Rheumatol Int (2012) 32:3799–3805
DOI 10.1007/s00296-011-2282-3

ORIGINAL ARTICLE

Serum anti-cyclic citrullinated peptide antibodies may predict disease activity in rheumatoid arthritis

Kamal Esalatmanesh · Raika Jamali · Arsia Jamali · Bardia Jamali · Mohammadreza Nikbakht

Received: 29 July 2011 / Accepted: 10 December 2011 / Published online: 21 December 2011

Abstract To define the relationship between serum anti-cyclic citrullinated peptide antibodies (anti-CCP) and disease activity, and to construct a new disease activity index by using anti-CCP in rheumatoid arthritis (RA). One hundred and five RA patients were included. Disease activity based on DAS28-ESR and serum anti-CCP was measured. There was correlation between serum anti-CCP and DAS28-ESR. ($R^2 = 0.71$, P value < 0.01). New disease activity index was developed by replacing anti-CCP with ESR in DAS28-ESR. There was correlation between new model and DAS28-ESR. ($R^2 = 0.91$, P value < 0.01) The new composite index best cut-off values corresponding to DAS28-ESR values of 2.6, 3.2, and 5.1 were 3.21, 3.38, and 4.74, respectively. There was agreement between new model and DAS28-ESR for determination of patients in different disease activity categories. (Kappa = 0.71, P value < 0.01). The new disease activity index that applies serum anti-CCP may predict disease activity in RA.

K. Esalatmanesh
Internal Medicine Ward, Division of Rheumatology,
Shahid Beheshti Hospital,
Kashan University of Medical Sciences, Kashan, Iran

R. Jamali (✉)
Anatomical Sciences Research Center, Students' Scientific Research Center, Internal Medicine Ward,
Kashan University of Medical Sciences, Kashan, Iran
e-mail: raika.jamali@gmail.com

A. Jamali · B. Jamali
Students' Scientific Research Center,
Tehran University of Medical Sciences, Tehran, Iran

M. Nikbakht
Anatomical Sciences Research Center,
Kashan University of Medical Sciences, Kashan, Iran

Keywords Rheumatoid arthritis · Disease activity · Anti-cyclic citrullinated peptide · Biomarkers · Antibodies

Introduction

Rheumatoid arthritis (RA) is a common cause of chronic inflammatory arthritis in Iran [1]. Early proper management according to disease activity could prevent irreversible damage to synovium and joint cartilage. Examination of the involved joints by a rheumatologist is the gold standard method for evaluation of disease activity in RA; however, new specific biomarkers in serum and synovial fluid of RA patients have recently attracted attention of the researchers [2–7]. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were among the pioneer biomarkers that seemed to be related to disease activity and response to treatment in RA [8–11]. These markers were not specific for RA and might increase in many other infectious or inflammatory conditions.

Disease activity score 28—ESR (DAS28-ESR) is a validated composite index and is an estimated number of actual disease activity. This model has some limitations due to the lack of specificity of ESR for this purpose [12]. Considering that ESR is not specific for predicting disease activity in RA, it seems reasonable to determine new specific biomarkers correlating with disease activity and to propose new composite index using these specific biomarkers for predicting disease activity more accurately. Anti-CCP is a more specific serologic marker than rheumatoid factor in diagnosing RA patients; however, reports about the correlation of anti-CCP and disease activity are controversial [13–19].

The aim of this study was to evaluate the correlation of serum anti-CCP and disease activity based on the DAS28-ESR.

Materials and method

Ethical considerations

This study was performed according to the ethical standards for human experimentation and was approved by the ethics committee of the Kashan University of Medical Sciences. Written consent was obtained from the participants after explaining the aim of the study.

