Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: Relation with disease aggressiveness

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Abstract Objectives

To analyse the value of the anti-cyclic citrullinated peptide antibody (anti-CCP) in patients with rheumatoid arthritis (RA) as a prognostic factor, as well as its relationship with disease activity.

Methods

A cross-sectional study was made on 89 patients with RA. The following values were assessed: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-CCP, Disease Activity Score 28 (DAS 28), Modified Health Assessment Questionnaire score (M-HAQ) and simplified radiologic score of Sharp/Van der Heijde (SENS: simple erosion narrowing score).

Results

Sixty-four percent of the patients were anti-CCP positive, from which 36.8% were negative for RF. Among negative RF patients, 48.3% had anti-CCP antibody. The average value of DAS 28 in anti-CCP positive patients was 4.31 (SD 1.27) compared to 3.30 (SD 1.55) for anti-CCP negative ($p \le 0.001$). There was a significant correlation between anti-CCP levels and CRP value ($p \le 0.011$). 78.9% of anti-CCP positive patients presented erosions as opposed to a 53.1% of those with negative anti-CCP ($p \le 0.011$), OR 3.3 (95% CI: 1.3-8.5). SENS in anti-CCP positive patients was significantly greater than in anti-CCP negative patients, 22.6 (SD 20.7) versus 13.88 (SD 19.24) ($p \le 0.054$). Patients with high levels of anti-CCP (> 200 U/ml) had higher SENS (p < 0.05). There was no correlation between M-HAQ and anti-CCP.

Conclusions

Prevalence of anti-CCP was higher among patients with higher activity. Patients with higher levels of anti-CCP antibody had more aggressive disease, with greater activity (elevated values in DAS 28 and CRP) and more severe radiological damage (more erosions and higher radiological damage, SENS).

Key words

Rheumatoid arthritis, anti-CCP antibody, rheumatoid factor, prognostic factor.

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Introduction

Rheumatoid arthritis (RA) patients are characterised by presenting some circulating autoantibodies in their serum. In clinical practice the most common diagnostic test is IgM rheumatoid factor (RF), which is an antibody directed against the constant region of IgG. It has an acceptable sensitivity of 60%-70%, but it is not disease specific (80%-90% specificity) (1).

Citrullinated proteins have recently been described as specific antigens of rheumatoid antibodies (2). Citrullination is a protein degradation mechanism in which a peptidylarginine is deimided to peptidylcitrulline by peptidylarginine deiminase enzymes. It happens in both the healthy and the arthritic population. Citrullination of synovial antigens, especially fibrin, is an active process during synovial inflammation that probably allows the induction of anti-cyclic citrullinated peptide (anti-CCP) antibody in RA patients, through an antigen-conducted activation of B cells (3, 4). There has been long speculation about the mechanism by which citrullinated epitopes break the tolerance. Possibly, multiple genetic and environmental influences are needed to achieve a rheumatoid phenotype (5). In a recent study, HLA of class II RA susceptibility alleles were associated to anti-CCP production (1). Moreover, a genetic factor could increase the ability to produce citrullinated proteins (6). Other RA related autoantibodies, like the antiperinuclear factor, antikeratin and anti-Sa, are known to recognise citrullinated epitopes at the molecular level (7).

It has been shown that anti-CCP antibody is highly specific for RA (98%) with similar sensitivity to RF (68%-80%) (7-10). Using stored serum samples from RA patients, anti-CCP antibody was detected 9 years before the arthritis onset (11, 12). This high specificity and its early presence in the disease, including the preclinical disease phase, make anti-CCP antibodies a new diagnostic marker for early RA (8, 13-15) and suggests that they play an important role in the RA pathogenesis (16).

Nowadays an early diagnosis and treat-

ment of RA is emphasised, before structural articular damage has occurred (17-20). Many reports have analysed the predictive factors of joint damage in RA (13, 21). This autoantibody could be of great value, if it was established as a predictor of worse evolution, in order to select patients who need early aggressive treatment. There have been contradictory reports until now.

