Relations of Serum COMP to Cardiovascular Risk Factors and Endothelial Function in Patients with Rheumatoid Arthritis Treated with Methotrexate and TNF-α Inhibitors

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ABSTRACT. ***Objective.*** To examine whether serum level of cartilage oligomeric matrix protein (S-COMP) is related to methotrexate (MTX) or to MTX and tumor necrosis factor-α (TNF-α) combination treatment for rheumatoid arthritis (RA); and to investigate whether S-COMP is related to cardiovascular risk factors including endothelial dysfunction and level of anticitrullinated protein antibodies (ACPA) in patients with RA.

Methods. Clinical and laboratory measures, including S-COMP and reactive hyperemic index (RHI), were examined in 55 consecutive patients with RA starting with either MTX (n = 34) or MTX and anti-TNF-α treatment (n = 21) at baseline, and after 6 weeks and 6 months.

Results. S-COMP was similar in the 2 treatment regimens during followup. We found a positive relationship between S-COMP at baseline and the use of disease-modifying antirheumatic drugs the last year preceding the study ($p = 0.001$), and a negative relation to current use of systemic glucocorticosteroids ($p = 0.044$). The nonsignificant change in S-COMP between baseline and the 6-month followup was positively and independently related to change in ACPA level ($p = 0.009$). There was no significant association between RHI and level of S-COMP at baseline.

Conclusion. The cartilage turnover marker S-COMP did not change significantly after 6 months' treatment with MTX with or without a TNF-α inhibitor in patients with RA. The positive association between S-COMP and ACPA suggests that these factors might interact, and could both be contributors to an unknown link between inflammation and cartilage destruction in patients with RA. S-COMP was not related to endothelial function in patients with RA, or to other cardiovascular risk factors studied. Clinical Trials registration number NCT00902005. (J Rheumatol First Release June 1 2012; doi:10.3899/jrheum.111401)

Key Indexing Terms:
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Rheumatoid arthritis (RA), a chronic inflammatory disease, often leads to disability and reduced physical capability, because of destruction of cartilage, tendons, and bone. Research during the last 2 decades has suggested that there are several subpopulations of patients with RA, characterized by more or less aggressive and erosive development[1,2]. A predictor with high specificity for joint destruction is therefore of great importance. Cartilage oligomeric matrix protein (COMP) has stood out as a promising marker for assessing the progression of joint tissue damage[3,4]. COMP is 1 of 5 extracellular matrix proteins, and was first described and measured in serum and synovial fluid in 1992[5]. The function of COMP is not completely understood; however, current data indicate that this protein plays important roles in organizing growth plate architecture, enhancing collagen fibril formation, and repair of cartilage[6]. However, the literature is inconsistent when it comes to COMP's ability to predict radiographic joint destruction in patients with RA[7,8,9]. Inconsistency also exists between studies that have assessed changes in serum COMP (S-COMP) during treatment with a tumor necrosis factor-α (TNF-α) inhibitor. Data regarding the effect of methotrexate (MTX) on S-COMP level are limited[10,11]. We investigated

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whether treatment of RA patients with MTX and MTX in combination with a TNF-α inhibitor could influence the level of S-COMP, and compared the 2 treatment groups.

COMP is present in human arteries, and has been detected in normal as well as atherosclerotic and restenotic human arteries[12]. Recent data suggest that COMP is pivotal for maintaining the homeostasis of vascular smooth muscle cells, and might be a novel inhibitor of vascular calcification[13,14]. Knowing that specific subpopulations of patients with RA have a particular susceptibility to develop accelerated atherosclerosis and also have increased cardiovascular morbidity and mortality[15,16,17], a second aim of this study was to investigate whether S-COMP levels might be associated with cardiovascular risk factors, including endothelial function, in patients with RA.

