

Pre-rheumatoid arthritis and its prevention

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Abstract

Pre-rheumatoid arthritis (pre-RA) is the preclinical period of the disease that precedes the onset of clinically apparent RA. It includes the interaction between genetic and environmental risk factors and development of disease-related autoantibodies and joint symptoms and signs, which may be considered nonspecific or unclassified for RA. A better understanding of the pre-RA stage will be useful in developing screening programs for early detection of RA. Identifying and modifying risk factors such as smoking, periodontitis, obesity, viral infections, and hormonal or dietary factors will be useful in preventing RA in susceptible population.

Keywords: Pre-rheumatoid arthritis, unclassified arthritis, rheumatoid arthritis prevention

Introduction

Pre-rheumatoid arthritis (pre-RA) is used to designate events before the clinical occurrence of RA. This stage is characterized by the presence of abnormalities in immune function and responses in the absence of clinical manifestations of autoimmune tissue injury (1). There is a preclinical period in the development of RA where the genetic and environmental factors interact, probably sequentially, to initiate and propagate the autoimmune process, resulting in tissue inflammation and injury. Moreover, disease-related autoantibodies such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) can develop in the absence of clinical signs and symptoms of tissue injury. At a later stage, minimal symptoms or signs can develop, which may be considered nonspecific or unclassified for any particular rheumatic disease before developing classical RA. Importantly, all patients need not experience each stage of the disease, and the phases can be in a combinational manner. For instance, a patient can have genetic risk factors, ACPA, and joint pain (2).

In the current medical literature, researchers used different terminologies, such as pre-RA, preclinical RA, autoantibody-positive arthralgia, probable RA, very early RA, and early undifferentiated arthritis progressing to RA, to describe the earlier phases of RA. To avoid confusion in terminologies, different professional associations such as EULAR recommend certain specific terminologies in the past few years (3).

The different phases of RA development in at-risk individuals from pre-RA to clinically apparent RA has been described in Figure 1. Phase I involves the interaction between genetic and environmental risk factors of RA. Phase II includes the production of RA autoantibodies such as RF and anti-cyclic citrullinated peptide (anti-CCP). Some of these individuals later enter into phase III where they develop arthralgia or joint stiffness without any clinical evidence of arthritis. In phase IV, patients develop arthritis in one or two joints, which is termed as early undifferentiated arthritis. In some cases, the arthritis can be intermittent at this stage and it is termed as palindromic rheumatism. Finally, some of these patients develop classical clinical features of RA, which is described as established RA (Phase V).

The EULAR study group recommends that in prospective studies, individuals at risk of developing RA should be described as having the following five stages (3).

- (a) Individuals with genetic risk factors for RA
- (b) Individuals exposed to environmental risk factors for RA
- (c) Systemic autoimmunity associated with RA
- (d) Symptoms without clinical evidence of arthritis
- (e) Unclassified arthritis



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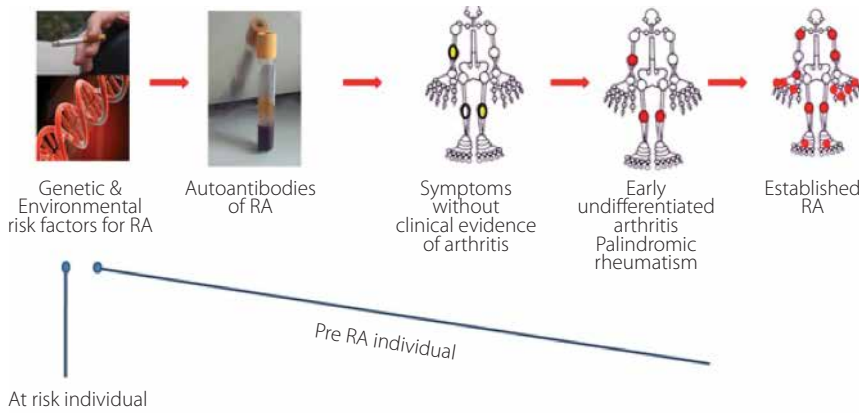


