Published in final edited form as:
Osteoarthritis Cartilage. 2007 July ; 15(7): 819–823.

The Ratio of Type II Collagen Breakdown to Synthesis and its Relationship with the Progression of Knee Osteoarthritis

September Cahue, MPH, **Leena Sharma, MD**, **Dorothy Dunlop, PhD**, **Mirela Ionescu, M.Sc**, **Jing Song, MS**, **Tatiana Lobanok, M.Sc**, **Lindsay King, PhD**, and **A. Robin Poole, PhD, D.Sc.**

Abstract

Objective.—To examine whether the baseline ratio of a type II collagen breakdown marker to a synthesis marker, or the level of these markers individually, is associated with the likelihood of knee OA progression between baseline and 18 months.

Methods.—Participants were recruited from community sources and had knee OA. Blood was drawn at baseline. Collagen synthesis was measured by commercial ELISA assay that detects c-propeptide of type II procollagen (CPII). Serum markers of collagenase cleavage of cartilage type II collagen [C2C epitope (COL2−3/4Clong mono) and C1,2C epitope (COL2−3/4Cshort)] were also assayed. Knee radiographs (semi-flexed with fluoro confirmation) were obtained at baseline and 18 months. OA progression was examined using worsening of joint space grade and worsening of Kellgren/Lawrence grade. The relationship between baseline serum markers and subsequent progression was analyzed from logistic regression.

Results.—Baseline levels of these markers, considered individually, were not associated with a change in the odds of progression. Belonging to the low synthesis tertile was associated with a greater likelihood of progression, approaching significance (adjusted OR 1.86, 95% CI 0.96, 3.63). A greater C2C:CPII ratio and C1,2C:CPII ratio were each associated with an increase in the odds of joint space grade progression, which approached significance (e.g. adjusted OR of C2C:CPII ratio was 3.15, 95% CI 0.91, 10.85).

Conclusion.—While the degradation markers individually, considered as continuous variables, did not predict OA progression, belonging to the lower synthesis marker tertile and greater degradation/synthesis marker ratios were associated with an elevation in the odds of progression albeit not achieving significance.

INTRODUCTION

Knee osteoarthritis (OA) is commonly associated with pain and loss of mobility. Approximately 300,000 total knee replacement surgeries are performed annually in the U.S. for OA that has progressed to advanced stages (1). At present, there are no disease-modifying agents to slow or stop OA progression. One important reason for this is the long duration required to demonstrate disease modification in therapeutic trials relying upon radiographic outcome measures. Body fluid markers of cartilage and bone metabolism may provide a means of identifying patients at greater risk for progression earlier than the time required to reveal radiographic changes and may also offer a way to gauge the aggressiveness of OA disease.

ADDRESS FOR REPRINT REQUESTS AND CORRESPONDING AUTHOR: Leena Sharma MD Feinberg School of Medicine, Northwestern University 240 E. Huron St., McGaw Suite M-300 Chicago, IL 60611 Phone: 312−908−5597, 312−503−8003 Fax: 312−503−0994 Email: L-Sharma@northwestern.edu.

Articular cartilage loss is the sine qua non of OA, and many molecular markers under study are constituents of cartilage, such as aggrecan epitopes, chondroitin sulfate epitopes, small proteoglycans, and cartilage collagens (2,3). Type II collagen is a major articular cartilage constituent, representing 90−95% of its total collagen content and forming the fibrils that give cartilage its tensile strength. In the process of collagen fibril formation, which is enhanced in OA cartilage (4), the c-propeptide is removed from the procollagen extracellularly and directly reflects the rate of type II procollagen synthesis (CPII) (4). Cleavage of type II collagen by collagenases is also excessive in OA cartilage (5). It yields fragments, such as the C2C epitope (COL2−3/4Clong mono) (6) and C1,2C epitope (COL2−3/4Cshort) (5), which reflect degradation. The C2C assay is specific for type II collagen, whereas C1,2C detects the cleavage of both types I and II collagens.

