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How to investigate: Pre-clinical rheumatoid arthritis

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A B S T R A C T

Multiple studies have shown that there is a pre-clinical period preceding the development of rheumatoid arthritis (RA). During this period, complex interactions between the environmental and genetic causes occur, and the expression “preclinical RA” has been proposed to define it. Early treatment intervention is associated with less joint damage and has an increased possibility of achieving remission. In this review, we provide an overview of the preclinical phases of RA, new immunological and imaging biomarkers, and the clinical features, and the management of individuals at-risk of developing RA.

Classification of preclinical RA

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that induces cartilage and bone damage, leading eventually to disability. Early diagnosis is key to optimal, therapeutic success, particularly in patients with well-characterized risk factors for poor outcomes such as high disease activity, the presence of autoantibodies, and early joint damage.

Multiple studies have identified environmental and genetic factors that are associated with the increased (or decreased) risk of RA [1]. Thus, it is reasonable to assume that individuals carrying those risk

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factors are potentially in an asymptomatic phase of a sequence of events that will ultimately lead to clinical manifestations compatible with the diagnosis of RA. The expression “preclinical RA” is used to define the period of abnormalities in immune function in the absence of clinical manifestations of autoimmune tissue injury [2–4]. To standardize the terminology for the phases leading up to RA, the European League Against Rheumatism (EULAR) Standing Committee on Investigative Rheumatology devised a recommendation for nomenclature, including six categories: genetic and environmental risk factors for RA (phases A and B, respectively), systemic autoimmunity associated with RA (phase C), symptoms without clinical arthritis (phase D), and both undifferentiated arthritis (UA) and RA (phases E and F, respectively) [5] (Fig. 1). These phases result from the construction made based on the current knowledge about RA etiology. It is relevant to note that this concept does not imply that all individuals progress through all phases, or that individual phases are mutually exclusive. In addition, the terms, preclinical RA and pre-RA, should only be used in a retrospective form, as many at-risk individuals will never develop clinical arthritis or RA. This is especially relevant for individuals in phases, A and B, who are healthy individuals with risk factors and may never present immunological disturbances. It is probable that to reach phase C, a trigger will be necessary to cross the threshold from risk to pathology (Fig. 1). Among several possible stimuli, systemic autoimmunity may be driven by smoking or initiating events at mucosal surfaces, such as the lung, periodontium, and gut [6,7].

Genetic and environmental factors relevant in the context of preclinical RA

Genetic factors

Multiple genetic studies have shown the genetic contribution to RA to be between 30% and 60% [8–10]. Many genetic variations showing an association with RA have been identified. The DRB1 allele that contains the “shared epitope” (SE) is the most important genetic factor associated with RA, with HLA-DRB1 molecules (*0101, *0102, *0401, *0404, *0405, *0408, *1001, and *1402) being the most strongly associated with RA. The SE alone is associated with a 3-fold increased risk of RA [11,12]. The SE represents the strongest risk factor for anticyclic citrullinated peptide antibodies (ACPA) positivity, with these autoantibodies developing preferentially in patients who have one or two SE alleles. A recent study examining the risk of developing ACPA-positive RA showed that the strength of association varied according to the different susceptibility HLA-DRB1 alleles, with HLA-DR1*0404, *0405, *0408 conferring the highest risk [13,14].

Genetic studies have revealed that, while ACPA-negative RA and ACPA-positive RA are two genetically distinct subsets of RA, each with its specific set of susceptibility polymorphisms, they also share several genetic associations. For example, AFF3, CCR6, CCL21, IL2RA, and CD28 are associated with ACPA-positive RA susceptibility but not with ACPA-negative RA, while markers at TNFAIP3, C5orf30, STAT4, ANKRD55, BLK, and PTPN22 are associated with both serotypes. By contrast, CLYBL, SMIM21, SPP1, CLEC16A, IRF5, DCIR, LEMD2, CSMD1, FCRL3, IL-33, PRL, and NFIA have been reported to be associated with ACPA-negative RA (although not at genome-wide significance thresholds), and many of these markers are not associated with ACPA-positive RA. An important unmet need in the research of genetic contributions to RA, is to investigate the specific functional role of each one of the genetic variants [11,12,15].

