Change in Serum COMP Concentration Due to Ambulatory Load Is Not Related to Knee OA Status

Annegret Mündermann,[1,2,3] Karen B. King,[4] R. Lane Smith,[3,5] Thomas P. Andriacchi[1,3,5]

[1]Department of Mechanical Engineering, Stanford University, Stanford, California, [2]School of Physiotherapy, University of Otago, 325 Great King Street, Dunedin 9001, New Zealand, [3]Bone and Joint Center, Palo Alto VA, Palo Alto, California, [4]Department of Orthopaedics—Bioengineering, University of Colorado, Denver, Aurora, Colorado, [5]Department of Orthopedic Surgery, Stanford University Medical Center, Stanford, California

Received 18 November 2008; accepted 20 March 2009
Published online 6 May 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jor.20908

ABSTRACT: The aim of this study was to test the hypothesis that a change in serum cartilage oligomeric matrix protein (COMP) concentration is related to joint load during a 30-min walking exercise in patients with medial compartment knee osteoarthritis (OA) and in age-matched control subjects. Blood samples were drawn from 42 patients with medial compartment knee OA and from 41 healthy age-matched control subjects immediately before, immediately after, and 0.5, 1.5, 3.5, and 5.5 h after a 30-min walking exercise on a level outdoor walking track at self-selected normal speed. Serum COMP concentrations were determined using a commercial ELISA. Basic time–distance gait variables were recorded using an activity monitor. Joint loads were measured using gait analysis. Serum COMP concentrations increased immediately after the walking exercise (+6.3% and +5.6%; $p < 0.001$) and decreased over 5.5 h after the exercise (−11.1% and −14.6%; $p < 0.040$ and $p = 0.001$) in patients and control subjects, respectively. The magnitude of increase in COMP concentration did not differ between groups ($p = 0.902$) and did not correlate with any variables describing ambulatory loads at the joints of the lower extremity. These results, taken together with a previous study of a younger healthy population, suggest the possibility that the influence of ambulatory loads on cartilage turnover is dependent on age. © 2009 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 27:1408–1413, 2009

Keywords: COMP; knee OA; walking; load

Osteoarthritis (OA) is characterized by degenerative changes in the cartilage that are likely influenced by mechanical and biological factors.[1,2] However, at an in vivo level, the interaction between mechanical and biological factors is poorly understood. Increased mechanical load on the medial compartment of the knee during gait, typically measured dynamically as extrinsic knee adduction moment,[3] has been related to OA presence,[4] OA disease severity,[4] and a higher rate of progression of knee OA.[5] However, it is still unclear if and how these increased loads affect biological processes.

Healthy cartilage undergoes constant turnover of cartilage constituents including collagen, proteoglycans, and cartilage oligomeric matrix protein (COMP), although at different rates. This equilibrium between synthesis and degradation is disrupted in osteoarthritic tissue.[6] Fragments of these structural proteins can be detected in blood serum and reflect cartilage degeneration.[7] While there are a number of markers for cartilage turnover, COMP is especially important in linking mechanical load to cartilage health, as it is found primarily in cartilage[8] and may play an important role in transducing mechanical forces from the extracellular matrix to the cell.[9] However, a direct link between functional in vivo loads at the knee in patients with knee osteoarthritis and changes in serum COMP concentrations has not been established.

Patients with knee osteoarthritis had elevated serum COMP concentrations following a 1-h physical exercise program.[10] Nevertheless, there are still significant gaps in our ability to interpret the relationships between changes in biomarkers and the loading environment of cartilage. For instance, load magnitude, number of loading cycles, frequency of loading, and the duration of exposure to load are some of the factors that may affect the regulation[9] and/or release of COMP. Serum COMP concentrations are higher during periods of radiographic progression in patients with knee osteoarthritis,[11] suggesting that serum COMP concentrations may be an important marker for cartilage degeneration.

The purpose of this study was to identify the role of functional loading of the knee during activities of daily living on changes in serum COMP concentration in patients with knee OA and in age-matched control subjects. We hypothesized that (1) the increase in serum COMP concentration immediately after a 30-min walking exercise is greater in patients with knee OA than in age-matched control subjects, and (2) the increase in serum COMP concentration during a 30-min walking exercise is related to lower extremity joint load during the exercise in both groups.