Patients and methods

This cross-sectional study was performed in consecutively selected patients with RA who were admitted in the rheumatology clinic of Shahid Beheshti Kashan hospital during 2010. RA was diagnosed based on the American College of Rheumatology criteria by an expert rheumatologist. Patients were assessed for the number of tender or swelling joints. Age and disease duration of the participants were asked and registered. Blood samples were collected from a peripheral vein after an overnight fast. The sera of the participants were separated by centrifugation with the speed of 1,500 rounds per minute for 10 min at room temperature. Then it was stored at −86° centigrade until the biochemical analysis was performed. Portions of blood samples were collected into tubes for evaluation of ESR.

ESR was measured based on the amount of erythrocytes sediment in 1 h and was reported as millimeter per hour (mm/h) according to Westergren.

Patient global assessment of pain and general health was measured using visual analogue scale (VAS) method and was reported as millimeter (zero = no pain, and 100 = worst pain possible).

Measurement of anti-CCP

Serum IgG antibodies against citrullinated protein (anti-CCP) were measured with a commercial kit (EDRA Genesis CPA kit; Genesis Diagnostics, UK). This quantitative assay was performed using enzyme-linked immunosorbent assay (ELISA) method according to manufacturer's instructions, and results were reported in unit per milliliter (U/ml). Principle of the test is explained as below:

Diluted serum samples were incubated with recombinant citrullinated rat filaggrin immobilized on microtitre wells. After washing away unbound serum components, rabbit anti-human IgG conjugated to horseradish peroxidase was added to the wells and this was bonded to surface-bound antibodies in the second incubation. Unbound conjugate was removed by washing, and a solution containing tetramethylbenzidine (TMB) and enzyme substrate was added to trace specific antibody binding. Addition of stop solution terminated the reaction and provided the appropriate pH for color development. The optical densities of the standards, controls, and samples were measured using a microplate at 450 nm.

Measurement of disease activity

Disease activity was calculated using DAS28-ESR composite index. DAS28-ESR is a commonly used scoring system for prediction of disease activity. The range of the test varies from zero to ten. DAS28-ESR scores less than 2.6 indicate patients in remission (comparable to American College of Rheumatology remission criteria). Scores between 2.6 and 3.2 indicate patients with low disease activity. Scores between 3.2 and 5.1 indicate patients with moderate disease activity. Scores above 5.1 indicate patients with high disease activity [11].

Statistical analyses

The Kolmogorov–Smirnov test was used to evaluate the normal distribution of the variables. Comparisons of mean age, disease duration, number of tender or swelling joints, serum anti-CCP, ESR, VAS, and DAS28-ESR between men and women were performed by *t* test. The correlation between disease activity (based on DAS28-ESR) and serum anti-CCP was analyzed by linear regression, and correlation coefficient (Pearson) was calculated. Comparisons of mean serum anti-CCP in different disease activity categories based on DAS28-ESR scores were performed by analysis of variances (ANOVA) using Tukey post hoc tests.

Considering the correlation between the disease activity based on DAS28-ESR with serum anti-CCP level in this study, and the correlation between the disease activity scores with the VAS, and number of tender or swelling joints in the previous studies [20, 21], we decided to construct a new composite index for predicting disease activity by replacing the serum anti-CCP level with the ESR in the DAS28-ESR composite index.

To construct the new composite index, we just replaced the serum anti-CCP concentration with the amount of ESR in the previous formula. Then we calculated the coefficient of the Neperian logarithm (Ln) of the serum anti-CCP and the constant of the new composite index by solver analysis using excel 2007 software.

To assess the correlation validity of the new composite index, the correlation of the absolute scores of the new composite index was compared with the DAS28-ESR scores by linear regression analysis, and correlation coefficient was calculated.

ROC curve analysis was performed to set cut-off values for new composite index (based on anti-CCP) to diagnose

RA patients in different disease activity categories (patients in remission, mild, moderate, and severe disease activity), considering the DAS28-ESR cut-off values as the gold standard. The best cut-off value was calculated through the contact point of the ROC curve and the line with slope equal to one in which the sum of sensitivity and specificity was the highest.