Smoking and environmental factors

There are several environmental factors that may potentially play a relevant role in RA susceptibility. Smoking is the most important environmental risk factor for the development of RA and it also

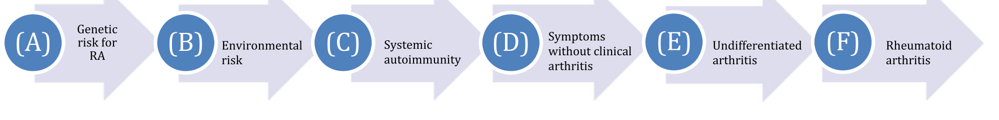

Fig. 1. The six specific phases of rheumatoid arthritis development as presented by the European League Against Rheumatism Standing Committee on Investigative Rheumatology.

increases the risk of severe disease. The risk is higher in ACPA-positive individuals [6,16]. Coffee consumption, according to some cohorts, showed association with the development of RA in ACPA-positive individuals [4]. One study demonstrated that the subjects consuming four or more cups of coffee a day have a relative risk of 2.06 of developing RA when compared with those who consumed fewer than four cups [17]. A more recent prospective study, on the other hand, did not find a significant association between total coffee and total caffeine consumption with the risk of RA [18]. So, we conclude that the actual data are still sparse, and findings are inconsistent across the few existing studies [17,18]. Occupational exposure to mineral oils (e.g., motor oils, hydraulic oils) was found to be a risk factor for ACPA-positive RA in men in a Swedish cohort. Professional exposure to silica was associated with an increased risk of developing RA in ACPA-positive people, according to studies performed in Malaysian and Swedish populations. The more recent study was made in a Swedish population of 2551 workers and the results demonstrated an increased risk of 57% for RA development [19,20]. Lower intake of vitamin D and antioxidants, and higher intake of sugar, sodium, red meats, protein, and iron were also associated with increased risk for RA. Furthermore, a finding that has been relatively consistent across many studies is that a higher intake of fish as well as omega-3 fatty acids have been consistently linked to decreased risk for RA across several studies, including studies where dietary data were collected prior to incident RA [21–25].

Infections are major candidates for the induction of autoimmunity and have, therefore, been intensively studied also in RA. Pathogens such as *Mycoplasma*, Epstein-Barr Virus (EBV) or *Proteus* have been associated with RA [4,26,27]. On the other hand, alcohol consumption was inversely correlated with the development of RA in ACPA-positive individuals [28]. This was particularly evident for those who drank >4 glasses of alcohol (1 glass = 15 g of ethanol) per week compared with those who drank < 1 glass per week or who never drank alcohol ($p = 0.04$). When the long-term alcohol consumption is analyzed, the results showed that women who reported drinking >3 glasses of alcohol per week had a 52% decreased risk of RA compared with those who never drank [29]. Women with lower age at menarche have a lower risk for the development of RA. In a Danish cohort, for example, women with a late menarche (≥15) had an almost twofold risk of developing RA as compared with women aged ≤12 years at menarche. Pregnancy is in itself a risk factor for the development of RA. During pregnancy, most women with RA experience a significant reduction in the disease activity, but almost all patients relapse within 3 months after delivery. Multiparity (>3 children) favors a more severe course of disease, but does not additionally increase the risk for developing RA. The other protective factor against the development of RA includes a history of oral contraceptive pill use [4,6,30–32].

The microbiome

Another field of interest is the interplay between the human microbiome (especially in the oral cavity, the gut, and lungs) and the host's immune system. A shift from a normal symbiotic toward a “dysbiotic” microbiome, characterized by the overgrowth of pathogenic, and a lack of commensal bacteria, may be responsible for changes in the innate and adaptive immunity contributing to the development of RA [33,34]. Periodontal disease has been reported in different studies as a risk factor of developing RA. It is particularly interesting to note that *Porphyromonas gingivalis*, one of the microorganisms involved in periodontal disease uniquely expresses a bacterial form of peptidylarginine deiminase (PAD) and enolase. *P. gingivalis* PAD can citrullinate different peptides in vitro and can thus, generate self-antigens. PAD can also be autocitrullinated, and antibodies against PAD have been detected in patients with RA [34–36]. Furthermore, *anti*-α-enolase antibodies cross-react with recombinant bacterial citrullinated enolase suggesting that *P. gingivalis* infection can induce autoimmune responses in susceptible individuals by “molecular mimicry”. Additionally, antibodies against *P. gingivalis* were detected in autoantibody (ACPA and Rheumatoid Factor (RF))-positive individuals at risk of developing RA (first-degree relatives of patients with RA) [37]. Periodontal disease, particularly in the presence of *P. gingivalis* is probably associated with an increased risk of developing RA, especially in smokers. Furthermore, there is evidence suggesting that smoking may be associated with the translocation of supraglottic bacterial species, such as *Prevotella* and *Porphyromonas* to the lungs, leading to increased activity of PAD and airway inflammation [33].

