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Determinants of disease course in rheumatoid arthritis

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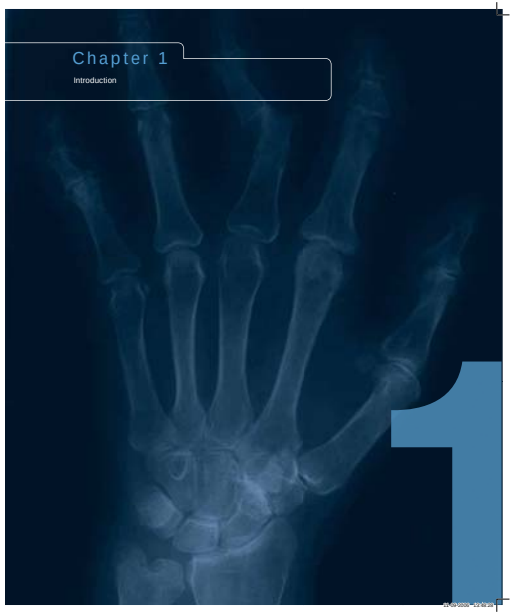
Chapter 1
Introduction
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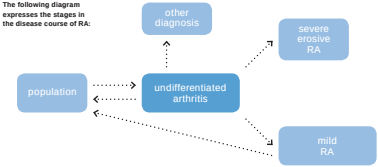
Introduction

Rheumatoid Arthritis (RA) is a chronic disease that may lead to loss of function because of chronic synovial inflammation that causes joint damage[1b] and even death[1c]. In many cases, RA is not imme-diately diagnosed when the first symp-toms occur because patients may present with non-specific symptoms like arthralgia, chronic monoarthritis, fever or flu-like complaints that have existed for a longer period. The ACR criteria for classifying RA that were defined in 1987 have a high sensitivity and specificity for diagnosing RA[1c]. However in patients with recent-onset RA, many patients with early arthritis that will later develop RA as defined by the ACR criteria, often do not qualify these criteria yet[1d]. RA is thus a heterogeneous disease with a wide spectrum in clinical presentation and severity (radiographic erosions, functional impairment, disease activity). The impression of many clinicians is that there are different phenotypes of RA. Possibly these phenotypes are related to the genetic background like HLA-DR3-positive patients (without anti-CCP antibodies) and shared epitope positive patients (with anti-CCP antibodies)[1b, 1c] or to patients with other serological markers like the presence of IgM rheumatoid factor.

Early recognition of RA is of vital importance because a "window of opportunity" may exist for early therapy preventing radiographic erosions and even reversing disease course[1c, 1d]. A recent study comparing treatment of probable RA (ACR 1958 criteria) with Methotrexate or placebo in 110 patients demonstrated that patients with UA benefit from treatment with Methotrexate. The Methotrexate treated patients have a lower disease activity at 3 months, less progression in radiographic joint damage and a lower proportion of patients develop RA according to the ACR 1987 criteria[1e].

The following diagram expresses the stages in the disease course of RA:



The importance of studying early arthritis that may or may not lead to RA has been widely recognised, and many early arthritis registers have been established in Europe, Australia and the USA to improve insight in disease course and etiological factors[1b]. These cohorts have been reviewed by K. Verpoort[2a]. Studying these cohorts has had a major impact on our knowledge of early arthritis, but many puzzles remain unsolved.

The knowledge of factors that influence each stage in this diagram is important for a better understanding of the aetiology of RA. In the following pages, a summary is given of the factors that are known to be or that are thought to be of influence on development of RA or on disease course in RA patients.

The following subjects will be discussed:

Epidemiology
- incidence and prevalence
- gender distribution
- age

Environmental factors
- diet
- smoking

Socio-economical factors and coping strategies

Serological markers

Genetic factors

Gene-environment interactions

Epidemiology

Incidence and prevalence

Depending on the geographic area and definition, the prevalence of RA is around 1% in most populations. A recent review of epidemiology of adult RA[3a] describes an annual incidence rate of 0.02-0.07 per 100 inhabitants and a prevalence rate of 0.5-1.1 per 100 inhabitants in most European and North American populations. In southern Europe, South America, Asian countries and in the Middle-East, the prevalence is lower ranging from 0.1-0.5[3a].

