions with destruction of the joint surface (DJS) 25%; 3 = DJS 26-50%; 4 = DJS 51-75%; 5 = DJS >75%. The score ranges from 0 to 160.

Few years later Rau et al developed a new method derived from the Larsen score including a quantitative appraisal of the percentage of loss of the joint surface. This method is known as a "Ratingen score" [106]. The score examines the following joints or areas: 10 PIP, 10 MCP, four sites in the wrist (navicular, lunate, radius, and ulna), eight MTP (2 to 5), and two IP on the great toe. This new method restricts scoring of an individual joint to definite changes of erosion and joint destruction. The extension of the erosion into the bone is not considered. The amount of joint surface destruction is defined by the length of the clearly visible interruption of the cortical plate in relation to the total joint surface. Grades are then assigned in this way: grade 1 = one or several definite erosions totalling destruction of <20% of the total surface; grade 2 = joint surface destruction 21-40%; grade 3 = 41-60%; grade 4 = 61-80%; grade 5>80%. Adding the scores from 38 areas gives a total score ranging from 0 to 190.

Table 3 summarizes the principal characteristics of the three common radiographic scoring methods used in RA.

An important disadvantage of the scoring methods for clinical trials is the fact that they require significant training, and that scoring according to these methods is very time consuming, making these techniques unfeasible for routine clinical practice. The scoring time is one drawback of both Sharp method and Sharp/van der Heijde method, related to their detailed evaluation [107, 108].

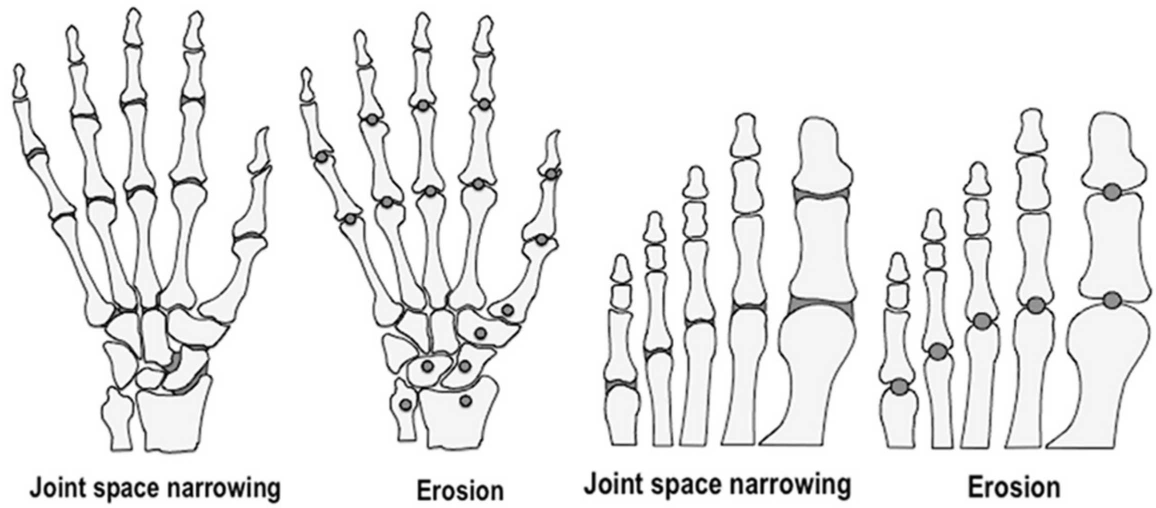

Figure 8. The Simplified Erosion and Narrowing Score (SENS) for scoring radiographic damage at the hands and feet in patients with RA. Erosions are assessed in 16 areas of each hand and 6 of each foot. Joint space narrowing is assessed in 15 areas of each hand and 6 of each foot.

