Genetics, autoantibodies and clinical features in understanding and predicting rheumatoid arthritis

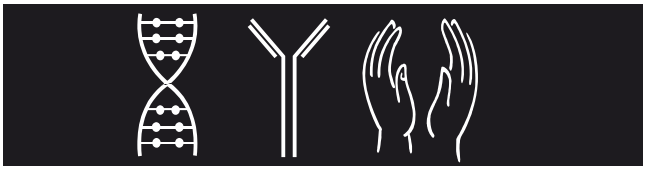
Helm-van Mil, A.H.M. van der

Chapter 11

Antibodies to citrullinated proteins and differences in clinical progression of rheumatoid arthritis

A.H.M. van der Helm - van Mil
K.N. Verpoort
F.C. Breedveld
R.E.M. Toes
T.W.J. Huizinga

Arthritis Res Ther 2005;7(5):R949-58.



ABSTRACT

Antibodies to citrullinated proteins (anti-CCP) are highly specific for rheumatoid arthritis (RA) and precede the onset of disease symptoms, indicating a pathogenetic role for these antibodies in RA. Recently we showed that distinct genetic risk factors are associated with either anti-CCP positive and anti-CCP-negative disease. These data are important as they indicate that distinct pathogenic mechanisms are underlying anti-CCP positive and negative disease. Likewise, these observations raise the question whether anti-CCP positive and negative RA are clinically different disease entities. Therefore, we investigated whether RA patients with anti-CCP antibodies have a different clinical presentation and disease course compared to patients without these auto-antibodies. In a cohort of 454 incident patients with RA, 228 patients were anti-CCP positive and 226 patients anti-CCP negative. The early symptoms, tender and swollen joint count and C-reactive protein level at inclusion, as well as the swollen joint count and radiological destruction during 4 years follow-up were compared for the 2 groups. There were no differences in morning stiffness, type, location and distribution of early symptoms, patients' rated disease activity and C-reactive protein at inclusion between RA patients with and without anti-CCP antibodies. The mean tender and swollen joint count for the different joints at inclusion was similar. At follow-up, patients with anti-CCP antibodies had more swollen joints and more severe radiological destruction. Nevertheless, the distribution of affected joints, for swelling, bone erosions and joint space narrowing, was similar. In conclusion, the phenotype of RA patients with or without anti-CCP antibodies is similar with respect to clinical presentation but differs with respect to disease course.

INTRODUCTION

Autoantibodies directed to citrullinated proteins (e.g. anti-cyclic-citrullinated peptide, anti-CCP antibodies) are highly specific serological markers for rheumatoid arthritis (RA) that are thought to be directly involved in the disease pathogenesis (1). Citrullinated proteins are not exclusively located in synovial tissue of RA patients, but can also be found in synovium samples of patients with other inflammatory joint diseases (2), suggesting that the specificity of anti-CCP antibodies for RA is not due to the expression of citrullinated proteins but might be the result of an abnormal humoral response. Intriguingly this antibody response may occur years before any clinical symptoms, as shown by the presence of anti-CCP antibodies several years before the clinical onset of arthritis (3,4). Furthermore, a proportion of RA patients do not harbour anti-CCP antibodies, suggesting that the presence of anti-CCP antibodies is not obligatory for the development of arthritis or that the pathogenic mechanisms underlying anti-CCP positive and negative RA are different.

These observations inspired subsequent research addressing the question whether RA patients with anti-CCP antibodies are different from those who are anti-CCP negative. Very recently, we demonstrated in two independent Caucasian populations that the shared epitope encoding HLA-DBR1 alleles associate with RA in patients with anti-CCP antibodies but not in patients without these antibodies (unpublished data, 5). These findings are important as they indicate that the shared epitope alleles are not associated with RA as such, but rather with a particular phenotype of the disease.

Given the findings suggesting a pathophysiological role for anti-CCP antibodies in RA and the reported immunogenetical differences between anti-CCP positive and negative patients, it is conceivable that anti-CCP positive and negative RA are different disease entities and have thus different phenotypical properties. Anti-CCP antibodies have been suggested to be associated with more severe radiological outcome (5,6). However, to our knowledge a detailed description of the distribution and degree of early symptoms and signs in both patient groups has not been published. Nevertheless, such an analysis is relevant as it might provide novel insight into the putative pathogenic role of anti-CCP antibodies in the aetiology of the disease. Therefore, in this study we set out to determine whether anti-CCP antibody positive and negative RA patients differ in different aspects of their phenotype, either the early symptoms of disease, the findings at physical examination at initial presentation or the acute phase reactant C-reactive protein at initial presentation. Moreover, we expanded the data on the influence of anti-CCP antibodies on disease course during 4-year follow-up for the distribution and extend of both inflammation (swollen joints) and radiological joint destruction. We show that the phenotype

of RA patients with or without anti-CCP antibodies is similar with respect to clinical presentation but differs with respect to disease course.