Other microbiome populations have been studied in the gut, offering new insights into the complex relationship between pathogens and commensals on one side and the host's immune system on the other. An abundance of *Prevotella copri* with loss of *Bacteroides* has been demonstrated in the stool of patients with new onset RA [38]. Interestingly, the gut and oral dysbiosis were shown to correlate with each other and with CRP, RF, and *anti*-CCP antibodies in a recent metagenomics study of RA patients; the same study also demonstrated a partial resolution of the dysbiosis after treatment with DMARDs [38,39]. Despite these findings, the beneficial effect of probiotics has not been unequivocally demonstrated in the treatment of RA. *Lactobacillus casei* was the only probiotic tested for effect on disease activity in a randomized trial [40]. However, the effect is probably strain- and dose-specific and this finding is not sufficient to recommend, at the moment, the routine use of probiotics in RA. What remains to be established is whether gut dysbiosis occurs as a consequence of the systemic inflammatory environment in early RA, or whether dysbiosis itself is the primary trigger for autoimmunity in some individuals. Tables 1 and 2 summarize the different environmental factors that could predispose or protect RA development.

The role of autoantibodies and inflammation in preclinical RA

Several studies have shown that RA-related antibodies, as RF or ACPAs, are present many years before RA diagnosis. Some case–control studies report a positive predictive value of 80% for ACPA and/or RF positivity in terms of the prediction of future RA [32]. Other studies of ACPA-positive individuals have shown a rate of RA development of 40–60% over 2–5 years of follow-up and confirm ACPA as a powerful marker for the future development of RA. Furthermore, this risk can be higher if the following factors are present in addition to ACPA positivity: the concomitant presence of RF, self-reported joint pain and tenderness on examination, smoking, obesity, SE, and the imaging findings of joint inflammation (e.g., power Doppler (PD) signal on ultrasound) [41–43].

New serum biomarkers in preclinical RA

Today, we know that early, aggressive treatment is more effective than delayed treatment. The use of biomarkers is useful to diagnose RA as early as possible and thus enable an early treatment, with consequent better outcomes. In recent years, multiple studies have assessed potential new biomarkers when RF and ACPA are negative, despite the presence of possible pre-RA subtle clinical manifestations.

A test for mutated citrullinated vimentin antibody (*anti*-MCV) was developed by Bang et al. Vimentin is an intermediate filament that is widely expressed in mesenchymal cells and macrophages [44–46]. Usually, it is not in a citrullinated state, but deamination of this protein occurs in macrophages undergoing apoptosis. Citrullinated vimentin (CV) may emerge as a consequence of the inadequate clearance of apoptotic material. CV can be encountered in RA pannus and the synovial fluid [47,48]. Previous studies suggested that *anti*-CV is one of the first antibodies to occur in the disease process and could be more sensitive than the ACPA antibodies. However, the sensitivity of the *anti*-Sa (anticitrullinated vimentin) antibody for detection of RA has been shown to be limited in established and early disease. A meta-analysis from 2010 that included 14 studies, in which *anti*-MCV and ACPA for RA

Table 1
Environmental factors associated with the development of RA.

Predisposing factors	Protective factors
Smoking (ACPA +)	Menarche ≤12 years
Periodontal disease (*P. gingivalis*) (ACPA+)	Alcohol consumption (ACPA +)
Exposure to mineral oils (ACPA+)	Fish and omega 3 fatty acid consumption
Older age at menarche (>15)	Oral contraceptive use
Pregnancy	
Silica dust (ACPA+)	
Low vitamin D intake and level	
High sodium, red meat and iron consumption	

ACPA, anticyclic citrullinated peptide antibodies; RA, rheumatoid arthritis.

Table 2
Environmental factors that could prevent the development of rheumatoid arthritis.

