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Radiological outcome in rheumatoid arthritis is predicted by the presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-rheumatoid factor at disease onset.

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Objective. To evaluate the significance of antibodies against cyclic citrullinated peptide (anti-CCP) and rheumatoid factors (RFs), in individuals before onset of rheumatoid arthritis (RA) and when presenting as early RA (baseline), for disease activity and progression.

Methods. Ninety-three of a cohort of 138 patients with early RA (*i.e.*, <12 months of symptoms) had donated blood before symptoms of RA (defined as pre-patients) and were identified from among blood donors within the Medical Biobank of northern Sweden. Disease activity (ESR, CRP, joint score, global VAS) and radiological destruction in hands and feet (Larsen score) were assessed at baseline and after 2 years. Anti-CCP antibodies and RFs were analysed using enzyme immunoassays. HLA shared epitope (SE) alleles (DRB1*0401/0404) were identified.

Results. Patients with anti-CCP antibodies before disease onset had significantly higher Larsen score at baseline and after 2 years. In multiple regression analyses baseline values of anti-CCP/IgA-RF/IgG-RF/IgM-RF, swollen joint count and Larsen score significantly predicted radiological outcome at 2 years. In logistic regression analyses baseline values of anti-CCP antibodies/IgA-RF, and therapeutic response at 6 months and, swollen joint count/ESR, respectively, and significantly predicted radiological progression after 2 years. The baseline titre of anti-CCP antibodies was higher in patients with radiological progression and decreased significantly in patients with response to therapy. SE allele carriage was significantly associated with a positive test for anti-CCP antibodies in pre-patients and in early RA patients.

Conclusion. Presence of anti-CCP antibodies before disease onset is associated with more severe radiological damage. The titre of anti-CCP antibodies is related to disease severity.

Key words: anti-CCP antibody, rheumatoid factors, early rheumatoid arthritis, radiological outcome, titre of anti-CCP antibodies.

Detection of antibodies against cyclic citrullinated peptides (CCP) has developed during recent years as a valuable tool in diagnosing rheumatoid arthritis (RA) and predicting the clinical outcome [1-3]. We have previously shown that anti-CCP antibodies and rheumatoid factors (RFs) of all isotypes predated the onset of RA by several years. The presence of anti-CCP antibodies and IgA-RF predicted the development of RA, with anti-CCP antibodies having the highest predictive value [4]. Anti-CCP antibodies have also been demonstrated to predict disease activity. Persistent arthritis after 2 years was strongly predicted by positive test for anti-CCP antibodies [5] and patients with anti-CCP antibodies had a significantly higher number of joints involved after 3 years [6]. In patients with undifferentiated arthritis the presence of anti-CCP antibodies significantly predicted development of RA after 3 years follow-up [7]. Several studies have demonstrated the prediction of radiological outcome by the presence of RF [8, 9] and anti-CCP antibodies [10, 11] at the time of diagnosis of early RA.

An association between certain alleles of the HLA-DRB1 locus, the so-called “shared epitope” (SE) and RA is well described [12, 13] and also associated with a more severe disease progression [14, 15]. We previously reported that presence of anti-CCP antibodies together with SE allele carriage is associated with a very high relative risk for the future development of RA [16]. An association between anti-CCP antibodies and SE allele carriage has been reported [16, 17] together with a more severe disease progression in patients with both anti-CCP antibodies and SE [18].

In this study of a cohort of patients with early RA we investigated the presence of anti-CCP antibodies and RFs, in blood samples collected before the onset of any symptoms of joint disease in those who had donated blood samples to the Medical Biobank, and in the whole cohort, at the time of diagnosis. The significance of the presence of these antibodies before and after disease onset for disease activity and radiological progression and outcome, as well as their relationship with SE, was evaluated. The impact of the titre of anti-CCP antibodies was also studied.