PATIENTS AND METHODS

Patients

In 1993 an Early Arthritis Clinic (EAC) was started at the department of Rheumatology of the Leiden University Medical Center, the only referral center for Rheumatology in a health care region of about 400 000 inhabitants in the western part of the Netherlands (7). General practitioners were encouraged to refer patients directly when arthritis was suspected. Patients referred could be seen within two weeks and were included in the program when the physician's examination of the patients revealed arthritis and the symptoms had lasted less than 2 years. At the first visit the rheumatologist answered a form with questions about the initial symptoms as reported by the patient (type of initial joint symptoms, localization and distribution of initial joint symptoms, presence of morning stiffness). Patients rated their global assessment of disease activity on a visual analogue scale (0-100). The Health Assessment Questionnaire, a self-assessed questionnaire asking about the ability of the patient to perform several daily activities over the past week, was used to obtain an index of disability. A tender joint count and swollen joint count (8,9) was performed on entering the study and yearly thereafter. For the tender joint count, each joint was scored on a 0-3 scale with 3 being maximal tenderness (0= no tenderness, 1= pain on pressure, 2= pain and winced and 3= winced and withdrew). For the swollen joint count the individual joints were scored on a 0-1 scale (0 = no swelling, 1= swelling). At inclusion from every patient blood samples were taken for routine diagnostic laboratory screening including C-reactive protein and were stored to determine antibodies to CCP2 at a later time point. The anti-CCP2 antibody ELISA (Immunoscan RA Mark 2; Eurodiagnostica, Arnhem, The Netherlands) was performed according to the manufacturer's instructions with a cut off value of 25 units. At present more than 1600 early arthritis patients are included in the EAC-cohort and have a follow-up of at least one year. 454 patients fulfilled the diagnosis of RA according to criteria of the 1987 American College of Rheumatology one year after inclusion in the study. The treatment of the patients in our longitudinal cohort study is characterized by a secular trend. The 122 RA patients (61 anti-CCP negative and 61 anti-CCP positive) included between 1993 and 1995, were treated initially with analgesics and subsequently with chloroquine or salazopyrine if they had persistent active disease (delayed treatment); the 135 (70 anti-CCP negative and 65 anti-CCP positive) RA patients included between 1996 and 1998, were promptly treated with either chloroquine or salazopyrine (early treatment) (for further description see 10). The 197 RA patients (97 anti-CCP negative and 100 anti-CCP positive) included after 1998

were promptly treated with either methotrexate or salazopyrine (early treatment). The rheumatologists that treated the patients were not aware of the anti-CCP status of their patients because anti-CCP antibodies were not routinely determined at inclusion but were assessed for research purposes years after inclusion using stored serum samples. Patients gave their informed consent and the local Ethical Committee approved the protocol.

Radiograpic progression

Radiographs of hands and feet were made at baseline, at one year and yearly thereafter. For 138 patients a complete radiological follow-up was available for 4 years. Inherent to an inception cohort, not all included patients had already completed 4 years of follow-up. Radiographs were scored using the Sharp-van der Heijde method (11). The rheumatologist that scored the radiographs was blinded to the clinical data and unaware of the study question. The distribution of radiological destruction of the small joints was studied by comparing the erosion score and joint space narrowing score of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of the hands.

Statistical analysis

Differences in means between groups were analysed with the Mann-Whitney test or t-test when appropriate. Proportions were compared using the chi square test. In the analysis of the tender joint count and the swollen joint count, for each joint location, the scores for the left and right joints were summed. Furthermore, the scores for the individual metacarpophalangeal joints were summed, as well as the scores for the metatarsophalangeal joints and the interphalangeal joints of the hands and feet. For the 138 RA patients with complete 4 year radiological follow-up, the swollen joint count, erosion score and joint space narrowing score were determined for the individual metacarpophalangeal and proximal interphalangeal joints of the hands at inclusion and 2 and 4 years follow-up, and expressed in mean with 95% confidence interval (95% CI). The distribution and degree of radiological destruction and swelling of these joints was studied by comparing the variance of these scores for the individual joints. The 95% CI was used as a measure of variance; as the number of observations in this study is constant (138 patients at all time points during 4 years follow-up), the extent of the confidence interval reflects the degree of variance. Correlations between joint swelling and erosion score or joint space narrowing score were determined for each MCP and PIP joint of the hands using the Spearman correlation test. The statistical Package for Social Sciences (SPSS) version 12.0 (SPSS, Chigaco, IL) was used to analyze the data. In all tests, p values less than 0.05 were considered significant.

