Novel molecular diagnostic marker in the evaluation of cartilage destruction in patients with rheumatoid arthritis

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Aim
The aim of this study was to evaluate the serum levels of cartilage oligomeric matrix protein (COMP) in rheumatoid patients in correlation with disease severity and cartilage destruction and to evaluate the therapeutic effectiveness of slow-remitting agents such as leflunomid on this marker of cartilage destruction.

Patients and methods
Fifty patients with rheumatoid arthritis (RA) diagnosed on the basis of the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria and 20 age-matched and sex-matched controls were enrolled in the study. C-reactive protein, erythrocyte sedimentation rate (ESR), rheumatoid factor, anti- cyclic citrullinated peptide, and COMP were determined. Patients were classified into two groups according to Disease Activity Score-28: group 1 (29 patients) included patients with severe activity with a score of greater than 5.1; and group 2 (21 patients) included patients with moderate activity with a score of greater than 3.2 and less than and equal to 5.1. The studied patients were classified into two groups on the basis of the time of receiving leflunomid therapy (20 mg daily after initial therapy 100 mg daily for 3 days) for 3 months: group 3 received before treatment and group 4 received after treatment.

Results
Serum COMP was significantly higher in patients with RA when compared with controls ($P = 0.000$). The COMP levels were found to be positively correlated with Joint space narrowing score (JSN) ($r = 0.832$, $P = 0.000$) and erosion score ($r = 0.863$, $P = 0.000$) of radiography and negatively correlated with rheumatoid factor (r=–0.313, $P = 0.027$); however, COMP levels did not correlate with age ($r = 0.231$, $P = 0.106$), duration of disease ($r = –0.060$, $P = 0.678$), Disease Activity Score-28 ($r = –0.098$, $P = 0.498$), C-reactive protein ($r = –0.242$, $P = 0.090$), ESR first hour ($r = –0.096$, $P = 0.509$), ESR second hour ($r = –0.101$, $P = 0.484$), or anti-cyclic citrullinated peptide ($r = 0.041$, $P = 0.775$).

Conclusion
COMP could be a useful biomarker for the detection of early cartilage and bone destruction and in the follow-up of disease severity and treatment in RA.

Keywords:
anti-cyclic citrullinated peptide antibodies, cartilage destruction, cartilage oligomeric matrix protein, Disease Activity Score-28, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune diseases affecting ~1–2% of the world's population. Although the precise etiology of RA is unknown, genetic and environmental factors seem to be involved in its pathogenesis. It is a chronic disease, and, if untreated, it can damage the cartilage, synovium, and bone of the joints causing pain, impairment, and disability in patients. For these reasons it becomes important to identify prognostic factors that can predict the damage of the cartilage and bone in early phases of the disease [1].

Cartilage oligomeric matrix protein (COMP) is one of the potential markers that have shown promise as a biomarker to assess and predict early severity and progression of the disease. COMP is a structural component of cartilage, where it catalyzes collagen fibrillogenesis. Elevated amounts of COMP are found in serum during increased turnover of cartilage associated with active joint disease, such as RA and osteoarthritis. COMP is considered a marker of cartilage breakdown, and is being studied as a biological marker; it has potential as a diagnostic and prognostic indicator and as a marker of the disease severity and the effect of therapy [2].

Aim

The aim of this study was to evaluate serum levels of COMP in rheumatoid patients in correlation with disease severity and cartilage destruction, and to evaluate the therapeutic effectiveness of slow-remitting agents such as leflunomide oral tablets (initially 100 mg for 3 days and then 20 mg daily, for 3 months) on this marker of cartilage destruction.

Patients and methods

Fifty patients with RA who were newly diagnosed and 20 apparently healthy age-matched and sex-matched individuals who served as controls were enrolled in this study. The patients fulfilled the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria [3]. There were 41 female and nine male patients. All patients were selected from the outpatient clinic of rheumatology and inpatient wards of Internal Medicine Department, Assiut University Hospitals. Informed consents were taken from all patients; this study was approved by ethical committee of Faculty of Medicine of Assiut University.