Figure 1. Phases of pre-rheumatoid arthritis

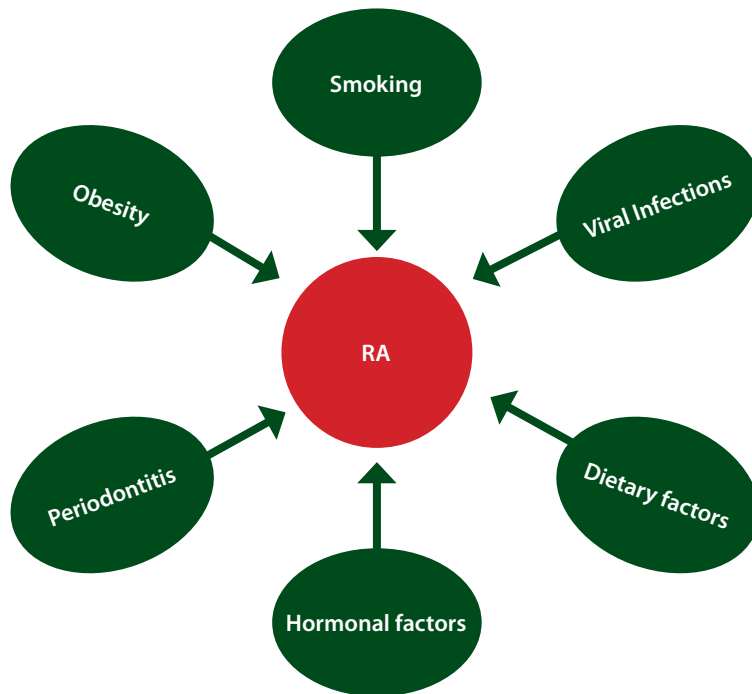


Figure 2. Environmental risk factors for rheumatoid arthritis

Table 1. Pre-RA

| | |
|--|--------------|
| a. Genetic risk factors for RA | Asymptomatic |
| b. Environmental risk factors for RA | |
| c. Systemic autoimmunity associated with RA | |
| d. Symptoms without clinical evidence of arthritis | Symptomatic |
| e. Early undifferentiated arthritis. | |

RA: rheumatoid arthritis

Table 2. Modifying risk factors to prevent rheumatoid arthritis

- Avoid/Quit smoking
- Good dental hygiene: Treat periodontitis early
- Balanced diet containing fish oil, antioxidants, and vitamin D
- Avoid excess coffee and food with high salt content
- Optimizing body weight
- Prevent infection

The term pre RA is used retrospectively to describe an earlier phase of the disease, at stage (a) to (e) or any of their combination, in a person who has developed RA. The term pre-RA is used to describe all phases before the development of a disease classifiable as RA, which will be asymptomatic (stages a, b, or c) or symptomatic (stages d or e) (Table 1)(4).

Genetic risk factors of RA (5)

It is well known that 70% of RA patients have genetic association with HLADR4 compared with 30% among controls, increasing the relative risk of developing RA with this gene by 4 to 5 fold. Susceptibility to RA is associated with the third hyper-variable region of DRβ1 allele, which is termed as the susceptibility epitope (SE). Other genes discovered later such as protein tyrosine phosphatase 22 and peptidyl arginase/deiminase (PADI-4) also carry approximately 2-fold risk of developing RA. Numerous other genes associated with lower risk are also described (6).

Twin studies show that 12-15% of identical twins develop RA compared with 4% in non-identical twins. The incidence of disease among first degree family members is 0.8%, when compared to 0.5% in the general population. It is found that the known genetic risk alleles and heredity factors can explain only 16% of the overall disease burden (5). Many other factors such as epigenetics can further alter the gene expression in favor of developing RA. It is now clear that genes only modestly increase the risk of RA and that the environment is likely to play a stronger role (7).

Environmental risk factors of RA (Table 2)

A number of environmental risk factors clearly contribute to RA susceptibility, including smoking, infections, periodontitis, obesity, and hormonal and dietary factors (Figure 2).