Subjects and methods

Subjects. The register of all patients (n=138; 98 females, 40 males) with early RA (duration of < 1 year) fulfilling the American College of Rheumatology (ACR) classification criteria for RA [19] at the Department of Rheumatology, University Hospital, Umeå (the only rheumatology department in the county of Västerbotten) and with a known date for the onset of symptoms, was co-analyzed with the register of individuals in the Northern Sweden Health and Disease Study (NSHDS) cohort and the Maternity cohort of northern Sweden (Medical Biobank), Umeå, Sweden. The NSHDS consists of three sub-cohorts which all are population-based. All adults in the county of Västerbotten are invited to participate and no one is excluded. The sub-cohorts and the conditions for recruitment into the cohorts and the collection and storage of blood samples have previously been described in detail [4]. Ninety-three (72 females, 21 males) of the 138 early RA-patients were identified as having donated blood before the onset of any symptoms of joint disease. The 93 individuals are referred to as pre-patients. The median time of blood sampling before onset of symptoms was 3.0 years (IQR: 1.1-5.3). Mean age at onset of symptoms was 54 years (range 23-73). The median time from onset of symptoms until the diagnosis of early RA (≥ 4 ACR criteria fulfilled) was 7.0 months (IQR; 5.0-9.0). The patients were followed for 2 years from the date of diagnosis. Follow-up data from the early RA clinic were missing for 5 individuals; two were not examined at correct time points because they had palindromic RA and another one was

examined only at baseline. Two were followed for only 6 months because one had died and the other refused to participate further. The patients were treated with the aim of achieving remission using disease-modifying-anti-rheumatic drug(s) (DMARDs), corticosteroids, non-steroidal anti-inflammatory drug(s) and analgesics with respect to the clinical situation. During the study, 92 % of the patients were treated for at least 6 months with DMARDs; 68 % received methotrexate, 30 % sulphasalazine, 14 % gold in either oral or parenteral form, 12 % antimalarials, 0.7% TNF-alpha-blockers, 12 % other DMARDs, and 30 % combination therapy. Forty-eight percent of the patients were receiving low dose prednisolone (≤ 10 mg/day) for at least six months during the study. The Ethics Committee of the University Hospital, Umeå, approved this study and the patients gave their written informed consent.

Methods.

Enzyme immunoassays (EIAs) for anti-CCP-2 antibody.

Anti-CCP antibodies were measured in plasma from pre-patients, Biobank samples, (n = 93) and at the diagnosis of RA (baseline; n = 85) using the Immunoscan RA (Mark 2) EIA from Euro-Diagnostica (cut-off value 25 units/mL) as previously described [4]. The Diastat kit from Axis-Shield Diagnostics Limited, (The Technology Park, Dundee, UK), (cut-off value 5 units/mL) was used for analyses both at baseline (n = 101) and after 2 years. Consequently, at baseline anti-CCP antibodies were analysed in a total of 127 patients and in 59 of the samples using both methods and there was total agreement between the results. The two methods are based on the same type of peptides [20]. All measurements were performed in duplicate.

Enzyme-linked immunosorbent assays (ELISAs) for isotype-specific RFs.

RFs of IgG, IgM and IgA isotypes were measured by in-house ELISAs as previously described [4]. The 95th percentile value of the controls, analysed previously, was used as the cut-off point for all three RF classes [4]. The analyses were performed in pre-patient samples (n=65) and samples collected at baseline (n=126).

HLA-DRB1 genotypes

HLA-DRB1 genotyping was performed on samples collected at baseline using polymerase chain reaction sequence specific primers from a DR low-resolution kit and DRB1*04 subtyping kit (Dynal, Oslo, Norway) [21,22]. The SE alleles were defined as HLA DRB1*0401 or DRB1*0404.

Measures of disease activity.

The erythrocyte sedimentation rate (ESR mm/h,) and blood levels of C-reactive protein (CRP, mg/L) were determined at baseline and after 0.5, 1 and 2 years. At the same time points, clinical examination including a 28-joint count for tender and swollen joints and assessment with a global visual analogue scale [VAS; EULAR (European League Against Rheumatism) criteria] were performed and the Disease Activity Score including 28 joints (DAS28) was calculated [23]. Therapy response was determined according to EULAR response criteria [24].

Measures of disease outcome.

