

RECENT PUBLICATIONS ON THE CLINICAL UTILITY OF SERUM COMP MEASUREMENTS IN RHEUMATOID ARTHRITIS PATIENTS.

In a recently published review (1) of COMP as a biomarker of arthritis, based on 26 clinical studies, Tseng, Reddi and Di Cesare conclude that COMP would be a valuable tool for identifying patients at high risk for rapid joint destruction and for monitoring treatment efficacy. They pointed out that COMP is not a diagnostic marker that should be compared to anti-CCP and Rheumatoid Factor (RF) but a disease activity marker only partially related to inflammation.

In this Focus Letter we will present three more recently published RA-studies, not included in the review above, which report results in line with this conclusion and based on AnaMar COMP[®] ELISA. Important findings in these publications were that cartilage alteration, expressed as serum COMP increase, starts before onset of clinical symptoms and even in sero-negative patients (2). This could also be verified by MRI-proven bone erosion in early RA (3). The results (3,4) also showed, in accordance with the review above, that systemic inflammatory biomarkers and serum COMP levels describe two different biological processes. Therefore the findings that serum COMP decreased in patients who showed remission after anti-TNF treatment but not the other patients is of special interest (4).

- 1 Tseng S, Reddi AH, Di Cesare PE.
Cartilage Oligomeric Matrix Protein (COMP): A Biomarker of Arthritis.
Biomark Insights. 2009;17;4:33-44.
- 2 Turesson C, Bergström U, Jacobsson LT, Truedsson L, Berglund G, Saxne T.
Increased cartilage turnover and circulating autoantibodies in different subsets before the clinical onset of rheumatoid arthritis.
Ann Rheum Dis. 2011;70:520-2.
- 3 Kawashiri SY, Kawakami A, Ueki Y, Imazato T, Iwamoto N, Fujikawa K, Aramaki T, Tamai M, Nakamura H, Origuchi T, Ida H, Eguchi K.
Decrement of serum cartilage oligomeric matrix protein (COMP) in rheumatoid arthritis (RA) patients achieving remission after 6 months of etanercept treatment: comparison with CRP, IgM-RF, MMP-3 and anti-CCP Ab.
Joint Bone Spine. 2010;77:418-20.
- 4 Fujikawa K, Kawakami A, Tamai M, Uetani M, Takao S, Arima K, Iwamoto N, Aramaki T, Kawashiri S, Ichinose K, Kamachi M, Nakamura H, Origuchi T, Ida H, Aoyagi K, Eguchi K.
High serum cartilage oligomeric matrix protein determines the subset of patients with early-stage rheumatoid arthritis with high serum C-reactive protein, matrix metalloproteinase-3, and MRI-proven bone erosion.
J Rheumatol. 2009;36:1126-9.

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). 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.

*Turesson C, Bergström U, Jacobsson LT, Truedsson L, Berglund G, Saxne T.
Increased cartilage turnover and circulating auto-antibodies in different subsets before the clinical onset of rheumatoid arthritis.
Ann Rheum Dis. 2011;70:520-522*

Clinical remission, as defined by DAS28, was related to a decrease in serum COMP in anti-TNF treated RA patients.

Anti-TNF therapy is nowadays widely used in the clinical routine to treat RA patients. It is known that certain subsets of patients can be predicted to achieve remission. However, the association of this clinical efficacy with serological variables is not fully elucidated. The aim of the present study was to evaluate if the clinical remission as defined by DAS28-ESR was related to a decrease in serum COMP in anti-TNF treated RA patients.

Most etanercept-treated (25mgx2/week in 6 months) RA patients (n=45) in this prospective study were classified as advanced stage with high disease activity as based on DAS28-ESR. Serum-COMP, CRP, ESR and MMP-3 were measured at baseline and after 6 months etanercept-treatment. There was a significant ($p<0.05$) decrease in serum COMP in patients (n=10) that respond to treatment and showed a remission but not in the rest of the patient population. CRP, ESR and MMP-3 showed a decrease both in the remission group and the group without remission. There was a very low but significant association ($r=0.33$, $p>0.028$) between the inflammatory biomarkers (ESR, CRP) used and serum COMP level indicating another biological background for serum COMP levels.

The authors conclude that serum COMP is a valuable biomarker to identify the subset of RA patients achieving remission during treatment with etanercept.

*Kawashiri SY, Kawakami A, Ueki Y, Imazato T, Iwamoto N, Fujikawa K, Aramaki T, Tamai M, Nakamura H, Origuchi T, Ida H, Eguchi K.
Decrement of serum cartilage oligomeric matrix protein (COMP) in rheumatoid arthritis (RA) patients achieving remission after 6 months of etanercept treatment: comparison with CRP, IgM-RF, MMP-3 and anti-CCP Ab.*

Serum COMP was significantly higher in early RA patients with MRI-proven bone erosions but was not related to DAS28CRP scores.

The background of this study is the difficulty to prove cartilage involvement with imaging techniques such as MRI in early RA since joint replacement surgery is not performed. The authors have in a recent study shown that MRI-proven bone erosions and edema was related to systemic inflammation biomarkers. The aim of the present study was to use serum COMP measurements as a marker of cartilage turnover and relate it to MRI detection of early joint damage.

In early (disease duration < 2 years) RA patients (n=98) recruited to the study the serum COMP level was significantly ($p < 0.017$) higher in patients with MRI-proven bone erosions (n=47) compared to patients without erosions. There was no significant difference in serum COMP levels in relation to DAS28CRP scores and MRI-proven edema. In an earlier study the authors has shown association between MRI-proven edema and inflammatory indices and DAS. The correlation to systemic inflammatory markers such as CRP ($r = 0.21$ $p = 0.035$) and MMP-3 ($r = 0.20$ $p = 0.046$) markers was very low but significant.

In conclusion the authors speculate that COMP reflects another aspect of the disease process than represented by MRI-proven edema and associated inflammatory indices.

Fujikawa K, Kawakami A, Tamai M, Uetani M, Takao S, Arima K, Iwamoto N, Aramaki T, Kawashiri S, Ichinose K, Kamachi M, Nakamura H, Origuchi T, Ida H, Aoyagi K, Eguchi K.

High serum cartilage oligomeric matrix protein determines the subset of patients with early-stage rheumatoid arthritis with high serum C-reactive protein, matrix metalloproteinase-3, and MRI-proven bone erosion.

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