Associations Between Joint Space Narrowing and Molecular Markers of Collagen and Proteoglycan Turnover in Patients with Knee Osteoarthritis

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ABSTRACT. ***Objective.*** We examined whether plasma concentrations of biomarkers of the collagenase cleavage of type II collagen (C2C), types I and II collagens (C1,2C), type II collagen synthesis (CPII), proteoglycan aggrecan turnover (CS846), and the ratio C2C:CPII would distinguish subjects with progressive radiographic osteoarthritis (OA) from those with stable disease.

Methods. Subjects were 120 obese middle-aged women with unilateral knee OA who participated in a 30-month clinical trial of structure modification with doxycycline, in which a standardized semiflexed anteroposterior view of the knee was obtained at baseline, 16 months, and 30 months. Subjects were selected from a larger sample to permit *a priori* comparisons between 60 OA progressors and 60 nonprogressors, as defined by joint space narrowing (JSN) in the medial tibiofemoral compartment. Each group contained 30 subjects who exhibited clinically significant increases in knee pain over 30 months and 30 who did not. Plasma samples were obtained every 6 months for determination of C2C, CPII, CS846, and C1,2C.

Results. None of the biomarkers was a significant predictor of progression of JSN. Over the interval from baseline to 16 months, the mean and the maximum of the intercurrent CS846 values were significantly associated with JSN (i.e., 0.12–0.14 mm of JSN per SD decrease in mean or maximum CS846; $p < 0.01$). The mean of serial CS846 levels was related to JSN also during the interval between months 16 and 30.

Conclusion. Markers of type II collagen synthesis/degradation and of proteoglycan aggrecan turnover were not predictive of JSN in knee OA in this pilot study. However, serial concentrations of proteoglycan aggrecan epitope CS846 were associated with JSN during both the intervals studied. (First Release May 1 2006; J Rheumatol 2006;33:1147–51)

Key Indexing Terms:
KNEE OSTEOARTHRITIS BIOMARKERS TYPE II COLLAGEN

In recent years it has become apparent that the potential exists to relate biomarker measurements in body fluids (such as blood and urine) of specific skeletal processes involving cartilage and bone matrix assembly, degradation, and turnover to clinical measures of joint damage, disease activity, and progression in patients with arthritis. These measurements primarily involve the use of sensitive immunoassays or analytical procedures, such as high performance liquid chromatography, to detect proteases, matrix molecules, and their degradation products that may originate from specific skeletal tissues, and which signify well defined extracellular molecular process involved in the physiology and pathology of hyaline cartilages and bone.

These protein based biomarkers have been developed and used to measure the resorption of cartilage and bone in osteoarthritis (OA) as well as matrix turnover and matrix synthesis in these tissues[1-5]. Specifically, immunoassays have been developed that detect and measure the cleavage of types I (C1,2C or COL2-3/4C-Short) and type II (C2C or COL2-3/4$C_{Long\ mono}$) collagens by collagenases in sera or plasma[6-8], other intrahelical[9] and C-telopeptide[10,11] cleavage products of type II collagen in urine, type II procollagen synthesis by measurement in sera or plasma of the c-propeptide[12] and N-propeptide[13], cartilage proteoglycan aggrecan turnover using the serum or plasma 846 epitope of this molecule[14,15], and the production in sera of cartilage matrix oligomeric protein[16]. These assays can be used to detect changes in extracellular matrix turnover in the skeleton in body fluids in patients with arthritis, as discussed in the aforementioned reviews.

We recently conducted a 30-month randomized placebo controlled trial (RCT) of doxycycline in subjects with knee OA, in which radiographic joint space narrowing (JSN) was

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the primary outcome variable. In that trial, doxycycline significantly slowed the progression of JSN and reduced the frequency of clinically important increases in knee pain[17]. A sample of plasma was obtained from each subject in the RCT at baseline and every 6 months thereafter. Although a full biomarker analysis of all subjects in the RCT was beyond the scope of the original investigation, we conducted this pilot study to determine whether measurements of these biomarkers at baseline or serially can distinguish subjects with progressive radiographic and symptomatic knee OA from those with stable disease.

MATERIALS AND METHODS

The procedures, benefits, risks, and associated safeguards in this trial were approved by institutional review boards affiliated with each of the 6 participating clinical research centers.

