Clinical Significance of Decreased Serum Concentration of Cartilage Oligomeric Matrix Protein in Systemic Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** Serum cartilage oligomeric matrix protein (COMP) concentration is elevated in patients with early osteoarthritis and early rheumatoid arthritis, and may be a biomarker of cartilage turnover. We investigated whether serum COMP concentration could be a clinically significant marker of arthritis and/or growth impairment in juvenile idiopathic arthritis (JIA).

Methods. Specimens were collected from 82 healthy blood donors under 22 years of age with no growth impairment who served as healthy controls, and from 24 patients with JIA (6 with oligoarthritis, 10 with polyarthritis, 8 with systemic JIA) presenting with active arthritis. Serum COMP concentration was determined using a human COMP assay kit.

Results. Serum COMP concentrations were significantly higher in all controls less than 16 years of age than in all controls aged 16 years or older. There was a significant negative correlation between serum COMP concentration and serum C-reactive protein in patients with JIA. Serum COMP concentrations in patients with systemic JIA were significantly lower than those in controls.

Conclusion. Serum COMP concentrations in healthy children reflected increased cartilage turnover in the growth phase. Because the serum COMP concentration was decreased in cases of systemic JIA in which growth impairment was pronounced, the systemic inflammation occurring in systemic JIA may have an effect on cartilage turnover, which plays an important role in growth. Serum COMP concentration may prove to be a marker that indicates growth impairment in systemic JIA. (J Rheumatol 2006;33:996–1000)

Key Indexing Terms:
CARTILAGE OLIGOMERIC MATRIX PROTEIN JUVENILE IDIOPATHIC ARTHRITIS
SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS INTERLEUKIN 6 GROWTH IMPAIRMENT

Cartilage oligomeric matrix protein (COMP) is a 524 kDa pentameric glycoprotein that is found predominantly in cartilage, but which is also present in tendons, ligaments, synovium, and menisci[1]. A member of the thrombospondin family of extracellular calcium-binding proteins, COMP is believed to play a vital role in the formation of the extracellular matrix and in the interactions between the matrix and matrix proteins[2,3]. COMP is predominantly synthesized by chondrocytes and synovial cells[4].

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Serum COMP concentration is elevated in patients with early osteoarthritis and early rheumatoid arthritis (RA), reactive arthritis, and traumatic arthritis, and may be a predictive factor of joint destruction[5-10]. At present, serum COMP concentration is considered to be a marker of synovitis and cartilage turnover[11,12].

Juvenile idiopathic arthritis (JIA) is the most widespread form of chronic arthritis occurring in childhood. According to its mode of onset, JIA is classified into categories including oligoarthritis, polyarthritis, and systemic JIA[13]. In the acute phase of JIA, several inflammatory-phase reactants such as C-reactive protein (CRP) increase, and various proinflammatory cytokines, such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1ß, are already activated. Additionally, matrix metalloproteinase-3 (MMP-3) and hyaluronic acid are used as specific biomarkers of arthritis in JIA[14-16]. As with these biomarkers, we hypothesized that serum COMP concentrations are elevated in JIA and may indicate an active arthritis in JIA. On the other hand, pronounced growth impairment occurs particularly in the active phase of systemic JIA[17-19], characterized by severe systemic inflammation and/or arthritis. Consequently, serum COMP concentrations may also reflect a

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decreased cartilage turnover associated with growth impairment. We investigated whether serum COMP concentration could be a clinically significant marker of arthritis and/or growth impairment in patients with JIA.

MATERIALS AND METHODS

Healthy controls. Serum samples were collected with donors' informed consent. Assurance was also given that patients' privacy would be maintained. Specimens were collected from 82 healthy donors (44 female, 38 male) under 22 years of age with no growth impairment. These subjects were evaluated as outpatients in the pediatric service of Okayama University Hospital and were designated the healthy controls.

Patients (Table 1). Serum samples were collected from 24 patients under 16 years of age with JIA (6 with oligoarthritis, 10 with polyarthritis, 8 with systemic JIA) presenting with arthritis symptoms. All patients satisfied the diagnostic criteria published by the International League of Associations for Rheumatology[13]. Serum COMP concentrations were quantitatively determined using a commercial assay kit. CRP and serum MMP-3 concentrations were assayed at the same time. Serum MMP-3 concentrations were measured by a commercial enzyme immunoassay kit according to the manufacturer's directions (Daiichi Fine Chemical Co. Ltd., Toyama, Japan). Specimens were collected when arthritis was in evidence. Arthritis was defined as the presence of joint swelling and pain.