In order to overcome these limitations, it has been developed the Simplified Erosion and Narrowing Score (called "SENS"), that is entirely based on the van der Heijde modification of the Sharp score [107] and the Short Erosion Scale (SES), a change of the Larsen method [109]. The SENS was developed by van der Heijde and is a simplified method by summing the number of eroded and narrowed joints on selected joints on hand and foot radiographs [107]. It exploits the same joints of hands and feet, but as opposed to applying a semiquantitative scale of 0-4 for joint space narrowing and 0-5 for erosions, the SENS simply dichotomizes (bimodal answer modality) whether an erosion is absent (score of 0) or present (score of 1), and whether joint space narrowing is absent (score of 0) or present (score of 1) [107]. The hand score per joint can, therefore, range from 0 to 2. Joint erosions are scored in 32 joints in the hands and wrists and 12 joints in the feet. JSN is scored in 30 joints in the hands and wrists and in 12 joints in the feet. Consequently, the maximum total erosion score is 44, the maximum total JSN score is 42 and the maximum total score is 86 (**Figure 8**) [107]. The SENS showed a good intra- and inter-reader reliability, and is sensitive to change [110].

The SES considers 12 joints: three of four regions of the wrist as defined by Larsen (medial-proximal, medial-distal, and lateral-proximal) and MCP 2, 3, and 5 [109]. Each joint is graded as in the 1995 Larsen system [104].

However, despite considerable effort to either reduce or at least define the intrinsic limitations of radiographic scores, problems remain with reader variability, floor and ceiling effects [56, 93, 111] and an inability to accurately quantify damage and its progression, particularly in the wrist.

Conclusions

Plain radiography remains the gold standard for the assessment of structural joint damage in RA even though this may not necessarily be the most sensitive imaging investigation in this setting [3]. It is generally safe, accessible and cost effective with the opportunity to provide timely and useful information which is helpful to a range of health professionals. Characteristic X-ray findings are part of the ACR/EULAR classification criteria for RA [5, 6], can be helpful in the differentiation of RA from other joint conditions, and can serve as an outcome parameter in clinical trials that investigate the potential of new drugs to preserve structural integrity of the joints. Appropriate scoring methods are designed to semiquantitatively measure radiographically visible changes, especially erosive destruction and-in part-cartilage loss. These methods are well validated, reproducible, and yield similar results in clinical trials.

Disclosure of conflict of interest

None.

Address correspondence to: Fausto Salaffi, Clinica Reumatologica, Università Politecnica delle Marche, Ancona, Ospedale "Carlo Urbani", Via Aldo Moro, 25, 60035, Jesi, Ancona, Italy. Tel: ++39/0731-534128/32/25; Fax: ++39/0731-534124; E-mail: fausto.salaffi@gmail.com

References

[1] Klareskog L, Catrina AI and Paget S. Rheumatoid arthritis. Lancet 2009; 373: 659-672.

[2] Salaffi F, De Angelis R and Grassi W; MArche Pain Prevalence; INvestigation Group (MAPPING) study. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. Clin Exp Rheumatol 2005; 23: 819-828.

[3] Colebatch AN, Edwards CJ, Østergaard M, van der Heijde D, Balint PV, D'Agostino MA, Forslind K, Grassi W, Haavardsholm EA, Haugeberg G, Jurik AG, Landewé RB, Naredo E, O'Connor PJ, Ostendorf B, Potocki K, Schmidt WA, Smolen JS, Sokolovic S, Watt I and Conaghan PG. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis 2013; 72: 804-814.

[4] Grassi W, Filippucci E, Carotti M and Salaffi F. Imaging modalities for identifying the origin of regional musculoskeletal pain. Best Pract Res Clin Rheumatol 2003; 17: 17-32.

[5] Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA Jr, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL and Hunder GG. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-324.

[6] Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, Birnbaum NS, Burmester GR, Bykerk VP, Cohen MD, Combe B, Costenbader KH, Dougados M, Emery P, Ferraccioli G, Hazes JM, Hobbs K, Huizinga TW, Kavanaugh A, Kay J, Kvien TK, Laing T, Mease P, Ménard HA, Moreland LW, Naden RL, Pincus T, Smolen JS, Stanislawska-Biernat E, Symmons D, Tak PP, Upchurch KS, Vencovský J, Wolfe F, Hawker G. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010; 62: 2569-2681.

