

Anti-Cyclic Citrullinated Peptide Antibodies (Anti-CCP) Are Highly Specific For Rheumatoid Arthritis in Combination With IgM Rheumatoid Factor Positivity

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Introduction

Anti-CCP has been reported to be highly specific (96%) and moderately sensitive (78%) for Rheumatoid Arthritis (RA), and importantly, is seen in 70% of early RA. It appears to be useful diagnostically in differentiating Seropositive RA from the arthritis of Hepatitis C with Rheumatoid Factor (RF) positivity. It may also be useful in differentiating other entities that can resemble RA and at times be RF positive (ie., Polymyalgia Rheumatica and Parvoviral Arthropathy), although this has not yet been formally studied. Furthermore, 30-40% of Seronegative RA are reported as Anti-CCP positivity. In addition, Anti-CCP positivity is predictive of erosive disease.

Our purpose was to evaluate the sensitivity and specificity of Anti-CCP combined with IgM RF positivity in RA, disease controls and normal controls.

Methods

Sera from 179 patients fulfilling the 1987 ACR criteria for RA were tested along with sera from 348 disease controls, and 100 normal controls for the presence of IgG Anti-CCP antibodies using a commercial assay (Diastat™ Anti-CCP EIA).

- ▶ All RA patients and all patients without RA but Anti-CCP positivity were tested for IgM RF by EIA.**
- ▶ All patients' sera were randomly selected from the practices of Drs. Morris and Metzger and stored at -70°C until testing.**
- ▶ Clinical correlation with the serological findings are in progress.**

Anti-Cyclic Citrullinated Peptide Antibodies in Rheumatoid Arthritis, Disease Controls and Normals

Table I

RA	Anti-CCP Positive	Sensitivity
Rheumatoid Arthritis	155/179	87%
Seropositive RA	144/155	93%
Seronegative RA	11/24	46%

Table II

Diseases	Anti-CCP Positive	Sensitivity
SLE	3/57	5%
Sjogren's Syndrome	0/11	0%
Progressive Systemic Sclerosis	1/16	6%
CREST Syndrome	0/22	0%
Dermatomyositis	0/11	0%
Polymyositis	0/5	0%
Seronegative Spondyloarthropathy		
A. Ankylosing Spondylitis	0/26	0%
B. Psoriatic Arthritis	1/28	4%
C. Reiter's Syndrome	0/15	0%
D. Inflammatory Bowel Disease with Arthritis	0/4	0%
Juvenile Rheumatoid Arthritis	1/9	11%
Polymyalgia Rheumatica	1/45	2%
Parvoviral Arthropathy	0/11	0%
Hepatitis C	0/4	0%
Gout	0/10	0%
Fibromyalgia	0/21	0%
Antiphospholipid Antibody Syndrome	0/10	0%
Wegener's Granulomatosis	0/11	0%
Vasculitis (various types)	0/11	0%
Sarcoidosis	0/4	0%
Seronegative Inflammatory Arthropathy	3/11	27%
Early Synovitis	1/7	14%
Normal Controls	1/100	1%

- ▶ **The specificity of Anti-CCP and IgM RF positivity for RA was 99.6% (only 2/448 controls were RF positive and Anti-CCP positive). Interestingly, both patients were weakly RF positive (8.2 IU/mL and 7.5 IU/mL) with the cutoff being <5 IU/mL.**
 - ▶ **The specificity of Anti-CCP alone was 97% relative to disease controls (11/348 were positive), and 99% specific versus normal controls (1/100 being positive).**
 - ▶ **The sensitivity of Anti-CCP positivity combined with RF positivity was 80.4% (144/179).**
 - ▶ **Anti-CCP was positive in 46% (11/24) Seronegative RA patients.**
 - ▶ **Anti-CCP was also positive in 3/11 seronegative inflammatory arthropathy patients suggesting a likely diagnosis of RA.**
 - ▶ **Of the eleven positive sera in the disease control group (11/348) only three were strongly positive, one with SLE, one with scleroderma and one with seronegative inflammatory arthropathy.**
 - ▶ **A substantial number of RA sera, 49% (76/155) was strongly reactive for Anti-CCP (>105 Units/mL), compared to disease control sera , 27% (3/11).**
 - ▶ **Only 12% (19/155) of RA sera had values <15 IU/mL, while in the disease control group 73% (8/11) were <15 IU/mL.**
 - ▶ **Interestingly, the sensitivity of Anti-CCP and RF were identical in RA, 87% (155/179).**
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Conclusion

Our results demonstrate that the presence of both RF and Anti-CCP is highly specific and moderately sensitive for RA, making this combination of auto-antibodies a powerful serologic tool in the serologic assessment of RA.

- ▶ **Anti-CCP alone is also highly specific and remarkably sensitive for RA.**
 - ▶ **A positive Anti-CCP result in seronegative RA strongly supports the diagnosis of RA serologically.**
 - ▶ **Most of the Anti-CCP positive RA patients had moderate to high reactivity to Anti-CCP, whereas the majority of the non-RA patients who were Anti-CCP positive had low reactivity.**
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Bibliography

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2. Information obtained from 8 clinical trials performed by Axis Shield involving 2,774 sera.
3. Eric, Jan, J.A. Kroot: The Prognostic Value of Anti-Cyclic Citrullinated Peptide Antibody in Patients with Recent Onset Rheumatoid Arthritis. *Arthritis & Rheumatism*, Vol. 43, No 8, Aug 2000, pgs. 1831-1835.
4. Quinn, Mark A., et al: Early RA: Anti-CCP Antibodies Predict Radiographic Progression. *ACR 65th Annual Scientific Meeting*, San Francisco, CA Nov. 10-15, 2001.

Anti-CCP Test Graph

- ▶ In a nine month period from November 21, 2002 through August 28, 2003, the total number of Anti-Cyclic Citrullinated Peptide Ab (Anti-Citrulline Ab) tests ordered was 15,024. Of those tests, 2,665 tests were positive (20 Units or higher). Of the positive tests, see the table below for the amount of tests with result values between 20 - 39 Units, 40 - 59 Units, 60 - 79 Units, and 80 Units and over.