Subjects. Subjects were 120 women, 45–64 years of age, all of whom had unilateral knee OA at baseline, based upon Kellgren and Lawrence (K&L) criteria[18], i.e., all exhibited K&L grade 2 or 3 changes in the index knee and K&L grade 0 or 1 in the contralateral knee and had completed the 30-month RCT. All subjects were in the upper tertile of the age, race, and sex appropriate norms for body mass index (BMI) established by the Second National Health and Nutrition Examination Survey[19].

Procedures. The subjects were selected from a larger sample (N = 431) in order to permit comparisons of biomarker concentrations between OA progressors versus nonprogressors. Sixty subjects (21 doxycycline and 39 placebo) were chosen to represent radiographic progressors, all of whom exhibited JSN $\geq$ 0.33 mm in the index knee (mean $\pm$ SD = 0.97 $\pm$ 0.75 mm), as determined by manual measurement of magnification-corrected joint space width (JSW)[17,20] in paired fluoroscopically standardized semiflexed anteroposterior (AP) knee radiographs[21] taken at baseline and 30 months later. In contrast, among the 60 radiographic nonprogressors selected for this analysis (30 doxycycline, 30 placebo), 30-month JSN in the index knee was $\leq$ 0.22 mm (mean $\pm$ SD = –0.03 $\pm$ 0.17 mm; $p < 0.0001$).

Because most subjects enrolled in the RCT were recruited from the community, rather than from among patients who had sought consultation for knee pain, baseline pain scores were low, affording little opportunity for improvement, and remained low in both treatment groups throughout the trial. Nonetheless, progressor and nonprogressor groups were constituted so as to contain 30 subjects (60 total) who reported increases $\geq$ 20% in 50-foot walk pain, relative to their previous examination, with a minimum increase of 1 cm on a 10-cm visual analog scale (VAS), on at least 2 of their 5 semiannual pain assessments. The remainder (30 subjects/group, 60 total) reported no increase in knee pain $\geq$ 20% on any of their followup visits. All pain assessments were conducted after a washout (5 half-lives) of all nonsteroidal antiinflammatory drugs and analgesics taken by the subject.

Plasma sample was obtained from each subject at the baseline visit and each semiannual followup visit. Each sample was stored at 4°C for centrifugation within 4 h, after which samples were kept at –70°C until shipped on solid CO_2 for assay at McGill University, Montreal.

Laboratory procedures. The immunoassays (C1,2C, C2C, CS846 aggrecan, and C-propeptide of type II collagen, CPII) were obtained as commercial kits from Ibex Technologies (Montreal, QC, Canada) and were used as recommended by the manufacturer. Assays were performed in triplicate. Details of the performance of these assays are published by the manufacturer. In our studies, the intraassay reproducibility of measurements of concentrations of C2C, CPII, CS846, and C1,C2 in 30 masked pairs of plasma samples was 9.7%, 6.4%, 11.5%, and 10.0%, respectively.

Statistical analysis. The predictive utility of baseline levels of the biomarkers with respect to radiographic progression of knee OA over 30 months was evaluated with multiple logistic regression analyses. The analyses calculated the change in odds of progression associated with a 1 standard deviation (SD) difference in baseline concentration. All odds ratios were adjusted for age, BMI, and baseline values of JSW. The odds ratios for prediction of progression based on the baseline CPII (and the C2C:CPII ratio) were also adjusted for race[22]. Separate analyses were performed on data from the placebo group and the combined treatment groups. Odds ratios for analyses of data from combined treatment group were also adjusted for treatment.

Repeated measures (mixed) models were used to determine whether variations in serial biomarker concentrations reflected concurrent JSN in the index and contralateral knee. Using the approach employed by Sharif, *et al*[23], we computed the within-subject mean and within-subject maximum of the 3 serial biomarker concentrations over each of the 2 discrete intervals between radiographic examinations (i.e., the baseline, 6 month, and 12 month samples for the 0–16 month interval; the 18, 24, and 30 month samples for the 16–30 month interval). Separate repeated-measures models were fitted with each candidate independent variable (mean and maximum biomarker concentrations) over each interval (0–16 months, 16–30 months). Knee (index or contralateral) was used as the repeated factor to account for correlations within subject. Results (i.e., parameter estimates) were adjusted for age, BMI, treatment group, and JSW at the start of the interval and were expressed as the loss of JSW, in mm, associated with a 1 SD increase in the mean or maximum of concurrent biomarker concentrations. Interactions of the biomarker measure with knee and treatment group were examined. When a significant interaction indicated a difference between subgroups with respect to the association between the marker level and JSN, separate models were fit for each subgroup.

