2 Pre-rheumatoid arthritis

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What is pre-rheumatoid arthritis?

In recent years, research in the field of rheumatoid arthritis (RA) has focused on the earliest stages of disease. Different terminologies for pre-clinical and very early clinical disease stages are used; 'pre-RA' is one of these terms. In order to facilitate communication, a European League Against Rheumatism (EULAR) task force has derived recommendations for terminology to be used during the preclinical and earliest clinically apparent phases of RA. The following phases in the development of RA were described (Figure 2.1) [1]:

- genetic risk factors;
- environmental risk factors;
- systemic autoimmunity;
- symptoms without clinical arthritis;
- unclassified arthritis (UA); and
- RA.

Importantly, not every patient has to experience each stage and the phases can be used in a combinatorial manner. For instance, a patient can have genetic risk factors, anticyclic citrullinated peptide antibodies (ACPA), and arthralgia. In this chapter, the presently available knowledge on these specific phases has been summarized.

Risk factors for rheumatoid arthritis

Genetic risk factors

At present, more than 100 genetic risk factors for RA have been identified and replicated (Table 2.1). The majority of these risk factors have a moderate

P. Emery, *Atlas of Rheumatoid Arthritis*,
DOI 10.1007/978-1-907673-91-7_2

minor allele frequency. This indicates that the risk alleles are not rare but are quite commonly present in the population. In contrast to the prevalence of these risk factors, the odds ratios are relatively small (in the range of 1.1–1.3). This indicates that carrying a single risk factor does not yield a dramatically increased risk of RA. Interestingly, several of the identified genes lie on the same pathway. For example, HLA class II histocompatibility antigen DRB1-9 beta chain (*HLA-DRB1),* protein tyrosine phosphatase non-receptor type 22 *(PTPN22),* signal transducer and activator of transcription 4 *(STAT4),* cluster of differentiation 40 *(CD40),* cytotoxic T-lymphocyte antigen 4 *(CTLA4),* interleukin (*IL*)2, *IL21,* and protein kinase C theta type (*PRKCQ*) are all involved in T-cell activation, while *CD40, CTLA4, IL 2, IL21, PRKCQ, PTPN22, STAT4,* tumor necrosis factor alpha-induced protein 3 *(TNFAIP3)*, and tumor necrosis factor receptor-associated factor 1 (*TRAF1)* are involved in cell-cycle regulation.

Importantly, the majority of the genetic risk factors are identified in ACPA-positive RA. It is suggested that ACPA-positive and ACPA-negative RA have dissimilar genetic risk factors but the heritability of both subgroups is similar (66% and 68%, respectively) [2]. This implies that the majority of genetic risk factors for ACPA-negative RA are as yet unidentified. Moreover, in ACPA-positive RA, the known risk factors do not explain the total genetic contribution to RA, suggesting that other genetic factors play a role as well. Therefore, more current ongoing genetic studies focus on rare genetic variants. Although these will be less common, it is expected that these variants will have a higher effect size. At the time of writing, no large-scale sequencing studies in patients with RA have been published.

Environmental risk factors

The known environmental risk factors for RA are summarized in Table 2.2 [3–16]. Given a heritability of 66%, up to 34% of the variance may be explained by environmental factors. Smoking is the only environmental factor that is widely replicated as a risk factor, particularly in persons that carry *HLA-DRB1* shared epitope alleles [6].

Systemic autoimmunity associated with rheumatoid arthritis

When examining serum of patients with RA that was collected before their arthritis became clinically apparent, a proportion of these patients had detectable rheumatoid factor (RF) or ACPA in the years before the development of arthritis (Figure 2.2) and the maturation of this auto-antibody response has taken place in the preclinical phase [9]. Similarly, acute phase reactants and bone degradation products have been found to be present in the phase before

arthritis occurs (Table 2.3) [17–23]. Together these data suggest that in patients with RA, the onset of the disease preceded the onset of clinically detectable arthritis. Although these data are highly interesting, prospective data are still scarce, leaving the question of what proportion of ACPA-positive persons in the general population will develop RA unanswered.

