

Recent data suggest the existence of different phenotypic subsets of RA at clinical onset and elevated serum COMP levels should be interpreted in relation to this new approach.

In recent years, data have been published to suggest that anti-CCP positive and anti-CCP negative RA constitute two different phenotypic manifestations of RA with respect to both clinical prognosis and underlying disease mechanisms. Anti-CCP antibodies have been proposed as a pathogenic factor that suppresses chondrocytes anabolism (1), and are also associated to a more intense lymphocyte accumulation in the synovial compartment (2). Some of these phenomena can be identified in patients before the onset of clinical symptoms and anti-CCP antibodies is today an established biomarker (3, 4) with high likelihood in the preclinical phase to predict the risk to develop clinical RA. An increase in pro-inflammatory cytokines in serum has also been shown in this preclinical phase (5). Since the release of COMP is a consequence of and not the cause of the underlying disease mechanism it is a logical hypothesis that COMP-value must be interpreted in relation to the underlying RA phenotype.

Two recent publications during the last year, from two independent research groups, have reported that anti-CCP negative RA patients compared to anti-CCP positive have a higher serum COMP level as measured by AnaMar's test when measured both in the preclinical phase (6) and early in the clinical onset before initiation of therapy (7). Despite a lower level of serum COMP in untreated seropositive RA, the COMP level increased in a parabolic shape during the first four years during therapy and was associated with MRI verified erosions which were not observed in anti-CCP negative RA patients (7).

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Cartilage oligomeric matrix protein associates differentially with erosions and synovitis and has a different temporal course in cyclic citrullinated peptide antibody (anti-CCP)-positive versus anti-CCP-negative early rheumatoid arthritis.

J Rheumatol. 2011;38:1563-8.

Elevated serum COMP was shown in anti-CCP positive RA patients at clinical onset before therapy start and increased in a parabolic course concomitant to MRI verified erosions and edema.

The authors have in a recent study demonstrated a negative correlation between the level of anti-CCP and a biomarker of cartilage collagen anabolism (PIIANP) indicating that anti-CCP might have a suppression effect on chondrocytes. The aim of this study was to investigate if they could verify a difference between positive and negative anti-CCP RA patients at the clinical onset and during the first four years with respect to serum COMP levels as a cartilage turnover marker. Serum COMP was significantly ($p < 0.001$) higher compared to controls at clinical onset of RA and remained increased after four years. Serum COMP was significantly lower in anti-CCP positive ($p < 0.048$) and IgM-RF-positive patients ($p < 0.47$) at clinical onset compared to sero-negative patients. In contrast to sero-negative RA patients the level of serum COMP followed a parabolic course during the first four years. They also found a significant but low association of the COMP level and MRI verified erosions and edema in sero-positive patients but not in sero-negative. The authors conclude that the results provides further evidence for the existence of different disease pathways between anti-CCP positive and anti-CCP negative subsets of RA-patients and that serum COMP might have different implications in these subsets.

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Increased cartilage turnover, measured as high serum COMP, may be a distinct process and thus a RA predictor in the pre-clinical phase of a subset of RA-patients with anti-CCP negative tests.

This study was based on an earlier reported observation that auto-antibodies such as anti-CCP and Rheumatoid Factor (RF) could be detected in the serum of RA-patients several years before onset of clinical symptoms and diagnosis. The aim of the present study was to use measurements of serum COMP as a marker of joint cartilage turnover and to investigate the extent of cartilage involvement before onset of clinical RA. Subjects, apparently healthy at inclusion, who developed RA within a median of 5 years (range 1-13) were recruited from a large prospective cohort (n=30447) and tested for anti-CCP, Anti-MCV, IgM RF, and COMP. In the subset of patients who developed anti-CCP negative clinical RA within 3 years, high serum COMP values (>12 U/l) were significantly ($p=0.04$) more common than in matched controls (10/20 vs 2/13). The overall sensitivity to detect RA within three years was 36% for raised COMP and 39% for anti-CCP but the specificity was much higher for anti-CCP, 100% vs 81%. Using a logistic regression model an increase in serum COMP was significantly associated to an increased development of clinical RA (OR 1.42 per U/l).

The authors conclude that increased cartilage turnover, measured as high serum COMP, may be a distinct process and thus a RA-predictor in the preclinical phase of a subset of RA-patients with anti-CCP negative test. As in the publication above, the results suggest the existence of various phenotypic subsets of RA at the clinical onset.

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