RESULTS

Early symptoms of disease

In total 454 patients fulfilled the ACR-criteria for RA; 228 of these patients had anti-CCP antibodies and 226 patients had no anti-CCP antibodies at inclusion. Patient characteristics and the type, localization and distribution of initial disease symptoms are depicted in Table 1. In both groups, 13% of patients reported to have no morning stiffness. In the patients that experienced morning stiffness the mean duration in the anti-CCP negative and anti-CCP positive patients was similar: 118 minutes and 123 minutes respectively. In both groups symptoms started with pain and swelling, predominantly symmetrical and in the small joints of the hands and feet. In the statistical analysis without correction for multiple testing, one difference in initial presentation between the two groups was observed: in anti-CCP positive patients symptoms started more often at both upper and lower extremities than in anti-CCP negative patients (20% vs. 11% respectively, $p<0.05$).

Table 1. Characteristics of the early symptoms in rheumatoid arthritis patients with and without anti-CCP antibodies.

	Anti-CCP– (N=228)	Anti-CCP+ (N=226)
Female n (%)	147 (64%)	150 (66%)
Age at inclusion Mean ± SD	57 ± 17	55 ± 16
Morning stiffness No n (%)	30 (13%)	30 (13%)
If yes, minutes (mean±SD)	118 ± 138	123 ± 128
Type of initial joint symptoms: n (%) #		
- pain	208 (91%)	205 (91%)
- swelling	146 (64%)	135 (60%)
- stiffness	106 (46%)	85 (38%)
- function loss	64 (28%)	57 (25%)
- redness or increased surface temperature of joints	19 (8%)	26 (12%)
Localization of initial joint symptoms: n (%)		
- small joints of hands and/or feet	105 (46%)	112 (50%)
- large joints	54 (24%)	50 (22%)
- both small and large joints	63 (28%)	59 (26%)
- unknown	6 (2%)	5 (2%)
Localization of initial joint symptoms: n (%)		
- upper limbs	114 (50%)	86 (38%)*
- lower limbs	72 (32%)	77 (34%)
- both upper and lower limbs	25 (11%)	45 (20%)*
- unknown	18 (8%)	18 (8%)
Localization of initial joint symptoms: n (%)		
- symmetric	145 (64%)	130 (58%)
- asymmetric	71 (31%)	83 (37%)
- unknown	10 (4%)	13 (6%)
VAS patients' rated global disease activity (0-100)	51.3 ± 39.9	46.7 ± 28.2
HAQ-score (mean ± SD)	1.0 ± 0.7	1.0 ± 0.7

Patients can have both swelling and pain at the start of the symptoms and therefore total can add to more than 100%. * P< 0.05, anti-CCP+ vs. anti-CCP–

Given the marginal p-value, that was not significant after correction for multiple testing, this finding was not considered a relevant difference. The mean patients' rated global disease activity on a VAS was not significantly different between the two groups. Likewise, the functional ability measured by a HAQ-score was similar in both groups. In conclusion, there are no fundamental differences in the early symptoms of disease between anti-CCP positive and anti-CCP negative RA patients.

Findings at physical examination at initial presentation

In each of the 454 patients a tender joint count and swollen joint count was performed at inclusion. The mean tender joint count per joint is presented in Table 2. There were no significant differences between RA patients with and without anti-CCP antibodies. Table 3 reveals the mean scores for joint swelling for both anti-CCP positive and anti-CCP negative patients, showing no statistical significant differences between the two groups. Thus, anti-CCP positive or negative RA patients cannot be distinguished at presentation by physical examination.

Table 2. Tender joint count (mean ± SD) at inclusion in rheumatoid arthritis patients with and without anti-CCP antibodies.

	Anti-CCP- (N=228)	Anti-CCP+ (N=226)
Temporomandibular joints	0.01 ± 0.41	0.08 ± 0.36
Sternoclavicular joints	0.23 ± 0.76	0.12 ± 0.47
Acromioclavicular joints	0.31± 0.63	0.55 ± 0.79
Shoulder joints	0.85 ± 1.5	0.86 ± 1.4
Elbow joints	0.42 ± 0.99	0.35 ± 0.81
Wrist joints	0.94 ± 0.94	0.80 ± 0.93
Metacarpophalangeal joints	4.3 ± 4.3	3.5 ± 3.4
Proximal interphalangeal joints of the hands	3.2 ± 3.6	3.3 ± 3.4
Distal interphalangeal joints of the hands	1.3 ± 2.4	1.2 ± 2.2
Hip joints	0.18 ± 0.73	0.11 ± 0.54
Knee joints	0.54 ± 0.88	0.59 ± 0.90
Ankle joints	0.41 ± 0.92	0.53 ± 1.1
Subtalar joints	0.31 ± 0.72	0.52 ± 0.76
Midtarsal joints	0.21 ± 0.40	0.18 ± 0.58
Metatarsophalangeal joints	4.2 ± 3.4	4.1 ± 3.7
Interphalangeal joints of the feet	0.91 ± 1.8	1.4 ± 3.2
Total Ritchie articular index score	10.4 ± 8.2	10.2 ± 8.0

Tenderness was scored per joint on a 0-3 scale; 0 = no tenderness, 1 = pain at pressure, 2 = pain and winced and 3 = winced and withdrew. The scores for the metacarpophalangeal joints were summed, as the scores for metatarsophalangeal joints and the interphalangeal joins of the hands and feet. The scores for the left and right joints were summed. The summed scores were divided by the total numbers of patients; the resulting means (± SD) are presented. There were no statistical differences between patients with and without anti-CCP antibodies.