In this study, we analyse if the presence and level of anti-CCP antibody is associated with higher activity or more severe joint damage in RA patients.

Patients and methods

Patients

We selected a sample of 89 patients fulfilling the 1997 ACR classification criteria for rheumatoid arthritis. The selection was made consecutively, taking into account the Disease Activity Score of 28 joints (DAS 28) in order to include patients with all levels of disease activity. We used the EULAR activity criteria, based on the DAS 28 (clinical remission values below 2.6, low activity between 2.6 to 3.2, moderate activity from 3.2 to 5.1 and high activity values over 5.1) (22). As we wanted to explore the relationship between anti-CCP antibodies and DAS-28, we needed to have enough people in each DAS-28 group. Remission and high activity patients were less prevalent than low or moderate activity level. Then, we selected patients in a consecutive way until having enough patients in every group. At the same time, functional evaluation was performed using the Modified Health Assessment Questionnaire score (M-HAQ). Serum samples for ESR, CRP, RF and anti-CCP antibody were obtained. Joint damage was measured with the Sharp/Van der Heijde simplified score (simple erosion narrowing score, SENS) (23). A new radiographic examination of hands and feet was done if the last one was older than 6 months. Age, sex and disease duration were demographic variables also analysed. All patients had been treated with disease-modifying anti-rheumatic drugs in function of disease activity, as is usual in clinical practice

Anti-CCP antibody and rheumatoid factor determination

Anti-CCP antibody was measured using a commercially available secondgeneration enzyme-linked immunosorbent assay (INNOVA[®]) which uses a purified synthetic citrullinated peptide. It was considered to be positive at a cut-off value of 20 u/ml. Anti-CCP antibody was not quantified over 200 U/ml, so we took a semi quantitative approach using the value 200 for all values \geq 200. Rheumatoid factor was measured using a standard nephelometry.

Statistical analysis

Firstly, an analysis was carried out between groups with positive and negative anti-CCP antibody. Secondly, the anti-CCP antibody was analysed using three categories: below 20 as negative, from 20 to 150 as low titer, and over 150 as high titer. Lastly, we analyse the anti-CCP antibody in a multivariate model.

The Student's t-test, Mann Whitney U test when necessary and chi square were used to analyse the significance of the different variables between anti-CCP positive and anti-CCP-negative patients. Variance analysis was used to compare mean DAS 28 among patients with negative, low or high anti-CCP antibody level. Comparisons of mean SENS among groups with negative, low or high anti-CCP antibody, and the comparisons of mean anti-CCP in patients with different degrees of activity, were done using the Kruskal-Wallis test. Odds ratio and 95% confidence interval (95% CI) were used to compare the risk of erosion in patients with anti-CCP antibody. Correlation between anti-CCP antibody and RF or CRP was analysed using Pearson's correlation coefficient.

A multiple regression analysis using the anti-CCP antibody titer as a predictive variable and SENS, DAS-28 and M-HAQ as dependent variables was developed. Age, sex, rheumatoid factor and disease duration were included in the model, as possible confounding or modifier effect variables to adjust. All the analyses were performed using the SPSS 11.0 statistical software.

Results

Eighty-nine RA patients were included. There were thirteen patients with inactive disease, 17 with low activity, 40 with moderate activity and 18 with a high level of activity. One patient had no DAS 28 determination and was included just for joint damage analysis. Basal demographic characteristics and the difference between patients with and without anti-CCP antibody are shown in Table I.

Relationship between anti-CCP antibody and disease activity

Patients with anti-CCP antibody had a higher DAS 28, 4.3 (SD 1.2) versus 3.3 (SD 1.5) (Table I). The difference 1.01 (95 % CI 0.3 - 1.65) was significant p = 0.001.