METHODS

Patients

Forty-two patients with radiographically diagnosed OA in the medial compartment of at least one knee participated in this study (Table 1) after giving written consent in accordance with the Institutional Review Board. All subjects fulfilled all inclusion criteria: definite osteophyte presence in the medial or lateral tibiofemoral compartment; a narrowest point inter-bone distance of the medial compartment less than the lateral compartment; pain in and around at least one knee for most of the days in the past months; at least some difficulty with two or more items in the WOMAC Physical Function scale.[12] Among the exclusion criteria: total knee or hip replacement in either leg; flexion contracture >15° in either knee; grade > moderate (scale none, mild, moderate, severe) of OA by exam in either ankle (by history) or either hip (American

Correspondence to: Annegret Mündermann (T: +64 3 456 4135; F: +64 3 479 8414; E-mail: anne.muendermann@gmail.com)

Table 1. Mean ± 1 SD and (Range) of Demographic Variables for Patients with Medial Compartment Knee OA and Age-Matched Control Subjects Participating in This Study

Variable	Patients	Control Subjects	p-Value (Patients vs. Control Subjects)*
Gender (female/male)	22/20	20/21	0.744**
Age [years]	60.7 ± 8.6 (40–74)	57.5 ± 7.0 (44–71)	0.070
Height [cm]	170.0 ± 10.5 (152–193)	172.6 ± 10.4 (152–193)	0.212
Mass [kg]	78.1 ± 15.0 (43–105)	76.6 ± 14.3 (52–109)	0.633
BMI[a] [kg/m^2]	27.0 ± 3.8 (17–36)	25.7 ± 4.2 (18–35)	0.148
Kellgren–Lawrence grade			
1	11		
2	7		
3	12		
4	12		

[a]Body Mass Index (BMI) = Mass [kg]/Height [m]^2.
*p-Values are based on independent samples Student's t-tests.
**p-Value is based on Mann–Whitney test.

College of Rheumatology criteria)[13]; morbid obesity (BMI > 35 kg/m^2); intraarticular corticosteroid injection within 2 months; knee surgery within 6 months; and plan for total knee replacement within the next year. Three patients presented with unilateral knee OA, and all other patients presented with bilateral knee OA.

Control Subjects

Forty-one age-matched control subjects (Table 1) without any symptoms or signs of knee OA (Kellgren–Lawrence grade 0) participated in this study after giving informed consent in accordance with the Institutional Review Board. All control subjects had no clinical diagnosis of OA or rheumatoid arthritis, or a history of knee trauma or pain. None of the control subjects had previously been treated for any clinical lower back or lower extremity condition, or had any activity-restricting condition. Magnetic resonance images[14] of both knees were obtained for each subject to confirm the absence of any early signs of OA in any of the compartments of the knee.

Procedures

Subjects were asked to limit their physical activity 36 h prior to the experiment. On the day of the experiment, subjects consumed breakfast within 1 h of waking, and the experiment started within 1 to 2 h of waking. Subjects were in a seated position for 30 min while completing the informed consent. Magnetic resonance images of both knees were then acquired with the subject in a prone position. Subjects were then in a seated position for 30 min before the first blood sample was taken. Five-milliliter blood samples were drawn from the same antecubital vein immediately before, immediately after, and 0.5, 1.5, 3.5, and 5.5 h after a 30-min walking exercise. During the walking exercise, subjects walked at their self-selected normal speed on a level paved outdoor walking track. An activity monitor (AMP331; Dynastream Innovations Inc., Cochrane, Canada) was attached to the ankle of the more severe side for patients and on the right ankle of control subjects to record basic time–distance measurements of gait. Subjects maintained a seated posture for 5.5 h after the 30-min walking exercise and performed a minimal amount of physical activity. During this resting time, basic time–distance measurements were recorded using the activity monitor. Following the last blood draw, subjects underwent gait analysis.

Enzyme-Linked Immunosorbent Assay

Blood was collected and allowed to clot for 30 min. Sera were separated and frozen to −20°C within 1 h of collection and then transferred for storage at −80°C until assayed. Serum COMP concentrations were determined using a commercial enzyme-linked immunosorbent assay (COMP® ELISA; AnaMar Medical AB, Lund, Sweden). Investigators were blinded to the samples, which were analyzed in duplicate and in random order. The detection limit of the assay was <0.1 Units/l (U/l), and the intra-assay and inter-assay coefficients of variation were <1.9% and <2.7%, respectively (10 U/l convert to approximately 1 μg/ml).[16] Differences due to inter-assay variation were eliminated by comparing concentrations within subjects and by testing all samples of any subject on the same plate.

