

# Review: Anti-cyclic citrullinated peptide antibody is a more specific test for rheumatoid arthritis than rheumatoid factor

Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* 2007;146:797-808.

**Clinical impact ratings:** Rheumatology ★★★★★★

## QUESTION

Are rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) accurate tests for rheumatoid arthritis (RA)?

## METHODS

**Data sources:** MEDLINE (to September 2006) and reference lists.

**Study selection and assessment:** Studies published after 1987 that evaluated the accuracy of RF or anti-CCP for diagnosis of RA in  $\geq 10$  participants. 50 studies of RF ( $n = 15\,286$ , median age 53 y, 68% women) and 37 studies of anti-CCP ( $n = 14\,949$ , median age 57 y, 59% women) met the selection criteria.

**Outcomes:** Pooled sensitivity, specificity, and positive and negative likelihood ratios (LRs). The reference standard for RA was the 1987 revised American College of Rheumatology criteria.

## MAIN RESULTS

Anti-CCP and IgM RF had similar sensitivity and -LR for diagnosing RA, but anti-CCP had higher specificity and +LR (Table). IgA RF and IgG RF had similar LRs to IgM RF (Table). Studies using second-generation anti-CCP antibody assays had a similar pooled +LR but lower -LR compared with

those using first-generation assays (Table). Studies requiring both anti-CCP positivity and RF positivity for a positive result had a pooled +LR slightly higher than that of anti-CCP alone (Table). Studies considering positivity in either test as a positive result had +LRs similar to that of RF alone (Table). Anti-CCP positivity was a stronger predictor than RF positivity for development of RA in asymptomatic persons (5 studies) and for radiographic progression of RA (15 studies).

## CONCLUSION

Detection of anti-cyclic citrullinated peptide antibody is a more specific test than rheumatoid factor for diagnosis of rheumatoid arthritis.

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*For correspondence:* Dr. K. Nishimura, Harvard School of Public Health, Boston, MA, USA, and Kobe University School of Medicine, Hyogo, Japan. E-mail knishimu@hsph.harvard.edu. ■

### Pooled test characteristics of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP) for diagnosis of rheumatoid arthritis\*

Test	Number of studies (n)	Sensitivity (95% CI)	Specificity (CI)	+LR	-LR
IgM RF	50 (15 286)	69% (68 to 70)	85% (84 to 86)	4.9	0.38
Anti-CCP	37 (14 949)	67% (65 to 68)	95% (95 to 96)	12.5	0.36
IgA RF	13 (5828)	—	—	5.0	0.44
IgG RF	13 (6046)	—	—	4.5	0.52
Anti-CCP1	5 (2098)	—	—	13.0	0.53
Anti-CCP2	29 (11 821)	—	—	12.8	0.32
Both tests positive	6 (1753)	—	—	15.7	0.46
Either test positive	8 (2837)	—	—	4.3	0.32

\*Anti-CCP1 = first-generation anti-CCP assay; anti-CCP2 = second-generation anti-CCP assay. Diagnostic terms and CI defined in Glossary.

## COMMENTARY

The diagnosis of RA is primarily clinical but is supported by serum RF positivity (anti-IgG antibodies), which is 1 of the 7 American College of Rheumatology diagnostic criteria. However, 3 common conditions (older age, hepatitis C, and primary Sjögren syndrome), as well as various infectious, malignant, and other rheumatic diseases, are often associated with RF positivity. In addition, RF-negative cases of RA are abundant, and measurement of RF is not standardized. These important limitations have been augmented by the shift toward early, more aggressive therapies in RA, which aim to control disease activity and mandate urgent and accurate diagnosis.

Thus, the rigorous meta-analysis by Nishimura and colleagues is timely and highly important, establishing anti-CCP as a new and promising player in the field. The selection of 87 studies and > 30 000 tests for review minimized possible bias and provided generalizable results. Very early RA, for which the sensitivity of anti-CCP may be lower, could have been better studied.

With no loss of sensitivity, anti-CCP was considerably more specific (95%) than RF (85%) and increased +LR for RA to 12.5, a more than 2.5-fold increase compared with RF. Up to 35% of patients with RF-negative RA demonstrated reactivity to CCP, another advantage of the test. Anti-CCP is also a better predictor of the development of RA

(range of odds ratios 16 to 39 for anti-CCP vs 1.2 to 8.7 for RF in 3 studies), radiographic progression (range of odds ratios 2.5 to 4.8 vs 0.7 to 2.7 in 3 studies), and functional impairment.

Although not yet reflected in American College of Rheumatology criteria or any consensus statement, the data suggest that, in suspect cases of RA, both RF and anti-CCP should be tested together (1). If both tests are positive or only anti-CCP is positive in a patient with a strong clinical probability, RA is highly likely. If only RF positivity is found, the higher the titer, the more likely the diagnosis, but alternatives must be ruled out. When both tests are negative, RA cannot be ruled out because this result has been reported in about one third of patients with RA (2); serial monitoring is recommended, and decisions must be clinically based. Although more studies are needed, Nishimura and colleagues are correct in their conclusion that anti-CCP should be incorporated into the diagnostic workup of RA.

Ami Schattner, MD  
Kaplan Medical Center  
Rehovot, Israel

## References

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