Symptoms without clinical arthritis

Symptoms that are specific for developing arthritis have not been explicitly described by the EULAR task force. From a clinical perspective, such information would be highly relevant, though at present data are scarce on this issue. The majority of existing data originate from cohorts in the Netherlands and Sweden [24,25]. In the Dutch cohort, it was observed that from a population of patients who were ACPA-positive with arthralgia, 20% developed RA; whereas from all patients who were ACPA-positive with symmetric arthralgia of small joints, 60% developed RA [24]. Because, clinically, there is no local inflammation detectable in this phase, the question is whether local subclinical inflammation can be detected in this phase using imaging techniques. Ultrasound was performed in the Dutch study; at a patient level, there were no significant differences in joint effusion, synovitis, or Power Doppler signals between those who did and did not develop RA [25]. In another study, patients who were auto-antibody-positive had magnetic resonance imaging (MRI) and an arthroscopic synovial biopsy on their knee joints, also revealing no subclinical inflammation in the knee [26].

A recent study that analyzed MRI images of small joints (extremities) of patients who were ACPA-positive with arthralgia found that the degree of synovitis, bone marrow edema, and erosions were higher in the patients with arthralgia compared to healthy persons, but lower than that of ACPA-positive patients with RA (Figures 2.3 to 2.5). As such, these data are in line with those of a study on monkeys showing that subclinical inflammation precedes clinical arthritis [27]. This study also showed that, in monkeys, the preclinical phase was characterized by synovial tissue infiltration of macrophages and the expression of macrophage-derived cytokines.

Unclassified arthritis

Knowledge about the processes taking place during the aforementioned preclinical phases is at present relatively limited. Much more data are available on the phase of unclassified (also called undifferentiated) arthritis (UA); the vast majority of these studies were performed when RA was defined according to the 1987 American College of Rheumatology (ACR) criteria.

Clinical and serological risk factors for progression to RA are summarized in Table 2.4 and relate to the extent of inflammation and the presence of auto-antibodies.

With regards to imaging, positive findings have been found using ultrasound, digital X-ray radiogrammetry (DXR), and MRI (Table 2.5). Ultrasound has a predictive value for RA development that is independent of and additive to known serological and clinical risk factors for RA [28]. Measuring bone mass density via DXR also seems to be relevant, though the present studies on UA are based on rather low patient numbers [29]. Two studies were done on the value of extremity MRI in early UA; in both studies, bone marrow edema was most predictive for progression to RA (Table 2.5) [28–31]. In regards to MRI, it should be noted that it is not completely clear which abnormalities are diagnostic or prognostic, as erosions and synovitis have also been observed in healthy persons, to some extent (mostly RA MRI scoring grade 1). When using MRI, the present data indicate that bone marrow edema is most strongly associated with the development of RA (Figures 2.6 to 2.8) and progression of RA (Table 2.6) [32–35].

With the development of the 2010 ACR/EULAR criteria for RA, not only did the definition of RA change, but also the definition of UA. Some patients who were formerly classified as UA at first presentation are now identified as having RA when using the 2010 criteria; this predominantly concerns ACPA-positive patients with early arthritis. However, the opposite also occurs. A proportion of patients who at disease-onset fulfilled the 1987 criteria do not fulfill the 2010 criteria; these are generally ACPA-negative patients. Overall, patients with UA according to the 2010 criteria have milder baseline characteristics and outcomes than patients with UA according to 1987 criteria (Figure 2.9) [31]. Importantly, although the majority of patients with UA using 2010 criteria are ACPA-negative, up to 25% of these patients progress to RA after 1 year. At present, we do not have adequate predictive tools to identify these patients. Whether imaging modalities are helpful in patients with UA is presently under investigation.

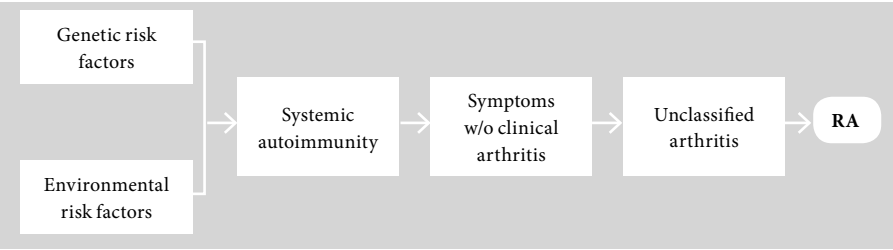

Figure 2.1 Different phases in the development of rheumatoid arthritis. RA, rheumatoid arthritis.