Smoking: Smoking is the best defined risk factor for seropositive RA (8). It is a strong stimulus for protein citrullination and generation of anti-CCP antibodies (9). HLA-SE has increased ability to bind the citrullinated protein. A smoker with two copies of HLA-SE has a 40-fold chance of developing RA, indicating the interaction between genetic and environmental risk factors in the development of RA (10, 11). There is also a long latency (up to 20 years) after cessation of smoking to return to the risk level of a non-smoker (12).

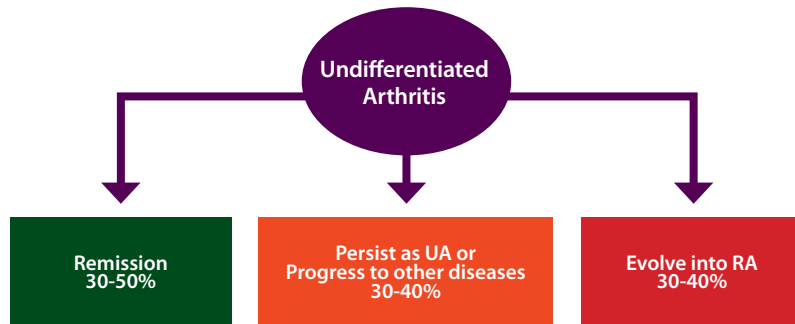


Figure 3. Fate of undifferentiated arthritis

A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis

| Variables | Score | |
|-----------------------------------|---------------------------|-----|
| Age (years) | X 0.02 | |
| Female | 1 | |
| Joint distribution | Small joints of hand/feet | 0.5 |
| | Symmetry | 0.5 |
| | Upper limb | 1.0 |
| | Upper&lower limb | 1.5 |
| Morning stiffness (on 100 mm VAS) | 26-90 mm | 1.0 |
| | >90 mm | 2.0 |
| Tender joints (n) | 4-10 | 0.5 |
| | >10 | 1.0 |
| Swollen joints | 4-10 | 0.5 |
| | >10 | 1.0 |
| CRP (mg/L) | 5-50 | 0.5 |
| | >50 | 1.5 |
| RF positivity | 1 | |
| ACPA positivity | 2 | |

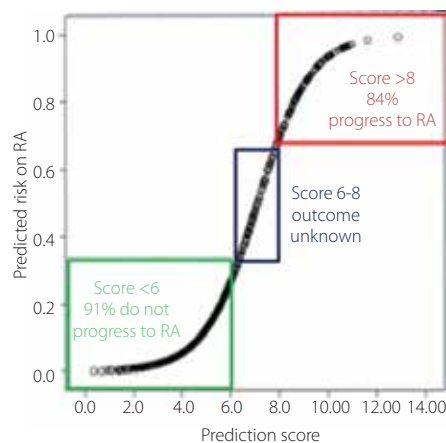


Figure 4. Leiden prediction rule

Infections

It is found that infective agents can contribute to the initiation or perpetuation of RA via a variety of mechanisms such as molecular mimicry, toll-like receptor activation, or direct invasion of the synovium. *Parvovirus 19*, *Mycoplasma*, Enteric bacteria, and Epstein-Barr virus are the commonly implicated infective agents. In India, an epidemic of chikungunya virus infection also contributed to the increase in the prevalence of RA in susceptible population (13).

Periodontitis

Periodontitis is a chronic inflammatory disease of the gingiva. It is a disease with similar pathogenesis, risk factors, and epidemiological association as RA (14). Various Indian studies and other countries showed that the occurrence and severity of periodontitis was found to be higher in RA subjects, suggesting a positive correlation between these two chronic inflammatory diseases (15, 16). RA patients with more periodontal symptoms have higher levels of RA disease activity. In RA patients, periodontitis is a strong predictor of ACPA (17). The bacterium causing periodontitis, namely *Porphyromonas gingivalis*, causes citrullination through its own PADI enzyme. Hence, management of periodontitis may reduce the risk of developing RA (18).

