Clinically suspect arthralgia: unraveling the development of rheumatoid arthritis

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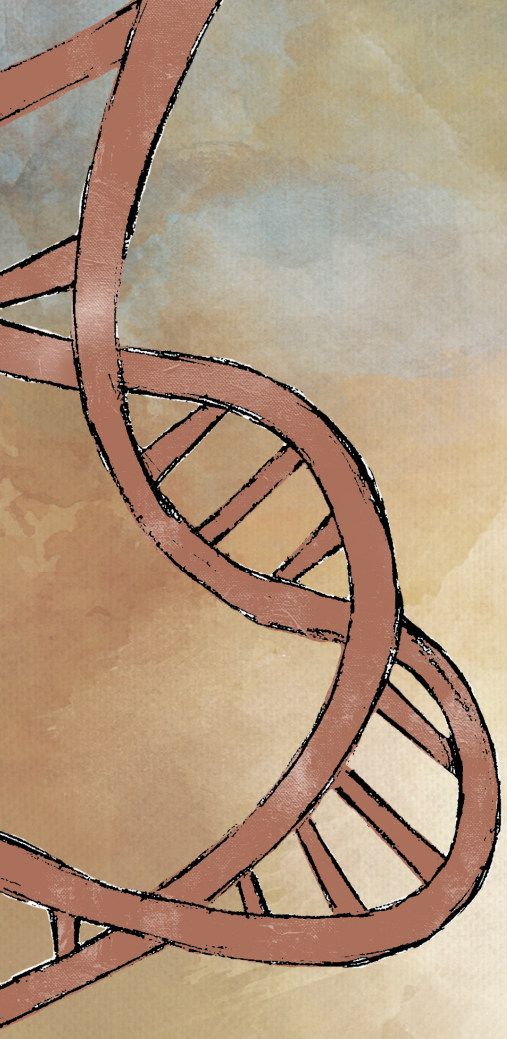

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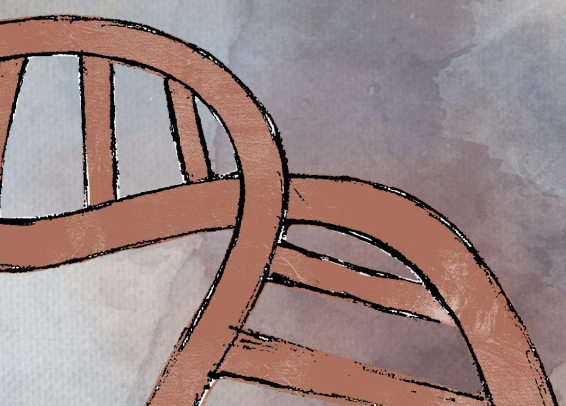
Summary and discussion



In this thesis two main aims were addressed. It has long been established that early treatment of rheumatoid arthritis (RA) improves disease outcomes. In **Part I** of this thesis we therefore further investigated the early detection of at-risk individuals by studying a large cohort of patients with clinically suspect arthralgia (CSA). We explored the value of two easy clinical tests, their potential to detect underlying inflammatory processes and to predict disease progression. In addition we investigated the presence of subclinical synovitis on imaging as starting point for treatment with disease modifying anti-rheumatic drugs (DMARDs) and the value of magnetic resonance imaging (MRI) detected erosions as new predictor for RA-development. In **Part II** of this thesis we aimed to determine which disease processes are involved in the different phases of RA-development. Knowledge on disease pathogenesis and timing of influencing factors can help to better target treatment during RA-development. We therefore evaluated whether autoantibody-response maturation occurred during the phase of CSA, and investigated the timing of genetic risk factor human leukocyte antigen-shared epitope (HLA-SE) and environmental risk factor smoking during the development of autoantibody-positive disease.