Several markers have been associated with OA presence and/or severity in cross-sectional studies; some markers have also been found to predict OA progression in longitudinal studies (7-13). Since OA may result from an imbalance in cartilage synthesis and degradation, marker approaches that capture both processes may better predict OA progression. In support of this, Garnero and colleagues (9) found that the combined Z scores of type II collagen degradation and type IIA collagen synthesis markers predicted progression more strongly than either marker individually. While combining Z scores is a powerful approach, the normative data needed may not be available and may vary between racial and ethnic groups. Ratios of biomarkers are another way of examining cartilage degradation and synthesis together.

Our overall aim was to examine the relationship of type II collagen A and B synthesis and degradation biomarkers with knee OA progression as part of the overall and ultimate research community goal of identifying biomarkers that could serve to predict disease progression and thereby shorten OA disease-modifying trials. The specific goal of this study was to examine whether the baseline ratio of serum markers of type II collagen breakdown (i.e. collagenase cleavage products) to type II collagen synthesis [i.e. carboxy (c) propeptide], or the level of these markers individually, was associated with the likelihood of knee OA progression between baseline and 18 months later.

METHODS

Sample.

Study participants were recruited from community sources (through advertising in periodicals targeting elderly persons, neighborhood organizations, letters to members of the registry of the Beuhler Centre on Aging at Northwestern University, via medical center referrals) and met the following inclusion criteria: definite osteophyte presence, Kellgren and Lawrence (K/L) radiographic grade ≥2 in one or both knees; and at least some difficulty (Likert category) with two or more items in the Western Ontario and McMaster University Osteoarthritis Index physical function scale. Exclusion criteria were: corticosteroid injection within 3 months, avascular necrosis, rheumatoid or other inflammatory arthritis, periarticular fracture, Paget's disease, villonodular synovitis, joint infection, ochronosis, neuropathic arthropathy, acromegaly, hemochromatosis, Wilson's disease, osteochondromatosis, gout, pseudogout, osteopetrosis, bilateral K/L 4 knee OA, or bilateral total knee replacement. Those with past unilateral knee replacement were eligible if they had OA in the non-replaced knee. Institutional Review Board approval was obtained. All participants gave informed consent.

Measurement of C2C, C12C, and CPII.

Each participant had blood drawn at baseline. Specimens were centrifuged for 10 minutes at 3,000 revolutions per minute to separate serum. Serum was then aliquoted into 1 ml cryotubes and stored in a −80 degree freezer until assayed. ELISA assays for C1,2C, and CPII were from

IBEX Technologies, Montreal, Canada. The principles of the C2C (COL2−3/4Clong mono) assay (for the cleavage of type II cartilage collagen by collagenases) (6), the C1,2C (COL2 −3/4Cshort) assay (similar to the C2C assay but also measures cleavage of type I collagen) (5), and the CPII (carboxy (c) propeptide) assay of type II procollagen (which measures the synthesis of this molecule) (4) have been previously described, as has the application and reproducibility for these serum assays (6,14,15). ELISA kits for C1, 2C and CPII were obtained from IBEX Technologies (Montreal) and the C2C assay (6) was used as described (14).

Radiographic acquisition and assessment of progression.

At baseline and at 18 months, radiographs of both knees were obtained following a protocol specifying knee position, criteria for beam alignment relative to knee center, and radiopaque markers to account for magnification (16). The knee was flexed until the tibial plateau was horizontal, parallel to the beam, and perpendicular to the film. To control for rotation, the heel was fixed and the foot was rotated until the tibial spines were centered within the femoral notch. Knee position (i.e. centering of the spines and superimposition of the anterior and posterior tibial rims) was confirmed by fluoroscopy before films were taken. Foot maps made at baseline were used to standardize repositioning at 18 months. All radiographs were obtained in the same unit by two trained technicians.

OA progression was examined using worsening of the joint space grade and worsening of K/L grade, as established and widely used radiographic outcome measures for natural history studies of knee OA. All available state-of-the-art acquisition protocols were designed and developed to measure joint space in the medial tibiofemoral compartment only. In contrast, joint space grade progression allows assessment of both medial and lateral compartments. The compartments were graded separately using the OARSI atlas-based scales from Altman et al (grade 0 joint space = no narrowing, 1 = possible narrowing, 2 = definite narrowing, 3 = severe narrowing) (17). Joint space grade progression was defined as worsening of grade of either compartment in one or both knees.