Dietary risk factors

Many dietary factors are found to modify the risk of RA in susceptible population. Studies show that omega-3 fatty acids ameliorate clinical symptoms of RA and fish oil consumption has a protective effect. Antioxidants in fruits and vegetables (vitamin C, vitamin E, carotenoids, and lycopene) also show a protective effect. Red meat intake and vitamin D deficiency increase the risk

of RA. Excessive coffee consumption is also a risk factor for ACPA-positive RA. High salt intake is found to be a risk factor in a recent study (19).

Hormonal factors

Although RA is three times more common in women than in men, estrogen containing contraceptives and other hormone replacement therapies do not reduce the risk of RA. Pregnancy ameliorates RA in majority of women. RA risk increases with breast feeding due to surge of proinflammatory prolactin. It is also found that nulliparity increases RA risk. Obesity is also an important risk factor for RA in western countries, as being overweight increases the levels of circulatory leptins and stimulates proinflammatory cytokines such as TNF α and interleukin-1 (20).

Systemic autoimmunity associated with RA

Individuals who are positive for RF and/or ACPA without any symptoms of RA are classified under this group. Multiple studies showed that RA-related antibodies are present years prior to the diagnosis of RA. Studies on stored prediagnosis blood samples from biobanks in Finland and Northern Sweden demonstrated that RF and anti-CCP were present years prior to the onset of clinically apparent RA (21). In prospective studies of initially healthy family members of patients with RA in UK, the presence of RF preceded the onset of clinically apparent RA. It is now clear that compared with controls, a combination of both anti-CCP and any RF isotype was highly specific for the future development of RA.

Symptoms without clinical evidence of arthritis

It is not uncommon to see patients presenting with arthralgia or joint stiffness with positive RF and/or ACPA, without any demonstrable arthritis on physical examination. Some of these patients later progress to classical RA after a variable period of time, and hence, it is considered as a "pre-RA" phase.

Unclassified arthritis (undifferentiated arthritis)

Unclassified arthritis is a situation where there is arthritis of more than one joint without fulfillment of criteria for RA or any other connective tissue disease. The diagnosis of unclassified arthritis is by exclusion, when the classification criteria for a well-recognized rheumatic condition can-

not be satisfied. However, these patients have a great potential for the development of persistent inflammatory arthritis (Figure 3). It is found that 30%-40% of patients with undifferentiated arthritis progress to classical RA on long-term follow-up (22, 23).

Leiden prediction rule (24) and other scoring systems are useful to identify people who will later progress to RA. If the Leiden prediction rule is ≤ 6 , 91% will not progress to RA. If the prediction score is ≥ 8 , 84% will progress to RA (Figure 4).

Prevention of RA

Screening and follow-up of people at risk of developing RA is appropriate for developing prevention programs for the disease (25). First degree relatives of RA patients, twins of RA patients, autoantibody-positive individuals, populations with high disease prevalence rate were screened in various prospective studies. However, these studies are expensive considering the yield as relatively low prevalence rate of RA and RA-related autoantibodies limit the statistical power of these studies (26). Large-scale screening to identify individuals at high risk of developing RA in the future (genetic factors and RA-related antibodies) will be very expensive. Low prevalence of autoantibodies in RA requires large-scale screening to identify at-risk individuals. As these studies are not suitable for developing countries, prevention of RA by modifying environmental factors is emerging as a cheap and effective strategy to prevent RA (27) (Table 2). Patients who are symptomatic definitely need treatment. Palindromic rheumatism patients often respond to antimalarials and other disease-modifying agents (28, 29). Many studies show that patients with undifferentiated arthritis benefit from methotrexate (30). Studies on the role of steroids alone are not very beneficial (31). Combining multiple DMARDs or DMARDs with corticosteroids may be even more beneficial. Among the biological agents, abatacept shows promising results (32). However, more randomized controlled trials with longer follow-up time are needed to prove which treatment provides best results or alters the disease course (33).

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