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Serum cartilage oligomeric matrix protein and clinical signs and symptoms of potential pre-radiographic hip and knee pathology

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Summary

Objective: To examine the cross-sectional relationship between serum cartilage oligomeric matrix protein (COMP) and hip and knee clinical signs and symptoms in a sample of adults without radiographic hip or knee osteoarthritis (OA).

Design: A total of 145 persons with available sera and no evidence of radiographic hip or knee OA (Kellgren–Lawrence grade 0) were randomly selected from the Caucasian participants of the Johnston County Osteoarthritis Project. COMP was quantified by a competitive ELISA assay with a monoclonal antibody 17-C10. Hip and knee clinical signs and symptoms were assessed by physical examination and interview, and their associations with Ln COMP analysed with general linear models.

Results: After adjustment for age, gender, body mass index (BMI), and other symptomatic joints, mean Ln COMP was statistically significantly higher among persons with hip-related clinical signs (P=0.018), among those with hip-related symptoms (P=0.046), and among individuals meeting American College of Rheumatology clinical criteria for hip OA (P=0.021). There were no statistically significant associations between any of the knee-related clinical signs and symptoms and Ln COMP.

Conclusion: Serum COMP may be useful as a biomarker of pre-radiographic hip joint pathology; its utility as a biomarker of pre-radiographic knee joint pathology is unclear.

Key words: Cartilage oligomeric matrix protein, Osteoarthritis, Hip, Knee.

Introduction

Cartilage oligomeric matrix protein (COMP) is a 524 kD glycoprotein found in cartilage, synovium, and tendon[1]. Elevated serum levels of COMP, potentially indicative of alterations in cartilage and bone metabolism and/or synovial inflammation, have been found in persons with knee osteoarthritis (OA) compared with healthy persons[2], in persons with OA-related type II collagen gene mutations[3], and in patients with knee OA accompanied by synovitis, compared with those with knee OA without synovitis[4]. Mean serum COMP has been found to correlate with yearly mean joint space narrowing in hip OA[5], and a rise in serum COMP has been observed in individuals with progressive radiographic knee OA[6,7]. We recently reported elevations in serum COMP concentration with the presence and severity of radiographic knee OA, bilateral radiographic knee OA, concomitant radiographic hip and knee OA, and the number of knees and hips with radiographic evidence of OA, in a large, population-based sample[8]. This report expands our previous work by examining the relationship between serum COMP concentration and hip- and knee-related clinical signs and symptoms in those participants without evidence of radiographic hip and knee OA.

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Participants and methods

PARTICIPANTS

The Johnston County Osteoarthritis Project is an ongoing population-based prospective study of hip and knee OA in a rural North Carolina community. Details of the study design and protocol have been published previously[9]. Individuals aged 45 and older were recruited into the project by probability sampling, without regard to prior joint pain or OA status, between May 1991 and December 1997. The institutional review boards of the University of North Carolina at Chapel Hill and the Centers for Disease Control and Prevention approved the study, which included two interviewer-administered home interviews, a clinical and radiographic assessment of hips and knees, and serum sampling.

Of the 3189 project participants, 305 Caucasians met the eligibility criteria for our present study, which were Kellgren and Lawrence (K–L) radiographic grade of 0 (no radiographic features of OA)[10] in both hips and both knees and a serum sample drawn at the time of radiography (the analysis was limited to Caucasians for comparability to the available literature to date; data on serum COMP in African-Americans from this project will be reported separately). The eligible participants were categorized by age (45–54 years, 55–64 years, and 65 years and older) and gender. We randomly selected 24 or 25 subjects from each category for evaluation of serum COMP concentration, for a total of 145 study participants.

RADIOGRAPHIC ASSESSMENT

Bilateral anteroposterior weight-bearing radiographs of the knees were performed on all participants. Anteroposterior supine pelvis radiographs were obtained from women 50 years of age or older and from all men. A single radiologist (JBR) scored all radiographs for K–L radiographic grade[10]. Inter-rater (weighted kappa=0.859) and intra-rater reliability (weighted kappa=0.886) for the radiologist were high, as previously reported[9].