The distributions of the within-subject mean and maximum values for CPII were not normally distributed. Accordingly, repeated measures models were run on square-root transformed CPII data.

RESULTS

Subjects selected for this study were, on average, 54.8 years old and had a mean BMI of 36.5 kg/m^2. Nineteen subjects (16%) were African American. Radiographic progressor and nonprogressor groups did not differ at baseline with respect to mean age, BMI, medial tibiofemoral compartment JSW, or plasma biomarker concentrations (Table 1). The criteria we employed to select subjects for this study assured that the mean rate of JSN over 30 months among progressors would be greater than that among nonprogressors (0.39 mm/yr vs –0.01 mm/yr). However, because of the stratified selection process, radiographic progressors and nonprogressors were similar with respect to the frequency with which they reported an increase of $\geq$ 20% in 50-foot walk pain over successive semiannual pain assessments (23% vs 22%).

Symptomatic progressors reported an increase in walk pain of $\geq$ 20% (and $\geq$ 1 cm on the 10-cm VAS) during 45% of their followup visits (Table 1). Symptomatic progressors had a higher mean BMI at baseline than nonprogressors ($p = 0.032$). By definition, nonprogressors did not report an increase in knee pain of this magnitude on any followup visit. Because of stratified sampling, these 2 subgroups were similar with respect to the rate of mean JSN in the index knee over 30 months (0.21 mm/yr vs 0.16 mm/yr; $p = 0.39$).

Predictive validity of biomarkers. The results of logistic regression analyses to determine the extent to which the baseline concentrations of the various biomarkers predicted progression of JSN in the index knee are shown in Table 2. Baseline levels of markers of Type II (C2C) and types I and II (C1, 2C) collagen degradation and type II procollagen synthesis (CPII) were unrelated to progression of JSN in the placebo

Table 1. Characteristics of progression subgroups at baseline.

	Radiographic Progression		Symptomatic Progression	
	Yes	No	Yes	No
No. of subjects	60	60	60	60
Age, yrs, mean ± SD	55.2 ± 5.6	54.4 ± 5.6	54.5 ± 5.7	55.1 ± 5.5
Body mass index, kg/m^2, mean ± SD	36.7 ± 6.6	36.3 ± 5.6	37.7 ± 6.4†	35.3 ± 5.7†
JSW, mm, mean ± SD*	3.42 ± 1.35	3.78 ± 1.16	3.74 ± 1.33	3.47 ± 1.19
30-month JSN, mm, mean ± SD*	0.97 ± 0.75	–0.03 ± 0.17	0.53 ± 0.88	0.41 ± 0.57
C2C, ng/ml, mean ± SD	78.3 ± 22.6	78.8 ± 22.7	76.0 ± 22.8	81.1 ± 22.2
C1,2C, ng/ml, mean ± SD	287 ± 107	278 ± 86	287 ± 72	278 ± 116
CPII, ng/ml, mean ± SD	1388 ± 810	1449 ± 809	1331 ± 727	1506 ± 877
C2C:CPII × 10^2, mean ± SD	7.6 ± 4.9	7.5 ± 5.7	7.4 ± 4.9	7.6 ± 5.7
CS846, ng/ml, mean ± SD	190 ± 100	219 ± 159	217 ± 138	192 ± 128

* Minimum medial compartment joint space width in the index knee. † $p < 0.05$ for comparison of symptomatic progressors and nonprogressors.

Table 2. Adjusted odds ratios (OR) from multiple logistic regression analyses to distinguish subjects who exhibited progression of 30-month JSN from those who did not on the basis of the baseline concentration of C2C, C1,2C, CPII, and CS846.

	Placebo Group, n = 69			Doxycycline Group, n = 51		
Biomarker	SD*, ng/ml	OR†	95% CI	SD*, ng/ml	OR†	95% CI
C2C	23.7	0.99	0.60–1.63	20.9	0.91	0.48–1.73
C1,2C	90.1	0.98	0.60–1.59	104.3	1.41	0.74–2.66
CPII	11.1	1.02	0.63–1.67	9.7	0.83	0.44–1.56
C2C:CPII	0.06	0.82	0.50–1.35	0.03	1.67	0.87–3.14
CS846	122.2	0.87	0.53–1.43	147.0	0.72	0.35–1.46

* Standard deviation of the distribution of baseline biomarker concentrations. † Odds ratio: changes in odds of progression of JSN per 1 SD increase in the baseline biomarker concentration, adjusted for age, BMI, and baseline JSW. Odds ratios for CPII and C2C:CPII also adjusted for race.

group (OR 0.98–1.02 per SD of the respective baseline marker distribution).

