Review

Anti-CCP antibody testing as a diagnostic and prognostic tool in rheumatoid arthritis

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Summary

Rheumatoid arthritis is both common and chronic, with significant consequences for multiple organ systems. Better understanding of its pathophysiology has led to the development of targeted therapies that have dramatically improved outcomes. The key to therapeutic success lies in identifying individuals who will have severe destructive disease as early as possible, so that effective treatment can be initiated before irreversible damage occurs. Anti-cyclic citrullinated peptide (anti-CCP) antibody testing is particularly useful in the diagnosis of rheumatoid arthritis, with high specificity, presence early in the disease process, and ability to identify patients who are likely to have severe disease and irreversible damage. However, its sensitivity is low, and a negative result does not exclude disease. Anti-CCP antibodies have not been found at a significant frequency in other diseases to date, and are more specific than rheumatoid factor for detecting rheumatoid arthritis. We discuss anti-CCP antibody testing in rheumatoid arthritis, with an emphasis on diagnostic performance, prognostic capability, and relevance to pathogenesis and new treatment paradigms in rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA) is a severe, progressive, systemic inflammatory disease of unknown aetiology. The morbidity and mortality it causes are a consequence of local and systemic inflammatory processes that damage cartilage, bone and soft tissue, as well as blood vessels and viscera. Until recently, treatment for RA was limited, and severe joint damage and overall debility were common. Early and aggressive intervention with new and effective biological treatments can alter the course of the disease, lengthen life, and improve function, but better molecular markers for diagnosis and prognosis are needed to identify RA patients earlier and fine-tune therapeutic choices to the individual patient. Serological testing for rheumatoid factor is complicated by moderate sensitivity and specificity, and high rates of positivity in other chronic inflammatory and infectious diseases such as Sjögren’s syndrome and chronic viral hepatitis. The reported sensitivity and specificity of rheumatoid factor in current studies may be falsely elevated by the inclusion of rheumatoid factor as a diagnostic criteria in the commonly used American College of Rheumatology diagnostic criteria for RA. Anti-cyclic-citrullinated-peptide (anti-CCP) antibodies hold promise for earlier and more accurate diagnosis of disease, improved prognostic information, and have been implicated in RA pathogenesis. If the physician is to intervene optimally during a patient’s window of opportunity before irreversible damage.
occurs, such a biomarker may be very useful, when used in combination with other diagnostic features.

**Historical background of citrullinated peptide antibodies and assays**

The discovery of anti-CCP antibodies evolved from previous work examining autoantibodies in sera from RA patients that were distinct from rheumatoid factor. The first citrulline-binding autoantibodies in RA sera were discovered by Nienhuis et al. in 1964, as an autoantibody able to bind to perinuclear granules in normal human buccal mucosa cells, and were named antiperinuclear factor. Antiperinuclear factor was found in 48% of patients with RA, and only 1% of healthy controls. The specificity of antiperinuclear factor for citrulline was not appreciated until years later, however. In 1979, Young et al. reported that RA sera contained antibodies that reacted to the keratinized layer of epithelium. These antibodies were called anti-keratin antibodies, and were only found in RA patients. Subsequent studies demonstrated that anti-keratin antibodies and antiperinuclear factor recognized a similar epitope, and were perhaps the same antibody. It was also discovered that conversion of arginine to citrulline on peptides was essential for anti-keratin antibody and perinuclear factor binding. Therefore, antiperinuclear factor and anti-keratin antibodies can be broadly categorized as anti-citrullinated-peptide antibodies. There is evidence for abnormal citrullination of various peptides in a diverse array of human diseases, including RA, psoriasis, and multiple sclerosis. The formation of antibodies to citrullinated peptides seems to be specific for RA patients, however.

Assays for the detection of anti-citrullinated peptide antibodies using linear stretches of citrullinated peptide proved difficult to standardize, but an assay using a cyclic citrullinated peptide (CCP) resulted in greater reproducibility. This test for anti-CCP antibodies was made commercially available, and is currently known as the anti-CCP1 assay. A second-generation assay was devised by screening a large library of citrulline-containing peptides with RA sera to identify the epitopes with the highest yield. This assay is now known as the anti-CCP2 assay, and has slightly better performance characteristics than anti-CCP1. Anti-CCP2 is currently the most widely used anti-citrullinated peptide assay.