Part I – Prediction and early detection of rheumatoid arthritis

Summary Chapter 2 and 3

The value of imaging in the prediction of RA has often been investigated. Subclinical inflammation can be detected even before the occurrence of clinically detectable arthritis and has been shown to predict disease progression.[1,2] However, imaging modalities as ultrasonography (US) and MRI are costly, time consuming and not always available. Moreover, it was hypothesized that subclinical features might underly clinical manifestations that are considered risk factors for development of RA. In **Chapter 2** we therefore investigated difficulties making a fist, one of the factors comprising the EULAR definition of arthralgia suspicious for progression to RA.[3] Although fist problems are considered a risk factor for RA-development in patients presenting with CSA, its predictive value and underlying cause were unclear. Difficulties making a fist was assessed in two ways: 1) fist closure was evaluated by visual inspection of the ability to completely close the fist, all fingertips touching the palm, 2) fist strength was determined by the patient squeezing the assessor's fingers. Incomplete fist closure and a decreased fist strength were both independently associated with progression to clinically apparent inflammatory arthritis (IA), though incomplete fist closure had a higher predictive value and better reliability. Fist problems associated significantly with flexor tenosynovitis; incomplete fist closure associated predominantly with flexor tenosynovitis of metacarpophalangeal (MCP)

joints, whereas decreased fist strength more strongly related to flexor tenosynovitis of the wrist. These results indicate that difficulties making a fist, and predominantly fist closure, is easily assessable in clinical practice and can provide information on both risk assessment for disease progression as well as underlying flexor tenosynovitis.

In addition to fist problems, the value of another simple clinical test in CSA was studied. Historically, the squeeze test, i.e. compression across the knuckles of MCP and metatarsophalangeal (MTP) joints, was used to assess presence of synovitis.[4] In early arthritis a positive squeeze test was indeed shown to associate with presence of synovitis in MCP- and MTP-joints, and even with local MRI-detected inflammation.[5] In the phase of CSA the squeeze test is considered a risk factor for development of RA, as it is also incorporated in the EULAR definition of arthralgia suspicious for progression to RA. It was therefore hypothesized that a positive squeeze test in CSA, in absence of clinical arthritis, might associate with presence of subclinical inflammation; this was investigated in **Chapter 3**. It was shown that >50% of CSA-patients had positive squeeze test in MCP- or MTP-joints, and that a positive test independently associated with local subclinical synovitis with an OR of 2. However, the sensitivity of the test was only 44%, indicating that subclinical synovitis is also often missed. In addition, a positive squeeze test in CSA was not independently associated with progression to IA. Nevertheless, despite its lack in predictive value, the squeeze test is a simple and quick test that can be used to obtain a first indication on presence of subclinical synovitis.

Considerations from Chapter 2 and 3

Chapter 2 and 3 describe two closely related tests that are part of the physical examination in clinical practice; difficulties making a fist and the squeeze test, both performed with different hand positioning. During development of the EULAR definition, experts indicated that both tests contributed to the recognition of CSA, and their independent contribution was confirmed in statistical analyses.[3] In **Chapter 2 and 3** we aimed to increase our understanding of these tests, and discovered that they both associate with different inflammatory features; fist problems with tenosynovitis and the squeeze test with synovitis. This confirms the notion that both tests are in fact different and correlate with different types of subclinical inflammatory features. This suggests that both tests could be of value in the recognition of CSA in clinical practice.

Together, assessment of fist problems and the squeeze test help provide a first impression of underlying subclinical inflammation. Importantly, both studies were performed in a population of CSA-patients. The results can therefore not be generalized to other populations without further research. Primary care is a population where both tests might be of value in establishing a first risk assessment,

since general physicians acknowledge the importance but also the difficulty of differentiating inflammatory diseases from other musculoskeletal problems.[6,7] However, the predictive value of a test is dependent on the prevalence of disease in a population, i.e. the pre-test probability. The incidence of RA, and presumably also the prevalence of subclinical inflammation in primary care is low. Therefore it is likely that the predictive value of these tests is also lower in primary care than in CSA. Nevertheless, since test characteristics are unaffected by prevalence, the sensitivity and specificity will remain the same in primary care.

