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Title

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Running head

Circulating COMP in JIA

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ABSTRACT

Objective. Raised serum cartilage oligomeric matrix protein (sCOMP) has been reported to predict erosive disease in early rheumatoid arthritis. In juvenile idiopathic arthritis (JIA), subnormal sCOMP levels have been associated with on-going inflammation and growth retardation. This study was done to assess sCOMP, C-reactive protein (CRP) and insulin-like growth factor I (IGF-1) in children/adolescents with JIA and in referents.

Methods. 52 JIA patients were enrolled at planned outpatient visits. 54 inpatients with on-going infection and 120 referents testing negative for IgE-mediated allergy ('IgE-referents') served as controls. All sera were analysed for COMP, IGF-1, and CRP.

Results. Average sCOMP was highest among 'IgE-referents' and lowest among 'infection-referents'. In JIA sCOMP was not reflected by CRP or clinical signs of disease activity.

Conclusion. The results of this study do not support clinical routine sCOMP analysis in patients with JIA.

Background

Juvenile idiopathic arthritis (JIA) designates a group of inflammatory joint diseases of unknown aetiology with onset before the age of 16 (1). The disease course is usually self-limiting although a substantial proportion has chronic progressive disease. Considerable efforts have been made to enable prospective structured assessments of disease activity, course and outcome of JIA (2). However, there is still a need to identify early predictors of aggressive disease leading to joint destruction.

'Cartilage oligomeric matrix protein' (COMP) is mainly located in hyaline cartilage, but also in tendons, skin, and synovial fibroblasts (3-5). Growth hormone (GH) and insulin-like growth factor type-1 (IGF-I) up-regulate COMP in cultured human chondrocytes. Serum COMP (sCOMP) increases upon paediatric GH therapy (6). Hepatic IGF-1 production increases as a response to pituitary-gland GH release, which stimulates bone growth and induces COMP gene expression (6).

In early adult rheumatoid arthritis (RA), elevated/rising sCOMP has been reported to predict erosive disease (7). Decreased sCOMP upon treatment with corticosteroids and/or tumour necrosis factor inhibitors has been interpreted as a sign of cartilage protection (8). However, Turesson *et al* reported raised sCOMP in pre-RA subjects testing *negative* for anti-citrullinated peptide antibodies, *i.e.* a risk marker of erosive disease (9).

This study was done to investigate sCOMP, IGF-1 and C-reactive protein (CRP) levels in prevalent JIA

METHODS

Subjects

JIA group: 52 children diagnosed with JIA were recruited, and categorised according to the ILAR classification criteria (1). Enrolment was done at planned visits to a paediatrician (PL) at Vrinnevi hospital, Norrköping, Sweden. Estimation of disease activity was based on presence of ≥1 palpable synovitis and/or motion-induced joint pain. By this definition, 69 % had active disease. 29% had x-ray proven erosions. Patient characteristics and on-going medications are summarized in Table 1.

Table 1. Characteristics of children with juvenile idiopathic arthritis, on-going infection, and referents testing negative for IgE-associated allergy

Mean age (years, 95% CI)	**Sex**	**Onset type** (number)	**Disease duration**	**Disease activity**	**CRP**	**IGF-1**	**sCOMP**	**Medication**
JIA 12.4 (2.0 – 18.2)	31 girls 21 boys	Oligoarticular (25) Enthesitis-related (8) Polyarticular RF+ (4) Polyarticular RF- (10) Systemic (0) Juvenile Pso-related (4) Undifferentiated (5)	3.9 (0.1-15)	Active: n=36 Inactive: n=16 Missing: n=2	≥ 10 mg/l n=11 < 10 mg/l n=39	330 ng/l (291-369)	12.2 U/l (3.7-28.7)	Predn n=5 MTX n=10 SSZ n=3 HCQ n=1 TNFi n=2
Infection-ref 10.6 (1.5-18)	33 girls 21 boys				≥ 10mg/l (n=54) < 10mg/l (n=0)	185 ng/l (146-224)	6.5 U/l (1.917.8)	
IgE-ref 9.2 (1.5-17.8)	60 girls 60 boys				≥ 10mg/l (n=6) < 10mg/l (n=102) missing (n=12)	245 ng/l (213-277)	13.7 U/l 4.9.29.6	

CI = confidence interval CRP = C-reactive protein HCQ = hydroxy-chloroquine IGF-1 = insulin-like growth factor JIA = juvenile idiopathic arthritis
MTX = methotrexate Predn = prednisolone Pso = psoriasis ref = reference group RF = rheumatoid factor SSZ = Sulfasalazine TNF = tumour necrosis factor

'Infection referents': 54 children hospitalized due to infection, but without signs of arthritis (33 girls; 21 boys, 1.5-18 years, mean 10.6/median 11.7).