Considering the calculated threshold values by ROC curve analysis for the new composite index, the patients were re-categorized. The numbers of patients in each disease activity categories in new composite index were compared with the numbers of patients in DAS28-ESR disease activity categories by using cross tabs and calculating kappa statistics. Kappa measures the agreement between the evaluations of new and previous composite indices when rating the same object.

Statistical analysis was performed using SPSS version 16 (SPSS, Chicago, IL, USA). The probability of the difference between the dependent and independent variables was considered significant if P value is less than 0.05.

Results

One hundred and five patients (19 men and 86 women) were included in the study. Serum anti-CCP, ESR, age, and DAS28-ESR scores were normally distributed that are shown in Fig. 1 ($Z = 1.03$, 1.22, 0.74, and 0.61, respectively, all P values > 0.05).

Comparison of mean (±SD) age, duration of disease, serum anti-CCP level, ESR, VAS, DAS28-ESR, and number of tender or swelling joints between men and women are shown in Table 1.

There was positive correlation between DAS28-ESR and serum anti-CCP concentration ($R^2 = 0.71$, P value < 0.01).

Mean serum anti-CCP concentrations and frequencies of the patients in different disease activity categories (based on DAS28-ESR) are shown in Table 2. There was statistically significant difference when mean serum anti-CCP concentration in DAS28-ESR remission group was compared with moderate group and when severe group was compared with other groups (All P values < 0.01).

Constructing new composite index

The new composite index for predicting disease activity was constructed as follows:

$$\begin{aligned}\text{DAS anti} - \text{CCP} = {} & 0.56 \times \sqrt{(\text{number of tender joints})} \\ & + 0.28 \\ & \times \sqrt{(\text{number of swollen joints})} \\ & + 1.63 \times \ln(\text{anti} - \text{CCP}) + 0.014 \\ & \times \text{VAS} - 3.06\end{aligned}$$

Anti-CCP was measured in unit per milliliter, and VAS was measured in millimeter in this formula.

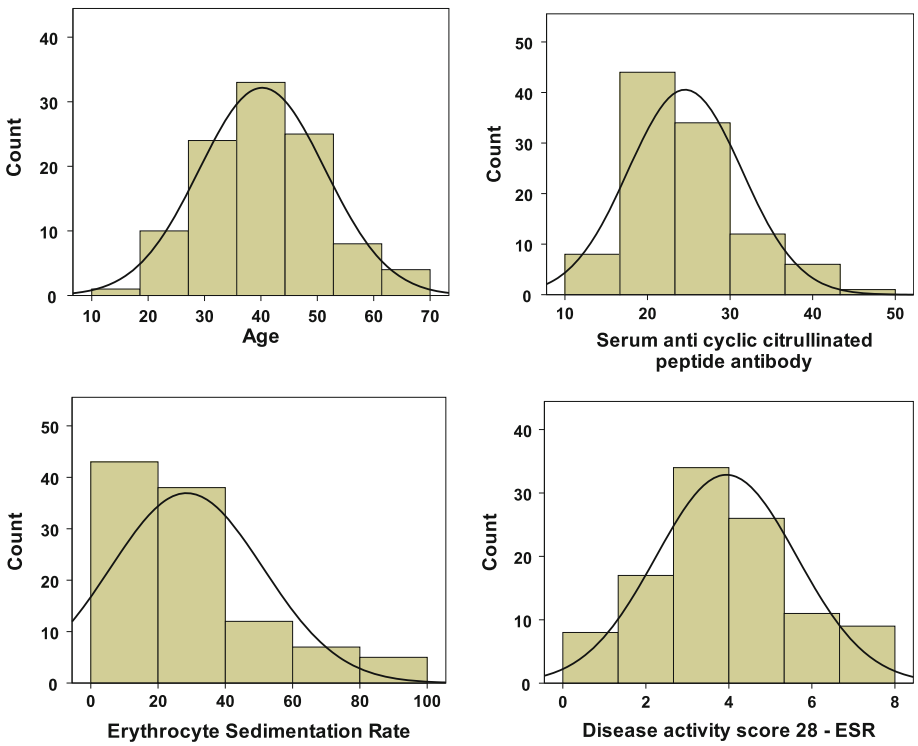

Fig. 1 Distribution of age, serum anti-cyclic citrullinated peptide antibody, erythrocyte sedimentation rate, and disease activity score 28-ESR in the study population