The selected patients and controls were subjected to the followings:

- Full history taking
- Thorough clinical examination including clinical assessment of disease activity using Disease Activity Score-28 (DAS-28) [4].

The DAS-28 is widely used as an indicator of RA disease activity and response to treatment, but is not always a reliable indicator of treatment effect. The joints included in DAS-28 are as follows (bilaterally): proximal interphalangeal joints (10 joints), metacarpophalangeal joints (10), wrists (two), elbows (two), shoulders (two), and knees (two). When looking at these joints, both the number of joints with tenderness upon touching (TEN28) and swelling (SW28) are counted. In addition, the erythrocyte sedimentation rate (ESR) was measured. Moreover, the patient makes a subjective assessment of disease activity during the preceding 7 days on a scale between 0 and 100, where 0 is 'no activity' and 100 is 'highest activity possible'. With these parameters, DAS-28 is calculated as follows:

$$\mathrm{DAS28} = 0.56 \times \sqrt{\mathrm{TEN28}} + 0.28 \times \sqrt{\mathrm{SW28}} + 0.70 \times \mathrm{In}(\mathrm{ESR}) + 0.014 \times \mathrm{SA}.$$

From this, the disease activity of the patient can be classified as follows:

Current DAS-28	DAS-28 difference from initial value		
	>1.2	>0.6 but ≤1.2	≤0.6
≤3.2			
Inactive	Good improvement	Moderate improvement	No improvement
3.2 but ≤5.1			
Moderate	Moderate improvement	Moderate improvement	No improvement
>5.1			
Very active	Moderate improvement	No improvement	No improvement

- Venous blood was collected by means of venipuncture. The following laboratory investigations were carried out for all participants
  (a) Complete blood count using Sysmex SF-3000 (Roche Diagnostics, Rotkreuz Switzerland)
  (b) ESR using the Westergren method
  (c) C-reactive protein (CRP) using nephelometry
  (d) Blood urea and creatinine using Integra 400 Plus
  (e) Liver enzymes SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) using Integra 400 Plus
  (f) Serum rheumatoid factor (RF) using nephelometry
  (g) Serum anti-cyclic citrullinated peptide (CCP) antibody using anti-CCP high sensitive using ORgbol ELISA kit (Mainz-Germany)
  (h) COMP assay using Human (COMP) ELISA kit (Del Rio, USA, catalog no. 11655)
- Radiography of the hands and feet to assess radiological bone and cartilage changes using Van der Heijde [5] modification of Sharp score of joint involvement by RA on plain radiographs

Statistical analysis

A data entry file, using EXCEL 2016 program, was prepared. Data were analyzed using SPSS (version 19, London). The frequencies, percentages, mean, SD, and median were computed. The χ^2-test was used to compare qualitative variables between groups. The Mann–Whitney test was used as the test of significance to compare quantitative data between groups. Spearman correlation was carried out to measure the correlation between quantitative variables. The 5% level was chosen as the level of significance and 95% confidence interval. The significance level was considered at *P* value less than 0.05.

Results

Significant differences were found as regards CRP, ESR, RF, and anti-CCP between patients and controls (Tables 1 and 2).

Table 1 Some clinical data of the patients (duration of disease, number of tender joints, number of swollen joints, Disease Activity Score-28, and ritchie articular index)

	N (%) (*n*=50)
Duration of disease (months)	
<6	32 (64.0)
≥6	18 (36.0)
Mean±SD (range)	4.78±3.02 (2.0-12.0)
Number of tender joints (mean±SD)	22.48±5.76
Number of swollen joints (mean±SD)	5.60±8.46
DAS-28 (mean±SD)	5.73±1.06
RAI (mean±SD)	19.04±4.72

DAS-28, Disease Activity Score-28; RAI, ritchie articular index.