Genetic variant	Located in/nearby gene(s)	Locus	Minor allele frequency	OR (95%CI)
HLA-DRB1 shared epitope alleles		6p21	0.22	2.88 (2.73–3.03)
rs2476601	*PTPN22*	1p13	0.10	1.94 (1.81–2.08)
rs3087243	*CTLA4*	2q33	0.44	0.87 (0.83–0.91)
rs10499194	*TNFAIP3-OLIG3*	6q23	0.27	0.91 (0.87–0.96)
rs7574865	*STAT4*	2q32	0.22	1.16 (1.10–1.23)
rs10818488	*C5-TRAF1*	9q33	0.40	1.45 (1.12–1.88)
rs2104286	*IL-2RA*	10p15	0.24	0.93 (0.87–0.97)
rs743777	*IL-2RB*	22q12	0.33	1.11 (1.05–1.17)
rs6822844	*IL-21*	4q27	0.18	0.90 (0.84–0.95)
rs4810485	*CD40*	20q13	0.25	0.85 (0.80–0.90)
rs2812378	*CCL21*	9p13	0.34	1.10 (1.05–1.16)
rs3890745	*MMEL*	1p36	0.33	0.90 (0.86–0.94)
rs4750316	*PRKCQ*	10p15	0.19	0.87 (0.82–0.92)
rs1678542	*KIF5A*	12q13	0.38	0.91 (0.87–0.96)
rs42041	*CDK6*	7q21	0.24	1.08 (NP)
rs13031237	*REL*	2p16	0.37	1.13 (1.07–1.18)
rs2736340	*BLK*	8p23	0.25	1.12 (1.07–1.18)
rs394581	*TAGAP*	6q25	0.30	0.91 (0.87–0.96)
rs1980422	*CD28*	2q33	0.24	1.12 (1.07–1.17)
rs540386	*TRAF6*	11p12	0.14	0.88 (0.83–0.94)
rs10919563	*PTPRC*	1q31	0.13	0.88 (0.82–0.94)
rs12746613	*FCGR2A*	1q23	0.12	1.13 (1.06–1.21)
rs548234	*PRDM1*	6q21	0.33	1.10 (1.05–1.16)
rs11586238	*CD2/CD58*	1p13	0.24	1.13 (1.07–1.19)
rs10865035	*AFF3*	2q11	0.47	1.12 (1.07–1.17)
rs6859219	*ANKRD55/IL-6ST*	5q11	0.21	0.85 (0.78–0.93)
rs26232	*C5-orf30*	5q21	0.32	0.93 (0.88–0.98)
rs3093023	*CCR6*	6q27	0.43	1.11 (1.06–1.16)
rs10488631	*IRF5*	7q32	0.11	1.25 (1.14–1.37)
rs13315591	*PXK*	3p14	0.10	1.13 (1.04–1.23)
rs874040	*RBJP*	4p15	0.30	1.18 (1.12–1.24)
rs934734	*SPRED2*	2p14	0.49	1.13 (1.06–1.21)
rs951005	*CCL21*	9p13	0.16	0.87 (0.81–0.93)

Table 2.1 The first genetic risk factors that were replicated in independent studies and their odds on rheumatoid arthritis. CI, confidence interval; NP, not provided; OR, odds ratio.

Risk factor	Degree of evidence
Environment	
• Air pollution	Inconclusive • Increased RA risk has been reported [7]
• Infections	Inconclusive • Indirect evidence by findings of increased rates of onset of RA in the winter [4,8] • Several microorganisms have shown increased titres of antibodies in RA compared to controls, however no single microorganism seems responsible for RA-development [9,10]
Lifestyle factors	
• Smoking	Established • This is the only well established environmental factor for RA [6] • Predisposition in HLA-DRB1 shared epitope-positive persons for development of ACPA-positive RA [11]
• Coffee	Inconclusive • Both positive and negative effects have been observed
• Alcohol	Inconclusive • RA patients report lower intake of alcohol, unclear whether alcohol is truly protective [12]
Hormonal	
• Parity	Inconclusive • Some studies reported a lower RA risk in parous women [13,14]
• Hormone replacement therapy/ oral contraceptives	Inconclusive • Some studies reported on a decreased risk of RA [14,15]
• Breast feeding	Inconclusive • A reduced risk for RA has been observed in women after long-term breast feeding [14,16]

Table 2.2 Environmental risk factors for rheumatoid arthritis. ACPA, anti-citrullinated peptide antibody; RA, rheumatoid arthritis.