Table 3. Joint swelling (mean ± SD) at inclusion in rheumatoid arthritis patients with and without anti-CCP antibodies.

	Anti-CCP- (N=228)	Anti-CCP+ (N=226)
Temporomandibular joints	0.01 ± 0.10	0.02 ± 0.18
Sternoclavicular joints	0.08 ± 0.34	0.04 ± 0.22
Acromioclavicular joints	0.06 ± 0.24	0.03 ± 0.17
Shoulder joints	0.08 ± 0.30	0.12 ± 0.40
Elbow joints	0.22 ± 0.54	0.20 ± 0.49
Wrist joints	1.0 ± 0.89	1.0 ± 0.90
Metacarpophalangeal jointss	3.2 ± 3.0	2.2 ± 2.2
Poximal interphalangeal joins of the hands	2.6 ± 3.1	2.0 ± 1.8
Distal interphalangeal joints of the hands	0.32 ± 0.60	0.21 ± 0.60
Knee joints	0.46 ± 0.74	0.49 ± 0.74
Ankle joints	0.31 ± 0.67	0.34 ± 0.63
Subtalar joints	0.24 ± 0.61	0.21 ± 0.55
Metatarsophalangeal joints	1.6 ± 2.2	1.8 ± 2.4
Interphalangeal joints of the feet	0.06 ± 0.24	0.18 ± 0.58
Total number of swollen joints	10.0 ± 7.2	8.6 ± 5.5

Swelling was scored for each joint on a 0-1 scale, 0 = no swelling, 1 = swelling. The scores for the metacarpophalangeal joints were summed, as the scores for metatarsophalangeal joints and the interphalangeal joins of the hands and feet. The scores for the left and right joints were summed. The summed scores were divided by the total numbers of patients; the resulting means (± SD) are presented. There were no statistical differences between patients with and without anti-CCP antibodies.

Acute phase reactant at initial presentation

The mean C-reactive protein level was 29.5 mg/L (SD 31.5) in the anti-CCP negative RA patients and 35.6 mg/L (SD 37.8) in the anti-CCP positive patients, and was not significantly different between the two groups (p=0.08).

Swollen joints at follow-up

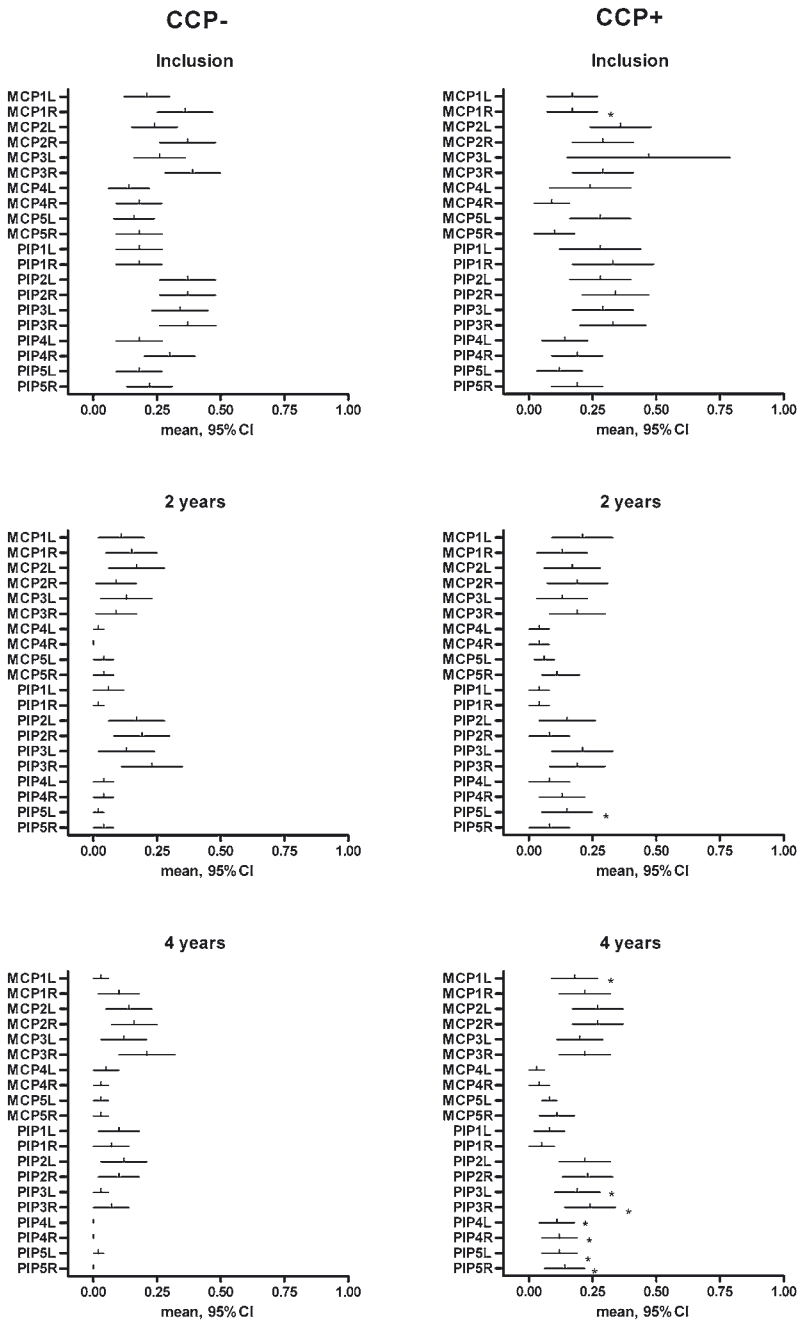
In the 138 early arthritis patients with complete radiological follow-up for 4 years the swollen joint count was assessed yearly. These patients had a mean age at inclusion of 53.7 ± 13.9 years, 67% (93 patients) were women and 74 patients (54%) were anti-CCP positive. The total number of swollen joints decreased during follow-up. At inclusion, in the anti-CCP negative patients the mean (±SD) number swollen joint was 10.0 ± 7.2; at 2 and 4 years follow-up the mean (±SD) number swollen joints was respectively 4.1 ± 6.7 and 3.1 ± 4.2. The mean (±SD) number swollen joints in the anti-CCP positive group was at inclusion 8.6 ± 5.5; this decreased to 5.2 ± 7.5 and 5.3 ± 6.8 at 2 and 4 years follow-up respectively. At 4 years follow-up the total number of swollen joints was significantly higher in the RA patients with anti-CCP antibodies (p=0.01).