Gait Analysis

The approach used to collect kinematic and kinetic data is identical to that described in previous investigations.[4,15,16] Briefly, reflective markers were placed on the leg along anatomical landmarks. Marker data was captured using seven high-speed cameras (120 frames/s; MCU240, Qualisys Medical AB, Gothenburg, Sweden). Ground reaction force data was collected using a force platform (sampling frequency: 120 Hz; Bertec Corporation, Columbus, OH). Each limb segment was idealized as a rigid body, and external moments at the ankle, knee, and hip in the sagittal and frontal planes were calculated from the position of the markers, ground reaction force measurements, and limb segment mass/inertia properties[17] using an inverse dynamics approach. Subjects performed three trials per speed at self-selected slow, normal, and fast walking speed. The trial with the speed that most closely matched the average walking speed during the 30-min walking exercise was used for further analysis. Joint moments were normalized to bodyweight and height (%Bw*Ht). Peak joint moments between the left and right knee were averaged for further analysis.

Statistical Analysis

All statistical computations were performed using SPSS 11.5 software (SPSS Inc., Champaign, IL). Serum COMP concentrations within each group and between groups were compared using two-way repeated measures ANOVA. Repeated measures and independent sample Student's t-tests

were used for post hoc comparisons. Stepwise multiple linear regression analysis was used to detect a significant relationship between the change in serum COMP concentration and variables describing joint load. The significance level α for all statistical tests was set a priori at 0.05.

RESULTS

Serum COMP Concentration at Baseline

Before the 30-min exercise, serum COMP levels were similar in patients with medial compartment knee OA and age-matched control subjects ($p = 0.755$). Mean (range) serum COMP concentrations were 10.8 (5.3–21.9) U/l in the patient group and 10.5 (4.5–19.1) U/l in the control group, respectively.

Serum COMP Concentration after 30-Min Walking Exercise

Immediately after the 30-min walking exercise, serum COMP concentrations increased in both groups (patients: +6.3%; control subjects: +5.6%; $p < 0.001$; Figs. 1 and 2). Within 30 min after the exercise, serum COMP levels returned to baseline in both groups (patients: $p = 0.009$; control subjects: $p = 0.001$; Fig. 1). Serum COMP concentration then continued to decrease up to 5.5 h after the exercise in both groups (patients: −11.1%, $p = 0.040$; control subjects: −14.6%, $p = 0.001$; Fig. 1). The change in serum COMP concentration during and after the 30-min walking exercise did not differ between the two groups ($p = 0.946$).

Ambulatory Load during the 30-Min Exercise

During the 30-min walking exercise, patients and control subjects took similar numbers of steps to travel similar distances (Table 2). Patients with medial compartment knee OA walked 8.9% slower and at a 4.7% lower cadence ($p < 0.027$; Table 2). Patients with medial compartment knee OA walked with lower peak knee flexion moments (−18.7%), peak ankle eversion moments (−5.3%), and peak hip flexion moments (−13.8) compared to control subjects ($p < 0.047$; Table 2). Subjects in both groups took a negligible number of steps during the 5.5-h rest following the 30-min walking exercise (Table 2).