The K/L grade is a global measure incorporating joint space assessment, bone changes, and joint deformity. It was important to apply K/L grade both to allow comparison of these results to other studies and also to describe the predictive value of these biomarkers in terms of a global progression measure. The K/L grade provides a global score incorporating joint space assessment, bone changes, and deformity of the joint surface: 0 = normal; 1 = possible osteophytes; 2 = definite osteophytes and possible joint space narrowing; 3 = moderate/multiple osteophytes, definite narrowing, some sclerosis, and possible attrition of joint surface; and 4 = large osteophytes, marked narrowing, severe sclerosis, and definite attrition. Progression was defined as a baseline-to-18-month increase (worsening) of grade in one or both knees. One experience reader assessed radiographs using an atlas. Reliability for these assessments was very good (κ coefficient, 0.80−0.86).

Statistical analysis.

Knees with a joint space grade of 3 (the most severe narrowing) in either the medial or lateral compartment or with a K/L grade of 4 at baseline were excluded from analyses, since they could not progress further. The relationship between baseline biomarkers (individual markers and marker ratios) and subsequent OA progression was analyzed from logistic regression. Participants were divided into biomarker tertile groups to specifically examine the impact of belonging to high versus low biomarker groups. Effects of ratios of biomarkers, calculated from individual assay values, on the odds of progression were investigated as continuous predictors. Odds ratios (OR) and associated 95% confidence interval (CI) were calculated for joint space progression and K/L progression. A 95% CI excluding 1 is statistically significant.

Analyses were adjusted for age (continuous), gender, BMI (continuous), and baseline disease severity (maximum of K/L grades of the two knees).

RESULTS

Sample characteristics.

202 persons (73% women) were studied. The mean age was 68.8 ± 10.6 (SD) years and the mean BMI was 30.1 ± 5.7 kg/m^2. The higher K/L grade (of the two knees) was 2 in 96 participants, 3 in 75, and 4 in 31. In 137 participants, K/L grade was 2 or 3 in both knees. The remainder of the participants had only one knee eligible for progression (the other knee was either K/L < 2, K/L of 4, or had undergone total knee replacement previously). Eighty-three (41%) participants had joint space progression between baseline and 18 months based on radiographic assessment of the tibiofemoral compartment. Mean levels of each type II collagen marker and the marker ratios in progressor and non-progressor groups are provided in Table 1.

The Prediction of Progression by Individual Markers.

We first examined each marker as a continuous variable. Marker level was not associated with any increase in the magnitude of the OR for progression (e.g. for joint space grade progression, the OR, adjusted for age, gender, BMI and disease severity, associated with C2C was 1.003, 95% CI 0.996, 1.011 and the OR associated with CPII was 1.00, 95% CI 0.997, 1.002). This was the case for both the degradation and synthesis markers, and for both approaches to assess progression.

Next, we applied a tertile approach. Upper limits for tertile 1 were: for C2C, 40; for C1,2C 93; and for CPII, 166. Tertile 2 upper limits were: for C2C, 63; for C1,2C, 132; and for CPII, 246. Tertile 3 upper limits were: for C2C, 330; for C1,2C, 289; and for CPII, 690. For the degradation markers, the impact of belonging to the higher tertiles (tertile 2 or 3) (with the lowest tertile as reference) on subsequent progression was examined. For the synthesis marker, the impact of belonging to the two lower tertiles (tertile 1 or 2) (with the highest tertile as reference) on subsequent progression was examined. Belonging to a low synthesis tertiles (but not to the high degradation tertiles) was associated with a greater likelihood of progression that approached significance (see Table 2).

Prediction of Progression by Degradation/Synthesis Ratio.

There was no correlation between either of the degradation markers with CPII (i.e. R = .09 for C2C and .12 for C1,2C). As shown in Table 3, the C2C:CPII ratio and C1,2C:CPII ratio were each associated with an elevation in the odds of joint space grade progression. Results were minimally affected by adjusting for age, gender, BMI, and baseline disease severity. A non-significant elevation in the OR was also seen when progression was examined as worsening of K/L grade. Analyses were repeated in a homogeneous subset of persons with K/L 2 or 3 in both knees (n = 137). Results were very similar, revealing no relationship between markers examined individually, and an elevation in OR for progression associated with degradation to synthesis marker ratio (i.e. OR 2.76 for C2C:CPII).