Category	Serologic abnormality
Inflammation	• Increased CRP • TNF-α levels, several interleukins (ILs) (eg, IL-1α, IL-1β, IL-6, IL-10, IL-15) are increased
Auto-antibodies	• Increased prevalence of rheumatoid factor • Increased prevalence of ACPA positivity • Maturation of ACPA response
Metabolism	• Lower HDLc levels, lower ApoA levels • Increased P1NP and osteoprotegerin levels

Table 2.3 Reported serological abnormalities in the preclinical phase of (rheumatoid) arthritis. ACPA, anti-citrullinated peptide antibody; ApoA, apolipoprotein; CRP, C-reactive protein; HDLc, high density lipoprotein cholesterol; P1NP, serum procollagen type 1 amino-terminal propeptide; TNF-α, tumor necrosis factor-alpha.

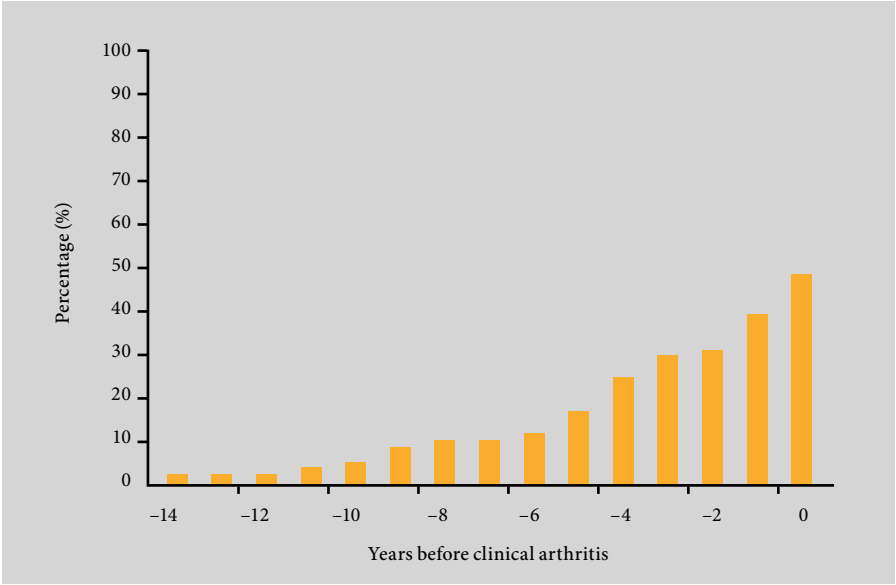

Figure 2.2 Percentage of patients with rheumatoid arthritis and positive for rheumatoid factor or anti-citrullinated peptide antibodies in the years before the onset of clinically detectable arthritis. Adapted with permission from Nielen et al [19] ©SAGE.