[7] Van der Heijde D, van der Helm-van Mil AH, Aletaha D, Bingham CO, Burmester GR, Dougados M, Emery P, Felson D, Knevel R, Kvien TK, Landewé RB, Lukas C, McInnes I, Silman AJ, Smolen JS, Stanislawska-Biernat E, Zink A and Combe B. EULAR definition of erosive disease in light of the 2010 ACR/EULAR rheumatoid arthritis classification criteria. Ann Rheum Dis 2013; 72: 479-481.

[8] Van der Heijde D, van Leeuwen M, van Riel P and van de Putte L. Radiographic progression on radiographs of hands and feet during the first 3 years of rheumatoid arthritis measured according to Sharp's method (van der Heijde modification). J Rheumatol 1995; 22: 1792-1796.

[9] Lard LR, Visser H, Speyer I, van der Host-Bruinsma IE, Zwindermann AH, Breedveld FC and Hazes JM. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: Comparison of two cohorts who received different treatment strategies. Am J Med 2001; 111: 446-451.

[10] Van Aken J, Lard LR, le Cessie S, Hazes JM, Breedveld FC and Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis 2004; 63: 274-279.

[11] Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, Emery P, Ferraccioli G, Hazes JM, Klareskog L, Machold K, Martin-Mola E, Nielsen H, Silman A, Smolen J and Yazici H. EULAR recommendations for the management of early arthritis: Report of a task force of the European standing committee for international clinical studies including therapeutics (escisit). Ann Rheum Dis 2007; 66: 34-45.

[12] Landewé R, Strand V and van der Heijde D. From inhibition of radiographic progression to maintaining structural integrity: a methodological framework for radiographic progression in rheumatoid arthritis and psoriatic arthritis clinical trials. Ann Rheum Dis 2013; 72: 1113-1117.

[13] Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, Emery P, Gaujoux-Viala C, Gossec L, Nam J, Ramiro S, Winthrop K, de Wit M, Aletaha D, Betteridge N, Bijlsma JW, Boers M, Buttgereit F, Combe B, Cutolo M, Damjanov N, Hazes JM, Kouloumas M, Kvien TK, Mariette X, Pavelka K, van Riel PL, Rubbert-Roth A, Scholte-Voshaar M, Scott DL, Sokka-Isler T, Wong JB and van der Heijde D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014; 73: 492-509.

[14] Gossec L, Fautrel B, Pham T, Combe B, Flipo RM, Goupille P, Le Loet X, Mariette X, Puéchal X, Wendling D, Schaeverbeke T, Sibilia J, Sany J and Dougados M. Structural evaluation in the