MATERIALS AND METHODS

Patients. Sixty-two consecutive patients with RA according to American College of Rheumatology (ACR) 1987 criteria[18] were enrolled in the ongoing PSARA (PSoriatic arthritis, Ankylosing spondylitis, Rheumatoid Arthritis) study at Lillehammer Hospital for Rheumatic Diseases, October 2008-November 2010[19]. The PSARA study is a prospective, open-label, observational study with consecutive inclusion of patients with RA and spondyloarthritis, starting with either combination therapy of TNF-α inhibitor and MTX or MTX alone. The aim of the study was to examine the association between inflammatory disease activity, cardiovascular markers (including endothelial function), and cartilage and bone markers in these patient groups during treatment. We describe results from the RA patient group.

Inclusion criteria were age range 18–80 years, RA according to the ACR 1987 criteria[18], and clinical indication for starting treatment with MTX monotherapy or MTX in combination with a TNF-α inhibitor (adalimumab, infliximab, or etanercept). The decision about treatment modality was based on conventional clinical judgment following prevailing European/Norwegian guidelines for RA treatment, and was made by rheumatologists at Lillehammer Hospital for Rheumatic Diseases who were not involved in the study. Doses were as follows: etanercept 50 mg subcutanous (SC) injection once a week; adalimumab 40 mg SC injection every other week; infliximab 3–5 mg/kg intravenous injection at baseline, then following prevailing dosing schedule. MTX was given in doses 15–25 mg orally once a week.

Exclusion criteria included lack of co-operability, any recent clinically significant infection, a history of tuberculosis (TB) or untreated TB, previously diagnosed immunodeficiency, pregnancy or breastfeeding, congestive heart failure, uncontrolled diabetes mellitus, recent stroke (within 3 months), systemic glucocorticosteroid (SGC; prednisolone) dose > 10 mg/day during the last 2 weeks, use of TNF-α inhibitor during the preceding 4 weeks, and a history of or current malignancy.

Of the 62 patients included, 55 completed the study period and were examined at baseline and at 6 weeks and 6 months. Seven patients did not complete the study period; 5 were excluded because of medication side effects and 2 because of treatment failure. These patients had baseline criteria similar to those who completed the study period.

The patients underwent examination by a rheumatologist. Data recorded were the Disease Activity Score for 28 joints (DAS28)[20]; complete medical history including alcohol, coffee, and tobacco use; physical activity; previous use of disease-modifying antirheumatic drugs (DMARD) and current use of SGC, nonsteroidal antiinflammatory drugs, statins, and other drugs known to affect the cardiovascular system; body mass index (BMI); Health Assessment Questionnaire (HAQ) score; and visual analog scales (VAS) for pain/fatigue[21].

The Regional Ethics Committee for Medical Research approved the study protocol, and all the patients gave oral and written informed consent.

Blood samples. Venous blood samples were drawn after fasting for 8 hours at baseline and at the 6-week and 6-month followup. Tobacco use was not allowed 12 hours before the blood samples were drawn. IgG class anticitrullinated protein antibodies (ACPA) and IgM rheumatoid factors (IgM RF) were determined consecutively by ELISA (QUANTA Lite™ CCP3 IgG ELISA and QUANTA Lite™ IgM RF ELISA; Inova Diagnostics, San Diego, CA, USA). S-COMP levels were determined in batches using the Quantikine ELISA assay (R&D Systems, Abingdon, UK; sensitivity 10 pg/ml). Routine test standards of the hospital laboratory were used to analyze erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), leukocytes, neutrophils, triglycerides, total cholesterol, high-density lipoprotein, low-density lipoprotein (LDL), lipoprotein(a) [Lp(a)], uric acid, homocysteine, glucose, and glycosylated hemoglobin (HbA1c). The laboratory assessor was blinded to the clinical data.