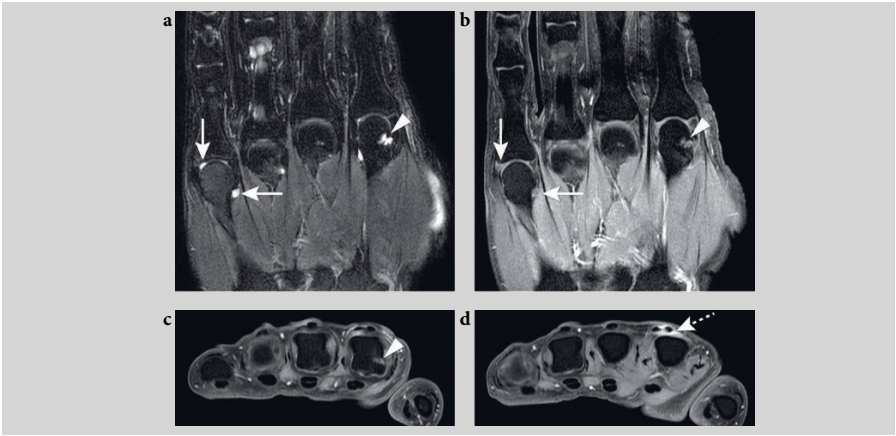

Figure 2.3 Magnetic resonance images of the left hand in a patient who is positive for anti-citrullinated peptide antibodies with arthralgia but without clinically-detectable arthritis. 1.5T extremity MRI with maximum field of view of 16 cm. Shown are the metacarpal bones 1 to 4 and the proximal phalanges. (**a**) Coronal T2 TSE fat saturation (fatsat) and (**b, c, d**) coronal and axial T1 TSE fatsat after intravenous administration of gadolinium. Some fluid is present in the fifth metacarpal phalangeal joint (**a**; arrows); the lack of enhancement after gadolinium shows there is no synovitis. In the head of metacarpal 2, subchondral cysts are appreciated (**a**), no enhancement is seen (**b, c**; arrow heads). However, on the axial images, the enhancement around the extensor tendons of the second finger is consistent with tenosynovitis (**d**; dotted arrow). In addition on the coronal T2 TSE, partial voluming of fluid, nonenhancing after gadolinium in the soft tissues dorsal to the fourth proximal phalanx is seen.

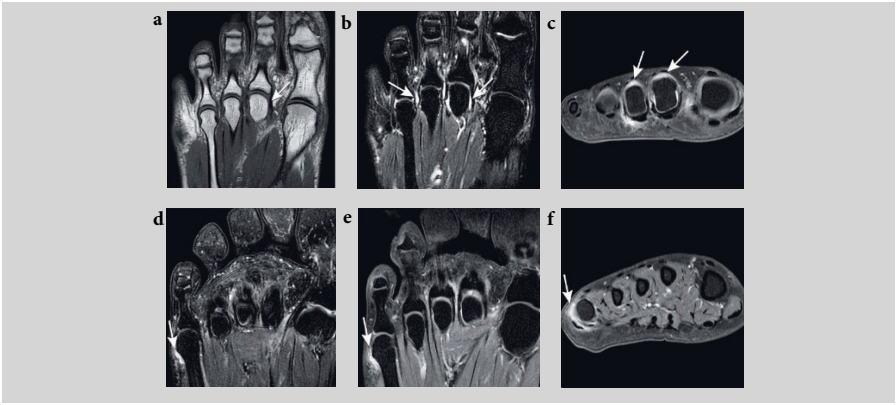

Figure 2.4 Magnetic resonance images (MRIs) of the left foot in a patient who is positive for anti-citrullinated peptide antibodies with arthralgia but without clinically-detectable arthritis. Axial T1 TSE (**a**), T2 TSE fat saturation (fatsat; **b, d**), and axial and coronal T1 TSE fatsat with gadolinium **(c, e, f)** of the forefoot on 1.5T extremity MRI. Intact cortical bone of the metatarsal phalangeal (MTP) joints on T1 TSE image (**a**). The high signal intensity on T2 TSE in the MTP joints (**b**), enhances after gadolinium (**c**) and is consistent with synovitis. This is well visualized on the coronal T1 TSE fatsat images with gadolinium at the level of the MTP 2 and 3 (**c**; arrows). The MTP 5 joint shows high signal intensity on (**d**) axial T2, and enhancement on (**e**) axial and (**f**) coronal T1 TSE fatsat (arrows), also consistent with synovitis.