DISCUSSION

This study examined whether the ratio of serum markers of type II collagen breakdown (i.e. collagenase cleavage [C2C; C1,2C]) to type II collagen synthesis (i.e. carboxy (c) propetide [CPII]), and these markers individually, at baseline were associated with the likelihood of knee OA progression between baseline and 18 months. There was no relationship between marker level and progression when the markers were examined individually as continuous variables.

Belonging to the lower synthesis (i.e. CPII) tertile was associated with an increase in the odds of progression that approached significance. The ratios were associated with an increase in the likelihood of progression in the next 18 months that approached significance, especially the C2C:CPII ratio for joint space grade progression.

The CPII tertile results introduce the possibility that this synthesis marker may have some predictive value but that its relationship with progression may be non-linear. Future studies should examine potential cut-offs for what constitutes high and low levels of CPII. Previous studies of CPII (4, which detects both type IIA and B collagens) and the N-propeptide of type IIA collagen (18, which only detects the minor type IIA collagen) have revealed that they are decreased in patients with knee OA. We were not able to identify a previous study applying a quantile approach for a synthesis marker. Previously, Reijman et al (10) found that persons in the highest quartile of urinary concentration of C-telopeptide, the type IIA and B non-helical degradation marker, had a 6-fold increased risk for progression of radiographic knee OA examined over a 6-year follow-up.

Our results suggest that biomarkers of type II collagen synthesis may be more informative than measuring intrahelical type II collagen degradation alone. This result is in keeping with the concept that proinflammatory cytokines, which, at low levels, are more effective in suppressing collagen synthesis than promoting collagen degradation (19), may play a role in loss of homeostasis reflected by OA progression.

The current findings for the ratios are in keeping with the concept that a failure of cartilage synthesis to keep pace with degradation may be associated with OA progression. This observation is of interest since it is known that degenerate articular cartilage in OA is characterized by an apparent imbalance in matrix catabolism and anabolism (20). For example, there is increased cleavage of type II collagen by collagenases (5,21) and increased synthesis of type II procollagen (4). Newly synthesized collagen is also rapidly degraded favoring catabolism (21). But, serum analyses have revealed a reduction in biomarkers of synthesis of type II collagen associated with a greater likelihood of progression of knee OA (4,9,18). Synthetic differences measured in serum may reflect genetically determined systemic differences in hyaline cartilage metabolism that in turn may influence disease onset and progression rather than reflecting pathology within the joint.

Two other longitudinal studies have examined the predictive value of concomitant consideration of synthesis and degradation markers. Garnero and colleagues (9) calculated an uncoupling index, using the Z scores of serum N-propeptide of Type IIA procollagen (PIIANP), a synthesis marker, and urinary C-terminal crosslinking telopeptide of Type II collagen (CTX-II), a degradation marker. A greater uncoupling index at baseline was associated with greater knee OA progression, evaluated either by joint space narrowing ($R = -0.46$) or by direct visualization arthroscopically ($R = 0.36$). Furthermore, patients with both low baseline levels of PIIANP and high baseline levels of CTX-II had an 8-fold increase in the likelihood of progression, suggesting that considering both degradation and synthesis may better at identifying persons most likely to progress (than markers considered individually). In another recent study in which progression was assessed over 30 months using medial tibiofemoral joint space narrowing (22), the C2C/CPII ratio was associated with an elevated but nonsignificant OR of 1.67 (95% CI 0.87, 3.14) in the 60 persons receiving doxycycline but not in the placebo group (also numbering 60) (OR 0.82, 95% CI 0.50, 1.45). The reason for this difference is unclear.

The present observations have interesting parallels for the same biomarkers when they have been used to study the progression of naturally occurring OA in the knee joints of guinea pigs (23). The Hartley strain develops more extensive knee OA than strain 13 over a period of one

year. Compared to Strain 13, this is also accompanied at 12 months by a reduction in the same serum CPII type II collagen biosynthesis marker and an increase in the serum C2C degradation marker in the Hartley strain. The ratio of C2C/CPII is also increased in Hartley guinea pigs as are a number of pro-inflammatory cytokines and chemokines (23).