Analysing DAS 28 among groups with

negative, low or high anti-CCP antibody level, a significant linear relationship was observed (Table II) p = 0.003. Patients in disease remission had lower anti-CCP antibody titer than those with low, moderate or high disease activity (Table III). There were a linear significant relationship p = 0.012. Multivariate regression analysis, after adjusting for disease duration and for rheumatoid factor, shows a positive relationship between the titer of anti-CCP antibody and the value of DAS 28 (R = 0.349, $R^2 = 0.122$, adjusted $R^2 = 0.091$, p = 0.012). Sex, age or RF did not modify significantly the relationship. There was no relationship between disease duration and anti-CCP titer or DAS 28. There was a significant correlation between the level of disease activity (remission, low, moderate or high) and the anti-CCP level (negative, low or high) r = 0.324 p = 0.02.

The prevalence of anti-CCP antibody was higher in patients with higher level of disease activity. It was not observed with the rheumatoid factor (Table IV).

Relationship between anti-CCP and M-HAQ

Mean M-HAQ in patients with anti-CCP antibody was 0.57 (SD 0.46) versus 0.43 (SD 0.45) in patients without anti-CCP. The difference was not significant. Nonetheless, a weak relationship was observed between anti-CCP titer and M-HAQ, r = 0.194 p = 0.034. Anti-CCP titer was not a predictive factor of M-HAQ. The only predictive

Table I. Demographic and disease-related characteristics in the whole group and in association with the presence of anti-CCP antibodies.

| | Total population (N = 89) | Anti-CCP positive $(N = 57)$ | Anti-CCP negative $(N = 32)$ | Р |
|------------------------------------|---------------------------|------------------------------|------------------------------|--------|
| Age, mean (SD), years | 61 (13) | 61.9 (12.7) | 58.3 (14.3) | NS |
| Female, % | 71.9 | 75.4 | 65.6 | NS |
| Disease duration, mean (SD), years | 7.6 (8.8) | 7.7 (9.1) | 7.1 (8.3) | NS |
| ESR, mean (SD),mm/hr | 28 (21) | 30 (19) | 24 (23) | NS |
| CRP, mean (SD), mgrs/L | 16.1 (19.7) | 18.92 (21.89) | 11.33 (13.69) | 0.05 |
| Rheumatoid factor, mean (SD), U/L | 132 (244) | 192.5 (305.5) | 53 (98.3) | 0.002 |
| Rheumatoid factor positive, % | 48.3 | 83.7 | 16.30 | 0.0001 |
| Anti-CCP antibody, mean (SD), U/ml | 93 (83) | | | |
| Anti-CCP antibody positive, % | 64 | | | |
| DAS 28, mean (SD) | 3.96 (1.46) | 4.31 (1.27) | 3.30 (1.55) | 0.001 |
| M-HAQ, mean (SD) | 0.53 (0.46) | 0.57 (0.46) | 0.43 (0.45) | NS |
| SENS, mean (SD) | 19.5 (20.5) | 22.6 (20.7) | 13.9 (19.24) | 0.05 |
| Erosions, % | 69.7 | 78.9 | 53.1 | 0.01 |

| Anti-CCP | DAS-28 * | SENS* | M-HAQ [#] | CRP* |
|----------|-------------|-------------|--------------------|-------------|
| < 20 | 3.3 (1.55) | 13.8 (19.2) | 0.43 (0.45) | 11.3 (13.7) |
| 20-150 | 4.06 (1.18) | 18.8 (16.6) | 0.49 (0.35) | 14.1 (16.8) |
| > 150 | 4.5 (1.33) | 25.7 (23.4) | 0.65 (0.53) | 22.8 (24.8) |
| All | 3.96 (1.46) | 19.5 (20.5) | 0.52 (0.46) | 16.1 (19.7) |

Table II. DAS-28, SENS and CRP in relation to anti-CCP level. Mean (SD).

Differences in DAS-28, SENS and CRP in patients with negative (< 20), low (20-150) or high (> 150) anti-CCP antibodies, showed a significant linear relationship.

* Linear association p < 0.05.

ns.