Severity of RA

Numbers on severity of RA depend on the definition of severe RA. The presence of bone and cartilage destruction or the rate of destruction are measures for severity that are often used.
Scott et al reviewed radiological progression in 5 pros-pective studies of established RA between 1977 and 1998. A total of 1395 RA patients were analysed. All RA cases were seen within 12 months of disease onset. Of these patients, 60-73% had developed one or more bony erosions in the hand or wrist. By 20 years follow-up, 18% of the wrists were completely destroyed whereas 25% of the wrists were non-erosive. Presence of rheuma-toid factor (RF) and elevated levels of C-reactive protein were risk factors for erosive disease. Presence of anti-CCP antibodies was not determined[3d].
Boonen et al analysed baseline erosions in 6 cohorts of inflammatory polyarthritis patients. At baseline, erosions were present in 8-15%[3e].

The numbers mentioned by Scott were found in patients that were treated at the time that the pyramid strategy was used. According to this treatment strategy, RA patients were initially treated with non-steroidal anti-inflammatory drugs (NSAIDs) until erosive damage occurred or persistent disease activity was present. Only then, treatment with disease modifying anti rheumatic drugs (DMARDs) was initiated. The reason to postpone treatment with DMARDs was that the disease course of RA was considered too benign to warrant medication with possible serious side-effects. A paradigm shift in the 1990's was caused by a heightened awareness of the serious consequences of RA: high morbidity, increased mortality and loss of economic capacity. This led to new treatment strategies commencing treatment in early RA with single or combination DMARD therapy. This caused a great improvement in overall treatment results: better functional capacity, less erosive damage, better remission rates and longer duration of remissions[16, 17, 18].

Remission in RA

Studies on remission in RA are complicated by difficulties of definition. Since this issue is addressed in this thesis, it will be discussed in some detail. In practice, remission is defined as "no arthritis", "cure of disease", "absence of disease activity", "low DAS 28 score"(values differ), "being symptom-free" or as "a state which approaches cure as closely as possible"[19]. The ARA 1981 preliminary criteria for remission (no fatigue, no arthritis, no joint tenderness, no joint pain (by history), low ESR, morning stiffness < 15 minutes) are frequently used, being the only official criteria, but have practical difficulties, due to the application of subjective parameters (fatigue, history of joint pain)[20]. However, the improvement of treatment outcome in RA in the past decade necessitates clear treatment goals and therefore it is necessary to define remission or low disease state in a simple and reproducible way.
Currently used scores to define remission are in general composite scores of objective and subjective parameters. This applies to any state of disease activity score used in RA and for this reason the disease activity score (DAS score)[21] has been implemented and widely used for monitoring disease activity in RA. The original DAS score included all 44 joints and took a long time to perform and calculate. For this reason the DAS score was altered for daily and trial use to a 28-joint count that was quicker and simpler to perform. It was validated for use in monitoring disease activity[22]. The formula for calculating the DAS 28 score is: 0.56 x √ (TJC28) + 0.28 x √ (SJC) + 0.70 x (ESR) + 0.014 x GH. TJC = tender joint count, SJC = swollen joint count, ESR = erythrocyte sedimentation rate and GH = general health on a visual scale 0-100 mm).