CLINICAL ASSESSMENT AND DEFINITION OF VARIABLES FOR ANALYSIS

A clinical examination by a trained clinical examiner, was performed on the same day as the radiographic assessment. Clinical examination of each hip included report of groin pain and hip pain on internal rotation; examiner's global assessment of the hip was recorded as normal or mildly, moderately, severely abnormal. Each knee was examined for five clinical signs: bony enlargement, crepitus, effusion, bony tenderness, and soft tissue tenderness at any of the anserine, infra-patellar, supra-patellar, and pre-patellar sites. Examiner's global assessment of the knee was defined as for the hip.

For the purposes of defining hip and knee OA by American College of Rheumatology (ACR) clinical criteria[11,12], hip flexion and internal rotation were each measured to the nearest degree using a long-arm goniometer, and the presence of morning stiffness (minutes) for each hip and each knee was also recorded.

The presence of other symptomatic joints was determined during the clinical examination by report of joint symptoms on a homunculus (shoulders, neck, upper-/mid-back, lower-back, elbows, wrists, ankles, hands, feet). Height was measured in centimeters and weight in kilograms using a balance beam scale, and body mass index (BMI) was defined as weight in kilograms/height in meters^2.

Symptoms of pain, aching, or stiffness in knees and hips was assessed in identical fashion during an interview done on average within 2 weeks of the clinical and radiographic examination, with the question, 'On most days do you have pain, aching, or stiffness in your right [left] hip [knee]?'.

For analysis, hip symptoms were defined as the report of groin pain or an affirmative response to the hip pain, aching, or stiffness question above. Hip-related clinical signs were defined as the presence of hip pain on internal rotation. Knee symptoms were defined as an affirmative response to the knee pain, aching, or stiffness question above. Knee-related clinical signs were defined as the presence of any one of the above five signs. Hip and knee global assessments were each defined as normal vs abnormal for hip and knee, respectively, and hip and knee OA by ACR clinical criteria were defined accordingly[11,12].

ELISA ASSAY

Sera were separated and stored on ice immediately, frozen to −20°C within 8 h of collection, and transferred to −86°C for long-term storage. COMP was quantified by an inhibition ELISA assay using monoclonal antibody 17-C10[8]. Samples were analysed in duplicate, blinded, and in random order; the means of the duplicate values for COMP for each individual were used in analyses. Intra-assay coefficient of variation was 3% and inter-assay was 9%.

STATISTICAL ANALYSIS

All statistical analyses were performed using SAS 6.12 software[13]. Descriptive statistics were used to summarize the non-normal distribution of serum COMP levels, including the median, first quartile (Q1) and third quartile (Q3). We used natural logarithmic transformation of COMP to satisfy the assumptions underlying the use of general linear model methodology. To evaluate the linear relationship of Ln-transformed serum COMP with continuous variables, we calculated Pearson correlation coefficients and performed tests for correlation. Differences between means of Ln COMP were assessed by the Student *t*-test.

Four separate linear models were used to assess the relationship of Ln COMP with hip- and knee-specific variables for symptoms, clinical signs, global assessment, and OA by ACR clinical criteria[11,12], adjusted for age, gender, BMI, and the presence of other symptomatic joints statistically significantly associated with Ln COMP in age-, gender-, and BMI-adjusted analyses. From every linear model, we calculated the differences between adjusted (least-squares) means and corresponding 95% confidence intervals (95% CI).

Results

Selected characteristics of the sample are depicted in Table I. Serum COMP ranged from 292 ng/ml to 2291 ng/ml, with an overall median of 959 ng/ml and first and third quartile cut-points of 824 ng/ml and 1272 ng/ml, respectively. The mean (S.D.) for Ln COMP was 6.92 ng/ml (0.33 ng/ml). Serum Ln COMP was positively correlated with age (r=0.35; P<0.0001) but not with BMI (r=0.03;

Table I
Selected characteristics of the sample, N=*145*

% female	50
% 45–54 years	33.3
% 55–64 years	33.3
% 65 years and older	33.3
Age range (years)	45–85
Mean (S.D.) age (years)	60.2(9.8)
Mean (S.D.) body mass index (kg/m^2)	27.2(4.8)

P=0.691) or associated with gender (*P*=0.326). These relationships persisted in all multivariable models.