Modifiable factors to prevent the development of Rheumatoid Arthritis
• Avoid smoking • Diet containing fish oil, antioxidants, and vitamin D • Body weight with an adequate body mass index • Dental hygiene to prevent periodontitis

diagnosis were tested, concluded that there is no difference between the two tests. The *anti*-MCV may be used as an alternative to ACPA, in the context of suspected RA with undetectable ACPA and RF [45–47].

The *14-3-3η protein* belongs to a conserved family of 7 isoforms with different functions (which occurs mainly at the intracellular level). However, its expression at the extracellular level can occur in the joint of RA patients and its expression in both serum and joint fluid correlates strongly with the expression of metalloproteinases. This protein activates proinflammatory signalling cascades and inflammatory mediators relevant to the pathogenesis of RA. A new ELISA-based assay has diagnostic utility for RA with sensitivity of 63.6% and specificity of 92.6%. Adding 14-3-3η to ACPA resulted in an identification rate of 72% compared to 59% for ACPA alone [48–50]. Adding RF to ACPA increased diagnostic capture from 59% to 72% and this increased further to 78% when 14-3-3η was added [51]. Positive 14-3-3η status is also significantly associated with radiographic progression in early RA at years 1, 3, and 5, indicating prognostic utility. Together with RF and/or ACPA, this test may result in the identification of 95% of patients with early RA [49–51].

Anticarbamylated protein (*anti*-CarP) antibodies have been described in RA and arthralgia patients at risk of developing RA. Carbamylation is a post-translational modification by which lysine residues in a given protein are nonenzymatically converted into homocitrulline in the presence of cyanate. Although trace amounts of carbamylated proteins were detected in healthy individuals (suggesting that carbamylation is a physiological process), excess of carbamylation has been described in three states: inflammation (generation of cyanate from thiocyanate and hydrogen peroxide by myeloperoxidase), cigarette smoking (direct inhalation of cyanate), and uremia (abundance of urea as a source of cyanate). As in the case of citrullination, an array of proteins is expected to be carbamylated in inflamed joints, although the exact identity of targeted proteins is yet to be explored. In a study performed on 2086 patients with early RA, *anti*-CarP, ACPA, and RF were tested. Results showed a sensitivity of 44% and a specificity of 89% for the *anti*-CarP, compared with the ACPA sensitivity and specificity of 54% and 96% and RF of 59% and 91%, respectively [52]. Furthermore, in a retrospective analysis, it was reported that RA patients had *anti*-CarP antibodies detectable 4 years before diagnosis, compared to 10 years for ACPAs. The presence of *anti*-CarP antibodies had a lower sensitivity (30%) than did ACPAs and RF, but a comparatively high specificity (95%) for the future development of RA. Importantly, the potential usefulness of *anti*-CarP antibody as a predictive biomarker was less convincing in the study by Gan et al. No ACPA/RF seronegative patients were *anti*-CarP antibody positive, and it did not add predictive power to ACPAs and/or RF. Further studies in different cohorts will be needed to validate these findings and improve our understanding of the etiological role and predictive power of these autoantibodies in RA development [53].

In addition to citrullination and carbamylation, malondialdehyde-acetaldehyde (MAA) adducts have recently been described as the third post-translational modification class serving as a target of antibodies in patients with RA. MAA are produced during oxidative stress typically caused by inflammation. The presence of *anti*-MAA antibodies was associated with ACPA and RF positivity, but *anti*-MAA did not cross-react with these antibodies [54]. Recent data suggest that serum *anti*-MAA antibodies measured with currently available assays do not appear to adequately discriminate RA from other rheumatic conditions, but with the identification of specific proteins that are MAA-modified in diseased tissues and assay refinement, *anti*-MAA antibody holds potential promise as a biomarker in RA [55]. Multiple studies in recent years have studied the expression of genes involved in interferon-mediated immunity. Lübbers et al. evaluated the association between type I IFN-signature and arthritis development in two independent cohorts, namely a cohort of seropositive persons at risk and a cohort of asymptomatic individuals who later evolved into RA. The results demonstrated a potential clinical utility for the IFN-signature as a biomarker in the prediction of arthritis development, since type-I IFN signature correctly identifies 52% of patients with arthralgia who will develop RA within 2 years [56]. Conversely, the expression of genes involved in B cell-mediated immunity was associated with protection against arthritis development. There is recent evidence indicating that stratifying the B cell signature in this way (B cell-high versus B cell-low) is similarly predictive, with a B cell-high signature associated with protection against arthritis development [57]. Notably, the combination of IFN and B-cell signatures can identify IFN-high/B cell-low individuals who appear to be at a higher risk of arthritis development than those with IFN-high signatures alone [56–58].