Quantification of serum COMP concentration. After collection, blood samples were centrifuged and the serum obtained was stored at –80°C. Serum COMP concentration was determined using a human COMP assay kit (Ideon, Wieslab AB, Lund, Sweden). The kit permits measurement of intact or fragmented COMP in serum or synovial fluid using a competitive ELISA technique.

Statistical analysis. As appropriate, data were analyzed by the Mann-Whitney U-test or one-way ANOVA. Spearman's rank correlation coefficient was used for determining correlation coefficients. (StatView software; SAS Institute Japan Ltd., Tokyo, Japan).

RESULTS

Serum COMP concentration in the control group (Figure 1). To evaluate development-associated differences, the study population was divided into 5-year age categories, and categories were compared for serum COMP concentration. This comparison showed that in all subjects under 16 years of age, serum COMP concentrations were significantly higher than in subjects aged 16 or older.

Similarly, serum COMP concentrations in subjects less than 16 years of age showed a tendency for being higher than the adult reference values published in the test kit documentation. For healthy controls less than 16 years of age, there were no differences between sex or age group, as follows (all mean ± SD): boys under 16 years, 1.68 ± 0.28 μg/ml; girls under 16 years, 1.79 ± 0.33 μg/ml; men over 16 years, 1.56 ± 0.13 μg/ml; women over 16 years, 1.27 ± 0.39 μg/ml.

Correlation between serum COMP concentration and laboratory and clinical measures of disease activity in JIA patients. There was no correlation between serum COMP concentration and the Steinbrocker functional class in JIA patients (R = –0.11, p = 0.25; Table 1).

Table 1. Profiles of different onset types in juvenile idiopathic arthritis.

No.	Onset Type	Sex	Age, yrs	CRP, mg/dl	COMP, μg/ml	MMP-3 mg/dl	Steinbrocker Stage	No. of Active Joints	Treatment
1	Oligoarthritis	F	6	1.9	1.25	257	I	2	Pretreatment
2	Oligoarthritis	M	5	0.1	2.42	12.5	I	1	NSAID
3	Oligoarthritis	F	6	0.1	1.59	37.6	I	1	NSAID/gold
4	Oligoarthritis	F	4	0.1	2.0	20.6	I	2	NSAID
5	Oligoarthritis	F	11	0.2	1.49	39.3	I	2	MTX
6	Oligoarthritis	F	3	0.3	2.18	127	I	2	NSAID
7	Polyarthritis	F	7	4.6	1.55	240	I	2	NSAID/MTX/PSL
8	Polyarthritis	F	15	1.3	1.46	110	I	3	NSAID
9	Polyarthritis	F	6	1.7	1.39	181	I	2	NSAID/MTX/PSL
10	Polyarthritis	F	8	0.6	1.57	194	I	0	NSAID/SZP
11	Polyarthritis	F	7	0.1	1.62	103	I	1	NSAID/MTX
12	Polyarthritis	F	5	0.6	1.50	202	I	2	NSAID/MTX
13	Polyarthritis	M	7	3.0	1.43	150	I	14	NSAID/MTX/PSL
14	Polyarthritis	F	7	1.05	1.67	40.8	I	2	NSAID/MTX
15	Polyarthritis	F	11	0.0	2.14	ND	I	4	NSAID
16	Polyarthritis	F	11	0.0	1.86	12.5	I	32	NSAID/MTX
17	Systemic JIA	M	6	6.2	1.37	90.7	I	5	NSAID/PSL/SZP
18	Systemic JIA	F	9	1.7	1.21	662	I	2	NSAID/MTX/PSL/CsA
19	Systemic JIA	F	4	8.5	1.61	548	I	2	NSAID/PSL
20	Systemic JIA	M	10	7.5	1.15	869	I	1	NSAID/MTX/PSL/MZB
21	Systemic JIA	F	12	10.0	0.55	14.6	I	2	Pretreatment
22	Systemic JIA	M	8	9.9	0.66	84.2	I	3	PSL/CsA
23	Systemic JIA	F	14	2.4	1.11	ND	III	6	NSAID/MTX/PSL/CsA
24	Systemic JIA	M	15	0.3	1.78	ND	I	1	NSAID

M: male; F: female; CRP: C-reactive protein; COMP: cartilage oligomeric matrix protein; MMP-3 metalloproteinase-3; CsA: cyclosporin A; MTX: methotrexate; MZB: mizoribine; Gold: sodium aurothiomalate; NSAID: nonsteroidal antiinflammatory drugs; PSL: prednisolone; SZP: salazosulfapyridine.