In addition, the scores for the individual MCP and PIP joints of the hands were compared. Overall the pattern of inflammation of the individual small joints is similar in CCP-negative and CCP-positive RA as is depicted by the means and 95% CI of the swollen joint count in Figure 1. Several individual joints had significant higher scores in the anti-CCP positive patients compared to the anti-CCP negative patients; this concerned at inclusion the 1st MCP joint at the right side, at 2 years follow-up the 5th PIP joint at the left side and at 4 years follow-up the 1st MCP, 3rd PIP, 4th PIP and 5th PIP joints at the left side and 3th PIP, 4th PIP and 5th PIP joints at the right side ($p<0.05$). Furthermore Figure 1 shows that in both anti-CCP positive and negative RA patients, the second and third MCP joints were more frequently swollen than other MCP joints. Likewise, in both groups the second and third PIP joints were more frequently affected than the other PIP joints. In conclusion, the pattern of inflammation of the individual small joints of the hand seems similar in anti-CCP positive and negative patients, however, particular at 4 years follow-up some MCP and PIP joints are significantly less frequently swollen in anti-CCP negative RA patients.

Radiographic progression

In the 138 RA patients with complete 4 years radiological follow-up, the total Sharp-van der Heijde scores between the RA patients with and without anti-CCP antibodies were compared (Figure 2). At 2 and 4 years follow-up anti-CCP positive patients had significantly higher radiological scores than anti-CCP negative patients ($p<0.001$).

The distribution of the radiological destruction in the MCP and PIP joints of the hands was further investigated. The erosion scores and joint space narrowing scores of the MCP and PIP joints are depicted in Figure 3. As the most pronounced radiological destruction was present in anti-CCP positive patients, the erosion scores and joint space narrowing scores are shown for the RA patients with anti-CCP antibodies. Figure 3 shows that at all time points, of all MCP joints, the second MCP joints had the highest erosion score, followed by the third MCP joints. Concerning the PIP joints, the highest erosion scores were present in the third and fourth PIP joints. Figure 3 further reveals that the second and third MCP joints are the MCP joints with the highest joint space narrowing scores at all time points during follow-up. The joint space narrowing scores of the PIP joints differ less, but there are slightly higher scores for the third and fourth PIP joints. The erosion scores and joint space narrowing scores for the patients without anti-CCP antibodies revealed the same distribution as for the anti-CCP positive RA patients (data not shown). In the anti-CCP negative patients the values for the mean and 95%CI were lower than in the anti-CCP positive patients, which is in concordance with the finding of lower total Sharp-van der Heijde scores in anti-CCP negative RA patients. Correlations between joint swelling and erosion score and between joint swelling and joint space narrowing score were determined for each MCP and PIP joint at 4 years follow-up. For all PIP joints and



For each joint swelling was scored on a 0 -1 scale, 0=no swelling, 1=swelling;
*p<0.05

Figure 1. Joint swelling (mean and 95%CI) of the metacarpophalangeal and proximal interphalangeal joints of the hands at inclusion, 2 and 4 years follow-up in rheumatoid arthritis patients with and without anti-CCP antibodies.

