Clinical utility of anti-CCP assay in patients with rheumatoid arthritis

Thesis Submitted By

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Summary and conclusion

Rheumatoid arthritis is a systemic autoimmune disease of unknown etiology. The major autoantibody detected in RA patients is rheumatoid factor. RF positivity is included in the American College of Rheumatology (ACR) classification criteria for the diagnosis of RA. RF assay is an easy, and convenient method. However, since RF is detected in only 50-80% of RA sera, and is frequently present in patients with other autoimmune disease and in the elderly healthy population, diagnosis of RA using RF assay remains suboptimal. Other autoantibodies detected in RA are anti RA33, anti-Sa, anti-p68, anti-calpastatin, AKA, and antiperinuclear factor, but these antoantibodies have demonstrated lower sensitivity for the diagnosis of RA (Choi et al., 2005).

A new group of autoantibodies that has generated particular interest are the anti-cyclic citrullinated peptide antibodies, First described by Schellekens et al, 1998. This discovery led to the development of assays employing cyclic citrullinated peptides (CCP) to measure antibodies recognising citrullinated antigens as a diagnostic test for RA. Further purification of the antigen led to the development of the second generation test, anti-CCP2, with better performance.

In this study, we aimed to evaluate the clinical utility of anti-CCP2 assay by ELISA method as a useful new serological test for the diagnosis of RA versus RF, and to correlate it with the disease activity parameters, functional disability, and radiological destruction.

This study included 50 patients with rheumatoid arthritis diagnosed according to the American College of Rheumatology (ACR) 1987 revised criteria for the classification of rheumatoid arthritis, 37 patients with a variety of rheumatic diseases, and 10 healthy controls.
The age of RA patients ranged between 22 and 70 years, with a mean of 42.5 ± 13.1 years, and their disease duration ranged between 1 and 15 years, with a mean of 6.2 ± 4.3. There was 6 males (12%) and 44 females (88%).

RA patients were evaluated by history, examination, questionnaires, laboratory and radiological examination. Disease activity was assessed by DAS28, pain by Numerical rating scale of pain, disability by HAQ-DI, and radiological damage by SENS method. In addition, complete blood count, ESR, C- reactive protein, rheumatoid factor, and anti-CCP were determined.

This study demonstrated the following:

- Anti-CCP2 was positive in 35 (70%) of RA patients, while RF was positive in 26 (52%). In healthy controls, anti-CCP2 was negative in all cases, while RF was positive in one case (10%). In patients with other rheumatic diseases, anti-CCP2 false positivity ranged from 0% (in OA and SSc) to 33.3% in PsA, whereas RF false positivity ranged from 0% (in AS, PsA, and SSc) to 20% (in SLE and OA).
- Agreement between anti-CCP2 and RF was modest but significant ($\kappa = 0.31$, $p = 0.02$) for RA patients and very highly significant ($\kappa = 0.42$, $p < 0.001$) for all groups.
- The sensitivity and specificity of anti CCP2 in RA patients was 70% and 91.5% respectively, while the sensitivity and specificity of RF in RA patients was 52% and 89.4% respectively.
- Combining the RF and anti-CCP2 diagnostic tests enhanced the sensitivity to 78%, with a negative predictive value of 0.78, and increased the specificity for diagnosis of RA to 100%, with a positive predictive value of 1.
- A highly significant correlation was observed between anti-CCP titre and parameters of disease severity (rheumatoid nodules, RF positivity, x-ray score, and extra-articular manifestations) and HAQ-DI, while no statistically significant correlation was found

with parameters of disease activity (duration of morning stiffness, Ritchie articular index, the number of swollen joints, numerical rating scale of pain, DAS28, ESR, anemia, and thrombocytosis).

- A significant correlation was observed between RF and the presence of rheumatoid nodules and x-ray score, while it was not correlated with parameters of disease activity or disability.

We concluded the following:

- Anti-CCP2 is a useful serological test for establishing the diagnosis of rheumatoid arthritis and is associated with disease severity, radiological damage, and disability.
- There is modest but significant agreement between RF and anti-CCP2, however anti-CCP2 is more sensitivite and more specific than RF in the diagnosis of RA, with better positive and negative predictive values.
- The combination of testing for both RF and anti-CCP2 is more useful than testing for either alone, since if either is present, sensitivity is increased, while if both are present, specificity is greatly enhanced.
- Anti-CCP2 also helps to diagnose other inflammatory and non-inflammatory rheumatic diseases by reducing the rate of false-positive results in comparison with RF.