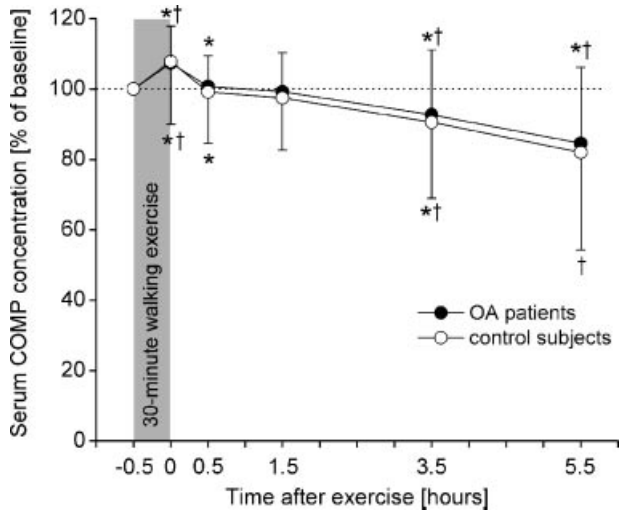

Figure 1. Mean (± 1 SD) serum COMP concentrations as percent of baseline before and after the 30-min walking exercise for patients with medial compartment knee OA and age-matched control subjects. *Indicates significant difference to previous time point. †Indicates significant difference to baseline values ($p < 0.05$). Note that statistical tests were performed on absolute values. Data was normalized to baseline values for visual presentation only.

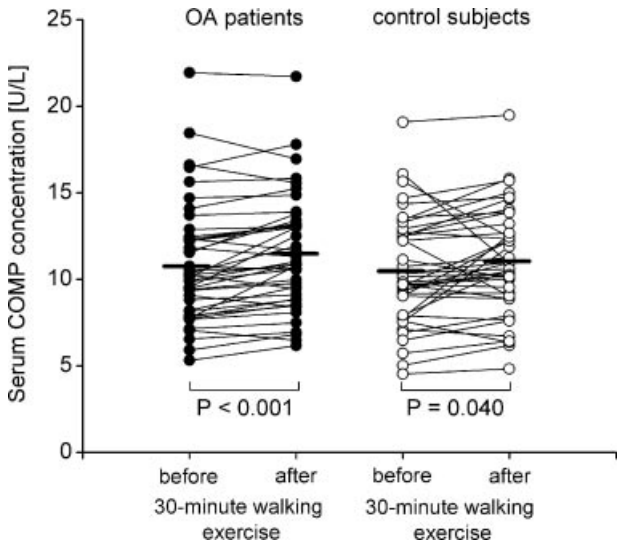

Figure 2. Serum COMP concentration before and immediately after the 30-min exercise in patients with medial compartment knee OA and age-matched control subjects. Each line represents an individual patient/subject. Horizontal bars show mean value for each group. p-Values are results of paired Student's t-tests.

Change in Serum COMP Concentration and Ambulatory Load

Stepwise multiple linear regression analysis did not reveal any correlation between the change in serum COMP concentration and any variable describing ambulatory loads at the joints of the lower extremity during the exercise (Fig. 3).

DISCUSSION

The results of this study showed that a 30-min walking exercise can cause elevated serum levels of COMP in patients with radiographically diagnosed OA in the medial compartment of the knee and in age-matched subjects with no signs of knee OA. However, the increase in serum COMP concentration during a well-defined exercise did not differ between patients and control subjects. Further, the change in serum COMP concentration during the exercise was not related to any of the variables describing ambulatory loads in patients or control subjects. Based on these results, hypotheses one and two were rejected.

Baseline serum COMP concentrations in patients with medial compartment knee OA and in age-matched control subjects were comparable to levels reported in other studies on patients with knee OA after 1 h of rest,[10] healthy younger adults after 3 h of minimal exercise,[18] and patients with nonprogressing knee OA[11] using the same assay as the one used in our study. Activity of

Table 2. Mean ± 1 SD of Basic Time–Distance Gait Measures and Variables Describing Lower Extremity Joint Load for Patients with Knee OA and Age-Matched Control Subjects Participating in This Study

Variable	Patients	Control Subjects	*p*-Value*
Basic time–distance gait measures during 30-min walking exercise			
Number of steps	3,428 ± 573	3,494 ± 455	0.567
Distance [m]	2,398 ± 506	2,543 ± 563	0.224
Walking speed [m/s]	1.3 ± 0.2	1.4 ± 0.3	**0.021**
Cadence [steps/min]	110 ± 10	116 ± 11	**0.027**
Basic time–distance gait measures during post-exercise rest			
Number of steps	71.8 ± 69.9	57.8 ± 49.6	0.459
Distance [m]	25.6 ± 32.6	19.2 ± 20.6	0.603
Variables describing lower extremity joint load			
Peak external knee adduction moment [%Bw*Ht]	2.65 ± 0.89	2.71 ± 0.65	0.717
Peak knee flexion moment [%Bw*Ht]	2.79 ± 1.27	3.43 ± 1.60	**0.047**
Peak ankle eversion moment [%Bw*Ht]	1.24 ± 0.49	1.31 ± 0.44	**0.015**
Peak ankle dorsiflexion moment [%Bw*Ht]	9.18 ± 0.92	9.73 ± 1.11	0.531
Peak hip adduction moment [%Bw*Ht]	4.45 ± 0.95	4.69 ± 1.18	0.322
Peak hip flexion moment [%Bw*Ht]	3.18 ± 0.81	3.69 ± 1.36	**0.044**

*p-Values are based on independent samples Student's t-tests. Significant differences between groups are indicated in bold.