Correlation validity of new composite index and DAS28-ESR

There was correlation between absolute scores of the new composite index and DAS28-ESR scores ($R^2 = 0.91$, P value < 0.01).

New composite index threshold values

Figure 2 shows ROC curves for determination of new composite index values corresponded to the DAS28-ESR values of 2.6, 3.2, and 5.1, respectively. The new composite index best cut-off values corresponding to DAS28-ESR values of 2.6, 3.2, and 5.1 were 3.21, 3.38, and 4.74, respectively. (Table 3).

New disease activity categorization

The patients were re-categorized based on new threshold values calculated by ROC curve analysis. The distribution of the patients in each disease activity category in new composite index based on the new threshold values and DAS28-ESR disease activity categories are shown in Fig. 3. There were agreement between the new composite index disease activity categories (according to the cut-off values calculated by the ROC curve analysis) and DAS28-ESR disease activity categories (Kappa $= 0.71$, P value < 0.01).

Table 1 Comparison of mean (±SD) age, disease duration, serum anti-cyclic citrullinated peptide antibody, erythrocyte sedimentation rate, visual analogue scale, disease activity score 28-ESR, and number of tender or swelling joints between men and women

	Men	Women	*P* value
Age (years)	40 ± 8.3	40.2 ± 11.6	0.9
Duration of disease (years)	7.1 ± 5.4	7.8 ± 5.1	0.6
Number of tender joints	5.6 ± 4	4.9 ± 4.7	0.5
Number of swollen joints	2 ± 1.6	1.7 ± 1.9	0.4
Serum anti-CCP level (U/ml)	26.4 ± 5.2	24.1 ± 7.1	0.1
Erythrocyte sedimentation rate	30.5 ± 18.6	28 ± 23.4	0.6
Visual analogue scale (mm)	34.7 ± 28.7	31.9 ± 29.9	0.7
Disease activity score 28-ESR	4.3 ± 1.3	3.8 ± 1.7	0.2

Anti-CCP anti-cyclic citrullinated peptide, *U/ml* unit per milliliter, *mm* millimeter

Table 2 Mean serum anti-cyclic citrullinated peptide antibody concentration (±SD) and frequencies of patients in different disease activity category measured by disease activity score 28-ESR

DAS28-ESR	Serum anti-CCP (U/ml)	Frequency (%)
Score < 2.6	18.2 ± 3	23 (22)
$2.6 \leq$ score < 3.2	21.6 ± 3.7	12 (11)
$3.2 \leq$ score ≤ 5.1	23.7 ± 3.9	48 (46)
Score > 5.1	34.3 ± 5.5	22 (21)

DAS28-ESR disease activity score 28—erythrocyte sedimentation rate, *Anti-CCP* anti-cyclic citrullinated peptide, *U/ml* unit per milliliter

Discussion

This study in definite RA patients with longstanding and medium active disease showed the correlation between serum anti-CCP levels and DAS28 scores. Considering the higher specificity of anti-CCP than other inflammatory biomarkers in predicting disability in RA patients [22], a new composite index for predicting disease activity was developed by replacing anti-CCP with ESR in DAS28 model. The positive correlation between the new composite index scores and the DAS28-ESR scores showed the correlation validity of the new model. Considering the DAS28-ESR as the gold standard, the high area under curve (AUC) in the ROC curve analysis indicates the great diagnostic accuracy of the calculated cut-off values for new disease activity score in determination of patients in different disease activity categories. Using kappa statistics, the number of patients in new disease activity categories was found to be in substantial agreement with DAS28-ESR disease activity categories.