Posterior-anterior radiographs of the hands, wrists and feet obtained at baseline (n=127) and after 2 years (n=112) were examined blind by two rheumatologists (EB and SRD) specially trained in the evaluation of X-rays, and graded according to the Larsen score [25] by comparison with standard reference films. The scoring system included 32 areas; metacarpal-phalangeal joints II-V (n = 8), all proximal interphalangeal joints (n = 8), the wrists divided

each in 4 areas ($n = 8$), metatarso-phalangeal joints II-V ($n = 8$). Each joint or joint area was graded from 0 to 5 [25]. The maximal score was 160.

Statistics

Differences in continuous data between two groups were analysed using an independent t-test. Differences in continuous data from two different time points in the same individual were analysed with a paired t-test. Variations over time between groups were assessed by analysis of variance for repeated measurements (StatView, version 4.51; Abacus Concepts, Inc, Berkeley, CA, USA). The chi-square test was used for testing categorical data between groups. Multiple regression analyses were performed using the ANOVA general linear model. Factors and covariates were chosen with respect to results of simple regression analyses and/or clinical assumptions. Backward logistic multivariate regression analyses were used to estimate the odds ratio for radiological progression at 2 years. Radiological progression was defined as present only if the difference in Larsen score at baseline and 2 years was greater than the median value. The degree of explanation of variations in the dependent variable given by the independent variables was expressed as Nagelkerke R^2 . All P-values are two-sided, and P-values equal to or less than 0.05 were considered statistically significant. All calculations, except analysis over time, were performed using the SPSS for Windows (version 11.5; Chicago, IL, USA).

Results

Among the individuals identified in the early RA cohort as donors of blood to the Medical Biobank before onset of any symptoms of joint disease (median 3.0 years [IQR 1.1-5.3]), anti-CCP antibodies were found in 32.3 % of the pre-patient samples ($n=93$). The corresponding figures for IgM-, IgA-, and IgG-RF were 20.0 %, 36.9 % and 16.9 %, respectively. When the patients were diagnosed as early RA (baseline) ($n=138$; median time after onset of symptoms 7.0 months [IQR 5.0-9.0]) the prevalence of all antibodies had increased with IgM-RF being the most prevalent, at 85.7 %. The corresponding figures for anti-CCP antibodies, IgA-RF and IgG-RF were 74.8%, 78.6% and 46.8%, respectively. The prevalence of SE allele was 54.8 % (51/93) in the pre-patient group and in the early RA group (containing 45 additional individuals, with no pre-patient samples) 58.7 % (81/138). There was a significant association between carriage of the SE allele and a positive test for anti-CCP antibodies both in the pre-patient group ($\chi^2 = 4.1$, $P<0.05$) and in the early RA group ($\chi^2 = 6.0$, $P<0.05$). SE allele carriage was also significantly associated with IgM-RF in the early RA group ($\chi^2 = 4.0$, $P<0.05$), but not in the pre-patient group. No significant associations were found between SE and IgG- or IgA-RF (data not shown).

Relationship between clinical data and anti-CCP antibodies and RFs in pre-patients

The Larsen score at baseline was significantly higher ($P<0.05$) in patients with anti-CCP antibodies predating symptoms than in those without (Table 1). Additionally, 2 years after diagnosis a significantly higher Larsen score was found in patients sero-positive for anti-CCP antibodies before disease onset. The Larsen score increased significantly from baseline to 2 years both in patients positive and negative for predating anti-CCP antibodies (Table 1). Patients positive for both predating anti-CCP antibodies and SE ($n = 15$) had a slightly greater radiological progression (see Statistics for definition) from baseline to 2 years, and higher Larsen score at baseline and at 2 years than patients without SE and without pre-dating anti-CCP antibodies ($n = 26$), although the difference was not statistically significant (data not shown).

Table 1. Larsen score (mean \pm SEM) at baseline and at 2 years in patients with early RA and who were positive or negative for anti-CCP antibodies, IgG-RF, IgA-RF or IgM-RF before symptoms of joint disease.