Another area of research is the synovial tissue. In addition to identifying potential pathogenic mechanisms, the synovial tissue biopsy might be useful for informing differential diagnosis in early inflammatory arthritis. An immunohistological analysis of synovial tissue concluded that synovial CD22 and CD38 expression could distinguish patients with RA from those with non-RA disease. Additionally, the activation of JUN N-terminal kinase (JNK) is elevated in the synovia of patients with early RA when comparing with the synovia of patients with undifferentiated arthritis [59].

Table 3 summarizes the new biomarkers described above.

Clinical presentation of at-risk individuals for RA

Frequently, it is possible to identify some symptoms that can present before the occurrence of arthritis. However, no large-scale prospective studies have explored which symptoms are characteristic of RA in a preclinical phase.

The UA phase is characterized by a clinical presentation where there is arthritis of one or more joints without fulfilling RA classification criteria or of any other rheumatic condition. In all, 30%–40% of patients with UA progress to classical RA on long-term follow-up. However, 40–50% of patients with UA experience spontaneous remission. Thus, adequate decision-making regarding the treatment of patients with early UA requires identification of those patients in whom RA will develop [60–62].

Van der Helm-van Mil et al. developed a prediction rule for the development of RA that includes 9 clinical variables (sex, age, localization of symptoms, morning stiffness, tender joint count, swollen joint count, C-reactive protein level, RF positivity and the presence of ACPA). 100% of patients with a score of $\geq$8.0 progress to RA, and 94% of patients with a score $\leq$6.0 did not develop RA. This indicates that if treatment decisions were based on the prediction rule using the cutoff levels of $\geq$8 for initiating

Table 3
New biomarkers with potential utility in pre-clinical RA.

New serum biomarkers with utility in pre-clinical RA	
Serum biomarker	Key findings
• *anti*-MCV	May be used as an alternative to ACPA, in the context of suspected RA, undetectable ACPA, and RF
• 14-3-3η protein	Diagnostic utility for RA with sensitivity of 63.6% and specificity of 92.6%; when positive it is a biomarker with prognostic value.
• *anti*-CarP antibodies	The presence of anti-CarP antibodies had a lower sensitivity than did ACPAs and RF, but a comparatively high specificity. Need more studies to clarify the predictive power.
• MAA adducts	This biomarker does not appear to adequately discriminate RA from other rheumatic conditions.
• (IFN)–mediated immunity	Potential clinical utility for the IFN-signature as a biomarker in the prediction of arthritis development
• B cell–mediated immunity	Genes involved in B cell-mediated immunity were associated with protection against arthritis development
• Synovial CD22 and CD38	Expression could distinguish patients with RA from those with non-RA disease
• JNK	Elevated in the synovia of early RA patients when comparing with the synovia of patients with undifferentiated arthritis

ACPA, anticyclic citrullinated peptide antibodies; *anti*-CarP, *anti*-carbamylated protein antibodies; MAA adducts, malondialdehyde-acetaldehyde adducts; *anti*-MCV, mutated citrullinated vimentin antibody; (IFN)-mediated immunity, interferon (IFN)-mediated immunity; JNK, JUN N-terminal kinase; RA, rheumatoid arthritis; RF, rheumatoid factor.

treatment and ≤6 for withholding treatment, treatment would be inaccurately withheld in only 6% of patients, and no patient would receive treatment inappropriately [63].

Looking for patients who presented at observation with arthralgia, we should have in mind that this is a non-specific symptom and the biological nature of joint pain is very diverse. Consequently, the risk of progressing to RA is different for patients with arthralgia in different settings. Most patients with arthralgia, who are referred to rheumatologists, have a diagnosis other than RA. In addition, the majority of patients presenting with arthralgia of uncertain cause are not considered to be at risk of RA by their rheumatologists. A recent study revealed that only 7% of arthralgia patients were identified as clinically suspicious of progressing to RA (clinically suspect arthralgia, CSA) [64]. Importantly, for patients with CSA, the odds for progression to RA were 55 times larger than the odds for patients with unexplained arthralgia. Recently, EULAR developed a definition of arthralgia suspicious for progression to RA that consists of seven clinical items that can be used in patients with arthralgia in whom imminent RA is considered the most likely explanation for the symptoms. Altogether, patients with arthralgia in secondary care who fulfill the EULAR definition of CSA represent a very small proportion of all individuals suffering from joint pain. Several studies have shown that the risk of developing RA in patients with arthralgia and presenting with autoantibodies (ACPA and/or RF) at evaluation is increased [65,66].