The correlation of anti-CCP level with disease activity in this study is in concordant with the results of some studies in the literature; however, studies that did not found

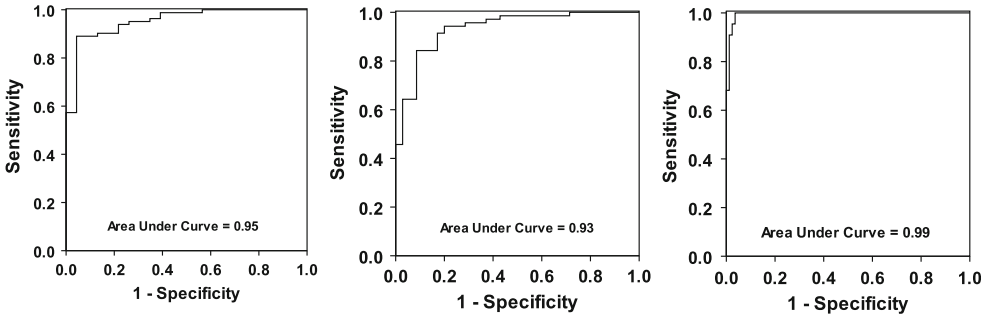

Fig. 2 Receiver operating characteristic (ROC) curves of the new composite index values corresponding to disease activity score 28-ESR cut-off values of 2.6 (*left*), 3.2(*middle*), and 5.1(*right*) as the gold standards

Table 3 New composite index values corresponding to disease activity score 28-ESR cut-off values

DAS28-ESR	New composite index	Sensitivity (%)	Specificity (%)
2.6	3.21	90	96
3.2	3.38	84	92
5.1	4.74	100	97

DAS28-ESR disease activity score 28-erythrocyte sedimentation rate

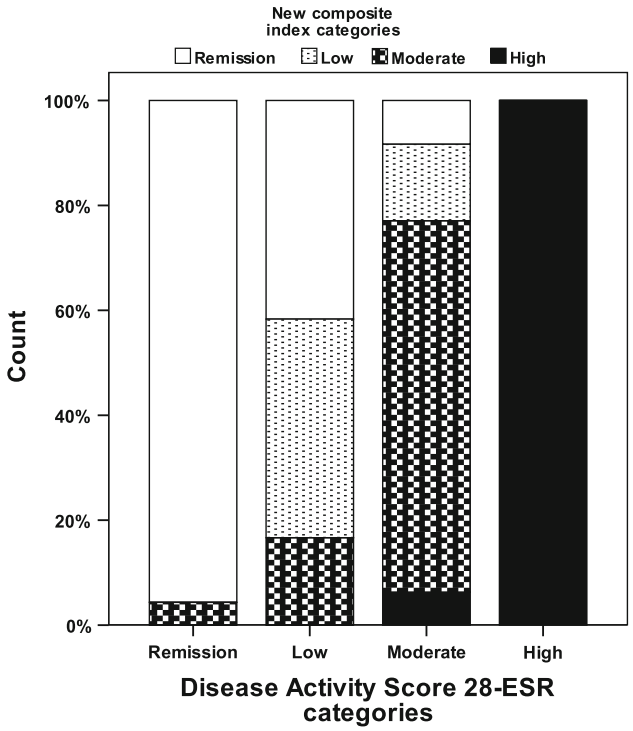

Fig. 3 Distribution of the patients in each disease activity category in new composite index based on the new threshold values and disease activity score 28-ESR categories