**Prevalence, sensitivity, and specificity of anti-CCP antibodies for RA**

Several studies have examined the performance characteristics of anti-CCP antibodies in RA, using both the anti-CCP1 and anti-CCP2 assays. Sensitivity and specificity using the anti-CCP1 assay ranged from 44% to 56% and 90% to 97%, respectively. Detection of antibody with CCP2 assays resulted in improved sensitivity (64–89%), and specificity (88–99%). Rheumatoid factor sensitivity ranged from 59% to 79% and specificity from 80% to 84% in the same groups. Many patients in the study groups had both rheumatoid factor and anti-CCP antibodies, but a significant number had only one or the other. Details of the studies are summarized in Table 1. Some of the variability in the sensitivity and specificity between studies may relate to slightly different cut-off points for positivity, and differences in disease duration, severity and other clinical characteristics of the groups being tested.

Studies of anti-CCP antibodies have been done in early arthritis patients with <6 months of joint symptoms. Many did not have an obvious clinical diagnosis at inception, but attempts were made to establish diagnoses at later dates, often 1–2 years after initial presentation. The physicians making the clinical diagnoses were usually blinded to the laboratory information. Anti-CCP antibody testing showed sensitivity ranging from 39% to 50%, and specificity from 93% to 98% in the patients who were eventually diagnosed with RA, compared to the other non-RA patients. Rheumatoid factor showed a sensitivity of 31% to 54% and specificity of 91% to 93% for the eventual diagnosis of RA when the test was done at first presentation, although rheumatoid factor was one of the criteria for the diagnosis of RA in these studies. Some patients who were eventually diagnosed with RA had either rheumatoid factor or anti-CCP antibodies. The combination of both rheumatoid factor and anti-CCP antibodies predicted RA with a sensitivity of 30% to 39% and a specificity of 98% to 100%. See Table 2 for a summary of the early arthritis cohort studies. Overall, the high specificity of anti-CCP antibodies for RA does not seem to differ significantly between early and established disease.

A number of papers have suggested diagnostic algorithms incorporating anti-CCP antibodies resulting in improved sensitivity and specificity for diagnosis. In a study of 196 RA patients, the 56% sensitivity and 90% specificity of anti-CCP
### Table 1a  Study designs evaluating anti-CCP antibodies in rheumatoid arthritis (RA)

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Assay</th>
<th>RA patients (n)</th>
<th>Control population 1</th>
<th>Control population 2</th>
<th>Anti-CCP Sensitivity</th>
<th>Specificity control 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Specificity control 2&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td>Bizzaro&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Italy</td>
<td>CCP1</td>
<td>98</td>
<td>Non-RA inflammatory disease + infectious disease</td>
<td>NA</td>
<td>44%</td>
<td>97%</td>
<td>NA</td>
</tr>
<tr>
<td>Bas&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Switzerland</td>
<td>CCP1</td>
<td>196</td>
<td>Non-RA inflammatory disease</td>
<td>Healthy donors</td>
<td>56%</td>
<td>90%</td>
<td>99%</td>
</tr>
<tr>
<td>Zeng&lt;sup&gt;15&lt;/sup&gt;</td>
<td>China</td>
<td>CCP1</td>
<td>191</td>
<td>Non-RA inflammatory disease + infectious disease</td>
<td>Healthy donors</td>
<td>47%</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>Lee&lt;sup&gt;16&lt;/sup&gt;</td>
<td>US</td>
<td>CCP2</td>
<td>103</td>
<td>Non-RA arthritis</td>
<td>NA</td>
<td>66%</td>
<td>90%</td>
<td>NA</td>
</tr>
<tr>
<td>Suzuki&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Japan</td>
<td>CCP2</td>
<td>549</td>
<td>Non-RA inflammatory disease</td>
<td>NA</td>
<td>89%</td>
<td>88%</td>
<td>NA</td>
</tr>
<tr>
<td>Vallbracht&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Germany</td>
<td>CCP2</td>
<td>295</td>
<td>Suspected rheumatic disease</td>
<td>Healthy donors</td>
<td>64%</td>
<td>96%</td>
<td>99%</td>
</tr>
<tr>
<td>De Rycke&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Belgium</td>
<td>CCP2</td>
<td>118</td>
<td>Suspected rheumatic disease</td>
<td>NA</td>
<td>74%</td>
<td>99%</td>
<td>NA</td>
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</table>