	Pre-patient antibodies							
	Anti-CCP-abs		IgG-RF		IgA-RF		IgM-RF	
	pos	neg	pos	neg	pos	neg	pos	neg
Baseline	8 \pm 1.5* (n=25)	5 \pm 0.7 (n=58)	6 \pm 1.2 ^{ns} (n=10)	4 \pm 0.7 (n=52)	5 \pm 1.6 ^{ns} (n=22)	4 \pm 0.8 (n=40)	7 \pm 1.7 ^{ns} (n=13)	4 \pm 0.7 (n=49)
2 years	14 \pm 2.3* (n=19)	9 \pm 1.2 (n=49)	10 \pm 2.3 ^{ns} (n=10)	10 \pm 1.3 (n=52)	12 \pm 2.0 ^{ns} (n=22)	9 \pm 1.4 (n=40)	14 \pm 3.0 ^{ns} (n=13)	9 \pm 1.2 (n=49)
P	<0.001	<0.001	<0.05	<0.001	<0.001	<0.001	<0.001	<0.01

* = P<0.05 (positives compared with negatives)

ns = not significant (positives compared with negatives)

P = significance of the difference between baseline values compared with scores at 2 years

There was no significant difference in the Larsen score at baseline or at 2 years in RF positive individuals, when compared with those without predated RFs of any isotype (Table 1). Nor was there any relationship between either predated anti-CCP antibodies or RF isotypes and measures of inflammation such as DAS 28, ESR, CRP, tender or swollen joint count at baseline or at 2 years (data not shown).

Relationship between anti-CCP antibodies and RFs at disease onset, and clinical data

Patients positive for anti-CCP antibodies, IgG- and IgA-RF at baseline had a significantly worse Larsen score at 2 years than patients without these antibodies (Table 2). At baseline the Larsen score was significantly higher in patients positive for IgG-RF compared with those negative for IgG-RF, but no differences were detected between patients positive or negative for anti-CCP antibodies, IgA-RF or IgM-RF (data not shown).

Table 2. Larsen score at 2 years (mean \pm SEM) for the whole early RA cohort stratified on different antibodies at baseline.

Antibody	pos	neg	P
Anti-CCP	11.2 \pm 0.9 (n = 83)	7.5 \pm 1.7 (n = 28)	<0.05
IgG-RF	13.4 \pm 1.2 (n = 54)	7.6 \pm 0.9 (n = 58)	<0.0001
IgA-RF	11.2 \pm 1.0 (n = 90)	6.2 \pm 1.0 (n = 22)	<0.001
IgM-RF	10.8 \pm 0.9 (n = 98)	7.2 \pm 1.6 (n = 14)	ns

ns = not significant

In multiple regression analyses, the baseline values of swollen joint count, Larsen score, and anti-CCP antibodies/IgA-RF/IgG-RF/IgM-RF significantly predicted a greater Larsen score at 2 years (Table 3).

Table 3. Result of four different multiple regression analyses with radiological outcome at 24 months as dependent variable, and as independent variables baseline values of Larsen score, swollen joint count and one of each: IgA-RF, IgG-RF, IgM-RF or anti-CCP antibodies, respectively in patients with early RA.

Variable	B	P	B	P	B	P	B	P
Larsen score	0.97	<0.0001	0.95	<0.0001	0.99	<0.0001	0.97	<0.0001
Swollen joints	0.28	<0.01	0.20	<0.05	0.30	<0.01	0.31	<0.01
IgA-RF	4.0	<0.01	-	-	-	-	-	-
IgG-RF	-	-	2.8	<0.05	-	-	-	-
IgM-RF	-	-	-	-	4.2	<0.05	-	-
Anti-CCP Abs	-	-	-	-	-	-	2.8	<0.05
R-squared	50.9%		50%		50%		49.4%	
R-squared adjusted	49.5%		48.6%		48.6%		48.0%	

Anti-CCP antibodies and RFs were not included in the same model because they were significantly associated ($\chi^2 = 38.0$, $P < 0.0001$ for anti-CCP and IgA-RF; $\chi^2 = 4.4$, $P < 0.05$ for anti-CCP and IgG-RF; and $\chi^2 = 22.9$, $P < 0.0001$ for anti-CCP and IgM-RF). In a backward stepwise logistic regression analyses to identify predictors for radiological progression at 2 years baseline values for anti-CCP antibodies/IgA-RF/IgG-RF/IgM-RF (yes/no), ESR, swollen joint count, Larsen score, SE (yes/no) and therapeutic response at 6 months (yes/no) were included. Anti-CCP antibodies and swollen joint count at baseline and therapeutic response at 6 months significantly predicted radiological progression at 2 years explaining about 21% of the variation (Nagelkerke R^2) and allowing correct classification in 73% of cases (Table 4). In the model with IgA-RF, ESR at baseline and therapeutic response at 6 months significantly predicted radiological progression at 2 years (Table 4). Nagelkerke R^2 was 24% and the accuracy 67%. In the model with IgG-RF, therapeutic response besides IgG-RF, significantly predicted radiological progression, however with lower Nagelkerke R^2 (14%) and accuracy (64%; data not shown). No significant prediction of radiological progression was found when IgM-RF was in the model.