this correlation exist. Miriovsky et al. [6] showed that higher anti-CCP was associated with increased disease activity in US veterans with RA. In the study of Onder et el in 61 Turkish RA patients with mean disease duration of 108.5 months, anti-CCP positivity was associated with higher scores of DAS28 [13]. Landmann et al. [15] showed a correlation between anti-CCP and DAS28 in Germany. The correlation was more positive in erosive RA patients than non-erosive ones, and median disease duration was 34 months. Chen et al. [23] demonstrated a low correlation between anti-CCP and DAS28 ($r = 0.37$) in 90 RA patients in Taipei, who did not responded to standard DMARD therapy. Inanc et al. [24] reported that mean DAS28 scores in anti-CCP-positive group of Turkish RA patients were higher than anti-CCP-negative group. Meanwhile, some studies showed no correlation between anti-CCP levels and disease activity based on DAS28 scores from Thailand, Greece, and Egypt [16–18, 25, 26]. Anti-CCP levels did not change in responders to anti-TNF therapy, although the DAS28 activity score and other inflammatory biomarkers decreased significantly [27–29]. There is one report that showed decrease of anti-CCP level in responders to Kampo (a traditional herbal medicine in Japan) therapy [30].

We suggest that the controversy about the correlation between anti-CCP and disease activity in the above mentioned studies may be related to the differences in patient characteristics (especially their ethnicity), duration of disease and follow-up, and disease severity in the studied populations. These parameters may influence on the power and type of immune response and thereby cause different levels of anti-CCP production.

This study included patients with longstanding and medium active disease, and those with early RA and high active disease were not included. This limitation is due to the patient selection method. The patients were consecutively selected, and there was no randomization. As a result, patients with early RA and high active disease were not enrolled unfortunately. Therefore, the results of this study cannot be generalized to all RA patients. Another limitation of this study was the cross-sectional design that could not determine the changes of anti-CCP during the course of disease. To define a new disease activity index, patients follow-up with longitudinal studies should be performed. Therefore, further studies are necessary to evaluate the correlation between serum anti-CCP concentration and radiographic damage (construct validity) and to define the discrimination validity of new model in larger cohorts of RA patients. We also suggest that the new results have to be compared with other validated scores. Further studies to define the best cut-off values for the new model in different patient populations are proposed. Recently, new more sensitive serum biomarkers like antibody against mutated citrullinated vimentin have attracted attention for early diagnosis and prognosis of RA [31, 32]. Prospective studies about the relationship of this antibody and disease activity are recommended.

In summary, this cross-sectional study showed the following: (1) There was correlation between serum anti-CCP and disease activity based on DAS28-ESR composite index. (2) New model for predicting disease activity was developed by replacing serum anti-CCP level with ESR in DAS28-ESR composite index, and correlation validity of the new model was determined. (3) Considering the DAS28-ESR scores as the gold standards, the best cut-off values for new composite index were calculated to diagnose RA patients in different disease activity categories. 4) There was agreement between new composite index and DAS28-ESR.

Conclusion

The new disease activity index that applies serum anti-CCP may predict disease activity in RA.

Acknowledgments This study was supported by the research funds of Kashan University of Medical Sciences. The authors extend their gratitude to Dr Hassan Ehteram and staff of rheumatology clinic in Kashan Shahid Beheshti Hospital for their special help and support of this study.

