

# Increased serum levels of cartilage oligomeric matrix protein in patients with psoriasis vulgaris: a marker for unknown peripheral joint involvement?

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## ABSTRACT

**Objective.** *Cartilage oligomeric matrix protein (COMP) is a parameter for the current extent of cartilage destruction. It has been shown that the release pattern of cartilage oligomeric matrix protein in serum reflects cartilage turnover. The aim of our study was to explore the utility of sCOMP as a marker for disease activity in patients with active psoriatic arthritis (PsA) in comparison to a control group only with psoriasis vulgaris (PV).*

**Methods.** *Serum levels of COMP were measured in 64 patients with PsA and psoriasis vulgaris. The control group consisted of a population with PV from a dermatological outpatient clinic. ELISA-tests were used to detect sCOMP levels according to the manufacturers instructions.*

**Results.** *In our 64 patients with PsA, we found increased sCOMP levels, which correlated significantly with inflammatory parameters and the number of swollen joints. Patients with active PsA had significantly higher sCOMP levels ( $p < 0.0001$ ) than the 39 patients with a low inflammatory status. In our control group with PV we also found elevated sCOMP levels, which correlated significantly with the increased C-reactive protein (CRP) levels in this group. The difference between the PsA and the PV group was not significant ( $p = 0.092$ ).*

**Conclusion.** *In our study, sCOMP has been demonstrated to be an indicator for disease activity in patients with PsA. Patients with active PsA showed significantly elevated sCOMP levels compared to the patients with low clinical and laboratory disease activity. The increased sCOMP levels in our control group with PV indicate that all patients with psoriatic lesions should be screened for additional joint involvement and should lead to an exact joint examination.*

## Introduction

Psoriatic arthritis (PsA) is an inflammatory joint disease, where manifestations in the skin and the joint can occur independently. PsA shows the frequent involvement of distal interphalangeal (DIP) joints with erosion and absorption of the terminal phalanges, coexisting

sacroiliitis, involvement of the proximal interphalangeal (PIP) joints of the toes, and a characteristic mutilating arthritis. T cells play an important role in the pathogenesis of PsA. Cytokine production and expression is increased in the skin and in the synovial membrane of patients with PsA (1, 2). This results in a matrix degradation and destruction of articular cartilage.

Articular cartilage consists of chondrocytes embedded in structured matrix. The major macromolecules are proteoglycans and collagen type II. The imbalance of breakdown of cartilage matrix and decreased synthesis of matrix components by chondrocytes results in destruction of cartilage in inflammatory joint diseases. Cytokine activation (IL-1, TNF, IL-17, Oncostatins) stimulates chondrocytes to release destructive proteases which lead to a loss of proteoglycans and destruction of collagen bundles. Detectable macromolecules of cartilage in synovial fluid and serum are aggrecan and COMP (3, 4). Cartilage oligomeric matrix protein (COMP) was shown to be a parameter for the current extent of cartilage destruction. It is a pentameric glycoprotein and one component of the extracellular articular cartilage matrix and belongs to the thrombospondin family (5). Increased levels of COMP have been found in human joint fluid (6, 7) and in serum of patients with osteoarthritis, active rheumatoid arthritis and after cartilage injury respectively (9-14). Elevated serum levels of COMP could also be detected in patients with psoriatic arthritis, but not in patients with reactive arthritis.

Raynaud's syndrome, scleroderma, systemic lupus erythematosus, vasculitis and Sjögren's syndrome (15). It has been shown that the release pattern of cartilage oligomeric matrix protein in serum reflects cartilage turnover (16-18). Inflammatory synovium has been considered as a potential tissue source of COMP since the molecule has been detected in the synovium (19-22).

However, much less is known about COMP production in synovial cells in other inflammatory rheumatic diseases. The aim of our study was to explore sCOMP as a marker for disease activity in patients with active psoriatic arthritis

Competing interests: none declared.

(PsA) in comparison to a control group with psoriasis vulgaris (PV) lacking clinical signs of arthritis.