Non-RA inflammatory disease, idiopathic inflammatory disease other than RA, such as systemic lupus, Crohn’s disease, etc. Infectious disease, chronic viral infections, tuberculosis, etc. Non-RA arthritis, other inflammatory and non-inflammatory arthritic disorders such as osteoarthritis, lupus, etc. Suspected rheumatic disease, patients being evaluated for possible rheumatic disease in the hospital or clinic setting. NA, not applicable. <sup>a</sup>If two control groups were studied, the specificity is calculated for each control group separately.

### Table 1b  Sensitivity and specificity of anti-CCP antibodies for rheumatoid arthritis

<table>
<thead>
<tr>
<th>Study</th>
<th>RF sensitivity</th>
<th>RF specificity</th>
<th>RF+ and CCP+</th>
<th>RF&lt;sup&gt;−&lt;/sup&gt; and CCP+</th>
<th>RF+ and CCP&lt;sup&gt;−&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>Bizzaro&lt;sup&gt;13&lt;/sup&gt;</td>
<td>62%</td>
<td>84%</td>
<td>36%</td>
<td>5%</td>
<td>27%</td>
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<tr>
<td>Bas&lt;sup&gt;14&lt;/sup&gt;</td>
<td>73%</td>
<td>82%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Zeng&lt;sup&gt;15&lt;/sup&gt;</td>
<td>59%</td>
<td>NA</td>
<td>38%</td>
<td>9%</td>
<td>21%</td>
</tr>
<tr>
<td>Lee&lt;sup&gt;16&lt;/sup&gt;</td>
<td>72%</td>
<td>80%</td>
<td>57%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>Suzuki&lt;sup&gt;17&lt;/sup&gt;</td>
<td>70%</td>
<td>82%</td>
<td>NA</td>
<td>69%</td>
<td>NA</td>
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<tr>
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<td>66%</td>
<td>82%</td>
<td>52%</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>De Rycke&lt;sup&gt;19&lt;/sup&gt;</td>
<td>79%</td>
<td>81%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

RF, rheumatoid factor; RF+ and CCP+, percentage of patients positive for both RF and anti-CCP; RF<sup>−</sup> and CCP+, percentage of patients negative for RF but positive for anti-CCP; RF+ and CCP<sup>−</sup>, percentage of patients positive for RF and negative for anti-CCP. NA, not applicable.
antibodies was improved when combined with rheumatoid factor seropositivity.\textsuperscript{14}

Anti-CCP antibodies have been tested in ethnically diverse RA cohorts from North America, Europe, and Asia, and rates of anti-CCP detection are remarkably consistent. Additionally, these investigations used several different controls, including healthy individuals and populations of various arthritic and non-arthritic inflammatory diseases, and used various methods of data collection and analysis. Despite this, no control population has shown an equivalent rate of anti-CCP positivity to that found in RA, and the specificity remains high even if controls with similar inflammatory disease processes are used.