 Table III. Anti CCP antibodies titres in patients with different activity disease level.

| DAS-28 | Anti-CCP u/ml Mean (SD)* | | |
|-----------|--------------------------|--|--|
| Remission | 27.8 (56.5) | | |
| Low | 90.6 (82.2) | | |
| Moderate | 99.8 (80.9) | | |
| High | 121.6 (83.3) | | |

Table IV. Prevalence of anti-CCP and RFwithin disease activity groups.

| DAS-28 | Anti-CCP | Rheumatoid Factor |
|-----------|----------|-------------------|
| Remission | 23.1 | 30.8 |
| Low | 58.8 | 58.8 |
| Moderate | 72.5 | 52.2 |
| High | 77.8 | 38.9 |

factor of functional ability in the model was disease duration p = 0.02.

Relationship between the anti-CCP antibody and joint damage

Erosions were observed in 69.4 % of patients. Patients with anti-CCP antibody had more frequent erosions, 78.9% versus 53.1% in patients without anti-CCP antibody (Table I) p = 0.011. The risk of erosions was higher in patients with anti-CCP antibody, OR 3.3 (95% CI 1.29-8.49). Among patients with positive RF, 79.1% had erosions versus 60,9% in negative RF patients. The difference was not significant. There was no more risk of erosions among positive RF patients (OR 2.4, 95 % CI 0.9-6.2).

Mean SENS in patients with anti-CCP antibody was higher than in anti-CCP-negative RA patients, the difference was 8.72 (95% IC: 0-17.4) p = 0.05 (Table I). The radiological damage (SENS) among groups with negative,

low or high anti-CCP antibody level showed a significant linear relationship (Table II) p = 0.03. The multivariate regression analysis, after adjusting for disease duration, showed a positive relationship between anti-CCP antibody titer and SENS (R = 0.522, $R^2 =$ 0.272, adjusted $R^2 = 0.246$, p < 0.0001). RF, age and sex, included in the model, did not modify the results. There was no relationship between disease duration and anti-CCP titer.

Figure 1 shows SENS in both groups, with and without anti-CCP over time.

Relationship between anti-CCP and

inflammatory acute phase reactants A relationship was found between anti-CCP titer and CRP values r = 0.269 p = 0.01, but not with ESR. Patients with anti-CCP antibody had higher levels of CRP (Table I). The difference 7.59 mg/L (95% CI 0.30-15.15) was significant p < 0.05. The CRP values showed a significant linear difference among groups with negative, low or high anti-CCP antibody (Table II) p = 0.05.

Relationship between anti-CCP and Rheumatoid Factor

Sixty four percent of patients had anti-CCP-positive antibody and 48.3% had positive RF. Anti-CCP antibody was present in 89.7% of patients with positive RF and in 45.7% of those without RF. Among patients with anti-CCP antibody, 36.8% had negative RF. Both tests were positive in 40.4% of patients and negative in 28.1%.

There was a significant correlation between the presence of RF and positive anti-CCP antibody r = 0.396 p < 0.0001. The mean anti-CCP antibody in patients with positive RF was higher than in negative RF patients: 123.3 U/ml (SD 78.4) versus 64.7 U/ml (SD 77.3), difference 58.65 (95% CI 25.8-91.5) p = 0.001.

Discussion

In this study we have found a significant association between the presence and the level of anti-CCP antibody and greater RA activity, with higher values of DAS 28 and CRP. The greater prevalence of anti-CCP antibody in patients with higher DAS 28 supports the hypothesis that this autoantibody could be associated with a poor prognosis. It was not observed with the RF, despite the well-documented association of RF with erosive disease.

A recent study examined the association of treatment response and disease duration with changes in RF and anti-CCP antibody, among patients with RA (24). Whereas treatment response was determinant for a decrease in RF levels, shorter disease duration predicted greater declines in anti-CCP antibody levels with treatment in RA. Another report analysed changes in RF and anti-CCP levels with Infliximab and Methotrexate treatment in RA (25). There was no significant effect on anti-CCP levels, but there were changes in RF with disease activity. In these longitudinal studies, anti-CCP levels do not experience significant changes with disease activity. In our cross-sectional analysis, we observed its greater prevalence and level in patients with higher DAS 28 and CRP values that means with more active disease. We have not observed a correlation between anti-CCP level and disease duration. This data suggests that patients with higher baseline anti-CCP levels have a more aggressive disease.