The relationships of serum Ln COMP with hip and knee symptoms are shown in Table II. Serum Ln COMP was statistically significantly higher in the presence of hip symptoms (*P*=0.003), and this result remained statistically significant after adjustment (Table II). In contrast, the association with knee symptoms did not reach statistical significance before or after adjustment. Similar results were seen when assessing the relationship between Ln COMP and hip and knee clinical signs (Table III).

Additionally, serum Ln COMP was slightly higher in those with an abnormal hip global assessment (*P*=0.025) but was unassociated with knee global assessment (*P*=0.238). Neither of these associations was statistically significant after adjustment.

Although by definition, no participants had radiographic OA of the hip or knee, 15% met the ACR clinical criteria for hip OA and 19% met the ACR clinical criteria for knee OA. Consistent with observations above, serum Ln COMP was statistically significantly associated with hip OA by ACR criteria (*P*=0.005), but not with knee OA by ACR criteria (*P*=0.598). The relationship between Ln COMP and hip OA by ACR clinical criteria remained statistically significant after adjustment (*P*=0.021).

Of other reported symptomatic joints, serum Ln COMP was positively associated with symptoms in the shoulder (*P*=0.014), upper/mid back (*P*=0.033), and elbow (*P*=0.045) in age-, gender-, and BMI-adjusted analysis, but none of these associations was statistically significant in any models after further adjustment, save for an association between Ln COMP and shoulder symptoms (*P*=0.035) in the model assessing hip and knee OA by ACR criteria.

Discussion

Ours is the first study to investigate the relationship between serum COMP concentration and symptoms and clinical signs of hip and knee pathology among persons with no radiographic evidence of hip and knee OA. Our finding of elevated serum COMP associated with hip symptoms and clinical signs in the absence of radiographic abnormality may reflect an underlying pathological process

Table II
Serum COMP levels and hip and knee symptoms

	Values	*N*	COMP median (Q1–Q3)	Difference of Ln COMP adjusted means (95% CI)*	*P* value*
Hip symptoms	No	89	919 (771–1108)	0.123 (0.002, 0.244)	0.046
	Yes	54	1104 (863–1415)		
Knee symptoms	No	96	951 (810–1231)	−0.058 (−0.178, 0.063)	0.345
	Yes	48	1003 (817–1340)		

*From linear model for Ln COMP containing variables for hip symptoms, knee symptoms, age, gender, body mass index, shoulder, upper/mid back, and elbow symptoms.

Table III
Serum COMP levels and hip and knee clinical signs

	Values	*N*	COMP median (Q1–Q3)	Difference of Ln COMP adjusted means (95% CI)*	*P* value*
Hip clinical signs	No	105	924 (793–1131)	0.146 (0.025, 0.266)	0.018
	Yes	35	1270 (870–1506)		
Knee clinical signs	No	42	959 (841–1263)	−0.005 (−0.115, 0.105)	0.932
	Yes	99	947 (796–1293)		

*From linear model for Ln COMP containing variables for hip clinical signs, knee clinical signs, age, gender, body mass index, and shoulder, upper/mid back, and elbow symptoms.