**Potential predictive value of anti-CCP antibodies to detect individuals at-risk for RA**

Ideally, screening healthy individuals at high risk of developing RA, for example those with a family history of RA, could allow for increased vigilance and the possibility of early intervention. A number of studies have documented the appearance of anti-CCP antibodies prior to the onset of RA. A cohort of 83 RA patients had blood samples available in a blood bank predating their diagnosis. Anti-CCP antibodies were positive prior to diagnosis in 33.7% of the RA patients vs. 1.8% in controls taken from the same pool of subjects ($p < 0.0001$).\textsuperscript{25} Median time between blood sampling and the development of disease was 2.5 years, with a maximum interval of 9 years. Rheumatoid factor was positive in 19.3% of donors who would eventually be diagnosed with RA, compared to 6% of control donors, which was not significant in logistic regression models. A second similar study identified 79 RA patients who had donated blood to a regional blood bank prior to their diagnosis.\textsuperscript{26} Forty percent of RA patients tested positive for anti-CCP antibodies prior to the onset of disease, compared with 0.6% in the control population. Anti-CCP antibodies were identified a median of 4.8 years before RA diagnosis, and one patient had anti-CCP antibodies 14 years prior to RA symptoms. Rheumatoid factor was positive in 27.8% of patients prior to diagnosis, and was positive in only 1.1% of controls. In a study using banked sera from the Nurses' Health Study, anti-CCP antibodies were detected up to 12 years prior to diagnosis, and were associated with an odds ratio of 5.1 for developing RA after adjusting for hormonal status and other confounding variables.\textsuperscript{27} Anti-CCP antibodies can appear years in advance of actual disease, and may eventually allow for identification of individuals who are likely to develop disease.

**Anti-CCP antibodies predict RA diagnosis in early arthritis**

Early in the disease process, RA is often difficult to distinguish from other types of inflammatory arthritis and systemic inflammatory conditions, as their initial presentations may be similar. Several studies have examined the utility of anti-CCP antibody testing in distinguishing RA from other inflammatory diseases, by studying cohorts of patients who presented with non-specific early inflammatory arthritis. In one such study, 524 patients with early undifferentiated arthritis of <2 years duration had anti-CCP antibody testing at inception, and were followed longitudinally for 2 years.\textsuperscript{28} After 2 years, 60% had self-limited inflammatory arthritis, 16% had persistent non-erosive arthritis, and 24% had persistent erosive arthritis. Anti-CCP positivity conferred an odds ratio of 4.58 for persistent vs. self-limited arthritis, as well as an odds ratio of 4.58 for erosive vs. non-erosive disease. Rheumatoid factor conferred an odds ratio of 2.99 for persistent vs. self-limited arthritis, and an odds ratio of 2.99 for erosive vs. non-erosive disease.

In another early arthritis study, 318 patients with undifferentiated inflammatory arthritis of <2 years duration were followed for 3 years.\textsuperscript{22} RA was eventually diagnosed in 64/69 (93%) of those with a positive initial anti-CCP antibody test. In this study, anti-CCP antibodies conferred an odds ratio of 38.6 for the diagnosis of RA, compared to an odds ratio of 9.8 for rheumatoid factor. These studies, and the others summarized in Table 2, demonstrate the significant predictive value of anti-CCP antibodies in early arthritis for the eventual diagnosis of RA. The ability to identify patients who are at greatest risk for progressive and destructive arthritis is especially useful, as these individuals will benefit most from early aggressive intervention.

**Anti-CCP antibodies correlate with disease activity parameters**

Patients with RA show considerable variability in disease activity, which can be difficult to predict at the onset of disease. Anti-CCP antibodies have proven useful in identifying those patients who are likely to have clinically significant disease activity. In 150 patients with long-standing RA, a strong
correlation was found between greater disease activity and anti-CCP positivity. In another study, anti-CCP2 assays were done on sera from 242 RA patients who were followed for 3 years. The patients were treated at the physician’s discretion, and the physicians were blinded to the patient’s anti-CCP status. Anti-CCP antibodies were positively correlated with higher erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), swollen joint count, and worse physician global assessment ratings. Presence of rheumatoid factor was positively correlated with increased ESR and CRP, but there was no association with other disease activity markers. In a similar study, anti-CCP status was correlated with disease activity parameters in 379 early RA patients. Statistically significant correlations were seen between anti-CCP positivity and higher CRP, ESR, and disease activity measurements. Of note, current or previous cigarette smoking was also associated with a positive anti-CCP test. This is especially interesting, as there is an association between tobacco use and the development of RA, as well as increased RA disease activity. In summary, anti-CCP antibodies identify patients with significantly greater disease activity more reliably than rheumatoid factor.