Summary Chapter 4

When presence of subclinical inflammation in at-risk populations is confirmed with imaging, treatment is sometimes considered, even in absence of clinical arthritis. Studies have shown that an increasing number of rheumatologists consider or initiate DMARD-treatment in patients with autoantibody-positive arthralgia,[8] their choices guided by US findings and presence of subclinical inflammation.[9] Indeed, subclinical inflammation can precede development of IA, but subclinical inflammation and symptoms also often spontaneously resolve.[10] In **Chapter 4** we therefore addressed the value of subclinical synovitis, its potential as starting point for DMARD-treatment and its potential for overtreatment. We studied three arthralgia cohorts in which the presence of subclinical synovitis was determined at baseline by either US or MRI. All patients were followed for one year for development of IA, during which DMARD-treatment (including corticosteroids) was not allowed. In anti-citrullinated protein antibody (ACPA) positive patients with subclinical synovitis 50-68% of patients did not develop IA, in ACPA-negative patients 66-89% did not progress. Even in patients with additionally ≥6 points on the 2010 EULAR classification criteria for RA, false positive rates remained considerable (≥37%). Results also remained similar when more stringent definitions of subclinical synovitis were used in sensitivity analyses. These findings indicate that DMARD-treatment in arthralgia-patients with subclinical synovitis would lead to considerable overtreatment.

Considerations from Chapter 4

In **Chapter 4** both MRI and US were used. It has been shown that MRI has a higher sensitivity than US.[11] Nevertheless, false-positive rates in all three cohorts were high, and the use of different imaging modalities with varying sensitivity has therefore unlikely influenced conclusions from this study. False positive rates might be further decreased by additional evaluation of other inflammatory features, e.g. tenosynovitis and/or BME. The latter can only be visualized by MRI, and the predictive value independent from tenosynovitis is limited.[2] Tenosynovitis is detectable by both imaging modalities, and the predictive value is highest of all inflammatory features.[2,12] It would therefore be valuable to repeat this study with subclinical tenosynovitis as

potential starting point for DMARD-treatment.

Summary Chapter 5

Subclinical inflammation as measured in **Chapter 2, 3 and 4**, even combined with ACPA-status, is insufficient for reliable identification of patients that progress to IA. Other imaging factors potentially increase the prognostic value of subclinical inflammation. Bone erosions are a hallmark of RA, and even RA-specific MRI-detected erosions have been established; these erosions were present in patients with early RA, but not in patients with other arthritides.[13] MRI is sensitive in detection of bone erosions, even in symptom-free persons[14] and in patients with CSA small MRI-detected erosions are detectable. In **Chapter 5** we investigated MRI-detected erosions in the phase of CSA. We determined the predictive value of MRI-detected erosions for development of IA, and evaluated whether the prognostic value of MRI-detected subclinical inflammation could be improved by evaluation of MRI-detected erosions. Any MRI-erosion, defined as erosions that were present in <5% of symptom-free persons in the same bone and age category, was present in 20% of CSA-patients. Presence of these erosions was not associated with IA-development. Erosion characteristics previously reported as specific for RA (grade ≥2 erosions, erosions in MTP5 and erosions in MTP1 in persons aged <40) were rarely seen in CSA-patients, and their presence was not associated with IA-development. When MRI-detected erosions were considered in addition to MRI-detected subclinical inflammation, the area under the curve (AUC) did not improve, and the prognostic accuracy decreased as shown by a net reclassification index (NRI) of -5.8; adding data on MRI-erosions resulted in a high number of false-positive predictions. Since erosions mainly occur early in ACPA-positive disease,[15-17] MRI-erosions were also evaluated in ACPA-positive and ACPA-negative CSA-patients separately. In neither subset MRI-detected erosions were predictive for development of IA. However, the median erosion score in ACPA-positive patients was significantly higher than in ACPA-negative patients. Notably, this difference was only seen in patients with subclinical inflammation; ACPA-positive patients without subclinical inflammation did not have a higher erosion score than ACPA-negative patients without subclinical inflammation.