Other predictive serum markers for progression which have been identified in longitudinal human studies include hyaluronic acid (hyaluronan) (7,12), C-reactive protein (11), stromeylsin-1 (MMP-3) (13) and cartilage oligomeric matrix protein (COMP) (8,24,25). Changes in molecular markers over time may also have better predictive value for progression than marker levels from one time-point. Bruyere et al (26) found that a one-year increase in serum osteocalcin or a one-year decrease in serum hyaluronic acid from baseline predicted progression at 3 years.

It is important to acknowledge that the results for the ratio of C2C to CPII in our study approached but did not achieve significance. We believe there are important reasons to report on these results. First, the OR for progression associated with the degradation to synthesis marker ratio was consistently elevated (deleterious effect), and may have achieved significance in a larger sample. In contrast, the OR for progression appeared to be unrelated to the levels of individual markers. Second, the longitudinal studies in the literature appear to describe somewhat striking results in one or only a few cohorts for each marker, introducing a concern that there may be underreporting of negative or less impressive results.

Our findings for the measurement of total type II collagen turnover are less impressive than those of Garnero et al (9). This difference may not only be related to the different markers themselves but rather to how the markers were combined; combining Z scores may be a superior approach. Moreover, in this previous study, only 16 progressors and 36 non-progressors were examined over one year. Clearly future appropriately powered studies should include head to head comparisons of these different markers and their combinations using the same methodologic approach to assess progression.

There are limitations to our study that may help to explain the relative weakness of the findings. We used radiographic measures of progression; quantitative assessment of cartilage volume by MRI may be a superior means of demonstrating the predictive value of these biomarkers. Also we did not adjust for total body burden of OA, which undoubtedly complicates the serum assessment of cartilage biomarkers.

In summary, the ratio of a marker reflecting type II collagen degradation (C2C) to a type II procollagen synthesis marker (CPII) was more closely related to knee OA progression over the next 18 months, than these markers examined separately. Future studies should consider ratio approaches and other methods of combining markers in an effort to identify synthesis and degradation combinations to more powerfully (than the current study approach) predict progression.

Acknowledgements

GRANT SUPPORT: Arthritis Foundation, NIH P60 AR48098

REFERENCES

1. NIH Consensus Statement on Total Knee Replacement. NIH Consens State Sci Statements Dec 8 −10;2003 20(1):1–32. [PubMed: 17308549]
2. Poole, AR. Biochemical/immunochemical biomarkers of osteoarthritis. In: Brandt, K., editor. Rheumatic Disease Clinics of North America. 29. Elsevier Science; 2003. p. 803-818.
3. De Groot J, Bank RA, Tchetverikov I, Verzil N, TeKoppele JM. Molecular markers for osteoarthritis: The road ahead. Curr Opinion Rheumatol 2002;14:585–589.