A study conducted in 15 seropositive patients (ACPA positive and often with arthralgia) and 11 newly presenting RA patients showed that symptoms common to both groups included joint pain, psychological distress, muscle cramps, abnormal skin sensations, stiffness, loss of motor control, weakness, fatigue, and sleeping difficulties. Seropositive arthralgia patients described pain as annoying, while RA patients described how the severity of pain intensified before diagnosis, to the point where symptoms were psychologically distressing. Patients with seropositive arthralgia described that the reddening of the skin and burning sensations that they felt were indicative of the onset of swelling. Intense pain appeared to precede the onset of swelling for those with RA, which was often palindromic and travelled between joints until it later became persistent. This study showed the large spectrum of symptoms that can be present in the early phases of RA [66].

In another cohort, clinical features, such as symptom duration, intermittent symptoms, symptoms in both the upper and lower extremities, early morning stiffness of approximately 1 h, and self-reported joint swelling, were all found to be independently predictive of progression to RA [67].

A prospective study investigated the effect of the presence and levels of ACPA on arthritis development in patients with arthralgia. Patients with arthralgia positive for ACPA or IgM RF were tested for SE and were followed for 12 months. In total, 147 patients with arthralgia (ACPA positive, IgM RF positive and positive for both autoantibodies) were included. After a median follow-up of 28 months, 20% developed arthritis and 90% of these were ACPA positive. In this study, the presence of ACPA was associated with arthritis development, whereas IgM RF and SE were not associated. However, the concomitant presence of IgM RF in ACPA-positive patients was associated with an enhanced risk for arthritis [68–70]. Currently, risk stratification of patients presenting at the first appointment without laboratory tests remains to be determined.

The value of imaging in preclinical RA

It is widely recognized that some patients present at medical observation with arthralgia but without clinical arthritis at physical examination by a rheumatologist. With disease progression, the inflammatory process sets in and synovitis becomes clinically evident. Imaging techniques may be more sensitive to identify these evolving inflammatory changes in the subclinical phase.

In a Dutch cohort of seropositive patients with arthralgia abnormalities detected on ultrasound (US) imaging (joint effusion, synovitis on gray-scale, and power Doppler) were predictive of arthritis development at the joint level but not at the patient level. The combination of gray-scale synovitis and PD abnormalities was the strongest predictor of arthritis (OR 12.9 and PPV 35%) [71].

Results of a systematic review of literature on US, and early arthritis indicate that a greater number of inflamed joints per patient was detected through US compared to clinical examination in populations ranging from ACPA/RF-positive patients with arthralgia, to patients with clinically observed arthritis. The presence of US signs of inflammation seems to increase the risk of progression to persistent arthritis or RA [72].

A recent study investigated whether US abnormalities assessed with a standard joint protocol can predict the development of arthritis in seropositive patients with arthralgia. Results showed that synovial thickening on US-predicted clinical arthritis development at patient level in seropositive patients with arthralgia, when metatarsophalangeal joints were excluded from the US assessment. Positive PD signs were infrequently seen in these at-risk individuals and were not predictive of RA [73].

The other image method that has received an increasing interest is magnetic resonance imaging (MRI), with the hope of providing a more sensitive method.

The first large study to use MRI in patients at risk of RA showed that subclinical inflammation as defined by MRI is present in 44% of patients with clinically suspected arthralgia (CSA), but no significant correlation with symptoms or other clinical characteristics was found. Additionally MRI was unable to differentiate those patients who progressed to chronic arthritis [74]. Another smaller MRI study performed in 22 patients with ACPA-positive arthralgia showed higher MRI inflammation scores in these patients compared with controls [75]. Hence, MRI seems to be a highly sensitive tool for identifying inflammation in at-risk individuals, but with low specificity as MRI can show synovitis in healthy individuals.