Table 2 Means of C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and anti-cyclic citrullinated peptide in patients and controls

	Patients (*n*=50)	Controls (*n*=20)	*P*
CRP (mg/dl) (mean±SD)	30.58±38.82	1.96±0.66	0.000*
ESR first hour (mm/h) (mean±SD)	59.62±28.44	7.55±2.76	0.000*
ESR second hour (mm/h) (mean±SD)	80.94±27.37	11.80±3.16	0.000*
RF (IU/l) (mean±SD)	230.77±434.44	8.38±1.58	0.000*
Anti-CCP (U/ml) (mean±SD)	223.90±388.09	12.59±2.15	0.000*

**P* value is statistically significant. CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Table 3 Means of cartilage oligomeric matrix protein in patients and controls

COMP (µg/l)	Patients (*n*=50)	Control (*n*=20)	*P*
Mean±SD	3.19±2.63	2.33±0.99	0.046*
Median (range)	2.5 (1.0-16.5)	2.0 (1.0-4.5)	

**P* value is statistically significant. COMP, cartilage oligomeric matrix protein.

Table 4 Means of serum cartilage oligomeric matrix protein in moderately and severely affected patients according to Disease Activity Score-28

COMP (µg/l)	DAS-28		*P*
	Moderate (*n*=21)	Severe (*n*=29)	
Mean±SD	2.41±0.56	3.76±3.33	0.342
Median (range)	2.5 (1.5-3.5)	2.5 (1-16.5)	

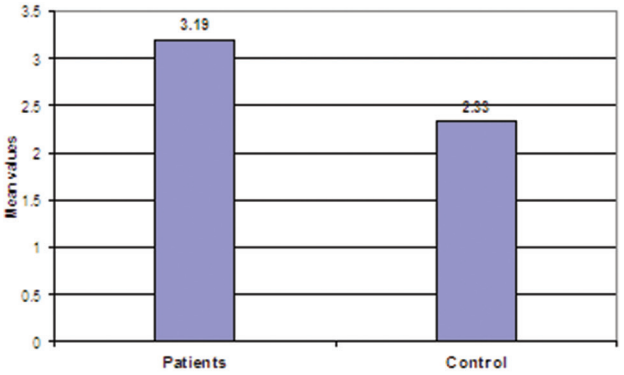
COMP, cartilage oligomeric matrix protein; DAS-28, Disease Activity Score-28.

There were significant differences in the mean COMP when comparing patients and controls (P = 0.046) (Table 3 and Fig. 1).

There were lower but nonsignificant differences in the mean COMP when comparing patients with moderate and those with severe activity (Table 4 and Fig. 2).

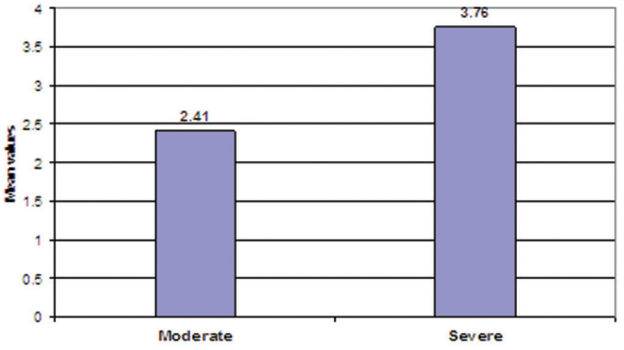
There were significant differences in the means of COMP when comparing patients before and after treatment (Table 5 and Fig. 3).