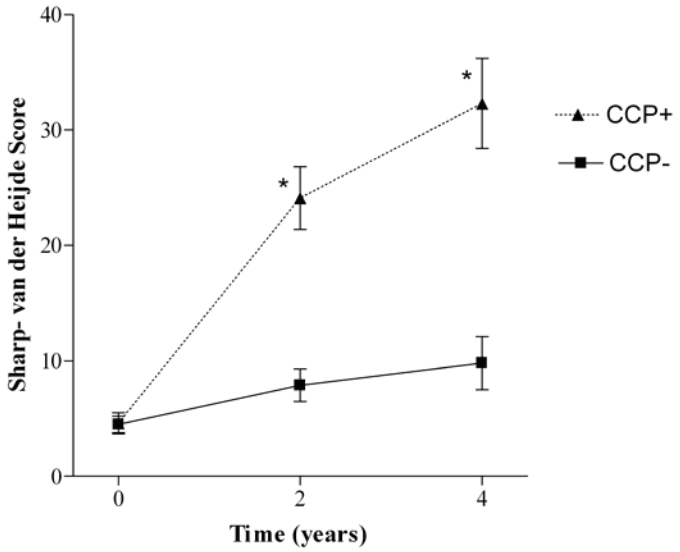


Figure 2. Total Sharp-van der Heijde scores (mean ± SEM) at inclusion, 2 and 4 years follow-up in rheumatoid arthritis patients with and without anti-CCP antibodies.

for all MCP joints, except the fourth MCP joints, the erosion score was significantly correlated with joint swelling ($p<0.05$). The joint space narrowing scores were significantly correlated with joint swelling in all MCP joints except the fourth MCP joint ($p<0.05$). This implies that at that time point the joints that were the most swollen were also the joints with the most severe radiological destruction.

DISCUSSION

This study shows that the phenotype of RA patients with or without anti-CCP antibodies does not differ at clinical presentation. In a large prospective early arthritis cohort we observed neither a significant difference in the reported first symptoms nor in the signs found at the physical examination at initial presentation between anti-CCP positive and negative patients. However, during follow-up anti-CCP positive RA patients have more swollen joints and show more radiological destruction than anti-CCP negative RA patients. Remarkable is that at follow-up, in spite of the difference in magnitude of disease characteristics, the distribution of swollen joints and the distribution of radiological joint space narrowing and bone erosions remains similar for RA patients with and without anti-CCP antibodies. This implies that, although different associations with known risk factors are reported for anti-CCP positive and negative RA patients, the presence or absence of anti-CCP antibodies is not associated with a distinguishable clinical phenotype at presentation of disease.

