ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should I order an anti-CCP antibody test to diagnose rheumatoid arthritis?

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A: Yes. Testing for anti-cyclic citrullinated peptide (anti-CCP) antibody can help diagnose rheumatoid arthritis (RA) because it is a highly specific test.

For many years, the diagnosis of RA has been based on the presentation of symmetrical small- and large-joint polyarthritis that spares the lower spine, further supported by the presence of characteristic joint damage on radiography and an elevated rheumatoid factor while also excluding clinical mimics. However, rheumatoid factor is often not detected early in RA, and detection of rheumatoid factor is not specific for RA. Testing for anti-CCP antibody can provide additional information and, in some cases, enable earlier and more specific diagnosis.

An important advance in our understanding of the pathogenesis of RA and in improving our ability to diagnose it early is the recognition that RA patients often produce autoantibodies directed against proteins and peptides containing the amino acid citrulline. Citrulline is generated in an inflammatory environment by the modification of the amino acid arginine by the enzyme peptidylarginine deiminase. Antibodies against cyclic citrulline are generated by patients with a certain genetic makeup, although citrulline can be detected in inflammatory tissues in conditions other than RA (without the antibody).

Anti-CCP antibody has been found in sera up to 10 years before the onset of joint symptoms in patients who later develop RA and may appear somewhat earlier than rheumatoid factor.[1] From 10% to 15% of RA patients remain seronegative for rheumatoid factor throughout the disease course.

INFORMAL GUIDELINES FOR ANTI-CCP ANTIBODY TESTING

The role of anti-CCP antibody testing in the management of RA is still being defined, but we suggest several informal guidelines.

Anti-CCP antibody testing can help interpret the significance of an inexplicably high rheumatoid factor titer in the absence of classic RA. In such situations, a negative anti-CCP antibody test suggests a nonrheumatic disorder such as hepatitis C virus infection or endocarditis, whereas a positive anti-CCP antibody test is more consistent with early or even preclinical RA since this test, unlike rheumatoid factor testing, is generally negative in the setting of infection.

In a new patient with symptoms and signs compatible with early RA (ie, a duration of less than 6 months), we believe anti-CCP antibody testing is the better test because it has equal or greater sensitivity (especially early on) and greater specificity[2,3] than rheumatoid factor testing (TABLE 1). Thus, the clinician can have more confidence initiating aggressive disease-modifying therapy.

However, in a patient who has documented RA and who is seropositive for rheumatoid factor, anti-CCP antibody testing has limited value, as the information it provides may be redundant. In a patient with a low to intermediate probability for RA and with a negative or low level of rheumatoid factor, a positive anti-CCP antibody test helps confirm the di-

In confirmed RA and a positive rheumatoid factor test, anti-CCP testing is not necessary

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TABLE 1

Comparison of rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibody testing for rheumatoid arthritis

	SENSITIVITY (%)	SPECIFICITY (%)
Rheumatoid factor	44–60[2,3]	79–89[2,3]
Anti-CCP antibody	65–70[2]	96–98[2]
	39–94[3]	81–100[3]

agnosis. Rheumatoid factor positivity and anti-CCP antibody positivity are each associated with more severe RA. Neither test varies with the activity of RA.

Finally, in smokers with a particular genotype, the presence of anti-CCP antibody predicts a particularly worse course for RA.

THE ROLE OF RHEUMATOID FACTOR TESTING

Anti-CCP antibody correlates with severe joint destruction and a poor prognosis

Rheumatoid factor, first described in 1940,[4] is an antibody against the Fc portion of immunoglobulin G. The cutoff value for positivity varies by laboratory but is usually greater than 45 IU/mL by enzyme-linked immunosorbent assay or laser nephelometry, or greater than 1:80 by latex fixation. However, serum titers or serum levels expressed as "IU/mL" cannot accurately be compared between laboratories; instead, when using tests for rheumatoid factor, physicians should refer to specificity and sensitivity measurements for each analyzing laboratory.

Around 50% of patients with RA become positive for rheumatoid factor in the first 6 months, and 85% become positive over the first 2 years. Also, rheumatoid factor testing suffers from low specificity, since it can be detected (although sometimes in low levels) in a variety of infectious and inflammatory conditions, such as bacterial endocarditis, malaria, tuberculosis, osteomyelitis, hepatitis C (with or without cryoglobulinemia), Sjögren syndrome, systemic lupus erythematosus, primary biliary cirrhosis, postvaccination arthropathy, and aging.

Current detection methods cannot differentiate between naturally occurring, transiently induced, and RA-associated rheumatoid factor. The levels are generally higher in RA than in many non-RA disorders, but significant overlap occurs. Rheumatoid factor positivity serves as a marker of poor prognosis, predicting generally more aggressive, erosive disease, and it is correlated with extra-articular manifestations such as rheumatoid nodules and lung involvement.