Table 4. Predictors of radiological progression at 2 years in patients with early RA. Variables remaining significant after backward stepwise logistic regression analyses including baseline values of anti-CCP antibodies/IgA-RF (yes/no), swollen joint count, ESR, Larsen score, SE (yes/no) and therapeutic response at 6 months (yes/no).

Variables	Model 1 ¹		Model 2 ²	
	OR (95% CI)	P	OR (95% CI)	P
Anti-CCP abs	5.4 (1.7-17.0)	<0.01		
Swollen joints	1.1 (1.0-1.2)	<0.05		
Therapeutic Response ³	0.35 (0.14-0.85)	<0.05	0.41 (0.17-0.97)	<0.05
IgA-RF			9.8 (2.1-45.5)	<0.01
ESR			1.02 (1.0-1.0)	= 0.05

¹ The model included anti-CCP antibodies(yes/no), but not IgA-RF

² The model included IgA-RF (yes/no), but not anti-CCP antibodies

³ EULAR response criteria, no v good/moderate response.

OR = odds ratio; CI = confidence interval

Patients with both SE allele and anti-CCP antibodies at baseline (n = 55) had a significantly (P<0.01) higher Larsen score (mean \pm SEM) at 2 years (12 \pm 1.1) than patients negative for both factors (n = 17; 6 \pm 1.3). The radiological progression from baseline was also significantly (P<0.001) higher in patients with anti-CCP antibodies and SE (6.0 \pm 0.79) than in patients negative for both factors (2.0 \pm 0.42). The Larsen score at baseline did not, however, differ significantly between positives for baseline anti-CCP antibodies and SE (6 \pm 0.65) and negatives for both factors (4 \pm 1.1).

The titre of anti-CCP antibodies decreased significantly between baseline and 2 years in those patients who had medium or good response to therapy at 6 months (mean 59 to 49 units/mL; P<0.01; n = 57) (Figure 1), at 12 months (mean 60 to 53 units/mL; P< 0.05; n = 65) and at 2 years (mean 62 to 54 units/mL; P<0.01; n = 71), respectively. Patients with radiological progression had significantly (P<0.05) higher titre (mean \pm SEM) of anti-CCP antibodies at baseline, (73 \pm 7.5 units/mL; Diastat ELISA) than patients without progression (51 \pm 6.4 units/mL).

In the early RA patients there was a significant reduction of DAS28 over time (P<0.0001), however the reduction was significantly less in patients positive for anti-CCP antibodies at baseline (P=0.05; Figure 2). Patients positive for IgM-RF at baseline also had significantly less reduction of DAS28 over time compared with IgM-RF negative patients (P<0.01; data not shown). The other RFs did not have any impact on DAS28 over time (data not shown).

Discussion

This is the first study in which the significance of the presence of anti-CCP antibodies before disease onset on the radiological outcome in RA has been investigated. Individuals positive for anti-CCP antibodies before the onset of symptoms of joint disease had significantly more joint erosions at the time of diagnosis of RA than individuals negative for these antibodies. Furthermore, 2 years after diagnosis the radiological outcome was worse for those sero-

positive for anti-CCP antibodies prior to the diagnosis of RA. The anti-CCP antibodies predated the onset of signs and symptoms of joint disease by up to several years. These observations suggest a sub-clinical process related to the presence of anti-CCP antibodies, whereby the formation of erosions has already started without a clinically evident inflammatory process. At their first visit to the early RA clinic, patients positive for anti-CCP antibodies as pre-patients and/or at baseline, did not have any higher level of inflammatory activity compared with antibody negative patients. However, the measurements of the inflammatory activity (*e.g.*, ESR, CRP, joint count) could be considered as relatively rough. In contrast to the present study, Kastbom *et al* [26] were able to demonstrate significantly higher baseline ESR and CRP in anti-CCP antibody positive patients compared with negatives when they presented at the early arthritis clinic.