Figure 1



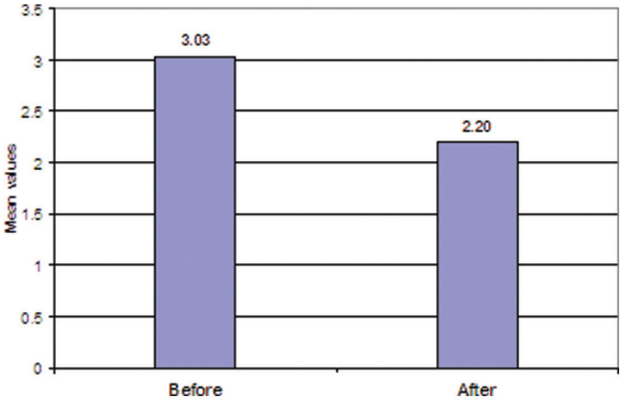
Means of cartilage oligomeric matrix protein in patients and controls.

Figure 2



Means of serum cartilage oligomeric matrix protein between moderately and severely affected patients according to Disease Activity Score-28.

Figure 3



The mean serum cartilage oligomeric matrix protein in patients before and after treatment.

There were significant positive correlations between COMP and radiography JSN score and radiography erosion score. However, a significant negative correlation was found between COMP and RF. No significant correlations were found between COMP and age, disease duration, DAS-28, ESR, CRP, or anti-CCP (Table 6 and Figs. 4–6).

Table 5 The mean serum cartilage oligomeric matrix protein in patients before and after treatment

COMP (μg/l)	Before (*n*=25)	After (*n*=25)	*P*
Mean±SD	3.03±1.35	2.20±1.16	0.004*
Median (range)	2.75 (1.0-5.5)	2.00 (0.0-4.5)	

**P* value is statistically significant. COMP, cartilage oligomeric matrix protein.

Table 6 Correlation between cartilage oligomeric matrix protein and age, duration of disease, Disease Activity Score-28, Van der Heijde modification of sharp score of joint involvement (radiography: JSN score and Erosion score), C-reactive protein, erythrocyte sedimentation rate (first and second hour), rheumatoid factor, and anti-cyclic citrullinated peptide

	COMP	
	r	*P*
Age	0.231	0.106
Duration of disease (months)	−0.060	0.678
ESR first hour	−0.096	0.509
ESR second hour	−0.101	0.484
DAS-28	0.098	0.498
Radiography JSN score	**0.832**	**0.000***
Radiography erosion score	**0.863**	**0.000***
CRP	−0.242	0.090
RF	**−0.313**	**0.027***
Anti-CCP	0.041	0.775

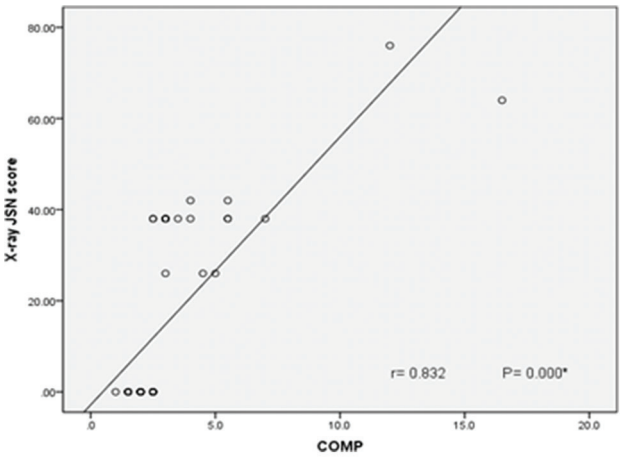
CCP, cyclic citrullinated peptide; COMP, cartilage oligomeric matrix protein; CRP, C-reactive protein; DAS-28, Disease Activity Score-28; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor.

Discussion

RA is the most common systemic autoimmune disease of unknown etiology. It affects up to 1–1.5% of world population, and the characteristic feature of classic RA is persistent inflammatory synovitis, which usually involves peripheral joints in symmetric distribution with intermittent exacerbations and remissions [6].