'IgE-referents': 120 children testing negative for IgE-antibodies against a panel of common allergens (60 girls/60 boys aged 1.5-17.8 years, mean 9.2/median 9.5).

Serum analyses

Enzyme-linked immunosorbent assays were used to analyse sCOMP (COMP®ELISA, AnaMar Medical, Göteborg, Sweden) and serum IGF-1 (IGF1-ELISA E20, Mediagnost®, Reutlingen, Germany). CRP was analysed turbidimetrically (Advia® 1800, Siemens Healthcare Diagnostics, Terrytown, NY, USA).

Statistics

Data are presented as mean values and 95% confidence interval. For two-group comparisons, unpaired t-test was applied. For three-group comparisons we used UniAnova, and Bonferoni test for multiple comparisons. For correlation analyses the Pearson test was used. The <5% level of significance was applied. Statistical analyses were performed using SPSS, version 19 (SPSS, Cary, IL, USA) and GraphPad Prism (GraphPad software Inc, La Jolla, CA, USA).

Ethics considerations

The study protocol was approved by the regional ethics review board in Linköping (registration number M70-7). Diagnostic COMP kits were provided by AnaMar Medical at a reduced rate without restrictions.

RESULTS

Average sCOMP was slightly lower in JIA than in IgE-referents ($p<0.05$) (Figure 1), but higher compared to infected children ($p<0.001$). Overall, sCOMP showed large inter-individual variations. Comparing the younger IgE-referents (0-15 years) with adolescents (16-18 years), average sCOMP was higher among the younger (14.2 U/l ±0.45 *vs* 11.6 ±0.7 U/l; $p=0.016$). Clinically active/inactive JIA patients did not differ regarding sCOMP levels.

Although not reaching statistical significance, a tendency to higher average CRP was recorded among the 36 clinically active compared to 16 clinically inactive JIA-patients ($p=0.053$). Average CRP was higher among infected children compared both to IgE-referents ($p<0.0001$) and JIA ($p<0.0001$).

Among IgE-referents there was a significant correlation between raised CRP and decreased sCOMP (rho -0.27;$p<0.005$), but *not* among infected children (rho -0.12;$p=0.4$) nor in JIA (Rho -0.023;$p=0.87$). CRP in JIA and IgE-referents differed significantly.

Regarding IGF-1, a low negative correlation was registered vis-à-vis CRP (rho = -0.25, p <0.01). IGF-1 levels correlated similarly with age (rho= 0.72, p<0.01) in all three populations, whereas no correlations were registered when comparing sCOMP and IGF-1 (rho=0.08, p=0.22). IGF-1 was significantly lower among infected children (mean 6.6 μg/l), compared both to IgE-referents (mean 13.6 μg/l, p<0.001) and JIA (mean 12.6 μg/l, p<0.001) after correction for age. Compared to IgE-referents, COMP:IGF-1 ratio was significantly lower in JIA as well as in infected children, even when corrected for age.

DISCUSSION

This study was undertaken to analyse sCOMP levels in JIA patients compared to children/adolescents hospitalised due to on-going infection, and children seronegative regarding IgE-mediated allergy. The few published studies on sCOMP in JIA, have all concluded that sCOMP is reduced during active inflammatory disease (10,11), and that it is related to growth retardation (6,11). Although confirming a tendency to lowered sCOMP in JIA-patients with raised CRP (p=0.053), this was not seen comparing patients classified clinically active/inactive. Discrepancies between different studies may depend on differences in patient materials, reference populations, disease duration, medication, etc.

Our study revealed that cases with infectious disease had markedly lower sCOMP compared to 'IgE-referents'. JIA-patients also had slightly (but statistically significant) lower sCOMP levels than the 'IgE-referents, but distinctly higher levels compared to the infection group. By dividing our JIA cases into a 'low-age group' (0-15 years) and a higher-aged group (16-18 years) we confirmed lower sCOMP among the older (presumably pubertised) adolescents compared to the lower-aged growing children.