### Anti-CCP antibodies predict disease damage

In addition to disease activity, irreversible damage from RA is an important outcome with significant impact on quality of life and functional capability. Predicting which patients will accrue damage is difficult, and disease activity parameters are not always accurate in predicting subsequent joint destruction. In a study addressing the progression of radiological damage in RA, anti-CCP1 antibodies were measured in 273 RA patients with <1 year of symptoms. The patients were followed for at least 6 years and had plain radiographs of the hands and feet performed every 6 months. X-rays were graded by a radiologist blinded to the clinical data. After 6 years, anti-CCP1 positive patients had significantly more radiographic damage than anti-CCP1 negative patients ($p<0.05$). Rheumatoid factor was also associated with increased radiological damage at 6 years ($p<0.0001$). Some 32% of patients in the study had both rheumatoid factor and anti-CCP antibodies, 33% had only anti-CCP, and 24% had only rheumatoid factor. Anti-CCP antibodies identified a large group of patients at increased risk of damage who would not have been identified using rheumatoid factor testing alone.
In another study, 104 early RA patients had anti-CCP antibodies and hand radiographs done at inception. Anti-CCP antibodies were positive in 36/67 (54%) of those who had at least one erosion at inception, compared with 8/37 (22%) with non-erosive disease. Rheumatoid factor was positive in 39/67 (58%) with erosive disease, vs. 11/37 (30%) with non-erosive disease. Among seropositive patients, 22% had only anti-CCP antibodies. Thus, anti-CCP antibodies may be useful in identifying a group of RA patients who are more likely to develop damage, and who may not be identified by rheumatoid factor testing alone.

Change in anti-CCP titres with treatment

Some reports describe a decrease in titre of anti-CCP antibodies following successful treatment of RA. In a RA treatment trial, 35% of patients had a decrease in anti-CCP2 titres of >15%, while 19% had an increase of >15%; 46% of patients had anti-CCP2 titres within 15% of the baseline values. All but 5 of 242 patients with a positive anti-CCP2 antibody test remained positive when tested serially over a 3-year period. In a similar study, serial anti-CCP2 levels were measured in 43 patients with RA who were treated for at least 2 years. Mean anti-CCP2 titres at inception were 107±9.5 U, which fell to a mean of 92±9.8 U (p=0.0001) after 24 months of treatment. Titres were more likely to decrease in patients showing a greater degree of clinical improvement. In summary, a decrease in anti-CCP titre can be seen with RA treatment, however, the decrease is usually modest and should not drive treatment decisions. Anti-CCP positive patients usually remain positive despite treatment.

Anti-CCP antibodies in other diseases

Several other inflammatory conditions have been studied for the presence of anti-CCP antibodies. Anti-CCP2 assays were done on 192 patients with psoriatic arthritis, 15 (7.8%) testing positive for anti-CCP2 antibodies. All anti-CCP2 positive patients had at least one feature of psoriatic arthritis thought to be useful in differentiating psoriatic arthritis from RA. However, many of these patients were also positive for rheumatoid factor. In another study, 160 psoriatic arthritis patients and 146 patients with psoriasis and no arthritis underwent anti-CCP2 antibody testing. Eleven (6.9%) patients with psoriatic arthritis were positive for anti-CCP2 antibodies, compared to a single patient with psoriasis and no arthritis. Of the psoriatic arthritis patients with anti-CCP2 antibodies, 8/11 fulfilled established criteria for RA. Thus, anti-CCP antibodies are uncommon in psoriatic arthritis, and are most frequently found in patients who also have features of RA.

Among 66 patients with systemic lupus erythematosus, 2/10 with erosive arthritis, and 1/56 with non-erosive disease tested positive for anti-CCP antibodies. Thus, similar to RA, anti-CCP antibodies may help identify lupus patients at risk for erosive joint disease.

Anti-CCP2 assays were also done on sera from 39 patients with chronic hepatitis C virus infection, 8 of whom had articular involvement thought to be related to hepatitis C, as well as 10 patients with co-existent RA and chronic hepatitis C. Although some of the patients with established RA and chronic hepatitis C tested positive, as would be expected, none of those with chronic hepatitis C only tested positive, regardless of articular involvement. Thus, anti-CCP antibodies may be useful in discriminating hepatitis-C-related arthropathy from RA.