management of patients with rheumatoid arthritis: Development of recommendations for clinical practice based on published evidence and expert opinion. Joint Bone Spine 2005; 72: 229-234.
[15] Wakefield RJ, D'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, Ostergaard M, Backhaus M, Grassi W, Dougados M, Burmester GR, Saleem B, de Miguel E, Estrach C, Ikeda K, Gutierrez M, Thompson R, Balint P and Emery P. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? Postgrad Med J 2012; 88: 482-486.
[16] Visser H, le Cessie S, Vos K, Breedveld F and Hazes J. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. Arthritis Rheum 2002; 46: 357-365.
[17] Combe B. Early rheumatoid arthritis: Strategies for prevention and management. Best Pract Res Clin Rheumatol 2007; 21: 27-42.
[18] Resnick D, Kyriakos M and Greenway GD. Rheumatoid arthritis. Diagnosis of Bone and Joint Disorders. 4th edition. Philadelphia: WB Saunders; 2002. pp. 891-974.
[19] Brown JH and Deluca SA. The radiology of rheumatoid arthritis. Am Fam Physician 1995; 52: 1372-1380.
[20] Smolen JS, van der Heijde DM, Keystone EC, van Vollenhoven RF, Goldring MB, Guérette B, Cifaldi MA, Chen N, Liu S and Landewé RB. Association of joint space narrowing with impairment of physical function and work ability in patients with early rheumatoid arthritis: protection beyond disease control by adalimumab plus methotrexate. Ann Rheum Dis 2013; 72: 1156-1162.
[21] Leak RS, Rayan GM and Arthur RE. Longitudinal radiographic analysis of rheumatoid arthritis in the hand and wrist. J Hand Surg 2003; 28A: 427-434.
[22] Ejbjerg BJ, Vestergaard A, Jacobsen S, Thomsen HS and Østergaard M. The smallest detectable difference and sensitivity to change of magnetic resonance imaging and radiographic scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe joints: a comparison of the OMERACT rheumatoid arthritis magnetic resonance imaging score applied to different joint combinations and the Sharp/van der Heijde radiographic score. Arthritis Rheum 2005; 52: 2300-2306.
[23] McQueen FM, Stewart N, Crabbe J, Robinson E, Yeoman S, Tan PL, McLean L. Magnetic resonance imaging of the wrist in early rheumatoid arthritis reveals progression of erosions despite clinical improvement. Ann Rheum Dis 1999; 58: 156-163.
[24] Wakefield R, Gibbon W, Conaghan P, O'Connor P, McGonagle D, Pease C, Green MJ, Veale DJ, Isaacs JD and Emery P. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: A comparison with conventional radiography. Arthritis Rheum 2000; 43: 2762-2770.
[25] Szkudlarek M, Narvestad E, Klarlund M, Court-Payen M, Thomsen HS and Ostergaard M. Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination. Arthritis Rheum 2004; 50: 2103-2112.
[26] Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y and Bijlsma JW. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 2000; 43: 1927-1940.
[27] Grassi W, Filippucci E, Farina A, Salaffi F and Cervini C. Ultrasonography in the evaluation of bone erosions. Ann Rheum Dis 2001; 60: 98-103.
[28] Zikou AK, Alamanos Y, Argyropoulou MI, Tsifetaki N, Tsampoulas C, Voulgari PV, Efremidis SC and Drosos AA. Radiological cervical spine involvement in patients with rheumatoid arthritis: a cross sectional study. J Rheumatol 2005; 32: 801-806.
[29] Nguyen HV, Ludwig SC, Silber J, Gelb DE, Anderson PA, Frank L and Vaccaro AR. Rheumatoid arthritis of the cervical spine. Spine J 2004; 4: 329-434
[30] Cassar-Pullicino VN. The spine in rheumatological disorders. Imaging 1999; 11: 104-118.
[31] Bouchaud-Chabot A and Liote' F. Cervical spine involvement in rheumatoid arthritis. Joint Bone Spine 2002; 69: 141-154.
[32] Reynolds H, Carter SW, Murtagh FR, Silbiger M and Rechtine GR. Cervical rheumatoid arthritis: value of flexion and extension views in imaging. Radiology 1987; 164: 215-218.
[33] Conlon PW, Isdale IC and Rose BS. Rheumatoid arthritis of the cervical spine: an analysis of 333 cases. Ann Rheum Dis 1966; 25: 120-126.
[34] Reichel H, Liebhaber A, Babinsky K and Keysser G. Radiological changes in the cervical spine in rheumatoid arthritis: prognostic factors obtained by a cross-sectional study. Z Rheumatol 2002; 61: 710-717.
[35] Younes M, Belghali S, Kriâa S, Zrour S, Bejia I, Touzi M, Golli M, Gannouni A and Bergaoui N. Compared imaging of the rheumatoid cervical spine: prevalence study and associated factors. Joint Bone Spine 2009; 76: 36-38.
[36] Neva MH, Kaarela K and Kauppi M. Prevalence of radiological changes in the cervical spine e a cross sectional study after 20 years from presentation of rheumatoid arthritis. J Rheumatol 2000; 27: 90-93.

[37] Park WM and O'Brien W. Computer-assisted analysis of radiographic neck lesions in chronic rheumatoid arthritis. Acta Radiologica Diagnosis 1969; 8: 529-534.