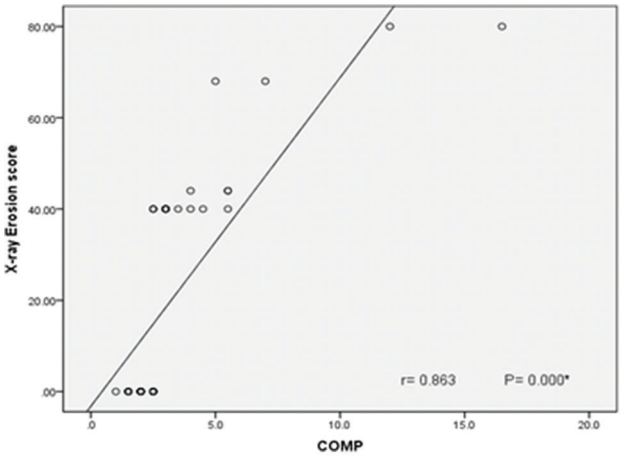
DAS-28 is a valid and reliable method to assess disease activity in RA [4]. The use of a single index has advantages because simultaneous interpretation of several measures of RA disease activity is difficult. It also has advantages for statistical analysis in studies. As the DAS-28 contains reduced joint counts, the DAS-28 is also feasible to use for monitoring of RA disease activity in daily clinical practice [7]. The DAS-28 showed a high predictive ability (0.88) in detecting a flare of RA disease activity [8]. The DAS-28 can be used as a guide in the suppression of RA disease activity with disease modifying antirheumatic drugs. However, it must be noticed that even firm suppression of disease activity may not be sufficient to totally stop the progression of joint damage. Furthermore, even when the DAS-28 is a useful guide for treatment decisions, it does not replace careful patient examination and inquiry [9].

Figure 4



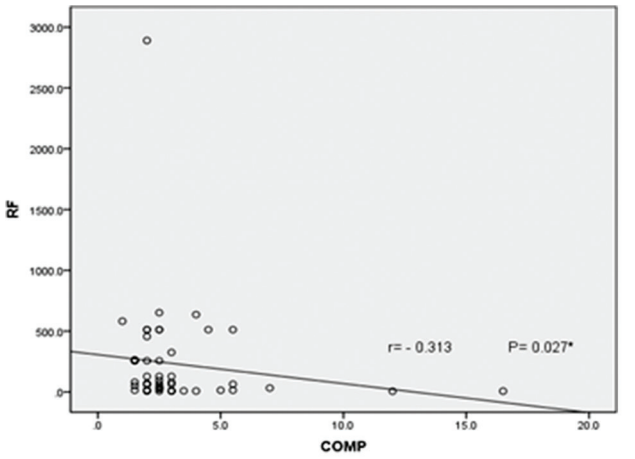
Correlation and linear regression between cartilage oligomeric matrix protein (COMP) and JSN score using the modified Sharp method.

Figure 5



Correlation and linear regression between cartilage oligomeric matrix protein (COMP) and erosion score using the modified Sharp method.

Figure 6



Correlation and linear regression between cartilage oligomeric matrix protein (COMP) and rheumatoid factor (RF).

Our study showed that 88% of patients had positive anti-CCP (44 patients) and 12% had negative values (six patients) at the time of diagnosis, and none of our healthy controls had positive anti-CCP. This is consistent with a study by Heidari *et al.* [10], who found that the anti-CCP test was positive in 164 of 201 patients, with a sensitivity of 81.6%, specificity of 87.5%, and overall accuracy of 84.6%. Thus, the anti-CCP test discriminated RA from non-RA patients with high accuracy. Moreover, our findings are in accordance with the results of Korkmaz and colleagues [11–14], who studied the prevalence of anti-CCP antibodies in RA patients and controls and showed the prevalence of anti-CCP antibody level in 80.4, 84, 81, and 80.4% of RA patients, respectively, but none of the controls had elevated levels of anti-CCP antibody. However, other studies have reported a lower sensitivity of anti-CCP when compared with RF [15].