Insights into pathogenesis

Citrullinated peptides have been found in synovial tissues from RA patients as well as non-RA controls, although the formation of antibodies against citrullinated proteins seems to be very specific for RA. Citrullination of synovial proteins has also been demonstrated in mouse models of inflammatory arthritis, however the mice do not form antibodies to citrullinated peptides. Whether anti-CCP antibodies are involved in pathogenesis and contribute to ongoing immune activation or are a by-product of inflammation in the synovium is not known. In a Japanese RA cohort, a haplotype of the enzyme that converts arginine to citrulline was associated with RA, but this association was not confirmed in an British RA cohort.

A number of investigators have found an association between anti-CCP antibody production and the presence of certain MHC class II alleles containing the ‘shared epitope’. The shared epitope refers to a conserved motif in the peptide binding cleft of the MHC molecule which is encoded by certain HLA class II alleles, and has been associated with risk of developing RA, as well as greater disease severity. In a blood donor cohort, the presence of both anti-CCP antibodies and the shared epitope in asymptomatic donors was associated with an
shared epitope alleles. RA patients with anti-CCP antibodies and no alleles had more destructive joint disease than with both anti-CCP antibodies and shared epitope than the two combined. Furthermore, RA patients were less predictive of the future onset of disease antibody production in RA patients. In this study, interaction between cigarette smoking and anti-CCP study has demonstrated a strong gene-environment a marker for this phenomenon. An interesting recent role in RA (Figure 1). Anti-CCP antibodies may be arthritogenic antigen exists and plays a pathogenic epitope MHC supports the hypothesis that an demonstration that citrullinated peptides bind to the shared epitope MHC. This binding could result in immune cell activation, and subsequently a directed immune response against citrullinated peptides and production of anti-citrullinated peptide antibodies. The production of anti-CCP antibodies.

In RA patients, shared epitope alleles are strongly associated with anti-CCP antibodies. In mice transgenic for shared epitope MHC, conversion of arginine to citrulline on synthetic peptides allowed high-affinity binding of the peptide to the MHC. This binding could result in immune cell activation, and subsequently a directed immune response against citrullinated peptides and production of anti-citrullinated peptide antibodies. The demonstration that citrullinated peptides bind to the shared epitope MHC supports the hypothesis that an arthritogenic antigen exists and plays a pathogenic role in RA (Figure 1). Anti-CCP antibodies may be a marker for this phenomenon. An interesting recent study has demonstrated a strong gene-environment interaction between cigarette smoking and anti-CCP antibody production in RA patients. In this study, the likelihood of having anti-CCP antibodies was related to previous smoking in a dose-dependent manner for RA patients carrying the shared epitope MHC, which was not the case for patients without the shared epitope. Citrullinated peptides were detected in the broncho-alveolar lavage fluid of the patients who smoked, and were not present in non-smokers, suggesting that smoking could cause citrullination of peptides in the lung, and that possibly these could promote an immune reaction to citrullinated peptides in the genetic background of the shared epitope MHC.

Conclusion

Anti-CCP antibodies are a highly specific marker for RA in several diverse patient groups. This specificity extends to patients with early disease, in whom a timely diagnosis is most needed. The low sensitivity of the test (40–50% in most published cohorts) indicates that a negative anti-CCP antibody test does not exclude disease, but its high specificity means that a positive result markedly increases the probability that the patient will have RA. Anti-CCP antibodies also identify a subset of patients who are likely to have substantial ongoing disease activity, accrue more damage, and who will probably benefit most from early aggressive treatment. A significant number of these patients do not have rheumatoid factor, and may not otherwise have been expected to develop severe aggressive disease. Anti-CCP antibodies tend to remain stable or decline slightly with treatment, and have not been found frequently in non-RA inflammatory or arthritic diseases. The presence of anti-CCP antibodies in serum years before the onset of RA suggests the possibility of pre-clinical detection, and may provide information about early events in the pathogenesis of the disease.

References