Considerations from Chapter 5

Findings in **Chapter 5** are supported by previous studies in undifferentiated arthritis (UA). The prevalence of RA-specific erosions was similar between UA- and CSA-patients,[18] which is in line with the finding that erosion-scores in CSA-patients did not increase during progression to IA.[19] Additionally, in UA-patients erosions also lacked predictive value for development of RA.[18] Nevertheless, more erosions were present in CSA compared to symptom-free controls. Even though the exact mechanism is unclear, the erosions in CSA might reflect previous subclinical inflammation that, due

to lack of other stimuli, spontaneously resolved. Intriguingly, a significantly higher number of erosions was seen in ACPA-positive CSA-patients, though only when subclinical inflammation was present. This supports the finding that development of erosions in ACPA-positive CSA is mediated by subclinical inflammation, as shown previously.[15] Potentially also a direct effect of ACPA on osteoclastogenesis and bone resorption exists, as indicated by a study from Harre et al.[20] However, since the number of erosions was not increased in CSA-patients with only ACPA (i.e. without subclinical inflammation), our data could not support this finding, Further research unravelling the mechanism between ACPA and development of erosions is needed. Because even though small MRI-detected erosions cannot be used as predictor for imminent RA, this study indicated that erosions already occur in the phase of CSA. Knowledge on the interplay between pro-inflammatory factors and ACPA in this process might direct future prevention of bone damage early in the disease.

Overall considerations from Part I

All longitudinal studies in **Part I** of this thesis were potentially influenced by the Treat Earlier trial, a randomized controlled trial (RCT) carried out in CSA-patients.[21] From April 2015 until September 2019 CSA-patients with MRI-detected subclinical inflammation could be included in this trial, in which the effect of Methotrexate (MTX) was studied. Baseline characteristics of included patients could be used for cross-sectional analyses within the CSA-cohort. However, since the outcome of the CSA-cohort (development of IA) was potentially influenced by the 50% chance of DMARD-treatment in patients participating in this trial, these patients had to be excluded from longitudinal analyses. Excluding part of the patients with subclinical inflammation, a known risk factor for development of RA, might have influenced the associations of investigated predictors. Robustness of our findings has been investigated by stratification for subclinical inflammation, evaluation of only patients included in the CSA-cohort before the start of the trial and/or validation in other at-risk cohorts; these analyses consistently indicated similar results. It is therefore considered unlikely that the exclusion of part of the patients in longitudinal analyses caused incorrect results.

The predictors investigated in this part of the thesis were insufficient in establishing a CSA-population that would progress to clinical arthritis with certainty. MRI-detected erosions were not helpful and even increased the number of false-positive predictions. Subclinical synovitis was present in a high number of CSA-patients that did not progress to IA, and the squeeze test as proxy of subclinical synovitis did not yield predictive value. Likewise, despite tenosynovitis having the highest predictive value of all investigated features, not all CSA-patients with subclinical tenosynovitis, or with difficulties making a fist as proxy thereof, progressed to IA. It seems necessary to combine multiple predictors to obtain high predictive values. Indeed, prediction

rules including known clinical and immunological predictors,[22] combinations of MRI features,[12] or even both[23] have been shown to increase the AUC and positive predictive values (PPVs). Newly discovered imaging features might further improve these models. The discovery of other juxta-articular features as intermetatarsal bursitis (IMB), which has been associated with early RA[24] and conferred risk for arthritis development in CSA,[25] might be used for this purpose.

In addition, imaging techniques continuously improve, which may further enhance implementation of imaging in clinical practice. Shorter MRI scanning protocols without contrast-enhancement using modified Dixon sequences provide similar results as MRI sequences used in this thesis, though less costly and more patient-friendly.[26] Additionally, a decrease in workload for physicians and researchers, as well as an increase in faster and more consistent scoring methods is pursued by investigating possibilities of automated scoring methods with artificial intelligence (AI).

Nevertheless, despite improvements of imaging methods and discovery of new predictive features, advanced imaging modalities are not always (directly) available. It remains important to keep investigating associations of clinical features with (new) predictive imaging features, such as the squeeze test and difficulties making a fist which proved useful in this thesis. Their value should be investigated in future prediction models, which can improve applicability of prediction models in clinical practice and optimize a first risk assessment. Since presence of subclinical extensor peritendinitis of MCP-joints has been shown to have a high predictive value,[12] determining a clinical proxy for this feature might prove valuable in clinical practice.