A number of studies have worked on defining the DAS 44 or DAS 28 score that correlates with the ARA Pinals criteria for clinical remission. Most have excluded fatigue in their analyses.
In a Dutch cohort that was studied to validate the original DAS score, 227 patients with established RA (median duration of follow-up 3.9 years) were studied. The ARA criteria for remission were fulfilled in 9.5% of the visits. 25% of the patients fulfilled the criteria in at least 1 visit. A DAS score of < 1.6 corresponded with the ARA remission criteria in this cohort[23].
In a Swedish cohort of 183 patients with early RA (mean disease duration 11 months), who were followed 6-monthly for at least 5 years, 39 patients (20%) achieved remission according to the ARA criteria for at least 6 months during follow up. In 21 patients this was spontaneous remission without treatment. 56% had relapsing and remitting disease and 44% persistent disease, which correlated with a worse outcome[24].
A Spanish study in 2004 with 788 RA patients from 34 centres compared the DAS 28 score to the Pinals criteria at one visit during follow-up. 32 patients (4.1%) satisfied the Pinals criteria, and 62 patients (7.9%) satisfied the Pinals criteria if fatigue was excluded. The frequency of any single criterion that patients in remission fulfilled: no fatigue and joint pain by history in 31 patients (96.9%); morning stiffness < 15 min in 26 (81.3%); no swelling in joints in 21 (65.6%); normal erythrocyte sedimentation rate (ESR) in 29 (90.6%); and no joint tenderness in 21 (65.6%) patients. The positive predictive value for remission of each criterion: normal ESR 6.1%); morning stiffness < 15 min 8.4%; no fatigue 8.7%; no joint tenderness 13%; no swelling in joints 15.8%; and no joint pain by history 27.7%. The DAS28 cut-off values with higher discriminatory power for remission were 3.14 (sensitivity 87%; specificity 67%) when all the ACR criteria were used, and 2.81 (sensitivity 84%; specificity 81%) when fatigue was omitted. It was concluded that the DAS 28 score is a good tool to define remission in established RA[25].
In 2004 the Dutch Nijmegen cohort that was mentioned earlier was analysed. This time, not the DAS score, but the DAS 28 score was determined that best corresponded with the ARA criteria for remission. Analysing 278 patients and 4378 visits, it was concluded that a DAS 28 score of 2.6 corresponded to the ARA criteria of remission in this cohort[26].
A Finnish cohort analysed the Positive Predictive Value (PPV) per ARA criteria in 127 patients with early RA who were followed for 5 years.
The highest PPV was again found for no history of joint pain (56%, 95% CI 38-74) and lowest for ESR (16%, 95% CI 1-24). Specificity of no history of joint pain for satisfying the ACR criteria was 90%. The study used 3 definitions of remission: The preliminary ARA criteria, a clinical score and a radiological score. Remission rates were 17%, 37% and 55% respectively demonstrating the importance of a uniform definition[27].
Remission in the Dutch Utrecht RA cohort was studied in 562 patients. The definition that was used for remission was morning stiffness ≤ 15 minutes, Mean VAS pain ≤ 10 mm, Thompson joint score ≤ 10 and ESR ≤ 30 mm/h during at least six months (an adaptation of criteria defined by Sokka et al in 1988)[28]. After a mean follow-up duration of 62 months, only 36% of the patients had fulfilled the remission criteria at least once.
Remission was predicted by good response to DMARD therapy in the first year[28].
From all these data it can be concluded that there is still no agreement on the definition of remission used in RA. In an editorial, van Riel stated that disease activity is a continuum, with remission a state at the end of it. In his opinion it would be best to follow disease activity regularly and calculate the mean and standard deviation. Uniformity should be reached on the level of the cut-off point in order to interpret trial results[18].
In conclusion, the ARA 1981 preliminary criteria are not useful for daily practice or monitoring in trials. The trend will go toward using DAS 28. The cut-off value needs to be determined, even if that means that some patients who have a swollen joint will be classified as remission. During the OMERACT meeting 2004, a preliminary definition of minimal disease activity (MDA) was agreed. MDA was defined as that state of disease activity deemed a useful target of treatment by both the patient and the physician given current treatment possibilities and limitations. Two preliminary equivalent definitions of MDA were stated, based on 60 profiles of RA patients, interpreted by 35 current rheumatologists from Europe and the USA, one based on clinical parameters: TJC, SJC, ESR, HAQ, GH (physician) and GH (patient) and one based on DAS 28. Further validation of these sets will be needed in the near future[29].

Gender distribution

The male: female distribution in most populations of RA patients is around 3:2. Gender distribution is similar in all geographical areas that have been studied.
Female hormones are likely to be of influence, since the disease begins more often in the postpartum period or after menopause and female RA patients often demonstrate great improvement in disease activity during pregnancy[30-35].