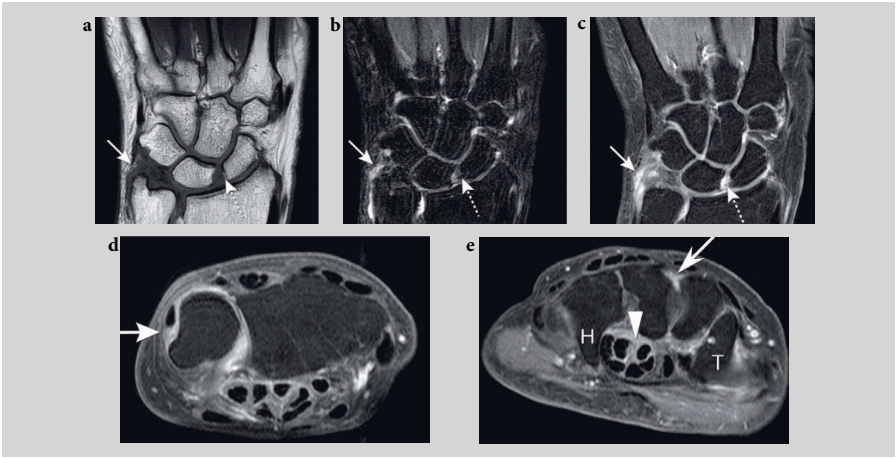

Figure 2.5 Magnetic resonance images (MRIs) of the left wrist with synovitis in a patient who is positive for anti-citrullinated peptide antibodies with arthralgia but without clinically-detectable arthritis. Coronal T1 TSE (**a**), T2-TSE fatsat (**b**) and T1 TSE fatsat with gadolinium, coronal (**c**), and axial (**d**) at the level of the distal radial ulnar joint and the carpal tunnel (**e**). The T2 images show some movement artefacts. Synovial thickening surrounding the distal ulna with irregularity of the triangular fibrocartilage, the signal intensity is intermediate on T1, inhomogeneous increased on T2, showing enhancement after intravenous gadolinium (**d, e**; arrow). Appreciate the cortical irregularity of the scaphoid and lunate **(a, b)** with enhancing synovium (**c**; dotted arrows). The radial styloid shows cortical irregularity as well **(a, c)**. The axial image at the level of the distal carpal tunnel (**H**, hook of hamate; **T**, trapezoid) shows enhancement around the flexor tendons (arrow head) and between the capitatum and trapezium, consistent with (teno)synovitis (**e**; arrow).

Risk factors:

- Older age
- Female gender
- Positive family history for rheumatoid arthritis
- Gradual symptom onset
- Involvement of small joints
- Symmetric symptoms and signs
- High (4 or more) number of tender joints
- High (4 or more) number of swollen joints
- Morning stiffness
- Increased CRP
- Increased ESR
- Presence of rheumatoid factor
- Presence of ACPA
- Smoking

Table 2.4 Clinical and serological risk factors for development of rheumatoid arthritis in patients with unclassified arthritis. ACPA, anti-citrullinated peptide antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

	Characteristics predictive for RA development	Additive prognostic value to clinical and serologic risk factors?
Ultrasound	Grayscale wrist and metacarpophalangeal joint involvement Power Doppler involvement of metatarsophalangeal joint	*Yes*, based on a study in 58 patients. The AUC significantly improved from 0.905–0.962 [28]
Magnetic resonance imaging (MRI)	Bone marrow edema in wrist or metatarsophalangeal joint	*Yes*, based on a study of 116 patients, after adjustments for other variables, bone marrow edema has an OR of 1.4 for RA development [30]. In a second study of 129 patients, bone marrow edema had an additive value to ACPA positivity (PPV increased from 92% to 100%) [31]
Digital X-ray radiogrammetry (DXR)	Highly elevated BMD loss is associated with a PPV of 85% on RA development (OR=6.1)	*Perhaps.* BMD has an independent effect of ACPA (OR=4.1, 95% CI 0.8, 21.2). Definitive conclusions cannot be drawn due to small numbers and a large CI [29]

Table 2.5 Prognostic value of different imaging modalities in unclassified arthritis. ACPA, anti-citrullinated peptide antibody; AUC, area under the curve; BMD, bone mineral density; CI, confidence interval; OR, odds ratio; PPV, positive predictive value; RA, rheumatoid arthritis.