Endothelial function. To examine endothelial function, a finger plethysmograph (EndoPAT 2000; Itamar, Caesarea, Israel) was used. Flow-mediated dilatation (FMD) of the brachial artery is the noninvasive "gold standard" technique for measuring endothelial function in clinical studies. It has been demonstrated that abnormalities in pulse-wave amplitude (PWA) using a novel finger plethysmograph (peripheral arterial tonometry, or PAT) are significantly correlated with FMD[22]. This method senses changes in the pulsatile arterial volume in the distal finger phalanx before and after 5-min occlusion of the upper arm. The signals are then transferred to a computer to be amplified and stored. A computer algorithm was used to analyze the PAT data in an operator-independent manner. The reactive hyperemic index (RHI) was calculated as the ratio between the magnitude of the average postobstructive PWA and the average of baseline PWA (preocclusion baseline period), further corrected to systemic changes recorded in the nonobstructed arm. The PAT method and the practical procedure have been described in detail[19,23,24].

Statistics. The chi-square test and Fisher's exact test were used to study categorical variables, and the independent samples t test, Mann-Whitney U test, and paired t test were used to identify differences in continuous variables between the 2 groups. Linear simple regression analysis was performed with S-COMP level at baseline as the dependent variable and the following independent variables: age, sex, previous use of DMARD, SGC, baseline ACPA level, rheumatoid disease duration (RDD), RHI, IgM RF level, homocysteine, ESR, Lp(a), CRP, HbA1c, BMI, extraarticular manifestations, and DAS28(ESR). In addition to age and sex, variables that showed a significant association ($p < 0.05$) with the dependent variable were included in the multivariate linear regression model. All statistical tests were 2-sided, and all analyses were performed with SPSS for Windows, version 19 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient baseline characteristics. Serum levels of COMP and ACPA antibodies were significantly higher in the patients with RA starting treatment with MTX + TNF-α inhibitor compared to those starting with MTX as monotherapy. The MTX + TNF-α inhibitor group also had significantly longer disease duration, more patients with erosive arthritis, higher total cholesterol, and higher LDL than the MTX group. All patients with RA in the MTX + TNF-α inhibitor group had used a DMARD the year preceding the study, and only 4 in the MTX group. Comparing the 2 RA treatment groups, a nonsignificant tendency of lower BMI and less fatigue was found in the MTX group. Otherwise, the demographic data, medication, inflammatory markers and scores, hypertension, and patient cardiovascular disease (CVD) or family history of CVD were similar in the RA treatment groups at baseline (Tables 1 and 2).

Comparison of treatment effects. There was no significant

Table 1. Baseline characteristics of patients with rheumatoid arthritis (RA) starting treatment with methotrexate (MTX) or MTX and tumor necrosis factor-α (TNF-α) inhibitor in combination. Except where indicated otherwise, values are mean ± SD.

Characteristics	MTX, n = 34	MTX + TNF-α Inhibitor, n = 21	p
Age, yrs	56 ± 11	58 ± 8	0.482
Women, n (%)	25 (71)	15 (71)	1.000
RDD, yrs	3 ± 6	9 ± 9	0.009
Erosive arthritis, n (%)	12 (35)	15 (71)	0.013
EAM, n (%)	2 (6)	1 (5)	1.000
SGC, n (%)	8 (24)	6 (29)	0.755
ACPA, n (%)	17 (50)	18 (86)	0.007
DAS28 (ESR)	5.1 ± 1.0	4.8 ± 1.2	0.239
VAS pain, mm	55 ± 22	53 ± 25	0.735
VAS fatigue, mm	45 ± 28	57 ± 24	0.089
HAQ	0.6 ± 0.4	0.7 ± 0.4	0.368
VAS global, mm	52 ± 20	53 ± 23	0.956
ESR, mm/h	26 ± 22	18 ± 14	0.119
CRP, mg/l	15 ± 16	13 ± 18	0.682
WBC, × 10^9 U/l	7.1 ± 1.4	7.2 ± 2.0	0.853
Neutrophils, × 10^9 U/l	4.2 ± 1.3	4.3 ± 1.5	0.794
ACPA, U/ml	103 ± 119	191 ± 98	0.004
IgM RF, U/ml	148 ± 190	211 ± 226	0.298
COMP, ng/ml	201 ± 63	317 ± 117	0.001

RDD: rheumatoid disease duration; EAM: extraarticular manifestations; SGC: systemic glucocorticosteroids; ACPA: anticitrullinated peptide antibody; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire score; VAS: visual analog scale; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cells; IgM RF: rheumatoid factor immunoglobulin type M; COMP: cartilage oligomeric matrix protein.