### Materials and methods

Serum levels of COMP were measured in 64 Austrian patients with PsA and psoriasis vulgaris (m/f: 39/25; age (median) 58 yrs). All patients showed typical radiological signs of psoriatic arthritis. The original diagnostic criteria of Moll and Wright (34) are the simplest and the most frequently used in current studies. The criteria are: an inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis), the presence of psoriasis, the (usual) absence of serological tests for rheumatoid factor. Additionally, we defined active PsA by a minimum of 2 swollen joints and CRP levels >20mg/dl, this could be observed in 25/64 patients. The control group consisted of a non arthritic population with PV from a dermatological outpatient clinic (n=39, m/f: 19/20, age (median) 50 yrs) without any typical joint symptoms. Additionally, routine laboratory monitoring and clinical assessment of the disease status (tender and swollen joint count) were performed. Serum was obtained from the routinely drawn blood samples, centrifuged immediately and the samples kept at -80°C prior to measuring of COMP. The serum, used for the measurement of COMP was only the rest from routinely drawn blood examinations on the day at hospitalisation, no blood sampling was done for quantification of COMP exclusively.

For the analysis a commercially available sandwich-type ELISA-kit developed by AnaMar Medical AB, Sweden was used for quantification of COMP. The ELISA test was performed according to the manufacturers instruction.

### Statistical analysis

The results were analysed by Spearman Correlation Statistics, Kruskal Wallis test, Chi square test, Wilcoxon rank sums and Wilcoxon two-sample test. A *p*-value below 5% was considered statistically significant.

### Results

In our 64 patients with PsA, sCOMP levels (U/l) ranged from 6.7-33.8

(median: 10.85±SD 5.84). Serum levels of COMP correlated significantly with erythrocyte sedimentation rate (ESR) (*p*=0.003), with C-reactive protein (CRP) (*p*<0.0001) and the number of swollen joints (*p*<0.0001) (Table I). The mean value of tender swollen joints was 5.5 (min 0 - max 18), of swollen joints 1.5 (min 0 - max 10). In the 25 patients with active PsA we observed significantly elevated sCOMP levels (*p*<0.0001) and CRP levels (*p*<0.0001), compared to the 39 patients with a low inflammatory status (Table II).

Interestingly we also found elevated sCOMP levels compared with the levels provided with the ELISA kit in our control group with PV with a range from 6.7-27.1 U/l (median 12.0±SD 4.81), which correlated significantly with the increased CRP levels in this group (median 17mg/dl) (Table III). The difference

between the total PsA and the PV group was not significant (*p*=0.092).

### Discussion

Psoriatic arthritis is defined as usually rheumatoid factor negative inflammatory arthritis associated with psoriasis vulgaris. Several studies have shown, that nearly 10% of patients with PV develop an inflammatory joint disease. Possible explanations for this finding could be a common etiologic trigger or the existence of a distinct entity. In general, most patients with PsA have mild to moderate skin disease, but there is no correlation between the extent of skin lesions and the number of arthritic joints (1). T cells and pro-inflammatory cytokines play an essential role in the pathogenesis of PV and PsA. The morphological vascular changes in the synovial membrane and skin lesions in

**Table I.** Difference of COMP in patients with active and not active psoriatic arthritis.

Active PsA	N	Mean	SD	COMP				
				Min	Q1	Median	Q3	Max
No	39	9.5	2.2	6.7	7.4	9.1	10.6	15.1
Yes	25	17.7	6.2	10.9	14.0	16.8	20.2	33.8
Total	64	12.7	5.8	6.7	8.7	10.8	14.6	33.8

  

Wilcoxon two-sample test	
Statistic	1258.5000
Normal Approximation	
Z	6.1315
One-Sided Pr > Z	<0.0001
Two-Sided Pr > Z	<0.0001
t Approximation	
One-Sided Pr >Z	<0.0001
Two-Sided Pr > Z	<0.0001

Significant difference of sCOMP levels (*p*<0.0001) and CRP levels (*p*<0.0001) in the active PsA group, compared to the 39 patients with a low inflammatory status. PsA: psoriatic arthritis; Active PsA n=39 patients with a low inflammatory status; Active PsA Yes: patients with a minimum of 2 swollen joints and CRP levels >20mg/dl; Q1: 25<sup>th</sup> percentile; Q3: 75<sup>th</sup> percentile.