Autoantibodies are among the first factors thought of in prediction of RA. ACPA and RF are among the strongest predictors for development of RA, and also play an important role in the 2010 EULAR classification criteria for RA.[27] Nevertheless, in up to 50% of RA-patients autoantibodies are absent. Even though the long-term outcomes of autoantibody-negative patients are less severe, clinical presentation and functional limitations are just as severe as in autoantibody-positive patients.[28] This underlines the importance of identifying not only early autoantibody-positive RA, but also early autoantibody-negative RA. At the moment most at-risk populations are composed of (arthralgia-)subjects with ACPA and/or RF, or relatives of RA-patients (e.g. first-degree relatives (FDR)). The CSA-cohort consists of a unique at-risk population, its inclusion based on clinical presentation rather than autoantibody status. While this cohort is useful in identification of predictors for autoantibody-negative RA, large cohorts for validation are lacking. Even though the recognition of autoantibody-negative RA is more complicated by the absence of known immunological risk factors, it deserves

more attention in pre-clinical research.

Even when existing prediction rules are improved, it is likely that part of at-risk patients will still not progress to arthritis, despite presentation with one or more known predictors. This complicates early preventive treatment, as it will partly result in overtreatment. Overtreatment is not without consequences; DMARD-treatment is expensive and may cause side effects. However, as functional limitations in patients with CSA that later progress to IA are already as severe as at the moment of arthritis development,[29] treatment may significantly benefit some at-risk patients. To what extent overtreatment is acceptable is an important topic of discussion. Apart from the risk for overtreatment, preventive treatment also complicates new studies in the pre-arthritis phase. The natural disease course that is presently studied in observational cohorts is then influenced by potential treatment responses in part of the patients. Moreover, ethical concerns may arise when initiating clinical trials investigating new preventive treatment in which part of the patients would receive placebo treatment. Lastly, the effectiveness of treatment in prevention of RA is not clear yet,[30-32] and currently still investigated in several trials.[21,33-35] It is therefore recommended to await clinical trial results and optimize prediction rules before starting DMARD-treatment in populations where clinical arthritis is not yet present.

Part II – Pathogenesis of rheumatoid arthritis

Adequate identification of patients at risk for development of RA can be improved by understanding the disease pathogenesis. Knowledge on disease processes and timing of contributing factors during initiation and progression of the disease help to better target treatment in pre-clinical stages, ultimately preventing RA.

Summary Chapter 6

Autoantibody development and response maturation, defined as an increase in number of autoantibodies and autoantibody levels, precede the development of RA.[36-38] It was unknown whether autoantibody-response maturation occurred in the phase of CSA, or whether the response was already fully matured at the onset of symptoms. In **Chapter 6** we therefore evaluated the presence and levels of autoantibodies in CSA at two timepoints; in patients that progressed to IA samples were taken at baseline and at the moment of IA-development, in patients that did not progress samples were taken at baseline and after two years. If maturation of the autoantibody-response played a role in disease progression, maturation was expected to be only present in CSA-patients that developed IA. We analyzed three autoantibodies (ACPA, anti-carbamylated protein antibodies (anti-CarP) and anti-

acetylated protein antibodies (AAPA)) in three different isotypes (IgM, IgG and IgA). Patients without any autoantibody at baseline rarely seroconverted to positive during follow-up. In patients with ≥1 autoantibody (out of nine) at baseline the median number of autoantibodies was 1, and an increase in number of autoantibodies was infrequent. Autoantibody levels did not significantly change over time. These findings were similar between patients that progressed to IA and patients that did not progress. We therefore concluded that autoantibody-response maturation was not responsible for the final hit in development of clinical arthritis. However, when the outcome RA was used, i.e. fulfilment of the 1987 and/or 2010 ACR/EULAR criteria[27,39] at the moment of IA-development, patients who did not progress showed a decrease in median number of autoantibodies over time. Possibly other factors involved in the continuation of the autoantibody-response were lacking in these patients.

Considerations from Chapter 6

Due to laboratory capacity autoantibodies at two time-points could only be measured in part of CSA-patients. This predominantly affected the selection of non-progressing CSA-patients that tested negative for RF and/or ACPA during routine laboratory measurements at baseline; from this group a random sample was studied. Preferably the entire CSA-population would have been studied. However, since baseline characteristics of included and excluded patients were similar, it is unlikely that replication of this study in the entire CSA-population would yield different results. Ideally, population-based studies are performed to confirm that autoantibody-response maturation occurs predominantly in the asymptomatic, and not in the symptomatic phase of RA-development.