Sixty four percent of patients had anti-CCP antibody, a similar sensitivity to previous studies (10). RF was positive in only 48.3% of patients. The low sensitivity of RF in this series could be related to the greater fluctuation of RF during the course of the disease probably in response to treatment. We emphasise the diagnostic value of positive anti-CCP antibody. In our study, among patients with negative RF, 45.7% had anti-CCP positive antibody and 36.8% of anti-CCP positive

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patients were RF negative, similar to previous reports (26).

A significant association between the presence and level of anti-CCP and joint damage were found, with a higher SENS and more risk of erosions in anti-CCP positive patients (OR 3.3, 95% CI 1.29-8.49). It could be expected that patients with positive RF had more erosions, but we did not find a significant increased risk of erosions in these patients. Probably, the explanation for our finding is again the fluctuation of RF during the disease course. Some RA patients became negative for RF over time. In this cross-sectional study, there were patients with negative RF at that moment, who were positive RF disease. In the regression analysis, rheumatoid factor did not modify the association between anti-CCP and SENS. Anti-CCP antibody seems to be more stable during disease course than RF (24, 25). In a recent report, Berglin E. et al. found a significant decrease in anti-CCP antibody titer in a group of early RA patients, with response to therapy. It is probable that in early states of disease they can be modified with treatment (24, 27).

Preliminary studies on this have been contradictory. Comparative studies between anti-CCP antibody and IgM RF concluded that the specificity of anti-CCP was useful to diagnose RA, but IgM RF was a better predictor of disease severity (24, 28). Another study concluded that positive anti-CCP antibody has a small additional predictive value above the IgM RF (29). Later studies, conversely, found that anti-CCP antibody were better predictors of disease course than RF over three years (30) independently of the RF subtype (26). It has been published that its presence in early disease was a marker of a more aggressive disease and highly predictive of more severe radiological damage (31, 32). Supporting this, in our study we observed that anti-CCP high level was associated to a more radiologic damage. In other report, more severe disease progression was found in RA patients with both anti-CCP antibody and shared epitope alleles (1). Lindqvist et al. investigated laboratory markers that provide prognostic information on joint damage in RA. Radiographic changes were evaluated in hands and feet at 5 and 10 years after inclusion. After 5 years, ESR, the presence of IgA RF, cartilage oligomeric matrix protein (COMP) and anti-CCP were significantly associated with more severe joint damage. Baseline CRP and anti-CCP antibody predicted radiographic outcome after 10 years (33). Interestingly, in our study we found a correlation between the anti-CCP antibody level and the CRP value but not with those of ESR. This association could be related to the greater presence of anti-CCP with more inflammation. CRP has a rapid response to inflammatory stimulus. Many studies have suggested that CRP levels correlate better with degree of activity than does ERS (34). The reports about correlation of anti-CCP antibodies and inflammatory acute phase reactants are contradictories. It has been found correlation with both ERS and CRP (35), or with any (36) of them.

We did not find a worse functional disability in positive anti-CCP antibody patients compared with negative anti-CCP patients, but there was a weak relationship between the titer of anti-CCP and M-HAQ. Only disease duration was clearly related to the functional ability. Probably, this is due to the fact that the mean M-HAQ in this series was low, with little difference in functional ability among patients. A greater sample would have been necessary to show a difference in M-HAQ, if that exists. It has been published that functional test does not appear to be useful in monitoring disease severity over time (37).

In summary, we can conclude that anti-CCP antibody could be a risk factor for a more aggressive disease. We show that it is significantly associated to a greater disease activity, more frequent erosions and a worse radiological damage score. As this is a cross-sectional study, we can not reach to a causeeffect conclusion. This is the main limitation of this study, but the association is strong enough to support the hypothesis that the anti-CCP antibody positivity is a risk factor of poor prognosis in RA patients.

It is possible that patients who present higher levels of this autoantibody could benefit from an early and more aggressive treatment, to prevent a more severe radiological damage and more active disease. Further studies, especially longitudinal surveys, are needed to know better the prognostic value of anti-CCP antibody.