Gender and severity of RA

A recent report on disease outcome in RA[36] states no major differences in disease pattern and radiological damage (Larsen score) in a retrospective study of 133 female and 133 male RA patients. The sicca syndrome was more frequent in men than in women (p=0.0003) and women underwent more frequently distal joint surgery.

Gender and remission in UA or RA

It has been reported that men are more likely to enter spontaneous remission[36-37].

Age

The mean age of onset of RA in most cohorts is around 55 years. The standard deviation is usually large. Late onset RA may clinically be very similar to polymyalgia rheumatica (PMR), with fever, weight-loss and other systemic complaints. This was already recognised by O'Duffy in 1977[38], who described 4 cases of osteo-arthritis, late onset RA (LORA), PMR and pseudogout. Recently, two papers were published on this subject. A paper from the UK that studied the accuracy of the initial diagnosis in patients presenting with LORA, PMR and temporal arteritis again described a great overlap in symptoms[39].
A recent Turkish paper compared clinical and laboratory parameters between patients with late onset RA and younger onset RA (YORA). Disease onset in the 150 patients with YORA was at 42.2 +/- 10.4 years and in the 124 LORA patients disease onset was at 68.4 +/- 4.6 years. LORA patients had more fever, weight loss and polymyalgia rheumatica-like symptoms. The frequencies of RF and ANA were lower in LORA patients, but ESR and C-reactive protein levels were higher.
Clinically, arthritis of small hand joints was more common in YORA patients; arthritis of wrist, knee and hip was equal in both groups[40].

Environmental factors

Diet

Diet and risk of developing RA

Studies on the role of diet in the prevention of autoimmune disease-including RA mention an important role for vitamin D. Preliminary data on vitamin D (1,25-dihydroxy vitamin D) suggested that the concentration is involved in regulation of T-helper cell and dendritic cell function as well as in inducing regulatory T-cell function.

The result is supposedly a decrease in the T-helper cell-driven auto-immune response and decreased severity of symptoms[41, 42]. Another possible role is mentioned for Selenium, an essential trace element involved in several key metabolic activities via selenoproteins, enzymes that are essential to protect against oxidative damage and to regulate immune function[43]. However, clinical studies showed no clinical benefit of selenium supplementation in 55 RA patients[44].
The preventive role of the Mediterranean diet, especially of the antioxidant effect of olive oil is also a topic of interest. This effect is probably due to a combination of its high oleic acid content and its content of a variety of plant antioxidants[45].
Two prospective cohorts, one from Denmark and one from the United Kingdom, were set up to investigate the association between dietary factors and the risk of RA/ inflammatory polyarthritis. The Danish cohort consisted of 57,053 persons who had filled out detailed information on food intake. Within this cohort, 69 persons had RA. The results suggest that the intake of 30 grams of fat fish per day was associated with a 49% (p=0.06) risk reduction of RA. Medium fat fish was associated with an increased risk of RA. An association was not found between intake of fruit, long chain fatty acids, olive oil and various vitamins, trace elements, coffee and risk of RA.The authors note that the limited number of patients who developed RA makes it difficult to draw definite conclusions on the influence of dietary factors in RA[46].
The cohort from the UK drew information from the European Prospective Investigation of Cancer Incidence (EPIC) in Norfolk, a population-based prospective study of > 25,000 subjects that included a baseline 7-day diet diary. In the population that was surveyed, 88 incident cases of inflammatory polyarthritis occurred. These cases were confirmed by the Norfolk Arthritis Register. It is concluded from the data obtained in this study that a modest increase in beta-cryptoxanthin intake (one glass of freshly squeezed orange juice) a day is associated with a reduced risk of developing inflammatory polyarthritis (Odds Ratio 0.51; 95% CI 0.25-1.02)[47]. The importance of recognising dietary factors as a potential risk factor in the development of RA is stressed in a review article by Choi[48].

Diet and severity of RA
Stamp et al review the evidence of influence of dietary factors on disease course in RA. A positive effect on disease course is found from consumption of n-3 fatty acids that can be found in fish oil[49, 50]. Some reports have been presented on introduction of diets without meat[51].