Summary Chapter 7

In **Chapter 7** we focused on the role and timing of the two most prominent genetic and environmental risk factors for development of RA; HLA-SE and smoking. Their association with RA is widely acknowledged, though it is unknown at which disease stage they exert their effect. To investigate a potential role of HLA-SE and smoking in autoantibody-development we studied literature on associations of HLA-SE and smoking with presence of ACPA in the asymptomatic population. Meta-analyses revealed that smoking, but not HLA-SE, was associated with ACPA-positivity in asymptomatic individuals. At presentation with symptoms (CSA-onset) both HLA-SE and smoking associated with presence of ACPA. Though previous studies showed gene-environment interactions for development of ACPA,[40,41] in CSA the association of smoking with ACPA was not dependent on presence of HLA-SE, and no significant interaction between HLA-SE and smoking was found. Likewise, previous findings in RA indicating that smoking was not associated with ACPA, but with RF or autoantibodies in general,[42,43] could not be replicated in meta-analyses of

asymptomatic populations or in CSA-patients. During follow-up HLA-SE associated with progression to IA in the total CSA-population, as well as in the ACPA-positive subset as indicated by meta-analyses in three arthralgia-cohorts. Smoking was not associated with IA-development, not in the total CSA-population, after ACPA-stratification or in meta-analyses with other cohorts. Together, results from this study imply that smoking is involved in autoantibody-development, and possibly symptom-development, but not with further progression to IA. The HLA-SE is not involved in autoantibody-development, potentially plays a role in autoantibody-maturation and symptom-development, and associates with IA-development.

Considerations from Chapter 7

Importantly, conclusions from **Chapter 7** are partly based on results from cross-sectional data. Associations of smoking and HLA-SE with autoantibody-development were investigated in cross-sectional studies of asymptomatic populations. However, we believe that autoantibody-development is the first step towards development of autoantibody-positive RA. Therefore it is likely that these cross-sectional data accurately reflect the roles of smoking and HLA-SE in autoantibody-development. Associations of smoking and HLA-SE with autoantibody-response maturation and symptom-development have been based on data obtained at CSA-onset. Though different studies support findings of smoking having a role in progression to CSA,[44] and HLA-SE being involved in autoantibody-response maturation,[45] longitudinal data are needed to confirm these findings. Ideally, population-based studies following individuals from an asymptomatic stage towards development of RA are performed. Such studies are complicated by the low prevalence of RA in the general population; an excessive number of subjects is needed to detect even a few that eventually develop RA.

In **Chapter 7** we could not find associations between smoking, HLA-SE and autoantibodies other than ACPA, i.e. RF, AAPA and anti-CarP. Even though our goal was to determine when certain risk factors exerted their effected, we also explored the predictive value of AAPA and anti-CarP. Thus far conflicting findings on predictive and additional value of anti-CarP were reported, and AAPA was never studied in arthralgia-patients. With data from two arthralgia-cohorts we showed that only AAPA, but not anti-CarP, associated with development of IA independently from ACPA and RF. Further research is necessary to validate our findings.

Overall considerations from Part II

Until large population-based studies are performed, we can only speculate about the biological mechanisms behind our findings in **Chapter 6 and 7**. Since no association was found between HLA-SE and autoantibodies in the asymptomatic stage, it seems

likely that smoking, rather than HLA-SE, stimulates the initial break of tolerance to citrullinated antigens. Autoantibody-response maturation is likely stimulated by HLA-SE, which is suggested by the tendency of HLA-SE to associate with higher ACPA-levels. An increase in autoantibody levels or number of autoantibodies and isotypes occurs before symptom-development. After symptom-onset the autoantibody-response, as measured in **Chapter 6**, generally remains unchanged and does not provide a final hit towards development of IA. Other forms of autoantibody maturation than measured in **Chapter 6**, e.g. changes in cross-reactivity, affinity maturation, epitope spreading and glycosylation profile, could occur in the symptomatic phase. It is tempting to hypothesize that these forms of maturation might be involved in the final hit towards development of clinical arthritis. However, since these autoantibody characteristics associate with autoantibody levels, it seems more likely that the final hit is influenced by factors other than the autoantibody response, e.g. by other processes of the adaptive immune system or other (yet) unknown factors unrelated to the autoantibody response.