characterized by altered cartilage or bone matrix catabolism or synovitis. Increased serum concentrations of COMP have been observed in Del1 mice (which harbor a short deletion in a type II collagen transgene) at the age of 4 months, correlating temporally with the onset of cartilage degeneration[14]. This study and our own suggest that serum COMP concentration may be a useful marker for altered cartilage or other joint tissue metabolism with developing joint pathology of the hip. While it is well-recognized that radiographic OA and joint symptoms may be discordant[15], epidemiological studies have indicated that knee pain predicts incident radiographic knee OA[16]. Joint pain has been found to be associated with muscle weakness[17], which may occur before OA is apparent radiographically[18]. Muscle dysfunction may be a cause of OA and under these circumstances, altered joint load could contribute to altered cartilage catabolism, reflected in increased serum COMP concentration. Subclinical cartilage degeneration could initiate synovitis in response to cartilage matrix components in the joint fluid, causing pain. Inflamed synovium is a potential source of COMP[4,9], although it appears that the concentration of COMP in cartilage exceeds that found in other joint tissues. Petersson and colleagues investigated the relative content of aggrecan and COMP in synovial fluid lavage samples from persons with knee pain with or without radiological knee OA defined by joint space narrowing; COMP concentration was higher among persons with radiological evidence of joint pathology[20]. However, differences in absolute levels of aggrecan and COMP between those radiographically negative individuals with and without knee pain could not be compared. We have ourselves detected highest serum COMP concentrations among persons with radiographic OA[8].

We found statistically significant associations between serum Ln COMP and hip-related symptoms, but not knee-related symptoms. This was surprising, since the hip symptom question was asked in identical fashion to the knee symptom question, and it was associated with serum COMP levels even though no specific location for the hip symptoms was sought with this question. The presence of groin pain was strongly associated with the hip pain, aching, or stiffness question, and we did note a somewhat stronger association between groin pain and serum Ln COMP than between the less-specific hip symptoms question and serum Ln COMP (data not shown). However, including groin pain in the hip symptoms definition did not change the relationships observed with hip symptoms defined by the hip pain, aching, or stiffness question alone. Further, hip-related clinical signs and hip OA defined by ACR clinical criteria, were also associated with serum Ln COMP. Serum COMP concentration has previously been shown to be higher in patients with bilateral (compared with unilateral) hip OA and to correlate with hip joint space width and yearly mean joint space narrowing[5].

Serum Ln COMP was not associated with knee-related symptoms, clinical signs, or knee OA defined by ACR clinical criteria. This may be because some of the knee-related clinical signs may be more common and less specific than the hip-related signs we evaluated. Knee soft tissue tenderness, but not knee swelling, was associated with serum COMP level in another cohort with established knee OA[4], but that study did not simultaneously evaluate hip clinical signs and symptoms. Other explanations for the stronger association between serum COMP and hip-related variables than knee-related variables may include differences in specificity of the K–L grading system for the hip and knee, lack of radiographic information about the patellofemoral joint, and use of the less precise K–L radiographic grading system, rather than direct measurement of joint space, to define radiographic OA, possibly resulting in some degree of misclassification of radiographic OA status.

Although the associations we observed between serum COMP and symptoms and clinical signs of hip pathology were not particularly strong, they were consistent across varying definitions, including symptoms, clinical signs and hip OA by ACR clinical criteria. In addition, adjustment for other symptomatic joints did little to alter the relationships noted for serum COMP and hip variables. For these reasons, we doubt that the associations between serum COMP and hip symptoms and clinical signs we observed were related instead to OA at other joint sites we did not investigate radiographically. Nonetheless, our results should be confirmed in other populations before firm conclusions can be drawn.

Our results have potential clinical implications and suggest that closer attention should be given to radiographically unaffected persons with hip symptoms and clinical signs, who may merit further evaluation or treatment for hip joint pathology. However, serum COMP cannot be used diagnostically or prognostically in an individual patient at this time because of lack of normative datasets and valid means of quantifying OA globally in an individual. Our results suggest further research into the OA process, imaging, and the use of serum biomarkers. For example, examination of the relationship between serum COMP concentration and OA status assessed with more sensitive OA definitions and/or joint imaging techniques, such as magnetic resonance imaging, might be a logical next step. Longitudinal analyses, to be done with the completion of the follow-up phase of the Johnston County Osteoarthritis Project, will elucidate whether increased serum COMP concentrations with concurrent joint symptoms might be reversible or instead portend the development of incident radiographic OA. Although our subjects were radiographically negative for both knees and hips (a more stringent requirement than any other radiographic study of serum COMP concentration to date, as most have focused only on radiographic knee OA), our results suggest that control subjects for future studies of OA and serum COMP should not only lack radiographic OA, but might in addition, also lack symptoms and clinical signs of OA.

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