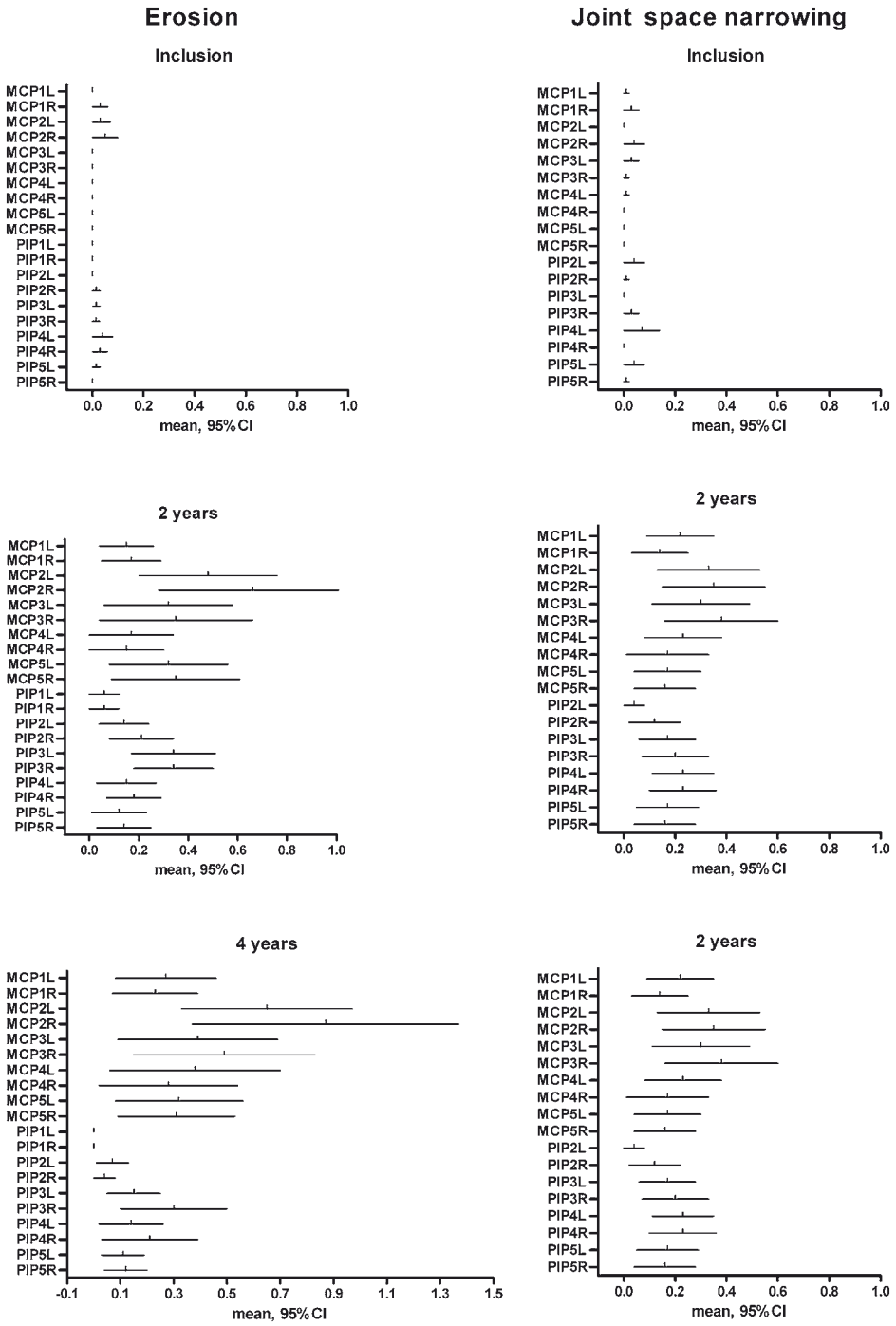


Figure 3. Erosion and joint space narrowing scores of the metacarpophalangeal and proximal interphalangeal joints of the hands (means and 95%CI) at inclusion, 2 and 4 years follow-up in rheumatoid arthritis patients with anti-CCP antibodies.

Pathophysiologically, this may have implications. It was recently observed that the prominent genetic risk factor HLA-Class II alleles only associate with susceptibility to RA in the presence of anti-CCP antibodies but not with RA in the absence of these antibodies (unpublished data, 5). In mice it has been shown that citrullination of arginine in a peptide can lead to a higher binding affinity of that peptide for HLA-DRB*0401, an important shared epitope allele (12), allowing peptide-specific T-cell induction. It can be speculated that also in humans citrullination may improve antigen presentation to CD4 positive T-cells and that the genetical background (presence of shared epitope alleles) provide the basis for a citrulline-specific immune reaction. It was demonstrated that anti-CCP antibodies occur years before disease onset (3,4). This last observation suggests that in anti-CCP positive RA patients the induction of disease occurs years before presentation, however the current study shows that the age of onset of clinical disease is similar in RA patients with and without anti-CCP antibodies. The risk factors such as HLA-alleles differ between anti-CCP negative RA and anti-CCP positive RA (5). Although differences in risk factors presume different pathophysiological pathways for anti-CCP positive and negative RA, the initial phenotypical presentation of both patient groups is similar and characterised by a symmetric poly-arthritis of the same small joints. At follow-up the clinical phenotype remains comparable with regard to joint distribution, but the anti-CCP positive patients have more inflamed joints and once there is inflammation also more rapid joint destruction. This leads to a pathophysiological model in which one or more triggers lead to arthritis in similar joints in anti-CCP positive and negative patients. Subsequently during inflammation antigens are citrullinated and in the presence of anti-CCP antibodies inflammation is aggravated, resulting in more severe radiological destruction. Further studies are needed to add insight into the pathogenic role of circulating anti-CCP antibodies in anti-CCP positive RA and to unravel risk factors associated with anti-CCP negative RA.

In a study by Kastbom et al (13) several baseline disease characteristics of anti-CCP positive and negative RA patients were compared. This study observed no significant differences in baseline total swollen joint count, C-reactive protein levels or DAS28 score between RA patients with and without anti-CCP antibodies, but showed a positive correlation between the number of fulfilled ACR-criteria and the frequency of anti-CCP positivity (13). Furthermore, in this study anti-CCP positive individuals were more often treated with disease modifying antirheumatic drugs than anti-CCP negative patients (13). Although in the present study secular trends in the initial treatment strategies with disease modifying antirheumatic drugs were present, these trends yielded the same effect for the anti-CCP positive and negative RA patients. Furthermore, the rheumatologists that treated the patients were not aware of the anti-CCP status of their patients. Therefore, the more severe disease course in patients with anti-CCP antibodies is not likely to be due to either a

more delayed treatment of these patients or confounding by treatment adapted to the anti-CCP status. We cannot exclude that during follow-up the anti-CCP positive patients that had more inflamed joints received more aggressive treatment. However, in case of a more aggressive treatment during follow-up in anti-CCP positive patients, this did not prevent the development of more severe radiological destruction in the RA patients with anti-CCP antibodies. The finding that the swollen joint count decreased during follow-up is probably due to the fact that at inclusion patients were not treated with disease modifying antirheumatic drugs.