References

1. Davatchi F, Tehrani Banihashemi A, Gholami J, Faezi ST, Forouzanfar MH, Salesi M, Karimifar M, Essalatmanesh K, Barghamdi M, Noorolahzadeh E, Dahaghin S, Rasker JJ (2009) The prevalence of musculoskeletal complaints in a rural area in Iran: a WHO-ILAR COPCORD study (stage 1, rural study) in Iran. Clin Rheumatol 28:1267–1274
2. Zamani B, Jamali R, Ehteram H (2010) Synovial fluid adenosine deaminase and high-sensitivity C-reactive protein activity in differentiating monoarthritis. Rheumatol Int. doi:10.1007/s00296-010-1602-3
3. Erer B, Yilmaz G, Yilmaz FM, Koklu S (2009) Assessment of adenosine deaminase levels in rheumatoid arthritis patients receiving anti-TNF-alpha therapy. Rheumatol Int 29:651–654
4. Zamani B, Jamali R, Jamali A (2011) Serum adenosine deaminase may predict disease activity in rheumatoid arthritis. Rheumatol Int. doi:10.1007/s00296-011-1912-0
5. Fernandes RM, Silva NP, Sato EI (2011) Increased myeloperoxidase plasma levels in rheumatoid arthritis. Rheumatol Int. doi:10.1007/s00296-011-1810-5
6. Miriovsky BJ, Michaud K, Thiele GM, O'Dell JR, Cannon GW, Kerr G, Richards JS, Johnson D, Caplan L, Reimold A, Hooker R, Mikuls TR (2010) Anti-CCP antibody and rheumatoid factor concentrations predict greater disease activity in men with rheumatoid arthritis. Ann Rheum Dis 69:1292–1297
7. Rodríguez-Rodríguez L, Lamas JR, Varadé J, López-Romero P, Tornero-Esteban P, Abasolo L, de la Concha EG, Jover JA, Urcelay E, Fernández-Gutiérrez B (2011) Plasma soluble IL-6 receptor concentration in rheumatoid arthritis: associations with the rs8192284 IL6R polymorphism and with disease activity. Rheumatol Int 31:409–413
8. Weinblatt ME, Keystone EC, Cohen MD, Freundlich B, Li J, Chon Y, Baumgartner SW (2011) Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate. J Rheumatol 38:242–246
9. Emery P, Gabay C, Kraan M, Gomez-Reino J (2007) Evidence-based review of biologic markers as indicators of disease progression and remission in rheumatoid arthritis. Rheumatol Int 27:793–806
10. Cylwik B, Chrostek L, Gindzienska-Sieskiewicz E, Sierakowski S, Szmitkowski M (2010) Relationship between serum acute-phase proteins and high disease activity in patients with rheumatoid arthritis. Adv Med Sci 55:80–85
11. Markatseli TE, Voulgari PV, Alamanos Y, Drosos AA (2011) Prognostic factors of radiological damage in rheumatoid arthritis: a 10-year retrospective study. J Rheumatol 38:44–52
12. Nishimoto N, Takagi N (2010) Assessment of the validity of the 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) as a disease activity index of rheumatoid arthritis in the efficacy evaluation of 24-week treatment with tocilizumab: subanalysis of the SATORI study. Mod Rheumatol 20:539–547
13. Ryu HJ, Takeuchi F, Kuwata S, Kim YJ, Lee EY, Lee EB, Song YW (2011) The diagnostic utilities of anti-agalactosyl IgG antibodies, anti-cyclic citrullinated peptide antibodies, and rheumatoid factors in rheumatoid arthritis. Rheumatol Int 31:315–319
14. Önder B, Kurtaran A, Kimyon S, Selçuk B, Akyüz M (2009) Association of anti-CCP positivity with serum ferritin and DAS-28. Rheumatol Int 30:223–227
15. Landmann T, Kehl G, Bergner R (2010) The continuous measurement of anti-CCP-antibodies does not help to evaluate the disease activity in anti-CCP-antibody-positive patients with rheumatoid arthritis. Clin Rheumatol 29:1449–1453
16. Vanichapuntu M, Phuekfon P, Suwannalai P, Verasertniyom O, Nantiruj K, Janwityanujit S (2010) Are anti-citrulline autoantibodies better serum markers for rheumatoid arthritis than rheumatoid factor in Thai population? Rheumatol Int 30:755–759