[38] Reiter MF and Boden SD. Inflammatory disorders of the cervical spine. Spine 1998; 23: 2755-2766.

[39] Winfield J, Young A, Williams P and Corbett M. Prospective study of the radiological changes in hands, feet, and cervical spine in adult rheumatoid disease. Ann Rheum Dis 1983; 42: 613-618.

[40] Fujiwara K, Fujimoto M, Owaki H, Kono J, Nakase T, Yonenobu K and Ochi T. Cervical lesions related to systemic progression in rheumatoid arthritis. Spine 1998; 23: 2052-2056.

[41] Hirano K, Imagama S, Oishi Y, Kanayama Y, Ito Z, Wakao N, Matsuyama Y and Ishiguro N. Progression of cervical instabilities in patients with rheumatoid arthritis 5.7 years after their first lower limb arthroplasty. Mod Rheumatol 2012; 22: 743-749.

[42] Stevens JC, Cartlidge NE, Saunders M, Appleby A, Hall M and Shaw DA. Atlanto-axial subluxations and cervical myelopathy in rheumatoid arthritis. Q J Med 1971; 159: 391-408.

[43] Floyd AS, Learmonth ID, Mody G and Meyers OL. Atlantoaxial instability and neurologic indicators in rheumatoid arthritis. Clin Orthop Relat Res 1989; 177-182.

[44] Weissman BN, Aliabadi P and Weinfeld MS. Prognostic features of atlantoaxial subluxation in rheumatoid arthritis patients. Radiology 1982; 144: 745-751.

[45] Neva MH, Isomaki P, Hannonen P, Kauppi M, Krishan E and Sokka T. Early and extensive erosiveness in peripheral joints predicts atlantoaxial subluxations in patients with rheumatoid arthritis. Arthritis Rheum 2003; 48: 1808-1813.

[46] Pisitkun P and Pattarowas C. Reappraisal of cervical spine subluxation in Thai patients with rheumatoid arthritis. Clin Rheumatol 2004; 23: 14-18.

[47] Bunton RW, Grennan D and Palmer DG. Lateral subluxation of the atlas in rheumatoid arthritis. Br J Radiol 1978; 51: 963-967.

[48] Vesela M, Stetkarova I and Lisy J. Prevalence of C1/C2 involvement in Czech rheumatoid arthritis patients, correlation of pain intensity, and distance of ventral subluxation. Rheumatol Int 2005; 26: 12-15.

[49] Meikle JA and Wilkinson M. Rheumatoid involvement of the cervical spine. Ann Rheum Dis 1971; 30: 154-161.

[50] McGregor M. The significance of certain measurements of the skull in the diagnosis of basilar impression. Br J Radiol 1948; 21: 171-181.

[51] Ranawat CS, O'Leary P, Pellicci P, Tsairis P, Marchisello P and Dorr L. Cervical spine fusion in rheumatoid arthritis. J Bone Joint Surg 1979; 61: 1003-1010.

[52] Kauppi M, Sakaguchi M, Konttinen YT and Hämäläinen M. A new method of screening for vertical atlantoaxial dislocation. J Rheumatol 1990; 17: 167-172.

[53] Karhu JO, Parkkola RK and Koskinen SK. Evaluation of flexion/extension of the upper cervical spine in patients with rheumatoid arthritis: an MRI study with a dedicated positioning device compared to conventional radiographs. Acta Radiol 2005; 46: 55-66.

[54] Zikou AK, Argyropoulou MI, Alamanos Y, Tsifetaki N, Tsampoulas C, Voulgari PV, Efremidis SC and Drosos AA. Magnetic resonance imaging findings of the cervical spine in patients with rheumatoid arthritis. A cross-sectional study. Clin Exp Rheumatol 2005; 23: 665-670.

[55] Jeromel M, Jevtič V, Serša I, Ambrožič A and Tomšič M. Quantification of synovitis in the cranio-cervical region: dynamic contrast enhanced and diffusion weighted magnetic resonance imaging in early rheumatoid arthritis--a feasibility follow up study. Eur J Radiol 2012; 81: 3412-3419.