Another imaging method that showed joint abnormalities with higher specificity in seropositive patients with arthralgia was macrophage positron emission tomography. Gent et al. demonstrated that subclinical arthritis in ACPA-positive arthralgia patients could be visualized by 11C- (R)-PK11195 PET scanning and was associated with the development of arthritis within 2 years of follow-up. This indicates that 11C-(R)-PK11195 PET may be useful in determining arthritis activity in the preclinical phase of RA. This method could discriminate at-risk individuals from controls and could identify with high specificity those who would progress to arthritis development [76]. However, for the detection of more subtle arthritis, (*R*)-[^{11}C]PK11195, was limited in its use due to high background uptake in the bone and bone marrow. A recent study investigated the value of [^{18}F]fluoro-PEG-folate PET-CT for imaging of inflamed joints in patients with clinically active RA. [^{18}F]fluoro-PEG-folate showed great potential as a macrophage tracer to image both clinical and presumably also subclinical arthritis in RA patients. This tracer had improved characteristics compared to the established macrophage tracer, (*R*)-[^{11}C]PK11195, for imaging arthritis because of a lower background signal [77].

The significance of imaging abnormalities (subclinical synovitis) in at-risk individuals who have not developed clinical synovitis has undetermined treatment implications. These at-risk patients with arthralgia who have demonstrated imaging abnormalities are a relevant fraction of the at-risk continuum group and should be monitored. Additional prospective studies in this area are needed.

Differential diagnosis of preclinical RA

The differential diagnosis of RA is extensive, particularly when RA does not present in its classical pattern. Many diseases can start as an undifferentiated arthralgia/arthritis and for that reason a comprehensive approach is necessary to differentiate RA from similar entities. When arthritis is of acute onset, it is particularly relevant to exclude infection. While bacterial (septic) arthritis most commonly affects one joint and is associated with a severe clinical presentation, viral arthritis usually occurs in a polyarticular fashion similar to RA and may occasionally be associated with a rash. Arthritis associated with HCV, HIV, as well as Lyme, and gonococcal arthritis may follow a more chronic pattern. Reactive arthritis is defined as an oligo-to polyarthritis of acute or subacute onset, most commonly affecting the ankles and knees in an asymmetric fashion, but may show a symmetric polyarthritis of the hands as well. Reactive arthritis is induced by a variety of infectious agents, usually 7–14 days following the (symptomatic or asymptomatic) infection of the urinary or gastrointestinal system caused more frequently by *Shigella*, *Salmonella*, *Campylobacter*, *Escherichia coli*, *Yersinia*, *Chlamydia*, *Mycoplasma* or *Ureaplasma* [78–80].

Hand osteoarthritis (OA) is the most frequent differential diagnosis of chronic polyarthritis affecting the hands. Several distinct features make the differentiation from RA relatively clear in the routine clinical setting: OA is characterized by non-inflammatory joint pain, normal levels of serum inflammatory markers, and a non-inflammatory synovial fluid pattern; it has a predilection for DIPs and first

CMC joints of the hands, sparing the radiocarpal and MCP joints. Differentiation between RA and OA may be less clear in the context of "inflammatory" OA when clinical signs of inflammatory polyarthritis, as well as erosive joint destruction occur.

Psoriatic arthritis has to be frequently and carefully differentiated both from RA and OA. The arthritis may be erosive as RA but has a greater predilection for DIPs and, despite resembling OA, is usually more destructive. Polymyalgia rheumatica is the most frequent differential diagnosis of recent onset symmetric polyarthritis in the elderly population, given its similarity to seronegative late-onset RA [81].

Connective tissue diseases are another relevant, but less frequent, differential diagnosis, the onset of which is more common in younger and middle-aged patients. Systemic lupus erythematosus (SLE) may present with arthralgia and symmetrical polyarthritis, as well as Jaccoud's arthropathy, a reversible mimic of RA deformities. SLE rarely is RF-positive, but increased RF titers are a common finding in Sjögren's syndrome. RF-positive erosive arthritis in patients with SLE is considered to be an overlap syndrome of RA and SLE and is often termed "rhupus". The "puffy" hands of systemic sclerosis, mixed connective tissue disease, and polymyositis should also be considered in the differential diagnosis. The *anti*-synthetase syndrome is the most important differential diagnosis of RA with lung involvement [82–84].

