Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis

CRD summary
This review concluded that antibodies against cyclic citrullinated peptide are more specific than rheumatoid factor for the diagnosis of rheumatoid arthritis, and may also be a better predictor of erosive disease. Limitations in the literature search and a failure to appropriately consider study quality and variability in the synthesis mean that these conclusions may not be reliable.

Authors’ objectives
To compare the accuracy of antibodies against cyclic citrullinated peptide (CCP) with rheumatoid factor (RF) for the diagnosis of rheumatoid arthritis and the prediction of radiological progression.

Searching
MEDLINE was searched to September 2006 for published studies; the search terms were reported and included a diagnostic filter. No language restrictions were applied. Reference lists of retrieved studies and review articles were screened for additional studies. Only studies published after 1987 were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Studies that included at least 10 participants were eligible for inclusion.

Specific interventions included in the review
Studies that assessed anti-CCP or RF were eligible for inclusion. The included studies assessed both first (CCP1) and second (CCP2) generation anti-CCP tests and different RF subtypes (immunoglobulins IgA, IgG and IgM).

Reference standard test against which the new test was compared
The authors stated that they used the 1987 revised American College of Rheumatology (ACR) guidelines as the reference standard; however, studies which did not specify these criteria as the reference standard were also included. The included studies used either the ACR criteria or a clinical diagnosis as the reference standard.

Participants included in the review
Studies of patients with known or suspected rheumatoid arthritis were eligible for inclusion. The studies included patients with both early (usually defined as symptom duration less than 1 year) and established arthritis. The median age of the participants was 57 years in the anti-CCP studies and 53 years in the IgM RF studies. The median proportions of women were 59% in the anti-CCP studies and 68% in the IgM RF studies. Control groups in the diagnostic case-control studies comprised patients with undifferentiated arthritis, other rheumatic conditions, healthy persons, hepatitis C carriers, or a mix of healthy persons and other diseases.

Outcomes assessed in the review
The studies had to report sufficient data for the calculation of a 2x2 table of test performance to be included.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened abstracts and full-text articles for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality using criteria developed for previous meta-analyses; any
discrepancies were resolved through discussion. The items assessed included the technical quality of the tests, application of the reference standard or index test, blinding of the observers, description of the study sample, and cohort assembly.

**Data extraction**
Two reviewers independently extracted the data using a standardised form. The authors did not report any details on how the results data were extracted. The sensitivity, specificity, and positive and negative likelihood ratios were calculated, along with the 95% confidence intervals (CIs).

**Methods of synthesis**
How were the studies combined?
The sensitivity, specificity, and positive and negative likelihood ratios, with 95% CIs, were pooled using a random-effects model. Analyses were stratified according to generation of anti-CCP antibody test (CCP1 or CCP2) and by RF subtype (IgA, IgG and IgM). Studies that evaluated both anti-CCP and RF were analysed separately. Publication bias was investigated using funnel plots for diagnostic odds ratios.

How were differences between studies investigated?
Subgroup analyses were restricted to patients with early rheumatoid arthritis. When heterogeneity was suspected, a meta-regression and stratified analysis for different thresholds and measurement methods was conducted.

**Results of the review**
Eighty-six studies were included: 37 studies (14,949 patients) assessed anti-CCP and 50 studies (15,286 patients) assessed RF.

Only 1 study fulfilled all quality criteria, 22 studies met at least 70% of the criteria, and 9 studies met less than 50% of the criteria.

Additional data are available online on the Annals of Internal Medicine website, but a subscription may be required for access.

**Anti-CCP.**
The sensitivity ranged from 39 to 100% and the specificity from 65 to 100%. The pooled sensitivity and pooled specificity were 67% (95% CI: 62, 72) and 95% (95% CI: 94, 97), respectively.

**RF.**
The sensitivity ranged from 20 to 100% and for IgM RF the pooled sensitivity was 69% (95% CI: 65, 73). The specificity ranged from 31 to 99% and for IgM RF the pooled specificity was 85% (95% CI: 82, 88). The likelihood ratios for the different RF subtypes were similar.

The results for patients with early arthritis were similar to those from all studies.

Three out of 4 studies found that the risk for radiographic progression was greater with anti-CCP antibody positivity than IgM RF positivity.

**Authors' conclusions**
The specificity of anti-CCP for the diagnosis of rheumatoid arthritis was greater than that of RF. Anti-CCP may also be a better predictor of erosive disease.

**CRD commentary**
The review addressed two separate clearly-defined questions. The inclusion criteria were explicit in relation to the diagnosis of rheumatoid arthritis but not in terms of prediction of disease: studies that answer this question will be very different in design to those on the diagnosis of rheumatoid arthritis, although it is possible to answer both questions in a single study. It was therefore unclear whether prediction studies had to fulfill the same criteria as diagnostic studies or whether alternative criteria were applied. The literature search was limited to one electronic database and a diagnostic filter was applied; no specific attempts were made to locate unpublished data. Many relevant studies were likely to have been missed by this search. The review methods were clearly reported and included appropriate steps to minimise bias at each stage of the review. A quality assessment was undertaken, but this was not appropriately considered in the analysis. In particular, diagnostic cohort and case-control studies were pooled together with no investigation of the differences between these types of study; this is likely to have led to an overestimation in estimates of both sensitivity and specificity.

Given the extreme heterogeneity between the studies it is questionable whether the meta-analysis was appropriate, and further investigation of the observed heterogeneity would have greatly improved this review. Publication bias was investigated, but the methods used were not appropriate for diagnostic accuracy studies. In view of the above limitations, in particular the limited literature search and failure to adequately investigate heterogeneity, the authors’ conclusions may not be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that anti-CCP antibody positivity should be included in the diagnostic criteria for rheumatoid arthritis and early rheumatoid arthritis.

**Research:** The authors stated that clinical trials and cost-effectiveness studies of the trade-offs between testing for anti-CCP alone or in combination with RF are needed.

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