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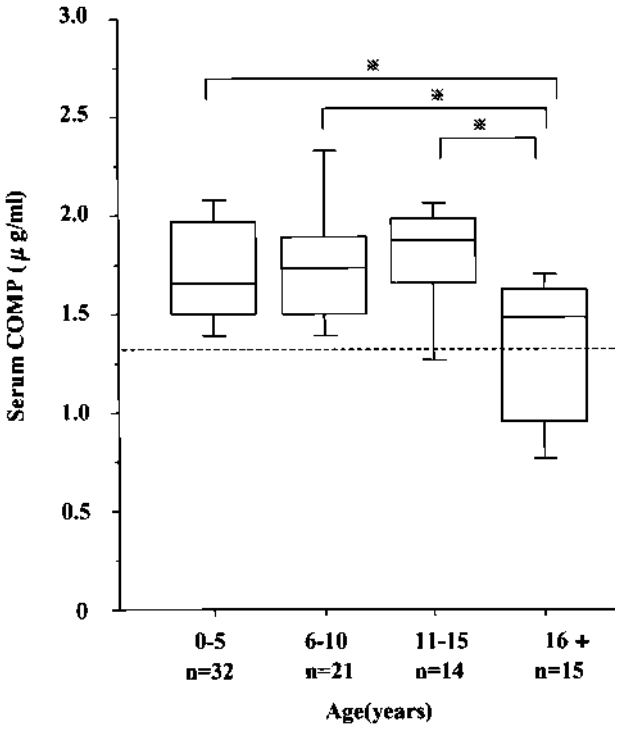

Figure 1. Variation of serum COMP concentrations with age in healthy controls by age group. Boxes show the mean (horizontal bar), 25th and 75th centiles (box), and 10th and 90th centiles (bars). Broken line indicates serum COMP level in healthy adults, 1.35 ± 0.4 μg/ml. n: number of patients per group. *p < 0.01 versus healthy controls aged > 16 years, Dunnett test.

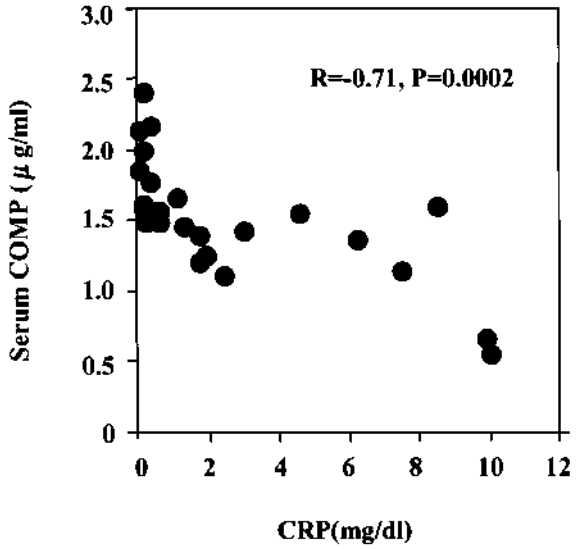

Figure 2. A negative correlation was found between serum COMP concentration and CRP in patients with JIA (n = 24). Spearman correlation coefficient R and significance level are shown.

There was no correlation between serum COMP concentration and the number of active joints (R = 0.03, p = 0.27) or serum MMP-3 concentration (R = –0.24, p = 0.092) in JIA patients.

There was a significant negative correlation between serum COMP concentration and serum CRP in JIA patients (R = –0.71, p = 0.0002; Figure 2).

Serum COMP concentrations in JIA (oligoarthritis, polyarthritis, systemic JIA). The serum COMP concentrations in patients with systemic JIA were significantly lower than those observed in healthy controls (Figure 3).

Serum COMP concentrations in the other 2 disease types of JIA (oligoarthritis and polyarthritis) were not significantly different from those of healthy controls.