Like all measurements of circulating biomarkers, interpretation of raised or lowered levels of sCOMP is intricate. Thus, results of serum measurements include aspects on rates of synthesis and degradation, as well as rates of uptake into and clearance from the circulation. Serum concentrations can also be affected by the nature and fate of the circulating analyte, which raises a number of questions, *e.g.:*

- do reported sCOMP levels reflect native protein and/or degradation fragments?
- can interaction between sCOMP and other circulating proteins (auto-antibodies?) or cells affect the results?
- is the elimination rate of sCOMP and COMP fragments affected by deficient organ function (liver; spleen; kidney)?
- do capture antibodies of the ELISA kit and/or circulating rheumatoid factor interfere with the test results?

Raised levels of sCOMP may thus be explained by increased synthesis *e.g.* during growth in infancy/adolescence or depending on tissue repair, but could also reflect on-going bone and cartilage destruction during local or systemic inflammation. Different sCOMP fragments may reflect different aspects on synthesis, degradation, elimination rates, etc. Overall, raised sCOMP levels can be induced by growth hormone, which is a likely explanation to elevated sCOMP recorded in children/adolescents during periods of high growth velocity (6). This may well explain the differences regarding positive COMP:CRP correlations reported in adult RA and the opposite in children with systemic inflammation, regardless of underlying cause. Tocilizumab therapy, which is efficiently CRP-lowering, has been shown to raise COMP levels to normal in young persons with JIA (12). Whether or not COMP interacts with CRP is unknown, but both of these molecules bind complement protein C1q, resulting in COMP-mediated inhibition of classical complement activation (13) and CRP-mediated activation of the classical pathway (14). Regarding the effects of GH, it is likely that lowered COMP in JIA relates to growth retardation in patients with on-going inflammation. GH induces IGF-1, which has been reported to be lowered in JIA (15) and, intriguingly, COMP gene expression is up-regulated by IGF-1 (16). Further, it is known

that sCOMP levels rise in children treated with growth hormone (6). Contrary to the predictive value of sCOMP in early RA with regard to erosive disease (4), Gilliam *et al* found that sCOMP in JIA patients who did not develop joint erosions and joint space narrowing were higher compared to patients with progressive joint damage (17). In our study, the average sCOMP level was slightly higher in the IgE-negative reference group compared to the JIA-group, which in turn had significantly higher COMP levels compared to children with on-going infection.

The results of this study confirm that clinical and biological correlates of sCOMP differ between children/adolescents and adults, and indicate that sCOMP is of limited clinical value as a biomarker in JIA.

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Figure Legends

Figure 1. Box plots illustrating 1st/3rd quartiles, medium and maximum levels of serum cartilage oligomeric matrix protein (COMP) in the IgE-negative control group, juvenile idiopathic arthritis (JIA), and hospitalized patients with ongoing infection respectively.

Figure 2. Diagram to illustrate circulating levels of cartilage oligomeric matrix protein in relation to C-reactive protein among referents with IgE-negative allergy tests (IgE referents), patients with juvenile idiopathic arthritis (JIA), and hospitalised patients with ongoing infection.