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References

- 1. VAN GAALEN FA, VAN AKEN J, HUIZINGA TW et al.: Association between HLA class II genes and autoantibody to cyclic citrullinated peptides influences the severity of rheumatoid arthritis. Arthritis Rheum 2004; 20: 2113-21.
- VAN VENROOIJ WJ, PRUIJN GJ: Citrullination: a small change for a protein with great consequences for rheumatoid arthritis. *Arthritis Res* 2000; 2: 249-51.
- 3. LOPEZ-HOYOS M, MARQUINA R, TAMAYO E *et al.*: Defects in the regulation of B cell apoptosis are required for the production of citrullinated peptide autoantibody in mice. *Arthritis Rheum* 2003; 48: 2353-61.
- VOSSERNAAR ER, NIJENHUIS S, HELSEN MM et al.: Citrullination of synovial proteins in murine models of rheumatoid arthritis. Arthritis Rheum 2003; 48: 2489-500.
- ZHOU Z, MENARD HA: Autoantigenic posttranslational modifications of proteins: does it apply to rheumatoid arthritis? *Curr Opin Rheumatol* 2002; 14: 250-3.
- 6. SUZUKI A, YAMADA R, CHANG X *et al.*: Functional haplotypes of PADI4, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat Genet* 2003; 34: 395-402.
- SCHELLEKENS GA, DE JUNG BA, VAN DEN HOOGEN KH, VAN DE PUTTE LB, VAN VEN-ROOIJ WJ: Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibody. J Clin Invest 1998; 101: 273-81.
- SCHELLEKENS GA, VISSER H, DE JONG BA et al.: The diagnostic properties of rheumatoid arthritis antibody recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000; 43: 155-63.
- JANSEN TL, BRUYN GA: Diagnostic value of anticyclic citrullinated peptide antibody in rheumatoid arthritis. *J Rheumatol* 2004; 31: 1012-3.
- 10. VOSSENAAR ER, VAN VENROOIJ WJ: Anti-CCP antibody, a highly specific marker for (early) rheumatoid arthritis. *Clin Appl Immunol Rev* 2004; 4: 259-62.
- RANTAPAA-DAHLQVIST S, DE JONG BA, BERGLIN E *et al.*: Antibody against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 2741-9.
- NIELEN MM, VAN SCHAARDENBURG D, REESINK HW et al.: Specific autoantibody precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004; 50: 380-6.
- VISSER H, LE CESSIE S, VOS K, BREEDVELD FC, HAZES JM: How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum* 2002; 46: 357-65.
- NEWKIRK MM: Rheumatoid factors: what do they tell us?. J Rheumatol 2002; 29: 2034-40.

- 15. VAN GAALEN FA, LINN-RASKER SP, VAN VEN-ROOIJ WJ et al.: Autoantibody to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004; 50: 709-15.
- 16. HILL JA, SOUTHWOOD S, SETTE A, JEU-NIKAR 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 Inmunol 2003; 171: 538-54.
- GOLDBACH-MANSKY R, LEE J, MCCOY A et al.: Rheumatoid arthritis associated autoantibody in patients with synovitis of recent onset. Arthritis Res 2000; 2: 236-43.
- AHO K, PALOUSO T, HELIOVAARA M, KENKT P, ALHA P, VON ESSEN R: Antifilaggrin antibody within "normal" range predict rheumatoid arthritis in a linear fashion. *J Rheumatol* 2000; 27: 2743-6.
- 19. KROOT EJ, DE JONG BA, VAN LEEUWEN MA et al.: The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. *Arthritis Rheum* 2000; 43: 1831-5.
- BUKHARI M, HARRISON B, LUNT M, SCOTT DG, SYMMONS DP, SILMAN AJ: Time to first occurrence of erosions in inflammatory polyarthritis: results from a prospective community-based study. *Arthritis Rheum* 2001; 44: 1248-53.
- 21. BUKHARI M, LUNT M, HARRISON BJ, SCOTT DG, SYMMONS DP, SILMAN AJ: Rheumatoid factor is the major predictor of increasing severity of radiographic erosions in rheumatoid arthritis: results from the Norfolk Arthritis Register Study, a large inception cohort. *Arthritis Rheum* 2002; 46: 906-12.
- 22. VAN GERSTEL AM, PREVOO MLL, VAN'T HOF MA et al.: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996; 39: 34-40.
- 23. VAN DER HEIJDE D, DANKERT T, NIEMAN F, RAU R, BOERS M: Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. *Rheumatology* 1999; 38: 941-47.
- 24. MIKULS TR, O'DELL JR, STONER JA *et al.*: Association of rheumatoid arthritis treatment respose and disease duration with declines in serum levels of IgM rheumatoid factor and anti-cyclic citrullinated peptide antibody. *Arthritis Rheum* 2004; 50: 3776-82.
- 25. BOBBIO-PALLAVICINI F, ALPINI C, CAPO-RALI R, AVALLE S, BUGATTI S, MONTECUC-CO C: Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. Arthritis Res Ther 2004; 6: R264-72.
- VALLBRACHT I, RIEBER J, OPPERMANN M, FORGER F, SIEBERT U, HELMKE K: Diagnostic and clinical value of anti-cyclic citrulli-