Available data indicate variations in the sensitivity and specificity of anti-CCP across different studies [16–20]. On the basis of a meta-analysis of 37 studies of anti-CCP antibody and 50 studies of RF by Nishimura *et al.* [15], anti-CCP was more specific compared with RF for diagnosing RA. The pooled sensitivity, specificity, and positive likelihood ratio for anti-CCP antibody were 67%, 95%, and 12.46, and for IgM RF the values were 69%, 85%, and 4.86, respectively.

In our study, the COMP level was found significantly higher in patients (mean ± SD = 3.19 ± 2.63) than in controls (2.33 ± 0.99) (P = 0.046). This is consistent with a study by Elsammak *et al.* [21] on 30 Egyptian RA patients and 20 healthy controls. They found a significantly elevated serum COMP in patients with RA compared with controls. In another study conducted on 24 Egyptian RA patients and 30 healthy controls by El Defrawy *et al.* [22], COMP was found significantly elevated in established compared with early-stage RA patients. Moreover, Al-Dalaen *et al.* [23] in a study that included 60 patients with rheumatoid arthritis and 20 matched normal population showed a significant increase in the levels of COMP compared with the controls; the sensitivity was 94.4% and specificity was 100%. They stated that patients at risk for progressive joint damage are diagnosed early by measuring synovial COMP. This finding is also in agreement with other previous studies that evaluated serum COMP in rheumatoid patients from different ethnic populations. The high serum COMP may reflect an increased breakdown of joint COMP in RA by the effect of matrix metalloproteinases (MMP) enzymes [24].

The elevated serum COMP may reflect a state of synovitis in RA patients [25], as synovial membrane is considered an important tissue source of COMP and may contribute to either synovial fluid or serum COMP levels. An increased level of COMP in the synovial fluid was described in early-stage RA [26]. The higher serum COMP levels in late-onset RA could be due to concomitant osteoarthritic processes in larger joints [27].

In the present study, there was no significant correlation of the COMP levels with the functional class of the RA patients according to DAS-28. This is in accordance with a previous study by Andrade *et al.* [28]. Moreover, the current study showed that COMP levels were not correlated to age, duration of disease, CRP, or ESR. Similarly, in a study by Tseng *et al.* [29], COMP levels did not correlate with ESR or other acute-phase indicators of inflammation. This is also consistent with the results of a study by Elsammak *et al.* [21], who found lack of correlation between serum levels of COMP and serum levels of CRP, which indicates that serum COMP does not reflect the inflammatory component of the disease. Thus, generalized systemic inflammation does not influence COMP turnover to the extent that can affect serum concentrations. These results are in accordance with those of Roux-Lombard *et al.* [30], who conducted a study aiming to investigate the relationship between COMP and variables reflecting generalized inflammation, such as CRP, IL-6, IL-10, the IL-1 receptor antagonist IL-1Ra, and others. The results showed lack of correlation between serum levels of COMP and the other variables. They concluded that COMP did not reflect the inflammatory CRP-related component of the disease and that COMP is a measure of tissue processes that are distinct from the acute-phase reaction. However, treating patients solely with anti-inflammatories and following them up both clinically and by measuring conventional markers of inflammation may be somehow misleading as the signs and symptoms of inflammation may decrease together with laboratory markers of inflammation, but still the undergoing process of joint destruction is taking place. Thus, serum COMP may provide a distinguished marker that reflects cartilage destruction without being biased by the anti-inflammatory given to nearly all patients [31]. Thus, COMP is better in the assessment of joint status compared with other markers, which may be masked by the treatment. Indeed, the previous conclusion was also supported by Vilím *et al.* [32] and Skoumal *et al.* [33], who examined whether COMP correlates with inflammation and/or joint destruction of patients with RA and found a significant correlation of COMP level with Larsen score after 5 years in patients with low clinical and laboratory prognostic factors. In contrast to our study and the previously mentioned studies, Al-Dalaen *et al.* [23] found significant positive correlations between serum levels of COMP with age, disease duration, DAS, CRP, and ESR.