The predictive value of C2C was not improved when Type II collagen degradation was expressed as a function of concurrent collagen synthesis (i.e., ratio of C2C to CPII). However, a 1 SD (122.2 ng/ml) increase in the baseline concentration of CS846 was associated with a 13% decrease in the odds of progression of JSN, although this change in odds was not statistically significant.

Parallel logistic regression analyses of data from the doxycycline treatment group showed larger changes in the odds of progression associated with standard increments in the baseline biomarker level than were found in the placebo group (Table 2). However, none of the changes in odds was significant.

Concurrent validity of biomarkers. The results of repeated measures analyses to relate the within-subject mean of biomarker values at baseline, 6 months, and 12 months to JSN between baseline and 16 months are shown in Table 3. Similar analyses for the interval between radiographic examinations at month 16 and month 30 also are given in Table 3. Among subjects in the placebo group, JSN over each interval was unrelated to intercurrent values of markers of collagen degradation and synthesis (C2C, C1,2C, and CPII). JSN also was unrelated to the C2C:CPII ratio. However, a 1 SD increase (132 ng/ml) in the within-subject mean of the CS846 values at baseline, 6 months, and 12 months was associated with a 0.14 mm decrease in JSN at 16 months ($p < 0.01$). This association was not seen in the ensuing 14-month interval (month 16 to month 30). Analyses of data from the combined treatment groups yielded similar results (Table 3).

The results were largely unchanged when the maximum, rather than the mean, of the serial marker values was examined in relation to concurrent JSN. The exception was for CS846 values in the placebo group, the maximum of which was significantly related to JSN in the interval between baseline and month 16 ($b = –0.12$, $p < 0.01$) and marginally related to JSN in the interval between month 16 and month 30 ($b = 0.13$, $p < 0.10$).

DISCUSSION

Investigations to identify and validate a reliable molecular biomarker of OA (i.e., a marker detectable in the synovial fluid, blood, or urine that may identify subjects likely to undergo rapid loss of articular cartilage) has been under way for more than 20 years. More than 15 years ago, Brandt[24] reviewed a variety of scientific and clinical issues that may confound the interpretation, and affect the utility, of biomarker measurements and concluded that no marker was then

Table 3. Parameter estimates from mixed models to predict radiographic JSN between baseline and 16 months and between 16 and 30 months, based upon intercurrent concentrations of biomarkers.

	Parameter Estimates (mm of JSN per 1 SD of the *mean* of intercurrent biomarker values)			
	Placebo Group, n = 69		Combined Treatment Groups, n = 120	
Biomarker	Months 0–16	Months 16–30	Months 0–16	Months 16–30
C2C	–0.03	–0.08	–0.01	0.02
C1,2C	–0.05	–0.04	–0.03	> –0.01
CPII	< 0.01	0.05	–0.01	0.06
C2C:CPII	–0.01	–0.07	0.01	–0.10
CS846	–0.14†	< 0.01	–0.12††	0.02

	Parameter Estimates (mm of JSN per 1 SD of the *maximum* of intercurrent biomarker values)			
	Placebo Group, n = 69		Combined Treatment Groups, n = 120	
Biomarker	Months 0–16	Months 16–30	Months 0–16	Months 16–30
C2C	–0.01	–0.08	–0.02	0.01
C1,2C	–0.08	–0.07	–0.02	–0.02
CPII	< 0.01	> –0.01	–0.01	0.03
C2C:CPII	0.02	–0.07	0.01	–0.06
CS846	–0.12†	0.13*∞	–0.11††	0.02

Parameter estimates were adjusted for age, BMI, and joint space width at the start of the interval. Parameter estimates for CPII and C2C:CPII were also adjusted for race. Parameter estimates for combined treatment groups were also adjusted for treatment. * $p < 0.10$; † $p < 0.05$; †† $p < 0.01$; ∞ contralateral knee only.

modifying effect of doxycycline seen in the full sample of the trial[2]. That possibility was negated by the stratified selection process we used. However, despite the clinical limitations inherent in all OA biomarker studies[9], our data suggest that variations in serial concentrations of CS846 may reflect concurrent progression of knee OA and should be evaluated in this context in larger, more representative samples of patients with knee OA.

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