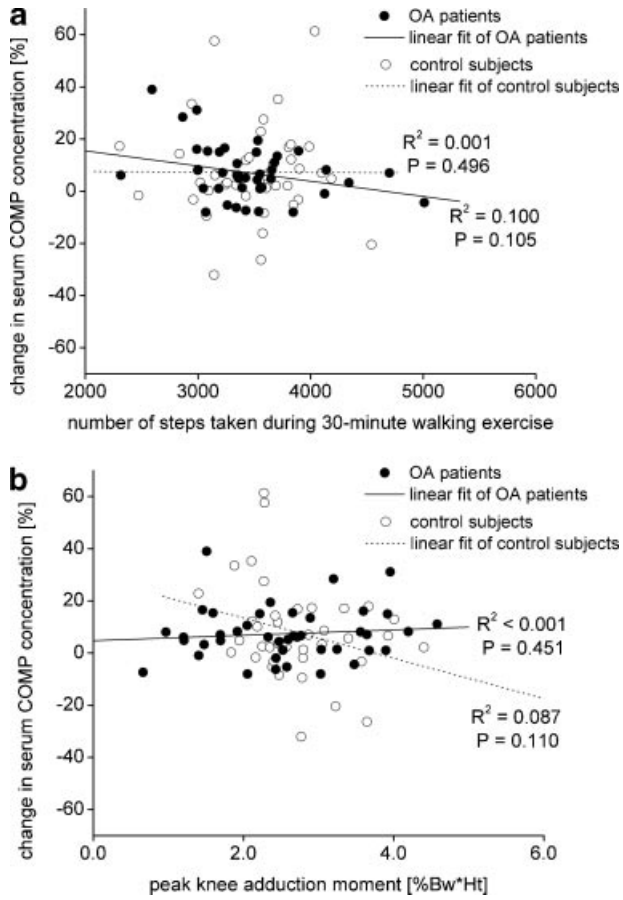

Figure 3. A relationship between change in serum COMP concentration during the 30-min walking exercise and ambulatory load was not observed ($p > 0.100$). Examples are shown for (a) number of steps taken during the exercise, and (b) peak knee adduction moment during walking for patients with medial compartment knee OA and age-matched control subjects.

participants in the current study 3 h prior to the first blood sample was controlled and minimized. The similarity of these baseline values provide further support for the importance of controlling physical activity prior to blood sampling as previously recommended.[10,18]

Some studies have reported greater COMP concentrations in patients with knee OA compared to control subjects.[19,20] One possible explanation for the discrepancy between previous and current results is the relatively small sampling size, inclusion of low Kellgren–Lawrence grade patients, and a mix of different age/ethnic groups. However, patients with knee OA in some previous studies[19] were older than control subjects. In addition, no significant interaction between age and arthritis status have been reported.[19] Thus, our results are in agreement with that study. However, it should be noted that the sample size in our study was too small to elucidate ethnic differences.

Physical exercise programs are often prescribed to patients with knee OA. The perceived benefits of these programs include reduction in pain, improved function, and altered joint load.[21,22] However, the effects of such programs on turnover of cartilage constituents including COMP are largely unknown. Serum COMP concentration in patients with knee OA increased during strengthening exercise and returned to baseline within 24 h.[10] In the current study, serum COMP concentrations increased similarly in patients with knee OA and in age-matched control subjects during a controlled walking exercise. This result supports previous statements[10,18] that exercise facilitates diffusion of COMP fragments from the tissue to the blood. Similar results have also been reported for other cartilage constituents including aggrecan, hyaluronan, and keratan sulfate in healthy athletes,[23] and for COMP in thoroughbreds free of orthopedic disease.[24]