Table 2. Baseline cardiovascular characteristics of patients with RA starting treatment with methotrexate (MTX) or MTX and tumor necrosis factor-α (TNF-α) in combination. Except where indicated otherwise, values are mean ± SD.

Characteristics	MTX, n = 34	MTX + TNF-α Inhibitor, n = 21	p
Current smokers, n (%)	13 (38)	4 (19)	0.229
BMI, kg/m^2	25 ± 3	28 ± 6	0.055
Hypertension, n (%)*	7 (21)	7 (33)	0.348
Hyperlipidemia, n (%)**	7 (21)	2 (10)	0.457
Angina pectoris, n (%)	1 (3)	1 (5)	1.000
Previous MI, n (%)	2 (6)	2 (11)	0.632
Family history of CAD, n (%)***	8 (24)	8 (38)	0.360
Statins, n (%)	6 (18)	2 (10)	0.696
NSAID, n (%)	26 (76)	16 (76)	1.000
Ca blocker, n (%)	2 (6)	1 (5)	1.000
ACE inhibitors, n (%)	4 (12)	2 (10)	1.000
Beta blocker, n (%)	3 (9)	1 (5)	1.000
Triglycerides, mmol/l	1.27 ± 0.52	1.29 ± 0.38	0.910
Cholesterol, mmol/l	5.1 ± 1.0	5.7 ± 0.8	0.014
LDL, mmol/l	3.1 ± 0.9	3.6 ± 0.7	0.025
HDL, mmol/l	1.4 ± 0.4	1.5 ± 0.4	0.519
Lp(a), mg/l	304 ± 352	561 ± 604	0.088
Uric acid, µmol/l	273 ± 67	281 ± 68	0.694
Homocysteine, µmol/l	12 ± 3	12 ± 3	0.318
HbAlc, %	43 ± 3	43 ± 3	0.548
RHI	1.88	1.94	0.646

* Hypertension ≥ 140/90, or antihypertensive treatment. ** Hyperlipidemia: total cholesterol > 5.5 mmol/l or lipid-lowering treatment. *** Coronary artery disease in male first-degree relatives before age 55 years, and/or female first-degree relatives before age 65. BMI: body mass index; MI: myocardial infarction; CAD: coronary artery disease; NSAID: nonsteroidal antiinflammatory drugs; ACE: angiotensin-converting enzyme; LDL: low-density lipoprotein; HDL: high-density lipoprotein; Lp(a): lipoprotein (a); HbAlc: glycosylated hemoglobin; RHI: reactive hyperemic index.

reduction in S-COMP levels during the followup period compared to the baseline level, neither in the RA patients treated with MTX nor in RA patients treated with MTX + TNF-α inhibitor (Table 3). Compared to baseline values, the inflammatory markers CRP and ESR were significantly reduced at both control points in the MTX group, whereas patients in the MTX + TNF-α inhibitor group showed nonsignificant changes. In both groups, DAS28(ESR), HAQ score, VAS pain, and VAS fatigue were improved at 6-week and 6-month followup (Table 3).