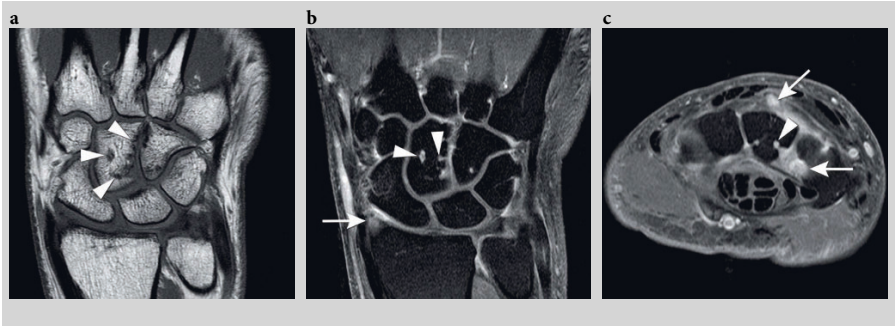

Figure 2.6 Magnetic resonance images (MRIs) of the right wrist in a patient with undifferentiated arthritis and erosions. Coronal T1 TSE (**a**), coronal (**b**) and axial (**c**) T1 TSE fat saturation (fatsat) with gadolinium. The multiple cortical defects are seen on coronal T1 TSE, enhancing on coronal and axial T1 TSE fatsat with gadolinium (arrow heads). Unsharply defined intraosseous enhancement is also present in the radial styloid (arrow), consistent with edema (**b**). Enhancing synovium is appreciated on the axial image intercarpal and at the dorsal side of the carpus (**c**; arrows).

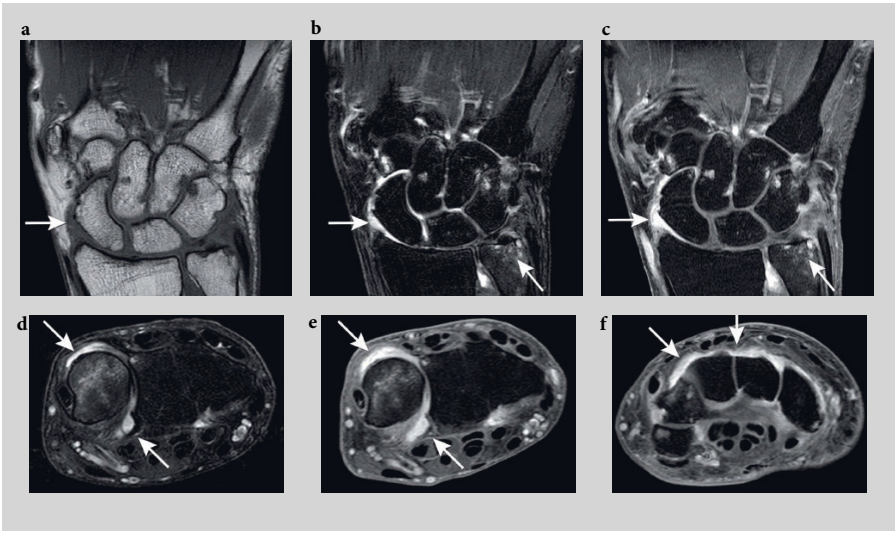

Figure 2.7 Magnetic resonance images (MRIs) of the right wrist in patient with undifferentiated arthritis and synovitis, intraosseous edema and erosions. Coronal T1 TSE (**a**), coronal and axial T2 TSE fat saturation (fat sat) (**b,d**) and coronal and axial T1 TSE fatsat with gadolinium (**c, e, f**). Multiple cortical erosions are visualized on T1 in the carpal bones and ulnar styloid process (**a**). On T2 (**b**) high signal intensity is present in the intercarpal, radiocarpal, and distal radial ulnar joints which enhances after contrast administration (**c**) (arrows), based on synovitis. Notice the intraosseous edema (bone marrow edema) and the enhancing erosions in the ulnar styloid (arrow). The high signal on T2 (**d**) is enhancing synovium (**e**) seen around the ulna and in the distal radial ulnar joint (arrows), as well as on the dorsal side of the carpalea (**f**).