Fig. 1

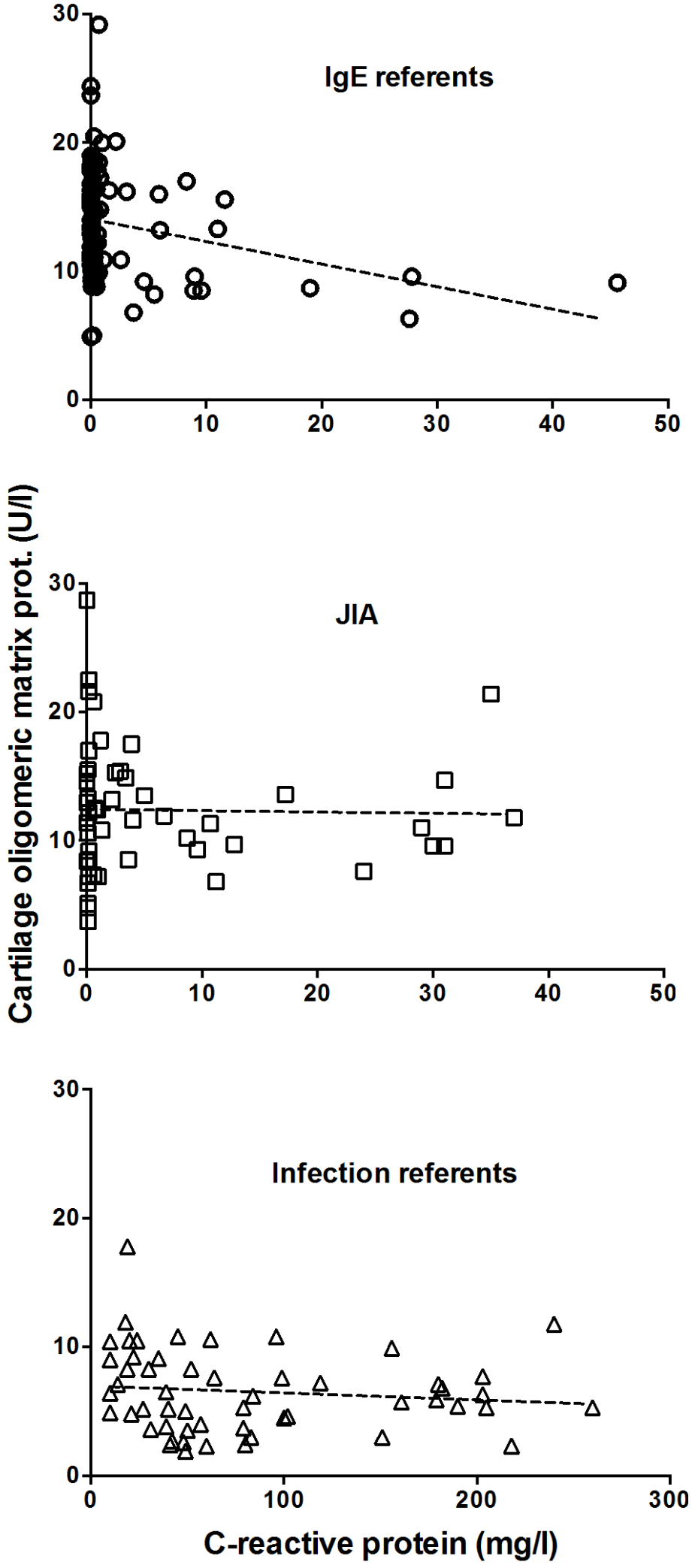
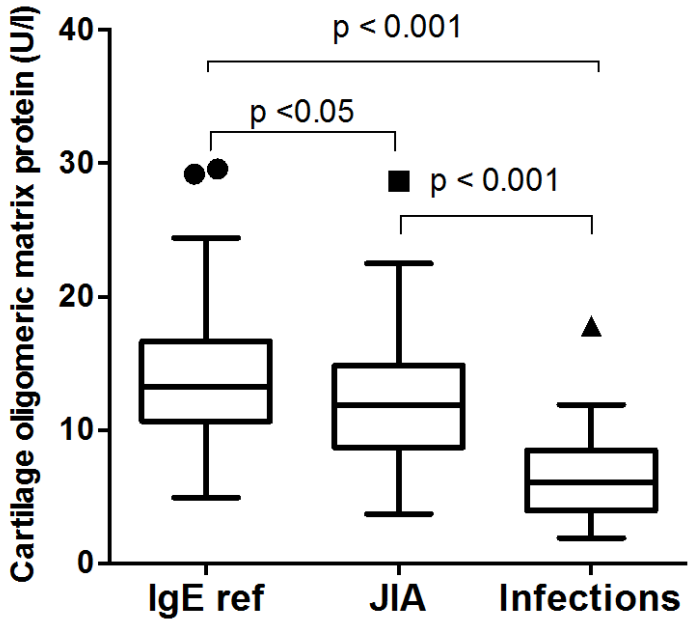

IgE referents
JIA
Infection referents
Cartilage oligomeric matrix prot. (U/l)
C-reactive protein (mg/l)
0
10
20
30
40
50
100
200
300

Fig 2.


Cartilage oligomeric matrix protein (U/l)
40
30
20
10
0
p < 0.001
p <0.05
p < 0.001
IgE ref
JIA
Infections