Diet and remission in UA or RA
No studies on this subject have been published to our knowledge.

Smoking

Smoking and the risk of developing RA
Exposure to tobacco smoke is an established risk factor for developing RA and for progressive disease course in RA. A Finnish study even reports an elevated risk for developing Juvenile Idiopathic Arthritis in girls but not in boys that were exposed to tobacco before birth.
The risk was highest for girls whose mother smoked > 10 cigarettes a day during pregnancy (Odds Ratio 4.64 (1.94-11.07))[52].
Smoking was first described to be a risk factor for RA in 1987[53]. Since then, smoking has been firmly established as a risk factor for the development of RA [54- 57]. A review article of the literature on the influence of smoking on the development of RA concluded that smoking is associated with the risk of developing RA, especially RF positive RA. The risk for patients with a higher cumulative exposure and for male gender may be increased. The study also confirmed these data[58].

Smoking and severity of RA
Smoking is associated with presence of rheumatoid factor and severity of RA. Wolfe demonstrated a linear relationship between RF and the number of years smoked. A similar relation was found with rheumatoid nodule formation. A nonlinear relationship was demonstrated between smoking and radiological damage (Larsen score). It is concluded that smoking does not contribute to alterations in disease activity measures, but appears to play a role in overall severity of RA[59]. A report from the Norfolk Arthritis Register in which 67% of the patients satisfied the ACR 1987 criteria for RA, found that smokers were more likely to be RF positive at baseline (47%) than were ex-smokers (34%) and never smokers (31%). After 3 years rheumatoid nodules were significantly more common in smokers (13%) than in non-smokers (4%). Smoking was not found to be of influence on the development of erosions or functional impairment in this cohort[60]. A new perspective on the influence of smoking on the severity of RA is described in the section on gene-environment interactions[61] and in this thesis (chapter 5).

Smoking and remission in UA or RA
There are no data available on the influence of smoking on disease remission. The influence of cessation of smoking has only been studied by one group[58].

This group has found that cessation of smoking reduced the risk of developing RA only after 10-15 years.

Socio-economic factors and coping strategies

There is increasing evidence that other than biomedical factors can contribute to physical functioning and disease activity in RA. Particularly the way patients cope and deal with the disease has been shown to play a possible additional role for the disease outcome in RA.
Most consistent evidence has been found for the role of passive coping and perceived helplessness as predictors of worse disease outcome in the longer term. For example, patients who have the tendency to retreat and rest when in pain and feel that nothing can be done to influence the consequences of RA in daily life have a worse prognosis. This contrasts with the beneficial effects of positive coping (e.g. ignoring pain, illness acceptance)[62-66].
RA patients from socially deprived areas and patients with a lower level of formal education have been described to have increased morbidity and mortality from RA[67-70], worse HAQ scores and higher tender and swollen joint counts[71]. These differences could not be explained by worse access to medical care or compliance with medication[72-75].
A Dutch study identified four styles of emotion regulation in rheumatoid arthritis patients: ambiguity, control, orientation and expression. These styles were not directly related to perceived somatic health, but may be of importance for psychological well-being and social functioning[76]. Emotion regulation is more interwoven with psychological health in women than in men[77].

Serological markers

Serological markers that predict the development of RA
The first paper that studied pre-RA sera from blood donors who later developed RA was conducted by a Finnish group[78]. They found the presence of Rheumatoid Factor (RF) in sera of RA patients before disease onset, thus demonstrating a clear relationship between RF and RA.
This concept was later utilised to demonstrate the presence of anti-cyclic citrullinated proteins (anti-CCP) antibodies in sera of patients who would later develop RA. In a Swedish nested case-control study, the presence of anti-CCP antibodies was found in 34% of the pre-RA individuals versus 2% in matched population controls[79].
A study undertaken in Amsterdam found anti-CCP antibodies in 41% of pre-RA patients versus less than 1% in controls[80].
In 318 Dutch patients with undifferentiated arthritis, the specificity of anti-CCP antibodies or developing RA was 97% (95% CI 95-99) and the positive predictive value for developing RA within 3 years was 93% (95% CI 87-99)[81].