In our search for factors that might influence the S-COMP level, we then analyzed all 55 patients with RA as 1 group, independent of treatment regime. In simple regression analysis, use of a DMARD in the last year preceding the study was positively associated with a higher level of S-COMP at baseline. This remained significant in the adjusted model (Table 4). RDD had a strong relationship to previous use of DMARD, and because of this, we did not adjust for RDD even though it was significantly associated with baseline S-COMP level. Use of SGC (prednisolone 10 mg/day or less) was significantly related to a lower level of S-COMP at baseline, which remained significant in the adjusted model (Table 4). A slightly higher level of S-COMP was found at baseline in those patients with RA who had erosive arthritis ($S\text{-}COMP_{erosive}$ = 266 ng/ml, SD 98, $S\text{-}COMP_{nonerosive}$ = 226 ng/ml, SD 106), although this result was nonsignificant. There were no significant associations between the following measures and level of COMP at baseline: RHI, ACPA level, IgM RF level, homocysteine, ESR, Lp(a), CRP, HbA1c, BMI, extraarticular manifestations, and DAS28(ESR).

Subsequently we examined whether any of the variables could be associated with changes in S-COMP from baseline to 6-month followup. Simple regression analysis showed a significant relationship between increase in ACPA level and an increase in S-COMP level at the 6-month followup (p = 0.005). A positive association was also found between longer RDD and increase in S-COMP at the 6-month followup (p = 0.045). In the adjusted model in which change in S-COMP level from baseline to 6-month followup was the dependent variable, and age of patient at inclusion, sex, RDD, and change in ACPA from baseline to 6-month followup were the independent variables, ACPA remained significantly related to S-COMP, while RDD still showed a strong tendency of relation to S-COMP ($p_{ACPAincrease}$ = 0.009, p_{RDD} = 0.050). We

Table 3. Followup values of clinical and biochemical variables in patients with RA during treatment with methotrexate (MTX) or MTX in combination with tumor necrosis factor-α (TNF-α) inhibitor, compared to baseline values.

	MTX				MTX + TNF-α inhibitor			
Factors	6 Weeks	p	6 Months	p	6 Weeks	p	6 Months	p
COMP, ng/ml	210	0.183	216	0.164	307	0.470	317	0.970
RHI	2.20	0.021	2.19	0.018	2.17	0.183	2.08	0.507
CRP, mg/l	7	0.001	6	0.011	4	0.007	6	0.120
ESR, mm/h	18	0.001	13	0.001	10	0.004	13	0.119
Lp(a), mg/l	253	0.001	259	0.007	477	0.027	512	0.204
Cholesterol, mmol/l	5.2	0.326	5.5	0.006	5.9	0.154	5.7	0.729
HDL, mmol/l	1.5	0.004	1.6	0.001	1.6	0.001	1.5	0.344
LDL, mmol/l	3.1	0.858	3.3	0.066	3.7	0.279	3.6	0.944
Homocysteine, μmol/l	11	0.001	11	0.001	12	0.489	12	0.224
Uric acid, μmol/l	284	0.054	284	0.059	298	0.052	288	0.465
WBC, × 10^9 μ/l	6.3	0.001	6.1	0.001	6.0	0.008	6.6	0.125
Neutrophils, × 10^9 μ/l	3.7	0.006	3.5	0.014	3.4	0.004	3.7	0.085
IgM RF, U/ml	—	—	92	0.047	—	—	169	0.286
ACPA, U/ml	—	—	126	0.146	—	—	192	0.554
HbAlc, %	5.8	0.253	5.6	0.073	5.8	0.471	5.8	1.000
DAS28 (ESR)	4.0	0.001	2.8	0.001	2.9	0.001	2.7	0.001
HAQ score	0.33	0.001	0.21	0.001	0.34	0.001	0.36	0.001
VAS pain, mm	27	0.001	18	0.001	18	0.001	21	0.001
VAS fatigue, mm	26	0.001	24	0.001	34	0.001	31	0.001

COMP: cartilage oligomeric matrix protein, RHI: reactive hyperemic index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Lp(a): lipoprotein a; HDL: high-density lipoprotein; LDL: low-density lipoprotein; WBC: white blood cells; IgM RF: rheumatoid factor immunoglobulin type M; ACPA: anticitrullinated protein antibodies; HbAlc: glycosylated hemoglobin; DAS28: 28-joint Disease Activity Score; HAQ: Health Assessment Questionnaire score; VAS: visual analog scale.