The sensitivity of anti-CCP2 antibodies for RA is reported to vary between 39% and 80% (14,15). The present study measured anti-CCP2 levels at inclusion (a very early stage of the disease) and reports a relatively low percentage (50%) of RA patients with anti-CCP antibodies. As CCP measurements were not repeated during follow-up, we cannot exclude that some RA patients that were anti-CCP negative at inclusion have become anti-CCP positive on a later stage in the disease. A relatively low prevalence of anti-CCP antibodies in early arthritis patients has been described before (14).

The present study shows that the second and third MCP joints have the highest erosion scores, as well as the highest joint space narrowing scores and are, of all MCP joints, most frequently swollen. Although the present study was not designed to study the correlation between inflammation and destruction, the observed similarity in joints that are affected by swelling, erosions and joint space narrowing supports the concept that in general the mechanisms leading to clinical inflammation and radiological destruction are related.

This study includes a detailed description on the distribution of affected joints in RA and shows that the MCP joints of the second and the third digits are most frequently inflamed and destructed. Although to our experience rheumatologists generally feel that the joints of the second and third digits are more frequently inflamed than other joints of the hands, to our knowledge this phenotypic characterisation has not been frequently described.

CONCLUSION

The present study shows that, although separate risk factors for anti-CCP positive and negative RA were recently described, the clinical presentation of RA patients with or without anti-CCP antibodies is not different. Patients with anti-CCP antibodies develop a more severe disease course with more radiological destruction compared to RA patients without these auto-antibodies. Nonetheless, also at follow-up the distribution of affected joints is similar.

REFERENCES

1. Vossenaar ER, Zendman AJ, Van Venrooij WJ. Citrullination, a possible functional link between susceptibility genes and rheumatoid arthritis. Arthritis Res Ther 2004;6:1-5.
2. Vossenaar ER, Smeets TJ, Kraan MC, Raats JM, van Venrooij WJ, Tak PP. The presence of citrullinated proteins is not specific for rheumatoid synovial tissue. Arthritis Rheum. 2004;50:3485-3494.
3. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, Sundin U, van Venrooij WJ. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48:2741-2749.
4. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, Habibuw MR, Vandenbroucke JP, Dijkmans BAC. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50:380-386.
5. Van Gaalen FA, van Aken J, Huizinga TW, Schreuder GM, Breedveld FC, Zanelli E, van Venrooij WJ, Verweij CL, Toes REM, de Vries RRP. Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. Arthritis Rheum 2004;50:2113-2121.
6. Forslind K, Ahlmen M, Eberhardt K, Hafstrom I, Svensson B; BARFOT Study Group. Prediction of radiological outcome in early rheumatoid arthritis in clinical practice: role of antibodies to citrullinated peptides (anti-CCP). Ann Rheum Dis 2004;63:1090-1095.
7. Aken J, Bilsen JAM, Allaart CF, Huizinga TWJ, Breedveld FC. The Leiden Early Arthritis Clinic. Clin Exp Rheumatol 2003;21(Suppl 31):S100-105.
8. Van Riel PL, van Gestel AM, Scott DG. In EULAR handbook of clinical assessments in rheumatoid arthritis. Alphen aan den Rijn, The Netherlands: Van Zuiden Communications; 2000, 10-11.
9. Hernandez-Cruz B, Cardiel MH. Intra-observer reliability of commonly used outcome measures in rheumatoid arthritis. Clin Exp Rheumatol 1998;16:459-462.
10. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, Hazes JM. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med 2001;111:446-451.
11. van der Heijde DM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. Baillieres Clin Rheumatol 1996;10:435-453.
12. Hill JA, Southwood S, Sette A, Jevnikar AM, Bell DA, Cairns E. Cutting edge: the conversion of arginine to citrulline allows for a high-affinity peptide interaction with the rheumatoid arthritis-associated HLA-DRB1*0401 MHC class II molecule. J Immunol 2003;171:538-541.
13. Kastbom A, Strandberg G, Lindroos S, Skogh T. Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedisch TIRA project). Ann Rheum Dis 2004;63:1085-1089.
14. Soderlin MK, Kastbom A, Kautiainen H, Leirisalo-Repo M, Strandberg G, Skogh T. Antibodies against cyclic citrullinated peptide (CCP) and levels of cartilage oligomeric matrix protein (COMP) in very early arthritis: relation to diagnosis and disease activity. Scand J Rheumatol 2004;33:185-188.
15. Nijenhuis S, Zendman AJ, Vossenaar ER, Pruijn GJ, vanVenrooij WJ. Autoantibodies to citrullinated proteins in rheumatoid arthritis: clinical performance and biochemical aspects of an RA-specific marker. Clin Chim Acta 2004;350:17-34.