In our study, there was a significant negative correlation of COMP levels with RF levels. This is in accordance with a cross-sectional study by Andrade *et al.* [28] and Heidari *et al.* [10], in which the average levels of COMP and anti-CCP were superior compared with RF in the diagnosis of RA as they are specific to RA, whereas RF is present in other rheumatic diseases as well. Skoumal *et al.* [34] suggested that serum COMP levels are highly specific markers for the cartilage degradation process in RA and are not related to a nonspecific inflammatory process in an arthritic joint, as they found elevated serum COMP levels only in patients with RA but not in inflammatory rheumatic diseases such as psoriatic arthritis, reactive arthritis, Raynaud's syndrome, scleroderma, systemic lupus erythematosus, vasculitis, and Sjögren's syndrome.

In our study, we found no significant correlation between serum levels of COMP and anti-CCP. This is in agreement with the findings of [35], who measured serum levels of antibodies against CCP (anti-CCP antibodies) and serum COMP in patients with recent-onset arthritis of less than 3 months' duration. The specificity of the anti-CCP antibody test for RA was 96%, and the sensitivity was 44%. There was a significant difference between groups of differentiated arthritis in the anti-CCP antibody test ($P < 0.001$), whereas no significant differences were found concerning COMP. This is in contrast to a study by Aref and Ahmed [36] on 40 RA patients who showed that COMP was positively correlated to anti-CCP.

Our study showed a highly significant positive correlation between COMP and JSN ($r = 0.832$, $P < 0.001$) and erosion score ($r = 0.863$, $P < 0.001$) of radiography findings of the joints involved using modified Sharp score. This is in accordance with a study by Andersson *et al.* [37] on 349 patients, in which radiographs of the hands and feet were obtained at inclusion and after 1, 2, and 5 years and scored according to s. They found that the group of patients with increasing COMP levels showed higher median change in total Sharp van der Heijde and erosion scores at 1, 2, and 5 years of follow-up compared with the groups with stable or decreasing COMP levels. Moreover, El Defrawy *et al.* [22] found that the modified Larsen score of radiography findings of affected joints was significantly higher in the established than in the early-stage RA patients and correlated significantly with both serum and synovial COMP levels.

Moreover, Fujikawa *et al.* [38] and Christensen *et al.* [39] found that serum COMP was associated with MRI-proven joint edema, erosion, and synovitis score. They reported that, in early RA, COMP may thus be used as a prognostic marker for cartilage degradation in patients with established RA [33].

Andersson *et al.* [37] reported that increasing COMP levels correlated with radiological joint damage progression and erosion score in patients with early RA. Krabben *et al.* [40] stated that the severity of RA can be measured objectively with radiographic progression, and biomarkers such as COMP could increase the prognostic ability of these approaches. However, another study found no association between radiographic progression and baseline serum levels of COMP in RA [41].

In our study, on comparing the two groups of patients both before and after receiving Leflunomide for 3 months, there was a statistically significant improvement in patients after receiving treatment as regards serum levels of COMP. This is consistent with the results of a study by Kullich *et al.* [42] on thirty-six patients with RA treated with leflunomide for 6 months. MMP-1, the activity of MMP-9, and COM*P* values were measured in serum using enzyme immunoassay. The measurements were performed before and after 3 and 6 months of leflunomide therapy. Reduced COM*P* values in serum after 3 months was observed, but the efficiency of the therapy improves distinctly from 3 to 6 months of treatment with leflunomide. This shows that leflunomide is an efficacious drug that interferes with the mechanisms involved in the destruction of joint integrity, a possible mechanism through which leflunomide slows down joint erosions in RA.

Conclusion

COMP has been shown to be beneficial in the detection of cartilage damage early in the disease, and hence there is a need to use an aggressive therapy to prevent bone and cartilage destruction in RA. Moreover, COMP can be used to monitor the response to treatment, as evidenced by its statistically significant decreased level after treatment with leflunomide.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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