Serological markers and severity of RA
The association between Rheumatoid Factor (RF) and severe disease course has been widely recognised through the years[1, 82-84]. More recently, it has become clear that the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies is even more powerful in predicting progressive erosive disease[84-87].

Serological markers and remission in UA or RA
In this thesis we will describe a group of 29 RA patients who enter sustained clinical remission. This group is characterised by the absence of IgM RF and the absence if anti-CCP antibodies[88].

Genetic factors

Arguments for genetic involvement in the aetiology of RA are predisposition to developing RA in certain families, high concordance rates in monozygotic twins and geographic clustering (e.g. high prevalence of RA among Pima Indians)[89-91]. In the description of this topic only an outline of this subject will be given.
Genetic predisposition can be studied by linkage studies[92], the candidate gene approach, and association studies (case–control studies)[93].
It has been proven that the HLA class II locus plays an important role in susceptibility for RA. Most well-known are the HLA-DRB1 shared epitope genotypes, the major RA susceptibility locus (94) and the protective effect from HLA-DRB1 alleles encoding the DERAA motif[95, 96].
Recent findings on genetic factors that may be associated with RA include: the PTPN 22 polymorphism, a genetic variant that regulates the threshold for T-cell activation (also a risk factor for diabetes) and the organic cation transporter gene SCL 22 A4 is found Japanese but not in UK patients with RA. The expression of the SCL 22 A4 gene is specific to haematological and immunological tissues and is highly expressed in the inflamed joints of mice with collagen induced arthritis.
Gene-gene interactions (for example between a haema-topoietic transcription factor called RUNX1 and the transcription binding site in the SCL22A4 gene) may increase the risk of RA[97].
Clinical benefits from knowledge on genetics in RA include: the possibility to predict disease susceptibility

and disease course, to predict response to therapy and the identification of pathways for possible future pharmacological interventions.

Gene-environment interactions

In studying aetiology of multifactorial diseases, the influence of interactions between genetic and environmental factors may improve insight[98-99]. The only gene-environment interaction that has been identified in RA at this moment is the interaction between smoking and shared epitope alleles, this combination is a risk factor for RF and anti-CCP antibodies in patients with RA. The interaction was not found in RA patients who did not carry the shared epitope alleles[100-102].

Purpose of this thesis

To elucidate additional factors that influence disease course in early and established RA.

Outline of the thesis

Chapter 2 discusses the fact that in an early stage, diagnosis of RA may be difficult because it can be hard to distinguish from other forms of arthritis. Auto-antibodies seen in RA can be detected years before clinical symptoms occur[79-80]. In our inception cohort of patients with recent-onset arthritis we assessed the predictive value of RA-specific auto antibodies to cyclic citrullinated peptides (CCP's) in arthritis patients that could not be readily diagnosed-patients with undifferentiated arthritis (UA).
In **chapter 3** the question is raised whether disease course in early arthritis and early RA can be predicted by distribution of arthritis. From the early arthritis population, two extreme phenotypes of RA were selected: those with sustained clinical remission and those with progressive erosive disease course. The outcome (progressive erosive disease) was validated in a larger group of patients with RA and in patients with undifferentiated arthritis.

RA is often considered to be a chronic disease with practically no chance of achieving sustained clinical remission. **Chapter 4** discusses the characteristics of patients with RA who achieve sustained clinical remission without the use of DMARDs. Serological and clinical parameters were compared between remitting patients and patients with persistent disease activity.

Chapter 5 chapter 5 studies the gene-environment interaction between tobacco exposure and shared epitope on auto-antibodies (IgM Rheumatoid Factor, anti-cyclic-citrullinated peptide antibodies) in RA, UA and on development of UA to RA.

Chapter 6 presents a theory concerning genetic drift as an explanation for decreased incidence of RA.

Chapter 7 summarizes the insights provided by chapter 2 to 6 in the factors influencing disease course in early and established RA

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