[56] Salaffi F and Carotti M. Interobserver variation in quantitative analysis of hand radiographs in rheumatoid arthritis: comparison of 3 different reading procedures. J Rheumatol 1997; 24: 2055-2056.

[57] Backhaus M, Kamradt T, Sandrock D, Loreck D, Fritz J, Wolf KJ, Raber H, Hamm B, Burmester GR and Bollow M. Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging. Arthritis Rheum 1999; 42: 1232-1245.

[58] Klarlund M, Østergaard M, Jensen KE, Madsen JL, Skjødt H and Lorenzen I. Magnetic resonance imaging, radiography, and scintigraphy of the finger joints: one year follow up of patients with early arthritis. The TIRA Group. Ann Rheum Dis 2000; 59: 521-528.

[59] Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, Quinn M, Karim Z, Green MJ, Proudman S, Isaacs J and Emery P. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum 2003; 48: 64-71.

[60] Salaffi F, Carotti M, Ciapetti A, Ariani A, Gasparini S and Grassi W. Validity of a computer-assisted manual segmentation software to quantify wrist erosion volume using computed tomography scans in rheumatoid arthritis. BMC Musculoskelet Disord 2013; 14: 265.

[61] Koski JM, Saarakkala S, Helle M, Hakulinen U, Heikkinen JO, Hermunen H, Balint P, Bruyn GA,

Filippucci E, Grassi W, Iagnocco A, Luosujärvi R, Manger B, De Miguel E, Naredo E, Scheel AK, Schmidt WA, Soini I, Szkudlarek M, Terslev L, Uson J, Vuoristo S and Ziswiler HR. Assessing the intra- and inter-reader reliability of dynamic ultrasound images in power Doppler ultrasonography. Ann Rheum Dis 2006; 65: 1658-1660.

[62] Perry D, Stewart N, Benton N, Robinson E, Yeoman S, Crabbe J and McQueen F. Detection of erosions in the rheumatoid hand; a comparative study of multidetector computerized tomography versus magnetic resonance scanning. J Rheumatol 2005; 32: 256-267.

[63] Døhn UM, Ejbjerg B, Court-Payen M, Hasselquist M, Narvestad E, Szkudlarek M, Møller J, Thomsen HS and Østergaard M. Are bone erosions detected by magnetic resonance imaging and ultrasonography true erosions? A comparison with computed tomography in rheumatoid arthritis metacarpophalangeal joints. Arthritis Res Ther 2006; 8: R110.

[64] Maillefert JF, Combe B, Goupille P, Cantagrel A and Dougados M. The 5-yr HAQ-disability is related to the first year's changes in the narrowing, rather than erosion score in patients with recent-onset rheumatoid arthritis. Rheumatology 2004; 43: 79-84.

[65] Salaffi F, Carotti M, Ciapetti A, Gasparini S, Filippucci E and Grassi W. Relationship between time-integrated disease activity estimated by DAS28-CRP and radiographic progression of anatomical damage in patients with early rheumatoid arthritis. BMC Musculoskelet Disord 2011; 12: 120.

[66] Scott DL. Prognostic factors in early rheumatoid arthritis. Rheumatology 2000; 39 Suppl 1: S24-S29.

[67] Van Zeben D and Breedveld FC. Prognostic factors in rheumatoid arthritis. J Rheumatol Suppl 1996; 44: 31-33.

[68] Young A and van der Heijde DM. Can we predict aggressive disease? Baillieres Clin Rheumatol 1997; 11: 27-48.

[69] Mottonen T, Paimela L, Leirisalo M-Repo, Kautiainen H, Ilonen J and Hannonen P. Only high disease activity and positive rheumatoid factor indicate poor prognosis in patients with early rheumatoid arthritis treated with "sawtooth" strategy. Ann Rheum Dis 1998; 57: 533-539.