**Table II.** Correlations of COMP in patients with PsA and PV.

Spearman correlation statistics								
	Variable 1		Variable 2			Correlation		
	Mean	SD	Name	Mean	SD	N	Coeff.	Prob> r
sCOMP	12.7	5.8	ESR	26.4	24.6	64	0.36	0.0030
			CRP	27.1	47.8	64	0.61	<.0001
			TJC	5.5	4.9	64	0.60	<.0001
			SJC	1.5	2.0	64	0.75	<.0001

sCOMP: Serum levels of cartilage oligomeric matrix protein; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count; SJC: swollen joint count; n: number of patients.

**Table III.** Correlations of COMP in patients with PV.

Spearman correlation statistics								
Variable 1			Variable 2			Correlation		
Mean	SD		Name	Mean	SD	N	Coeff.	Prob> r
COMP	13.3	4.8	ESR	24.1	20.3	39	0.30	0.0618
			CRP	17.1	18.1	39	0.33	0.04

sCOMP: Serum levels of cartilage oligomeric matrix protein; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; n: number of patients.

patients with PsA show minimal hyperplasia and hypertrophy of synoviocytes, the wall of capillaries have perivascular infiltrates (2). TNF alpha, platelet derived growth factor, IL-1beta, IL-6, transforming growth factor beta, as well as vascular endothelial growth factor could be isolated and may be responsible for the vascular changes (22). In psoriatic skin the concentrations of TNF-alpha is also increased, which leads skin cells to multiply rapidly, forming the characteristic psoriatic plaques which is responsible for the inflamed skin lesions. Therapeutic use of TNF alpha antagonists like adalimumab, infliximab or etanercept lead to a significant improvement of the inflamed skin lesions and are highly effective in the treatment of PsA (23).

Protease activity like metalloproteinases, cathepsin K and other cysteine proteases lead to a specific cleavage of matrix molecules like aggrecan and COMP. COMP has been found elevated in the serum (sCOMP) and synovial fluid (synCOMP) of patients with rapidly destructive rheumatoid arthritis and was suggested to be a predicting factor for the outcome of the disease (24-26, 28, 35). Furthermore, it is a marker for early destruction of cartilage (27) in patients with PsA, and osteoarthritis (36). COMP is known as an indicator for the current extent of cartilage destruction. High COMP levels are also correlated with the future development of osseous joint destruction (16).

In our study, sCOMP has been demonstrated as an indicator for disease activity in patients with PsA. Patients with active PsA showed significantly elevated sCOMP levels compared to the patients with low clinical and laboratory disease activity. This reflects the increased cartilage turnover in inflammatory joint

diseases with high activity similar to findings in rheumatoid arthritis (30).

Patients with psoriasis vulgaris, but no history of arthritis were included in the control group. None of these patients had clinical signs of an inflammatory joint disease. Surprisingly we found increased levels of sCOMP in this control group as well, with no significant difference to the PsA group. Farina *et al.* found accumulated COMP protein in the skin of patients with systemic scleroderma, but not in normal skin. COMP is overexpressed in scleroderma skin and cultured fibroblasts possibly due to autocrine TGF beta stimulation (33). We could not find any evidence in the literature to support the view that extended skin lesions of psoriasis have any influence on sCOMP levels (31). Cytokines like TNF alpha, which are responsible for skin and joint inflammation, stimulate chondrocytes to release destructive proteases which lead to a loss of proteoglycans, to destruction of collagen bundles and to the release of COMP (32).

### Conclusion

The increased sCOMP levels in the control group with PV and the PsA group indicate that all patients with psoriatic lesions should be screened for additional joint involvement. The inflammatory parameters in this group may not only reflect the dermal inflammation of PV. In addition to sCOMP it could also be a hint for cartilage destruction and should give rise to an exact joint examination. All patients with PV should be screened for osseous involvement in the inflammatory process even when joints are symptom free. Further studies with patients with psoriasis vulgaris without history of arthritis are needed to clarify the source and etiology of the increased sCOMP levels in this group.

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