17. Aridoğan BC, Kaya S, Savaş S, Cetin ES, Akkuş S, Demirci M (2008) The role of anti-cyclic citrullinated peptide (anti-CCP) antibodies in serologic diagnosis and evaluation of disease activity in rheumatoid arthritis. Mikrobiyol Bul 42:669–674
18. Serdaroğlu M, Cakirbay H, Değer O, Cengiz S, Kul S (2008) The association of anti-CCP antibodies with disease activity in rheumatoid arthritis. Rheumatol Int 28:965–970
19. Sghiri R, Bouagina E, Zaglaoui H, Mestiri H, Harzallah L, Harrabi I, Ghannouchi M, Mokhtar F, Ghedira I (2007) Diagnostic performances of anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis. Rheumatol Int 27:1125–1130
20. van der Heijde DM, van't Hof MA, van Riel PL, van Leeuwen MA, van Rijswijk MH, van de Putte LB (1992) Validity of single variables and composite indices for measuring disease activity in rheumatoid arthritis. Ann Rheum Dis 51:177–181
21. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL (1995) Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 38:44–48
22. Shidara K, Inoue E, Hoshi D, Sato E, Nakajima A, Momohara S, Taniguchi A, Yamanaka H (2010) Anti-cyclic citrullinated peptide antibody predicts functional disability in patients with rheumatoid arthritis in a large prospective observational cohort in Japan. Rheumatol Int. doi:10.1007/s00296-010-1671-3
23. Chen HA, Lin KC, Chen CH, Liao HT, Wang HP, Chang HN, Tsai CY, Chou CT (2006) The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis 65:35–39
24. Inanc N, Dalkilic E, Kamali S, Kasapoglu-Günal E, Elbir Y, Direskeneli H, Inanc M (2007) Anti-CCP antibodies in rheumatoid arthritis and psoriatic arthritis. Clin Rheumatol 26:17–23
25. Alexiou I, Germenis A, Ziogas A, Theodoridou K, Sakkas LI (2007) Diagnostic value of anti-cyclic citrullinated peptide antibodies in Greek patients with rheumatoid arthritis. BMC Musculoskelet Disord: 8:37
26. Abdel-Nasser AM, Mahmoud MH, El Mansoury TM, Osman AM (2008) Anti-CCP2 is an adjunct to, not a surrogate for, rheumatoid factor in the diagnosis of rheumatoid arthritis: diagnostic utility of anti-CCP2 antibodies in Egyptian patients with rheumatoid arthritis. Scand J Rheumatol 37:329–336
27. Kolarz B, Majdan M, Dryglewska M, Darmochwal-Kolarz D (2010) Antibodies against cyclic citrullinated peptide don't decrease after 6 months of infliximab treatment in refractory rheumatoid arthritis. Rheumatol Int. doi:10.1007/s00296-010-1509-z
28. Dejaco C, Duftner C, Klotz W, Schirmer M, Herold M (2010) Third generation anti-cyclic citrullinated peptide antibodies do

not predict anti-TNF-alpha treatment response in rheumatoid arthritis. Rheumatol Int 30:451–454
29. Caramaschi P, Biasi D, Tonolli E, Pieropan S, Martinelli N, Carletto A, Volpe A, Bambara LM (2005) Antibodies against cyclic citrullinated peptides in patients affected by rheumatoid arthritis before and after infliximab treatment. Rheumatol Int 26:58–62
30. Kogure T, Sato H, Kishi D, Ito T, Tatsumi T (2009) Serum levels of anti-cyclic citrullinated peptide antibodies are associated with a beneficial response to traditional herbal medicine (Kampo) in rheumatoid arthritis. Rheumatol Int 29:1441–1447
31. van der Linden MP, van der Woude D, Ioan-Facsinay A, Levarht EW, Stoeken-Rijsbergen G, Huizinga TW, Toes RE, n Mil AH (2009) Value of anti-modified citrullinated vimentin and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. Arthritis Rheum 60:2232–2241
32. Wagner E, Skoumal M, Bayer PM, Klaushofer K (2009) Antibody against mutated citrullinated vimentin: a new sensitive marker in the diagnosis of rheumatoid arthritis. Rheumatol Int 29:1315–1321