Crystal deposition disorders (gout and calcium pyrophosphate deposition disorder (CPPD)) may present in approximately 10% of cases with a polyarticular pattern and may resemble RA. Gout is more frequent in the context of metabolic syndrome, whereas CPPD is frequently seen in the elderly. A joint tap may reveal intra-articular crystals. US may help detect the signs of crystal deposition. If not treated adequately, gout can evolve into a chronic tophaceous disorder that can mimic RA with rheumatoid nodules [84]. Finally, fibromyalgia and paraneoplastic syndromes (particularly associated with lung cancer) can be difficult to discriminate from preclinical and early RA.

Intervention in preclinical RA

Identifying individuals at risk for RA is beneficial. The intervention in the preclinical phase may result in better outcomes than when intervening in clinically apparent arthritis. Prevention may include pharmacological targets, dietary, and lifestyle interventions. Preventive measures should also take into account the genetic and environmental factors (including micro-organisms) that might contribute to the initiation of RA.

To adequately intervene in preclinical RA, highly accurate prediction models for future RA are crucial. We will need to estimate the overall risk for future RA, as well as the timing for the onset of future RA, so that interventional studies can be designed around specific time intervals and estimates of outcomes of RA. Rheumatology experts, primary care, health care systems (including governmental), public health agencies, and industry may work together to ameliorate the prevention of RA. Ultimately understanding the overall efficacy and cost-effectiveness of RA prevention will have a positive impact on public health.

Another preventive strategy is to look for a therapeutic window for preclinical RA therapy. A glucocorticoid trial in one group of seropositive patients with arthralgia was ineffective in the prevention of RA onset. To test whether rituximab treatment could be used as a preventive approach in preclinical RA patients, a randomized, double blind, placebo-controlled clinical trial in individuals at a high risk of developing RA (defined by the presence of both serum autoantibodies as well as elevated CRP) was designed (the PRAIRI study: NTR 1969). Results showed that a single infusion of 1000 mg of rituximab significantly delayed the development of arthritis in subjects at risk of developing RA, providing evidence for the pathogenetic role of B cells in the earliest, prearthritis stage of autoantibody-positive RA [85–87]. More recently, the APPIPRA study (Arthritis Prevention in the Pre-Clinical Phase of RA with Abatacept, International Standard Randomised Controlled Trials Number 46017566) was launched; a randomized, placebo-control trial, including ACPA-positive patients with joint pain, without clinically obvious arthritis, comparing 125 mg Abatacept vs placebo in the prevention or delay of RA onset. Results are expected in 2020 [88].

Other possible ways of intervening in the preclinical phase of the disease that have been suggested include induction of tolerance by vaccination with dendritic cells, promoting bystander immunity by inducing autoantigen-specific Tregs, or desensitization using various antigens, which might be more effective in the phases preceding the diagnosis compared with the fully established disease [89]. None of these interesting potential approaches have been studied yet.

Summary

There is a preclinical period in RA development, where immune dysregulation and inflammation is ongoing without typical manifestations of the disease. Genetic and environmental factors play a role in this process and the first pathological events may occur at mucosal surfaces. Clinical, laboratorial, immunological, and imaging variables can be used as predictors of the evolution toward RA. Preventive measures including treatment interventions are being evaluated to prevent the onset of full-blown RA in patients identified at the preclinical RA phase.

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Research agenda

- Development and validation of clinical and/or biological markers to help general practitioners in the early recognition and reference to the rheumatologists of patients with pre RA, CSA, and early forms of arthritis;
- Development of accurate prediction models for the evolution from pre RA and CSA into RA including genetic, environmental, biological, and clinical factors;
- Validation of a management strategy for the preclinical phase of RA;
- Evaluation of innovative remission inducing treatment regimens for pre and early RA, which can be subsequently tapered with the goal of achieving a drug-free remission;
- Prevention trials evaluating the effectiveness of pharmacological and/or the change of lifestyle risk factors in RA prevention.

Practice points

- Preclinical RA is defined by abnormalities of autoantibodies and other biomarkers in the absence of and prior to the appearance of clinically demonstrable inflammatory arthritis.
- There are currently limited evidence-based effective, preventive interventions for RA. However, there are several lifestyle changes that may be protective against the development of RA, as well as improve overall health:
  - Avoid smoking
  - Keep a normal body mass index
  - Healthy eating habits
- Immediate referral to rheumatologists of patients with ACPA positivity and/or with suspected arthralgia.

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