Our findings suggest that the HLA-SE might play a role in the final hit, since it significantly associated with IA-development in ACPA-positive patients in **Chapter 7**. An HLA-SE restricted T-cell response potentially stimulates the already existing ACPA-response. ACPA-IgG variable-domain glycosylation has indeed been shown to increase towards symptom-onset and significantly associates with HLA-SE.[46] While the exact mechanism remains to be elucidated, influences of HLA-SE on the ACPA-response could explain why ACPA-positive patients with HLA-SE more often develop RA than ACPA-positive patients without HLA-SE. Nevertheless, since also RA-patients without HLA-SE and/or autoantibodies present with similar clinical manifestations, other triggers remain to be elucidated.

As previously addressed in **Part I** of this thesis, a large part of RA-patients is autoantibody-negative. Apart from improving prediction in this RA-subset, knowledge on disease pathogenesis of autoantibody-negative disease needs to be enhanced. In **Chapter 7** initial analyses suggested that HLA-SE was somewhat predictive for development of ACPA-negative IA. However, this could not be replicated with the outcome RA. Since most at-risk cohorts only include autoantibody-positive patients we were not able to further explore these findings. Nevertheless, previous research suggested that HLA-SE is also involved in ACPA-negative RA, though with a smaller effect size.[47] This suggests that an effect of HLA-SE with RA-development might be found when studying a larger group of autoantibody-negative at-risk patients.

Future perspectives

Early detection and knowledge on disease pathogenesis of RA have tremendously improved over recent years, and first steps towards prevention have been taken. Nevertheless, further research is necessary to improve risk stratification and understanding of disease development.

The following points might be topic of future studies:

- A search for new clinical tests that associate with predictive imaging features, e.g. for MCP extensor peritendinitis which has shown high predictive value in CSA.
- The value of difficulties making a fist and the squeeze test may be tested in other populations, i.e. primary care, where they might prove valuable in determining presence of subclinical inflammation or risk for inflammatory disease.
- Further optimization of prediction rules, in which the value of newly discovered imaging features (e.g. juxta-articular inflammation as inter-metatarsal bursitis) or biomarkers (e.g. AAPA and/or ACPA-IgG glycosylation) need to be determined. With the prospect of preventive treatment in the future, the risk of overtreatment must be evaluated during development of new prediction rules.
- Findings on autoantibody-response maturation and timing of effects of HLA-SE and smoking as described in this thesis are ultimately confirmed in longitudinal population-based studies.
- Further research on disease pathogenesis to establish which factors are involved in the final hit towards development of RA. Factors may concern other forms of autoantibody maturation than addressed in this thesis, other processes of the adaptive immune system or even (yet) unknown factors entirely unrelated to the autoantibody response. Knowledge on timing of contributing factors may help to better target treatment in pre-clinical stages.
- Development of autoantibody-negative at-risk cohorts. While the CSA-cohort is useful in identification of predictors for autoantibody-negative RA, large cohorts for validation are lacking. Apart from identification of predictors, additional autoantibody-negative cohorts can be used to further elucidate disease processes in development of autoantibody-negative RA.

Final conclusions

In this thesis we have investigated CSA-patients and reported on the value of several clinical, imaging and immunological factors for prediction of RA. We also added to knowledge on disease pathogenesis and timing of disease processes by investigating immunological, genetic and environmental factors contributing to RA-development

in both asymptomatic and symptomatic disease phases. Although progress has been made, with the current knowledge and risk stratification it is not yet recommended to start preventive DMARD-treatment outside research settings in the absence of clinically apparent inflammatory arthritis. To prevent overtreatment, it is necessary to refrain from DMARD-treatment until adequate risk assessment is established, and clinical trials investigating the effect of preventive treatment have proven its value. Until such times, research should focus on the natural disease course of RA-development, further optimizing prediction and knowledge on disease mechanisms. In time, this could ultimately lead to prevention of RA in a high risk population, with the right treatment, at the right time.

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