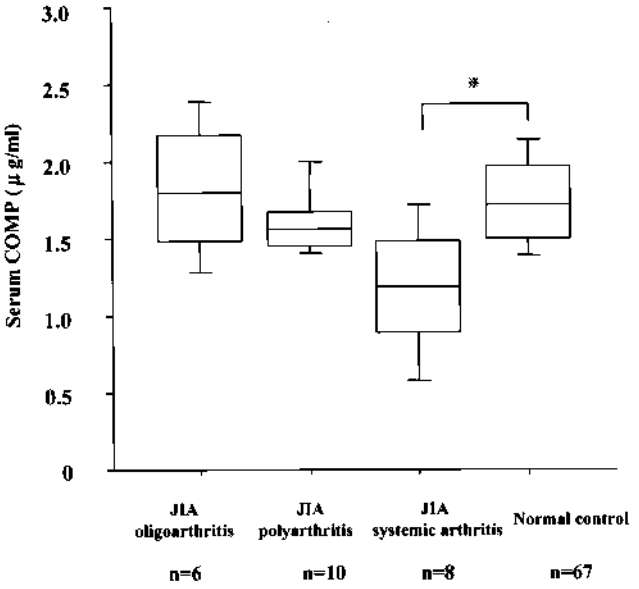

Figure 3. Serum COMP concentrations in patients with juvenile idiopathic arthritis (oligoarthritis/polyarthritis and systemic arthritis) and healthy controls (< 16 years of age). Boxes show the mean (horizontal bar), 25th and 75th centiles (box), and 10th and 90th centiles (bars). *p < 0.01 versus healthy controls, Dunnett test.

DISCUSSION

Longitudinal growth results from chondrocyte proliferation and differentiation in the growth plate[20]. The growth plate is a cartilaginous template that is located between the epiphysis and the metaphysis of the long bones, the so-called "epiphyseal cartilage." The highest level of COMP mRNA is detected in chondrocytes in the central region of the growth plate[21]. On the other hand, an increased serum COMP concentration during growth hormone treatment suggests that COMP produced by chondrocytes in the growth plate may play an important role in longitudinal growth[22].

The results shown in Figure 1 suggest that longitudinal growth in the growth phase is associated with an increased production of COMP, mainly from chondrocytes in the growth plate. As the growth phase passes, epiphyseal carti-

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lage is replaced with bone and disappears, and longitudinal growth therefore ceases, probably resulting in the reduction of serum COMP. Therefore, serum COMP concentration in children apparently reflects the turnover of chondrocytes in the growth plate.

In adult RA, the serum COMP concentration is elevated in the active phase[23]; however, our study showed that serum COMP concentration was not elevated even in patients with active JIA (Figure 3). Moreover, there was no correlation between serum COMP concentration and arthritis activity (Table 1). These differences from previous reports on adult RA[23] may be attributed to fundamental differences in the pathological states of RA and JIA with respect to cartilage turnover. Because adults are past the growth phase, epiphyseal cartilage is no longer present. Thus, serum COMP concentration in cases of adult RA may reflect the degree of destruction in articular cartilage. However, in cases of JIA, the serum COMP concentration may reflect not the arthritis so much as the longitudinal growth.

In JIA, various proinflammatory cytokines such as IL-6, TNF-α, and IL-1ß are activated. IL-6 plays a role in the growth impairment associated with chronic inflammation, and the action of IL-6 in inhibiting bone growth has been determined using IL-6 transgenic mice[19,24]. On the other hand, TNF-α and IL-1ß also decrease chondrocyte proliferation[25]. These proinflammatory cytokines have also been shown to induce the production of acute-phase proteins such as CRP; the results illustrated in Figure 2 suggest that the overproduction of proinflammatory cytokines may result in both increased CRP and reduced serum COMP concentration associated with inhibition of the proliferation of chondrocytes in epiphyseal cartilage.

In systemic JIA, systemic inflammation is the greatest factor promoting growth impairment that may be a major complication. Additionally, reports have shown that growth impairment is most apparent in patients with systemic JIA, and is either related to the disease activity or corticosteroid therapy[26,27]. In our study, however, there was only a tendency toward lower mean height standard deviation score for chronological age (HSDS/CA) in systemic JIA patients in comparison with the other subgroups, as follows (all mean ± SD): oligoarthritis, –0.43 ± 0.89; polyarthritis, –0.12 ± 1.02; systemic JIA, –1.44 ± 2.89. The reason there were no apparent differences in the HSDS/CA may be the limited period of corticosteroid therapy or the active phase of systemic JIA. The results in Figure 3 show that serum COMP concentrations were lower in systemic JIA than in the other types of JIA, suggesting that systemic JIA in the active phase is associated with both a pronounced growth impairment and a lower serum COMP concentration. Accordingly, serum COMP concentration may become a useful marker that indicates growth impairment in patients with systemic JIA.

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