In the present study, RFs of all isotypes were also present in pre-patient samples, but no significant differences in the Larsen scores at baseline or at 2 years were detected between individuals with pre-dating RFs of any isotype and those without. One interpretation of this finding is that presence of anti-CCP antibodies in pre-patient samples predicts a more aggressive form of RA. However, for diagnostic sensitivity the cut-off level for positive RFs was at the 95th percentile. To analyze the severity of the disease perhaps higher cut-off levels for RFs with a reduced sensitivity would be more appropriate. This should be further investigated in another study. Another point to take into consideration is the rather low number of individuals in the analyses of RFs decreases the possibility to obtain statistically significant differences.

The results presented here that presence of anti-CCP antibodies at disease onset is associated with radiological progression confirm earlier reports [11, 28]. Their finding that radiological progression was also predicted by initial radiological joint damage was not, however, confirmed in our study. We found that radiological damage at 2 years, but not radiological progression was predicted by baseline radiological damage. One interpretation of this discrepancy might be that our patients had a better response to pharmacological therapy, which slowed the joint damaging process. Using multiple regression analyses in the present study, showed that baseline values of swollen joint count, Larsen score and anti-CCP antibodies or RFs of each isotype independently predicted the higher Larsen score at 2 years and accounted for approximately half of the variation. There was a correlation between anti-CCP antibodies and RFs in baseline samples, which explains the similar results. However, the results of logistic regression analyses favour anti-CCP antibodies and IgA-RF as the most important predictors, which is consistent with the results of Lindqvist *et al* [28]. In several previous studies an association between initial inflammation, measured as ESR, CRP or number of swollen joints, and radiological outcome or progression has been reported [5, 10, 11, 27, 28]. In multiple regression analyses [10, 28], however, anti-CCP antibodies and RFs (IgM-RF and IgA-RF) have been better predictors for radiological outcome and progression than measures of inflammation, which is in agreement with our results. Patients with anti-CCP antibodies or IgM-RF at baseline had a significantly smaller reduction in the DAS28 during the follow-up period compared with antibody negative patients, indicating a more persistent disease activity in patients with these antibodies. These results are similar to those reported by others [5, 11, 26]. The aim of this study was to investigate the significance of anti-CCP antibodies and RFs for disease activity and severity. Since anti-CCP antibodies and RFs are strongly correlated comparisons between them as predictors are difficult to perform, however, the results of this study favour the interpretation that IgA-RF in addition to anti-CCP antibodies could be related to radiological progression whilst both IgM-

RF and anti-CCP antibodies could be related to inflammatory activity as measured by DAS28, and to SE allele.

High titres of anti-CCP antibodies at baseline are related to greater radiological progression at 2 years. The titres declined during the study in those patients with therapeutic response. This is in agreement with the results of other studies showing significant decrease in anti-CCP antibody titres in patients with early RA who had a decrease in disease activity [5, 6, 26]. In our study the therapeutic response predicted less radiological progression after 2 years, in contrast with the presence of anti-CCP antibodies or IgA-RF at baseline, which predicted increased radiological progression. This suggests that repeated measurements of the anti-CCP antibody titre could be of clinical use for assessing disease activity and severity. Contrary to our findings Mikuls *et al* [29] reported that disease duration but not treatment response to conventional DMARDs was associated with declines in the anti-CCP-antibody levels. Unfortunately corresponding data for the course of the titres of RFs is missing in the present study.