4. Nelson F, Dahlberg L, Laverty S, Reiner A, Pidoux I, Ionescu M, Fraser G, Brooks E, Tanzer M, Rosenberg LC, Dieppe P, Poole AR. Evidence for altered synthesis of type II collagen in patients with osteoarthritis. J Clin Invest 1998;102:2115–2125. [PubMed: 9854047]
5. Billinghurst RC, Dahlberg L, Ionescu M, Reiner A, Bourne R, Rorabeck RC, Mitchell P, Hambor J, Diekmann O, Tschesche H, Chen J, Van Wart H, Poole AR. Enhanced cleavage of type II collagen by collagenases in osteoarthritic articular cartilage. J Clin Invest 1997;99:1534–1545. [PubMed: 9119997]
6. Poole AR, Ionescu M, Fitzcharles MA, Billinghurst RC. The assessment of cartilage degradation *in vivo*: development of an immunoassay for the measurement in body fluids of type II collagen cleaved by collagenases. J Immunol Meth 2004;294:145–153.
7. Sharif M, George E, Shepstone L, Knudson W, Thonar EJ-M, Cushnaghan J, Dieppe P. Serum hyaluronic acid level as a predictive of disease progression in osteoarthritis of the knee. Arthritis Rheum 1995;38:760–767. [PubMed: 7779118]
8. Sharif M, Saxne T, Shepstone L, Kirwan JR, Elson CJ, Heinegard D, Dieppe P. Relationship between serum cartilage oligomeric matrix protein levels and disease progression in osteoarthritis of the knee joint. Br. J. Rheumatol 1995;34:306–310. [PubMed: 7788143]
9. Garnero P, Ayral X, Rousseau J-C, Christgau S, Sandell L, Dougados M, Delmas PD. Uncoupling of type II collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis. Arthritis Rheum 2002;46:2613–2624. [PubMed: 12384919]
10. Reijman M, Hazes JMW, Bierma-Zeinstra SMA, Koes BW, Christgau S, Christiansen C, Uitterlinden AG, Pols HAP. A new marker for osteoarthritis: cross-sectional and longitudinal approach. Arthritis Rheum 2004;50:2471–2478. [PubMed: 15334460]
11. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, Pepys MB. Low-level increases in serum C - reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum 1997;40:723–727. [PubMed: 9125256]
12. Pavelka K, Forejtove S, Olejarova M, Gatterova J, Senolt L, Spacek P, Braun M, Hulejova M, Stovickova J, Pavelkova A. Hyaluronic acid levels may have predictive values for the progression of knee osteoarthritis. Osteoarthritis Cartilage 2004;12:277–283. [PubMed: 15023379]
13. Lohmander LS, Brandt KD, Mazzuca SA, Katz BP, Larsson S, Struglies A, Lane KA. Use of the plasma stromelysin (matrix metalloproteinase 3) concentration to predict joint space narrowing in knee osteoarthritis. Arthritis Rheum 2005;52:3160–3167. [PubMed: 16200596]
14. Cibere J, Thorne A, Kopec JA, Singer J, Canvin J, Robinson DB, Pope J, Hong P, Grant E, Lobanok T, Ionescu M, Poole AR. Glucosamine sulfate and cartilage type II collagen degradation in patients with knee osteoarthritis: randomized discontinuation trial results employing biomarkers. J. Rheumatol 2005;32:896–902. [PubMed: 15868627]
15. Verstappen SMM, Poole AR, Ionescu M, King LE, Abrahamowicz M, Hofmann DM, Bijlsma JWJ. Lafeber FPJG. Radiographic joint damage in rheumatoid arthritis is associated with differences in cartilage turnover and can be predicted by serum biomarkers: A 3 year follow-up study. Arthritis Res Ther 2006;8:R31. [PubMed: 16507130]
16. Buckland-Wright CB. Protocols for precise radio-anatomical positioning of the tibiofemoral and patellofemoral compartments of the knee. Osteoarthritis Cartilage 1995;3(suppl A):71–80. [PubMed: 8581753]
17. Altman RD, Hochberg M, Murphy WA, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3:3–70. [PubMed: 8581752]
18. Rousseau J-C, Zhu Y, Miossec P, Vignon E, Sandell LJ, Garnero P, Delmas PD. Serum levels of type IIA procollagen amino terminal propeptide (PIIANP) are decreased in patients with knee osteoarthritis and rheumatoid arthritis. Osteoarthritis Cartilage 2004;12:440–447. [PubMed: 15135140]
19. Poole, AR.; Alini, M.; Hollander, AP. Cellular biology of cartilage degradation. In: Henderson, B.; Edwards, JCW.; Pettipher, ER., editors. Mechanisms and Models in Rheumatoid Arthritis. Academic Press; New York: 1995. p. 163-204.
20. Goldring MB. The role of chondrocyte in osteoarthritis. Arthritis Rheum 2000;43:1916–1926. [PubMed: 11014341]

21. Dahlberg L, Billinghurst RC, Manner P, Nelson F, Webb G, Ionescu M, Reiner A, Tanzar M, Zukor D, Chen J, van Wart HE, Poole AR. Selective enhancement of collagenase-mediated cleavage of resident type II collagen in cultured osteoarthritic cartilage and arrest with a synthetic inhibitor that spares collagenase 1 (matrix metalloproteinase 1). Arthritis Rheum 2000;43:673–682. [PubMed: 10728762]