The classification criteria for RA published in 2010 by the American College of Rheumatology and the European League Against Rheumatism provide references for the measurement of rheumatoid factor: "low-level positive" refers to values less than or equal to three times the upper limit of normal for a particular laboratory; "high-level positive" refers to values more than three times the upper limit of normal.[5] This is an attempt to provide a clinically useful benchmark for the measurement of rheumatoid factor, the values of which may vary between laboratories.

STUDIES COMPARING THE TWO TESTS

Several studies have evaluated the utility and validity of anti-CCP antibody testing vs rheumatoid factor testing.

In a study of 826 US veterans with RA,[6] 75% tested positive for anti-CCP antibody and 80% were positive for rheumatoid factor. It was found that a higher anti-CCP antibody titer was associated with increased disease activity and inversely correlated with remission, especially in those also positive for rheumatoid factor.[6]

In another study,[1] in which blood samples from 79 patients with RA who had been blood donors were analyzed, 39 patients (49.4%) were positive for either rheumatoid factor or anti-CCP antibody, or both, a median of 4.5 years (range 0.1 to 13.8 years) before the onset of RA symptoms; 32 patients (40.5%) became positive for anti-CCP antibody before symptom onset.

Whiting et al,[7] in a systematic review of 151 studies, showed that anti-CCP antibody testing had greater specificity than rheumatoid factor testing (96% vs 86%), with similar sensitivity (56% vs 58%)—most notably in eight cohort studies of patients with early RA.[7] In the 15 cohort studies analyzed, the test was found to have a positive likelihood ratio of 12.7 and a negative likelihood ratio of 0.45, supporting this as a test of high positive predictive value for RA.

In view of the evidence from these studies, it is not surprising that the 2010 collaborative classification of RA of the American College of Rheumatology and the European League Against Rheumatism places equal weight on anti-CCP antibody testing and rheumatoid factor testing in the early diagnosis of RA.[5]

GENETICS AND THE PROGNOSIS OF RHEUMATOID ARTHRITIS

In recent years, there has been a growing recognition that the pathogenesis of RA in patients who are seropositive for rheumatoid factor or anti-CCP antibody is different from the pathogenesis of RA in patients who are seronegative for rheumatoid factor and anti-CCP antibody. This may help us guide therapy.

Patients positive for rheumatoid factor or anti-CCP antibody who have a specific allelic subset of a region of the immune-response gene *DRB1*04* appear to be highly vulnerable to smoking as an environmental trigger or to worsening RA.[8]

Patients positive for anti-CCP antibody tend also to have severe joint destruction and, hence, have a worse prognosis. Kaltenhäuser et al[9] found that determining the presence of the shared epitope (an RA-specific genetic marker) and positivity for anti-CCP antibody facilitates prediction of the disease course and prognosis.[9]

Studies have shown that patients with confirmed RA who test positive for anti-CCP antibody may also have more-severe extra-articular manifestations. Recent studies have found anti-CCP antibody positivity in 15.7% to 17.5% of patients with psoriatic arthritis and in 85% of patients with RA. Patients with psoriatic arthritis who were positive for anti-CCP antibody had more joints that were tender and swollen, erosive arthritis, deformities, and functional impairment of peripheral joints.[10,11]

THE COST DIFFERENCE IS TRIVIAL IN THE LONG RUN

Cost is the major differentiating factor between rheumatoid factor testing and anti-CCP antibody testing. Rheumatoid factor testing costs around $43, and anti-CCP antibody testing costs $102 in the reference laboratory at Cleveland Clinic. However, the difference in cost is trivial, since this is only a one-time cost, whereas the information anti-CCP antibody testing provides can have a major impact on predicting the prognosis and determining the choice of therapy for a disease associated with high direct and indirect costs over a lifetime. Also, Medicare and other insurers would likely reimburse for anti-CCP antibody testing as long as it was associated with a related diagnosis such as arthralgia or arthritis.

Given that there will be a small number of patients with confirmed RA who will be negative for rheumatoid factor yet positive for anti-CCP antibody, one can support ordering both tests in tandem in a patient whom you strongly suspect of having RA. Or, at $100, one could make the argument that it would be cost-effective to order anti-CCP antibody testing only if rheumatoid factor testing is negative.

Testing for rheumatoid factor and anti-CCP antibody should not be done serially to assess treatment response or disease activity in these patients: these markers do not vary with inflammatory activity or disappear with clinical "remission."

Testing for rheumatoid factor and anti-CCP antibody should not be done serially to assess treatment response or disease activity

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