[70] Bukhari M, Lunt M, Harrison BJ, Scott DG, Symmons DP and Silman AJ. Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis. Arthritis Rheum 2002; 46: 906-912.

[71] Knijff-Dutmer E, Drossaers-Bakker W, Verhoeven A, van der Sluijs Veer G, Boers M, van der Linden S and van de Laar M. Rheumatoid factor measured by fluoroimmunoassay: a responsive measure of rheumatoid arthritis disease activity that is associated with joint damage. Ann Rheum Dis 2002; 61: 603-607.

[72] Molenaar ET, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M and Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. Arthritis Rheum 2004; 50: 36-42.

[73] Welsing PM, Landewé RB, van Riel PL, Boers M, van Gestel AM, van der Linden S, Swinkels HL and van der Heijde DM. The relationship between disease activity and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2004; 50: 2082-2093.

[74] Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ and Emery P. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis Rheum 2008; 58: 2958-2967.

[75] Mulherin D, Fitzgerald O and Bresnihan B. Clinical improvement and radiological deterioration in rheumatoid arthritis: evidence that the pathogenesis of synovial inflammation and articular erosion may differ. Br J Rheumatol 1996; 35: 1263-1268.

[76] Fuchs HA, Kaye JJ, Callahan LF, Nance EP and Pincus T. Evidence of significant radiographic damage in rheumatoid arthritis within the first 2 years of disease. J Rheumatol 1989; 16: 585-591.

[77] Salaffi F, Ferraccioli G, Peroni M, Carotti M, Bartoli E and Cervini C. Progression of erosion and joint space narrowing scores in rheumatoid arthritis assessed by nonlinear models. J Rheumatol 1994; 21: 1627-1630.

[78] Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. Ann Rheum Dis 2001; 60: 924-927.

[79] Landewé R. Predictive markers in rapidly progressing rheumatoid arthritis. J Rheumatol Suppl 2007; 80: 8-15.

[80] Courvoisier N, Dougados M, Cantagrel A, Goupille P, Meyer O, Sibilia J, Daures JP and Combe B. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 2008; 10: R106.

[81] Combe B, Cantagrel A, Goupille P, Bozonnat MC, Sibilia J, Eliaou JF, Meyer O, Sany J, Dubois A, Daurès JP and Dougados M. Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. J Rheumatol 2003; 30: 2344-2349.

[82] Gremese E, Salaffi F, Bosello S, Ciapetti A, Bobbio-Pallavicini F, Caporali R and Ferraccioli G.

Very early rheumatoid arthritis as a predictor of remission: a multicentre real life prospective study. Ann Rheum Dis 2013; 72: 858-862.

[83] Combe B, Benessiano J, Berenbaum F, Cantagrel A, Daurès JP, Dougados M, Fardellone P, Fautrel B, Flipo RM, Goupille P, Guillemin F, Le Loet X, Logeart I, Mariette X, Meyer O, Ravaud P, Rincheval N, Saraux A, Schaeverbeke T and Sibilia J. The ESPOIR cohort: a ten-year follow-up of early arthritis in France: methodology and baseline characteristics of the 813 included patients. Joint Bone Spine 2007; 74: 440-445.

[84] Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, Meyer O, Sany J, Daures JP and Dubois A. Prognostic factors for radiographic damage in early rheumatoid arthritis. A multiparameter prospective study. Arthritis Rheum 2001; 44: 1736-1743.

[85] Forslind K, Ahlmen M, Eberhardt K, Hafstrom I and Svensson B. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004; 63: 1090-1095.

[86] Guillemin F, Gerard N, van Leeuwen M, Smedstad LM, Kvien TK and van den Heuvel W. Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. J Rheumatol 2003; 30: 2585-2589.

[87] Kaarela K. Prognostic factors and diagnostic criteria in early rheumatoid arthritis. Scand J Rheumatol 1985; 57: 1-54.

[88] Lindqvist E, Jonsson K and Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003; 62: 611-616.

[89] Visser H. Early diagnosis of rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005; 19: 55-72.

