Systematic review: accuracy of anti-citrullinated peptide antibodies for diagnosing rheumatoid arthritis


CRD summary
This well-conducted review concluded that second-generation anti-cyclic citrullinated peptide antibody tests should be included in the diagnostic work-up of patients with early symptoms of rheumatoid arthritis. The results of the review are likely to be reliable.

Authors' objectives
To compare the accuracy of anti-citrullinated peptide antibodies and rheumatoid factor in diagnosing rheumatoid arthritis in patients with early symptoms of the disease.

Searching
MEDLINE, EMBASE, Science Citation Index, BIOSIS Previews, Web of Science, SIGLE, Zetoc, NTIS, and Dissertation Express were searched without language restrictions from inception to September 2009; specific search terms were not reported. References lists of included studies were also searched.

Study selection
Diagnostic accuracy studies that compared any method to detect any type of anti-citrullinated peptide antibodies to diagnose rheumatoid arthritis in people with suspected or confirmed rheumatoid arthritis (of any duration) were eligible for inclusion. The reference standard for diagnosing rheumatoid arthritis had to be the revised 1987 American College of Rheumatology classification criteria. Sufficient data to produced 2x2 tables of test performance were required. Randomised controlled trials (RCTs) comparing testing protocols with and without anti-citrullinated peptide antibodies were also eligible.

Most participants in the cohort studies had early rheumatoid arthritis (disease duration under two years). Control participants in case-control studies were healthy or had other conditions. Where reported, the mean age ranged from 27 to 71 years, and the proportion of women from 33 to 96%.

Two reviewers independently screened titles and abstracts, and full texts were screened by one reviewer and checked by a second reviewer; disagreements were resolved through consensus.

Assessment of study quality
Study quality was assessed by one reviewer and checked by a second reviewer using the 14-criteria QUADAS tool; disagreements were resolved through consensus.

Data extraction
Data to construct 2x2 tables of test performance were extracted by one reviewer and checked by a second reviewer, from which sensitivity and specificity were calculated.

Methods of synthesis
Summary estimates of sensitivity and specificity, with 95% confidence and prediction regions, were calculated using the bivariate model. Where there were four or more studies, hierarchical summary receiver operating characteristic curves were derived; otherwise pooled estimates were produced using random-effects logistic regression. Summary positive and negative likelihood ratios were calculated from the estimates of sensitivity and specificity. Estimates were calculated for all studies, and different study designs and subgroups separately.

When pooling all studies, a single 2x2 table was selected from each study on a hierarchical basis, using type of anti-citrullinated peptide antibody, manufacturer, biochemical test, and anti-citrullinated peptide antibody threshold. Analyses were stratified by disease stage and anti-citrullinated peptide antibody test. Heterogeneity was assessed by
visual inspection of summary receiver operating characteristic plots and the variance of logit-transformed sensitivity and specificity.

Sensitivity analyses were conducted to investigate the impact of the classification of patients with undifferentiated arthritis, different types of control groups (where used), and combining immunoglobulin M rheumatoid factor and second generation anti-cyclic citrullinated peptide antibodies.

P-values were calculated using likelihood ratio tests.

**Results of the review**

The review included 151 studies; 27 cohort (n=9,524 participants; range 32 to 1,025), 15 cross-sectional studies (n=3,527 participants; range 34 to 715), 104 case-control studies (n=12,674 cases, 18,118 controls; range 29 to 1,077), and five nested case-control studies (n=393 cases, 3,305 controls; range 294 to 2,217). Most studies avoided partial and differential verification bias and incorporation bias. Only 24 studies included an appropriate patient spectrum, and most did not report on blinding of the interpreters of the tests, withdrawals, or uninterpretable/indeterminate results.

**Anti-citrullinated peptide antibodies diagnostic accuracy:**

Across all studies, sensitivity and specificity varied widely; sensitivity ranged from 12 to 93%, and specificity from 63 to 100%. Pooled estimates (138 studies) were sensitivity 67% (95% CI 64 to 69) and specificity 96% (95% CI 95 to 96). Pooled sensitivity was significantly higher in case-control (68%, 95% CI 65 to 71; 97 studies) and cross-sectional studies (69%, 95% CI 62 to 76; 14 studies) compared with cohort studies (60%, 95% CI 54 to 64; 27 studies). Estimates of specificity were similar across study designs.

For the detection of early rheumatoid arthritis, pooled estimates from 19 cohort studies were sensitivity 54% (95% CI 48 to 60) and specificity 95% (95% CI 93 to 97). From 24 cross-sectional and case-control studies, pooled estimates were sensitivity 66% (95% CI 59 to 72) and specificity 94% (95% CI 92 to 95).

For the detection of established rheumatoid arthritis, pooled estimates from 11 cohort studies were sensitivity 66% (95% CI 58 to 73) and specificity 98% (95% CI 95 to 99). From 99 cross-sectional and case-control studies, pooled estimates were sensitivity 69% (95% CI 66 to 72) and specificity 95% (95% CI 94 to 96).

**Second generation anti-cyclic citrullinated peptide antibodies diagnostic accuracy:**

For early rheumatoid arthritis (15 cohort studies), pooled sensitivity was 57% (95% CI 51 to 63) and specificity 96% (95% CI 93 to 97).

For established rheumatoid arthritis (seven cohort studies), pooled sensitivity was 77% (95% CI 74 to 79) and specificity 96% (95% CI 94 to 98). Data from cohort studies were limited for first and third generation anti-cyclic citrullinated peptide antibody tests.

Results for a large number of other subgroups were also presented, as were the positive and negative likelihood ratios.

**Authors’ conclusions**

Second generation anti-cyclic citrullinated peptide antibody tests should be included in the work-up of patients with early symptoms of rheumatoid arthritis.

**CRD commentary**

The authors addressed a clear review question which was supported by appropriate inclusion criteria. Several relevant sources were searched without language restrictions or diagnostic filters, and unpublished data was sought. Each stage of the review was conducted in duplicate, reducing the risk of error and bias.

Study quality was assessed using appropriate criteria, although the results for individual studies were not available. The authors stated that 27 cohort studies were included in the review; details of 29 were included in the table of study...
characteristics. Appropriate methods of synthesis were used, and heterogeneity was extensively investigated. The pooled results from all studies were based on very heterogeneous data, and some of the subgroup analyses included very few studies, whose quality was unknown. There were a number of limitations with the available data which were discussed by the authors.

Overall, this was a well-conducted review, and the results are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that: the American College of Rheumatology criteria should be updated for use earlier in the course of rheumatoid arthritis and to incorporate modern diagnostic technologies. In practice, a physician could presumptively diagnose rheumatoid arthritis early if the second generation anti-cyclic citrullinated peptide antibody test result was positive, and start therapy accordingly; and if the test result was negative, a physician could adopt a policy of regular review and assessment.

Research: The authors stated that further research is needed into the accuracy of second generation anti-cyclic citrullinated peptide antibodies as an indicator of disease progression or severity, and the potential for second generation anti-cyclic citrullinated peptide antibody tests to detect very early-stage rheumatoid arthritis (up to three months’ duration) and predict the onset of rheumatoid arthritis before symptom onset. The authors recommend that future studies are of a cohort design, enrol patients with suspected rheumatoid arthritis, include an evaluation of rheumatoid factor and the combined accuracy of anti-citrullinated peptide antibody and rheumatoid factor, and adhere to the STARD guidelines for reporting diagnostic test accuracy studies.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.