22. Mazucca SA, Poole AR, Brandt KD, Katz BP, Lane KA, Lobanok T. Associations between joint space narrowing and molecular markers of collagen and proteoglycan turnover in patients with knee osteoarthritis. J. Rheumatol 2006;33:1147–1151. [PubMed: 16652436]

23. Huebner JL, Kraus VB. Assessment of the utility of biomarkers of osteoarthritis in the guinea pig. Osteoarthritis Cartilage 2006;14:923–930. [PubMed: 16679035]

24. Vilim V, Olejarova M, Machacek S, Gatterova J, Kraus VB, Pavelka K. Serum levels of cartilage oligomeric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis. Osteoarthritis Cartilage 2002;10:707–713. [PubMed: 12202123]

25. Sharif M, Kirwan JR, Elson CJ, Granell R, Clarke S. Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurement of serum cartilage oligomeric matrix protein levels over five years. Arthritis Rheum 2004;50:2479–2488. [PubMed: 15334461]

26. Bruyere O, Collette JH, Ethgen O, Rovati LC, Giacovelli G, Henrotin YE, Seidel L, Reginster J-YL. Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee osteoarthritis. J Rheumatol 2003;30:1043–1050. [PubMed: 12734904]

TABLE 1

Sample Mean of Type II Collagen Markers. Mean and standard deviation of each marker and marker ratio is shown for the full sample (n = 202), progressors (n = 83), and non-progressors (n = 119).

Type II Collagen Marker	Mean ± SD (Full sample)	Mean ± SD in progressors	Mean ± SD in non-progressors
C2C epitope (degradation marker)	59 ± 41 pmol/ml	63 ± 53 pmol/ml	57 ± 30 pmol/ml
C1,2C epitope (degradation marker)	119 ± 56 pmol/ml	118 ± 57 pmol/ml	120 ± 55 pmol/ml
CPII (synthesis marker)	223 ± 108 ng/ml	217 ± 121 ng/ml	227 ± 99 ng/ml
C2C:CPII ratio	0.31 ± 0.24	0.35 ± 0.30	0.29 ± 0.19
C1,2C:CPII ratio	0.64 ± 0.41	0.69 ± 0.48	0.60 ± 0.35

TABLE 2

Odds Ratio for Joint Space Grade Progression Associated with Marker Tertile. The odds ratio (OR) for joint space grade progression associated with belonging to the given marker tertile is shown with the 95% confidence interval (CI) first unadjusted then adjusted for age, gender, BMI, and baseline disease severity. A 95% CI excluding 1 is significant.

Marker Tertile	OR (95% CI)	Age, gender, BMI, disease severity-adjusted OR (95% CI)
C2C Tertile 2 or 3 (reference tertile1)	0.81 (0.45, 1.47)	0.90 (0.49, 1.67)
C1,2C Tertile 2 or 3 (reference 1)	0.73 (0.40, 1.32)	0.78 (0.42, 1.43)
CPII Tertile or 2 (reference 3)	1.85 (0.99, 3.46)	1.86 (0.96, 3.63)

TABLE 3

Odds Ratios for Knee OA Progression Associated with Marker Ratio (n = 202) The table shows the odds ratio (OR) for joint space grade progression and for K/L grade progression per unit change in marker ratio, first unadjusted and then adjusted for age, gender, BMI, and baseline disease severity.

Marker Ratio	JOINT SPACE GRADE PROGRESSION		K/L GRADE PROGRESSION	
	OR (95% CI)	Adjusted* OR (95% CI)	OR (95% CI)	Adjusted* OR (95% CI
C2C : CPII ratio	2.82 (0.86, 9.25)	3.15 (0.91, 10.85)	1.98 (0.62, 6.35)	2.18 (0.65, 7.3)
C1,2C : CPII ratio	1.68 (0.84, 3.38)	1.79 (0.87, 3.69)	1.70 (0.84, 3.46)	1.79 (0.86, 3.72)

* Adjusted for age, gender, BMI, and baseline disease severity. A 95% CI excluding 1 is significant.