Table 4. Factors influencing serum COMP level at baseline in patients with RA.

	Unadjusted Analyses			Adjusted Analyses*		
Factors	Beta	95% CI	p	Beta	95% CI	p
Age	1.759	–1.141, 4.66	0.229	1.140	–1.437, 3.716	0.378
Sex	–35.129	–97.905, 27.647	0.267	–17.011	–71.823, 37.800	0.536
Previous DMARD	104.430	55.443, 153.417	0.001	96.312	45.030, 147.594	0.001
Smoking	–54.005	–113.383, 5.374	0.074	–9.745	–66.423, 46.933	0.731
SGC	–63.936	–126.441, –1.43	0.045	–57.158	–112.769, –1.547	0.044
ACPA	0.129	–0.109, 0.367	0.281	—	—	—
RDD	5.649	2.416, 8.881	0.001	—	—	—

* R^2 = 0.342 (adjusted for age, sex, previous use of DMARD, smoking, and SGC). COMP: cartilage oligomeric matrix protein. Previous DMARD: use of disease-modifying antirheumatic drug within the year preceding the study; SGC: systemic glucocorticosteroids; ACPA: anticitrullinated protein antibodies; RDD: rheumatoid disease duration.

found no relationships between RHI, CRP, DAS28, IgM RF, age, sex, smoking, BMI, and changes in S-COMP level.

Current use of SGC. Fourteen of the 55 patients with RA were using a sustained dose of SGC ≤ 10 mg/day at inclusion and during the followup. These patients had significantly lower S-COMP level at all control points compared to the patients with RA not using SGC ($p_{baseline}$ = 0.007, p_{6weeks} = 0.001, and $p_{6months}$ = 0.005). There was no difference in RDD between these groups (p = 0.402).

DISCUSSION

The initiation of MTX or MTX combined with a TNF-α inhibitor in patients with RA was not related to reduction in S-COMP during our 6-month followup study, and there were no differences in effect between the 2 treatment regimes. S-COMP was significantly higher in the MTX + TNF-α inhibitor group compared to the MTX group at baseline, probably indicating a more erosive disease in this group, which we confirmed in Table 1. This group also had higher ACPA levels at baseline, indicating a worse prognostic outcome in terms of joint destruction. This is in contrast to Christensen, *et al*, who found significantly lower S-COMP in ACPA-positive patients with RA compared to ACPA-negative patients with RA[25]. They speculate whether these autoantibodies may have a modifying effect on cartilage metabolism, or whether COMP may have different implications in the ACPA-positive versus the ACPA-negative patients with RA. This calls for further investigation because of the many studies indicating S-COMP as a marker of cartilage destruction and ACPA as a predictor of development of future erosions in RA.

Comparing our results with den Broeder, *et al* we would have expected a reduction in S-COMP level in the MTX + TNF-α inhibitor group[26]. However, their followup period was 2 years, and 6 months could be too short to detect any decrease in this cartilage turnover marker. A Japanese study group found a decline in S-COMP in 10 patients with RA who had entered remission after 6 months of etanercept treatment[27]. None of our RA treatment groups reached remission (DAS28 < 2.6) at 6-month followup, so this is in line with the fact that the remaining 35 patients with RA in the Japanese study who did not reach remission showed no significant reduction in S-COMP. Our result is also in line with another study in which 29 patients with RA were treated with adalimumab for 12 months[11]. In that study, no change in mean S-COMP level was found after 3, 6, or 12 months of treatment. However, Crnkic, *et al* found a significant decrease in S-COMP level in patients with RA after 3 months of treatment with either infliximab or etanercept[10]. We found no differences in S-COMP reduction between our treatment regimens, perhaps because we used another type of ELISA assay than Lindqvist and Saxne[4,5].