However, the delayed increase in serum COMP concentration, as reported in our previous study[18] of a younger population, was not observed in the OA patients nor in the age-matched healthy control subjects in the present study. This discrepancy suggests the possibility that the influence of exercise on cartilage turnover is dependent on age. The delayed response in the younger population,[18] using the same protocol as in this study, suggests the possibility that the older control subjects have cartilage that responds to load in a way that is closer to a patient with knee OA than a younger healthy subject. Hence, we speculate that cartilage in the younger population is more metabolically active than cartilage in patients with knee OA and older asymptomatic persons and, therefore, has the ability to adapt to the loading associated with the exercise. Thus, the influence of physical exercise on the turnover of aging cartilage requires further analysis.

Serum COMP concentration decreased below baseline following the exercise in patients and control subjects. Similar observations were made previously in healthy subjects during a 6-h resting protocol.[18] In contrast to that study, activity prior to the first blood sample in patients and subjects in the current study was controlled and minimized. It is possible that the further decrease in serum COMP concentration throughout the day in the current study reflects the diurnal variation in COMP concentration.[25] In addition, activity following the walking exercise in the current study was minimized and closely monitored. It is possible that patients in a previous study[10] were more active following the exercise than patients in the current study, resulting in the return of serum COMP levels to baseline only 6 h after the exercise.

Patients in the current study walked at significantly lower self-selected speed than age-matched control subjects. It is possible that this difference in walking speed might represent a behavior that prevents the elevation of markers of cartilage degeneration. Osteoarthritis is a progressing disease, and the rate of progression varies between individuals. Thus, some aspect of mechanical load that is outside of this very thorough and precise analysis could potentially contribute to cartilage breakdown. Further, it is feasible that COMP release and/or synthesis may not adequately reflect a low level but a persistent change in a degenerative pathway that modifies the tissue/matrix capacity for distribution of joint loads.

Joint load was not quantified in any other previous studies[10,18,26] on the effects of exercise on serum COMP concentration. Increases in serum COMP concentrations were observed in all of these studies despite a wide variety of loading modes during these exercises. The results of the current study combined with the results reported in the literature suggest that while serum COMP concentration does not seem to be related to ambulatory loads, exercise still may be critical for the transport of waste products from the tissue to the blood. It has been suggested[27] that exercise may increase clearance of degraded matrix constituents through increased rate of diffusion through the synovium and increased lymphatic flow. Further, physiologic exercise such as walking increased the rate of synovial fluid in effusive joints of patients with arthropathy.[28] Thus, physical activities such as walking or strengthening exercises are likely beneficial for the healthy and osteoarthritic joint as long as normal joint mechanics are maintained, that is the load is well-distributed between the medial and lateral compartments of the knee.

ACKNOWLEDGMENTS

The authors thank Jessica Asay, Susan Ward, Louise McManus, Lise Worthen-Chaudhari, and Joe Guerricabeitia for their assistance in data collection and processing. This work was funded by Department of Veterans Affairs grant #A04-3583R; AnaMar Medical AB (Lund, Sweden) provided COMP ELISA kits, and Dynastream Innovations Inc. (Cochrane, Canada) provided activity monitors.

REFERENCES

1. Andriacchi TP, Mündermann A, Smith RL, et al. 2004. A framework for the in vivo pathomechanics of osteoarthritis at the knee. Ann Biomed Eng 32:447–457.
2. Aigner T, Fundel K, Saas J, et al. 2006. Large-scale gene expression profiling reveals major pathogenetic pathways of cartilage degeneration in osteoarthritis. Arthritis Rheum 54:3533–3544.
3. Schipplein OD, Andriacchi TP. 1991. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 9:113–119.
4. Mündermann A, Dyrby CO, Hurwitz DE, et al. 2004. Potential strategies to reduce medial compartment loading in patients with knee OA of varying severity: reduced walking speed. Arthritis Rheum 50:1172–1178.
5. Miyazaki T, Wada M, Kawahara H, et al. 2002. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. Ann Rheum Dis 61: 617–622.
6. Cahue S, Sharma L, Dunlop D, et al. 2007. The ratio of type II collagen breakdown to synthesis and its relationship with the progression of knee osteoarthritis. Osteoarthritis Cartilage 15:819–823.
7. King KB, Lindsey CT, Dunn TC, et al. 2004. A study of the relationship between molecular biomarkers of joint degeneration and the magnetic resonance-measured characteristics of cartilage in 16 symptomatic knees. Magn Reson Imaging 22: 1117–1123.
8. Saxne T, Heinegård D. 1992. Cartilage oligomeric matrix protein: a novel marker of cartilage turnover detectable in synovial fluid and blood. Br J Rheumatol 31:583–591.
9. Wong M, Siegrist M, Cao X. 1999. Cyclic compression of articular cartilage explants is associated with progressive consolidation and altered expression pattern of extracellular matrix proteins. Matrix Biol 18:391–399.
10. Andersson ML, Thorstensson CA, Roos EM, et al. 2006. Serum levels of cartilage oligomeric matrix protein (COMP) increase temporarily after physical exercise in patients with knee osteoarthritis. BMC Musculoskelet Disord 7:98.
11. Sharif M, Kirwan JR, Elson CJ, et al. 2004. Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years. Arthritis Rheum 50:2479–2488.
12. Bellamy N, Buchanan WW, Goldsmith CH, et al. 1988. Validation study of WOMAC: a health status instrument for

measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 15:1833–1840.
13. Altman R, Alarcon G, Appelrouth D, et al. 1991. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 34: 505–514.
14. Koo S, Gold GE, Andriacchi TP. 2005. Considerations in measuring cartilage thickness using MRI: factors influencing reproducibility and accuracy. Osteoarthritis Cartilage 13: 782–789.
15. Prodromos CC, Andriacchi TP, Galante JO. 1985. A relationship between gait and clinical changes following high tibial osteotomy. J Bone Joint Surg 67:1188–1194.
16. Wang JW, Kuo KN, Andriacchi TP, et al. 1990. The influence of walking mechanics and time on the results of proximal tibial osteotomy. J Bone Joint Surg 72:905–909.
17. Dempster WT, Gaughran GRL. 1967. Properties of body segments based on size and weight. Am J Anat 120:33–54.
18. Mündermann A, Dyrby CO, Andriacchi TP, et al. 2005. Serum concentration of cartilage oligomeric matrix protein (COMP) is sensitive to physiological cyclic loading in healthy adults. Osteoarthritis Cartilage 13:34–38.
19. Jordan JM, Luta G, Stabler T, et al. 2003. Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project. Arthritis Rheum 48:675–681.
20. Clark AG, Jordan JM, Vilím V, et al. 1999. Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. Arthritis Rheum 42:2356–2364.
21. Thorstensson CA, Henriksson M, von Porat A, et al. 2007. The effect of eight weeks of exercise on knee adduction moment in early knee osteoarthritis—a pilot study. Osteoarthritis Cartilage 15:1163–1170.
22. Jan MH, Lin JJ, Liau JJ, et al. 2008. Investigation of clinical effects of high- and low-resistance training for patients with knee osteoarthritis: a randomized controlled trial. Phys Ther 88:427–436.
23. Roos H, Dahlberg L, Hoerrner LA, et al. 1995. Markers of cartilage matrix metabolism in human joint fluid and serum: the effect of exercise. Osteoarthritis Cartilage 3:7–14.
24. Helal IE, Misumi K, Tateno O, et al. 2007. Effect of exercise on serum concentration of cartilage oligomeric matrix protein in thoroughbreds. Am J Vet Res 68:134–140.
25. Andersson ML, Petersson IF, Karlsson KE, et al. 2006. Diurnal variation in serum levels of cartilage oligomeric matrix protein in patients with knee osteoarthritis or rheumatoid arthritis. Ann Rheum Dis 65:1490–1494.
26. Neidhart M, Müller-Ladner U, Frey W, et al. 2000. Increased serum levels of non-collagenous matrix proteins (cartilage oligomeric matrix protein and melanoma inhibitory activity) in marathon runners. Osteoarthritis Cartilage 8:222–229.
27. Engström-Laurent A, Hallgren R. 1987. Circulating hyaluronic acid levels vary with physical activity in healthy subjects and in rheumatoid arthritis patients. Relationship to synovitis mass and morning stiffness. Arthritis Rheum 30:1333–1338.
28. James MJ, Cleland LG, Gaffney RD, et al. 1994. Effect of exercise on 99 mTc-DTPA clearance from knees with effusions. J Rheumatol 21:501–504.