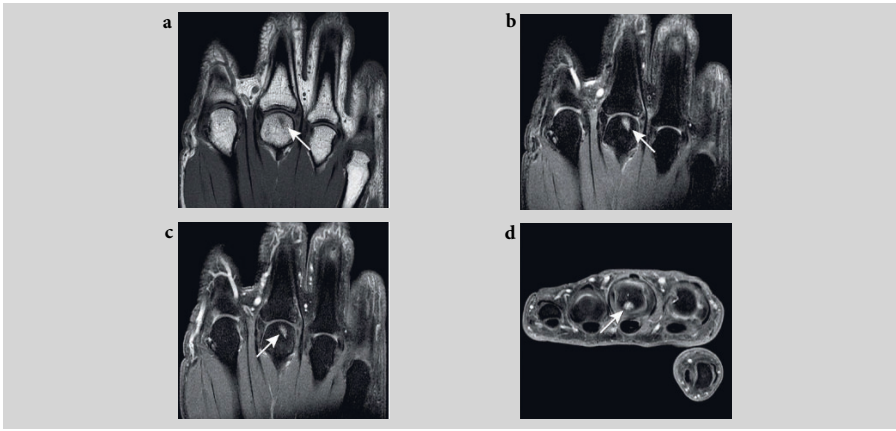

Figure 2.8 Magnetic resonance images (MRIs) of the right metacarpophalangeal joints in a patient with unclassified arthritis. Focal area in the head of metacarpal 3 of low signal intensity on T1 TSE (**a**), high on T2 TSE fat saturation (fatsat) (**b**), enhancing after gadolinium on T1 TSE fat sat (**c, d**). On the axial images, the volar subchondral location is appreciated, a cortical defect is not seen (however cannot be excluded). This finding is aspecific and can be based on a synovial cyst of no clinical importance or aspecific intraosseous edema. Its location, not at the level of ligamentous insertion, is less convincing for an erosion. There is no pathologic enhancing synovium. Follow-up in time may be of additional value.

Study [reference]	n	Disease duration (median)	Joints scanned	MRI scoring	Follow up	Outcome measure	Main finding
Haavardsholm et al [32]	84	<12 months	Wrist	RAMRIS	1 year	X-ray progression	BME independent predictor erosive progression
Syversen et al [33]	82	<12 months	Wrist	RAMRIS	1 year	X-ray progression	BME independent predictor erosive progression
Bøyesen et al [34]	55	<12 months	Wrist	RAMRIS	3 years	X-ray progression	BME independent predictor erosive progression
Døhn et al [35]	52	7 years	Wrist, MCP	RAMRIS	1 year	X-ray progression	Especially BME predictive for erosive progression

Table 2.6 Overview of studies on magnetic resonance imaging in progression of rheumatoid and the main findings. BME, bone marrow edema; MCP, metacarpophalangeal joint; MRI, magnetic resonance imaging; RAMRIS, rheumatoid arthritis MRI score.

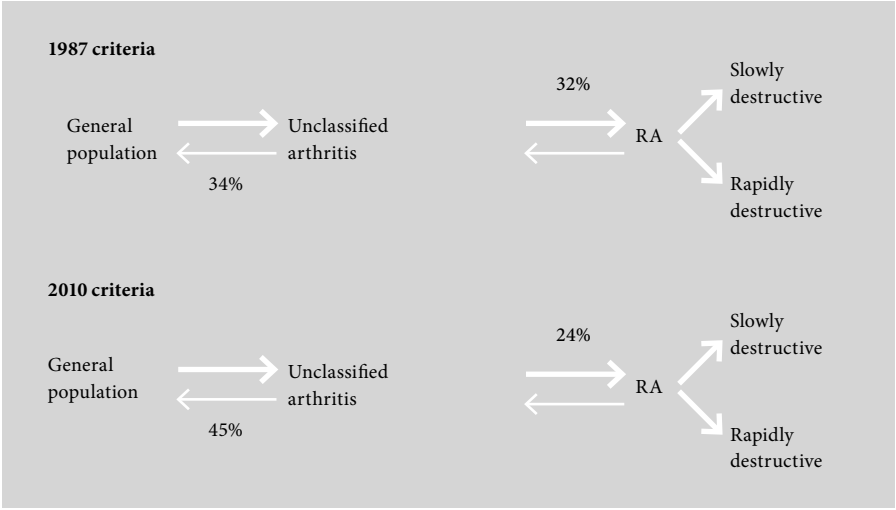

Figure 2.9 Outcomes of unclassified arthritis, depending on the classification method for rheumatoid arthritis. 1987 or 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria. RA, rheumatoid arthritis. Indicated are the percentages of patients with unclassified arthritis that achieved sustained remission after 7 years and the percentages of patients with unclassified arthritis that developed RA after 1 year [31].

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http://www.springer.com/978-1-907673-90-0

Atlas of Rheumatoid Arthritis

Emery, P. (Ed.)
2015, XI, 264 p. 166 illus., 115 illus. in color., Softcover
ISBN: 978-1-907673-90-0