The inflammatory markers CRP and ESR and the inflammatory clinical score DAS28 did not show any significant relationship to the level of S-COMP. This is in line with studies indicating that S-COMP mainly reflects the cartilage degradation process and is somehow unrelated to the inflammatory process itself[5,10,11]. Still, a possible link between inflammation and cartilage degradation needs further investigation. Recently published data might indicate that COMP could after all play an active role in inflammation by interacting with the complement system[28].

We found a strong relationship between previous use of DMARD the last year before entering the study and higher S-COMP levels at baseline. Also, most of those patients were in the MTX + TNF-α inhibitor group. This means that treatment with conventional DMARD had not been sufficient to achieve reduction of disease activity for those patients. The association between longer disease duration and higher S-COMP at baseline was somehow expected. Erosions develop over time and this could explain the higher cartilage turnover in the patients with longer disease duration.

The 14 of our 55 patients with RA using a sustained dose of SGC during the study had significantly lower S-COMP levels at all control points, including at baseline, compared to those patients not using SGC. The RDD was similar in these 2 groups, so the chondroprotective effect of SGC seems to be strong and might create a relatively instant reduction in the cartilage turnover. One study has shown that intravenous treatment with SGC in patients with highly active RA resulted in reduction in S-COMP within 10 days[29].

In our search for factors associated with changes in S-COMP level during our followup period, ACPA stood out as the most significant association. Elevation in S-COMP thus was associated with elevation in ACPA level. ACPA might have a direct role in the pathogenesis of RA in a majority of patients with RA, and is likely to be a predictor of future joint destruction[2,30]. One might hypothesize that our result could indicate a link between COMP and ACPA. Whether this hypothetical connection is of direct or indirect character remains to be explored. However, there are studies indicating that ACPA activates the complement system *in vitro*, through the classical and alternative pathways[31]. Because COMP might also activate the complement system[30], the possible interaction between ACPA and COMP could go through the complement system. Another explanation could be that ACPA directly influences the cartilage metabolism, causing interruption or stimulation of COMP's different roles[25]. It is also possible that S-COMP concentration is a reflection of major joint destruction in which ACPA participates in the inflammatory processes.

To our knowledge, this is the first study to examine a possible relationship between S-COMP and endothelial function. We did not find any association between low RHI values and high S-COMP values, which might suggest that the endothelial function is not influenced by circulating COMP levels. Except for ACPA, none of the other cardiovascular risk factors we analyzed were associated with S-COMP. Thus S-COMP might have a role in the atherosclerotic process at a later stage, e.g., in the vascular calcification process, as suggested by other authors, and not in the early phase characterized by endothelial dysfunction[14]. We know that there is a positive association between inflammatory activity and cardiovascular risk in patients with RA. Even so, our result might indicate that this risk is independent of the cartilage destruction itself.

The limitations of our study are several. The number of patients was relatively low, and the study was not a randomized controlled trial (RCT). The low number of patients could explain why the relationship between S-COMP at baseline and presence of erosive arthritis showed only a tendency and not significance. Selection of patients by traditional clinical judgment might lead to a potential selection bias, e.g., higher DAS28 in 1 of the treatment groups, even though that was not the case in our study. The strengths of our study are that it reveals new information regarding S-COMP and endothelial function and, to our knowledge, is the first study directly comparing effects of MTX and MTX + TNF-α inhibitor treatment on level of S-COMP in patients with RA. In addition, observational studies mirror real life and are less affected by selection bias than are RCT.

Treatment of RA patients with MTX or MTX combined with a TNF-α inhibitor did not reduce the cartilage turnover marker S-COMP during our 6-month followup study, although disease activity was reduced by the treatment regimens. There were no differences in therapeutic effect between the 2 types of treatment. S-COMP was related neither to endothelial function in patients with RA nor to the other cardiovascular risk factors studied. The positive association between S-COMP and ACPA levels suggests that these factors might interact in rheumatoid inflammation and cartilage destruction. Further studies are needed to explore these associations.

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