nated peptide antibody compared with rheumatoid factor isotypes in rheumatoid arthritis. *Ann Rheum Dis* 2004; 63: 1079-84.

- 27. BERGLIN E, JOHANSSON T, SUNDIN U et al.: 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. Ann Rheum Dis. Published Online First: 21 September 2005; doi: 10.1136/ard.2005.041376.
- BAS S, PERNEGER TV, SEITZ M, TIERCY JM, ROUX-LOMBARD P, GUERNE PA: Diagnostic tests for rheumatoid arthritis: comparison of anti-cyclic citrullinated peptide antibody, anti-keratin antibody and IgM rheumatoid factors. *Rheumatology* 2002; 41: 809-14.
- 29. JANSEN LM, VAN SCHAARDENBURG D, VAN DER HORST-BRUINSMA I, VAN DER STADT RJ, DE KONING MH, DIJKMANS BA: The predictive value of anti-cyclic citrullinated peptide antibody in early arthritis. *J Rheumatol* 2003; 30: 1691-5.
- 30. KASTBOM A, STRANDBERG G, LINDROOS A, SKOGH T: Anti-CCP antibody test predicts the disease course during 3 years in early rheumatoid arthritis (the Swedish TIRA project). Ann Rheum Dis 2004; 63: 1085-9.
- VENCOVSKY J, MACHACEK S, SEDOVA L et al.: Autoantibody can be prognostic markers of an erosive disease in early rheumatoid arthritis. Ann Rheum Dis 2003; 62: 427-30.
- 32. MEYER O, LABARRE C, DOUGADOS M et al.: Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. Ann Rheum Dis 2003; 62: 120-6.
- LINDQVIST E, EBERHARDT K, BENDTZEN K, HEINEGARD D, SAXNE T: Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005; 64: 196-201.
- 34. LARSEN A: The relation of radiographic changes to serum acute-phase proteins and rheumatoid factor in 200 patients with rheumatoid arthritis. *Scand J Rheumatol* 1988; 17: 123-9.
- 35. AOTSUKA S, OKAWA-TAKATSUJI M, NAGATANI K et al.: A retrospective study of the fluctuation in serum levels of anti-cyclic citrullinated peptide antibody in patients with rheumatoid arthritis. Clin Exp Rheumatol 2005; 23: 475-81.
- 36. GREINER A, PLISCHKE H, KELLNER H, GRU-BER R: Association of anti-cyclic citrullinated peptide antibodies, anti-citrillin antibodies, and IgM and IgA rheumatoid factors with serological parameters of disease activity in rheumatoid arthritis. *Ann N Y Acad Sci* 2005; 1050: 295-03.
- 37. HUSTED JA, GLADMAN D, COOK RJ, FAREWEL VT: Responsiveness of health status instruments to changes in articular status and perceived health in patients with psoriatic arthritis. J Rheumatol 1998; 25: 2146-55