There was a significant association between carriage of SE allele and a positive test for anti-CCP antibodies in both the pre-patient samples and in samples collected at baseline, which is consistent with our earlier results [14] and those of others [11, 17]. Hill *et al.* [30] demonstrated that conversion of arginine to citrulline in HLA-DRB1*0401 transgenic mice significantly increased peptide-MHC affinity and led to activation of CD4+ T-cells. This finding may explain B-cell activation and the production of anti-CCP antibodies found preferentially in individuals carrying SE allele. Patients with both the SE allele and anti-CCP antibodies at baseline showed a more severe radiological outcome than patients lacking both. This concurs with the study by van Gaalen *et al.* [18], who reported an association between HLA class II RA susceptibility alleles and the production of anti-CCP antibodies as well as an increased rate of joint destruction in patients with both SE allele and anti-CCP antibodies. In an earlier study [16], we found that the combination of SE allele and anti-CCP antibodies in individuals without symptoms of joint disease was associated with a very high relative risk for future developing of RA. The results of the present study suggest that the combination of SE allele and anti-CCP antibodies also is associated with disease severity.

Conclusions

In conclusion, the presence of anti-CCP antibodies before and at disease onset is associated with a more aggressive disease as measured by a significantly higher Larsen score. Anti-CCP antibodies together with SE allele carriage are markers for severe disease outcome. The titres of anti-CCP antibodies decreased significantly in patients with therapeutic response, suggesting that anti-CCP-antibodies could be a useful marker of disease progression. Anti-CCP antibodies or any of the RFs and swollen joint count and Larsen score at baseline significantly predicted radiological outcome at 2 years. Radiological progression was significantly predicted by both anti-CCP antibodies and by IgA-RF, respectively in combination with clinical data.

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Figure legends.

Figure 1

The titre of anti-CCP antibodies (units/mL; Diastat ELISA; median values, 25:th and 75:th percentile and range) at baseline (a-CCP 0) and at 2 years (a-CCP 24), stratified for different groups of response to treatment at 6 months (EULAR response criteria). No response: n = 43; median or good response: n = 57. ** P<0.01.

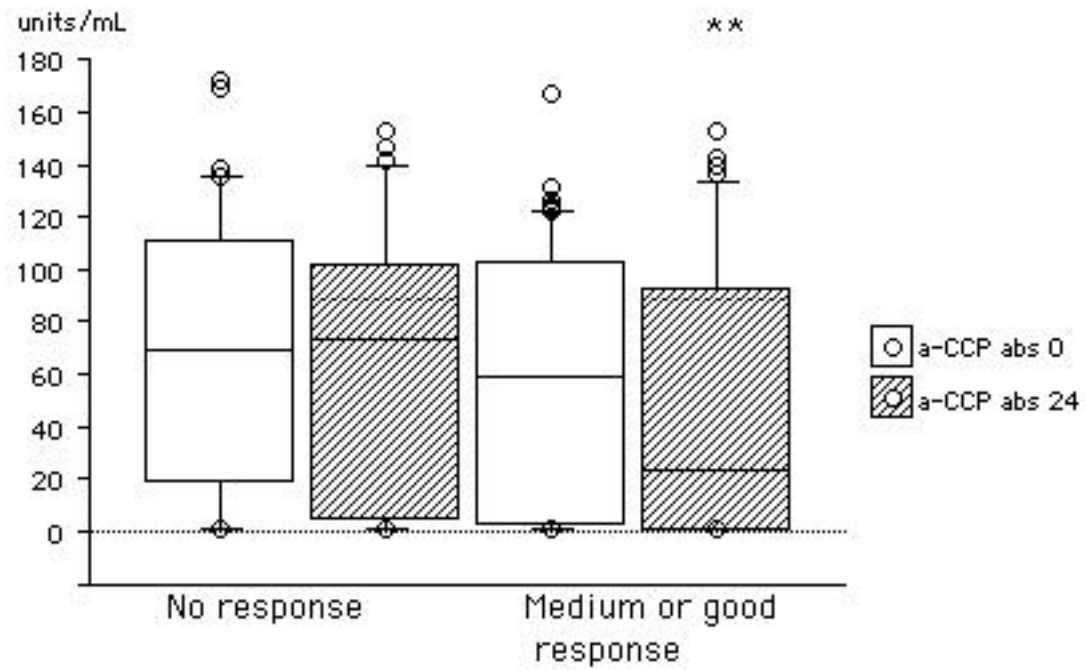
Figure 2

Disease activity expressed as DAS28 (mean \pm SEM) at different time points after diagnosis of early RA in patients positive (a-CCP pos; n = 95) or negative (a-CCP neg; n = 32) for anti-CCP antibodies at baseline. * P<0.05; *** P<0.001

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