[90] Guillemin F, Suurmeijer T, Krol B, Bombardier C, Briançon S, Doeglas D, Sanderman R and van den Heuvel W. Functional disability in early rheumatoid arthritis: description and risk factors. J Rheumatol 1994; 21: 1051-1055.

[91] Steinbrocker O, Traeger C and Batterman R. Therapeutic criteria in rheumatoid arthritis. JAMA 1949; 140: 659-662.

[92] Kellgren J and Bier F. Radiological signs of rheumatoid arthritis: a study of observer differences in the reading of hand films. Ann Rheum Dis 1956; 15: 55-60.

[93] Van der Heijde D. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheum 1996; 10: 435-453.

[94] Knevel R, Kwok KY, de Rooy DP, Posthumus MD, Huizinga TW, Brouwer E and van der Helm-van Mil AH. Evaluating joint destruction in rheumatoid arthritis: is it necessary to radiograph both hands and feet? Ann Rheum Dis 2013; 72: 345-349.

[95] Scott D, Laasonen L, Priolo F, Houssein D, Bacarini L, Cerase A and Cammisa M. The radiological assessment of rheumatoid arthritis. Clin Exp Rheumatol 1997; 15 Suppl 17: S53-S61.

[96] Van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 1999; 26: 743-745.

[97] Salaffi F, Carotti M, Lamanna G and Baldelli S. Quantitative analysis of radiologic progression in rheumatoid arthritis: controversies and perspectives. Radiol Med 1997; 93: 174-184.

[98] Sharp JT, Lidsky MD, Collins LC and Moreland J. Method of scoring the progression of radiologic changes in rheumatoid arthritis. Arthritis Rheum 1971; 14: 706-720.

[99] Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, Decker JL, Genant HK, Gofton JP, Goodman N, Larsen A, Lidsky MD, Pussila P, Weinstein AS and Weissman BN. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum 1985; 28: 1326-1335.

[100] Genant HK, Jiang Y, Peterfy C, Lu Y, Redei J and Countryman PJ. Assessment of rheumatoid arthritis using a modified scoring method on digitized and original radiographs. Arthritis Rheum 1998; 41: 1583-1590.

[101] Van der Heijde D, van Riel PL, Nuver-Zwart IH, Gribnau FW and van de Putte L. Effects of hydroxychloroquine and sulfasalazine on progression of joint damage in rheumatoid arthritis. Lancet 1989; 1: 1036-8.

[102] Larsen A, Dale K and Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by reference films. Acta Radiol Diagn 1977; 18: 481-491.

[103] Larsen A, Edgren J, Harju E, Laasonen L and Reitamo T. Interobserver variation in the evaluation of radiologic changes of rheumatoid arthritis. Scand J Rheumatol 1979; 8: 109-112.

[104] Larsen A. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J Rheumatol 1995; 22: 1974-1975.

[105] Rau R and Herborn G. A modified version of Larsen's scoring method to assess radiologic changes in rheumatoid arthritis. J Rheumatol 1995; 22: 1976-1982.

[106] Rau R, Wassenberg S, Herborn G, Stucki G and Gebler A. A new method of scoring radiographic change in rheumatoid arthritis. J Rheumatol 1998; 25: 2094-2106.

[107] Van der Heijde D, Dankert T, Nieman F, Rau R and Boers M. Reliability and sensitivity to

change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford) 1999; 38: 941-947.
[108] Van der Heijde D, Boonen A, Boers M, Kostense P and van der Linden S. Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. Rheumatology (Oxford) 1999; 38: 1213-1220.
[109] Wolfe F, van der Heijde DM and Larsen A. Assessing radiographic status of rheumatoid arthritis: introduction of a short erosion scale. J Rheumatol 2000; 27: 2090-2099.
[110] Barnabe C, Hazlewood G, Barr S and Martin L. Comparison of radiographic scoring methods in a cohort of RA patients treated with anti-TNF therapy. Rheumatology 2012; 51: 878-881.
[111] Boini S and Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis 2001; 60: 817-827.