Department of Veterans Affairs

Journal of Rehabilitation Research and Development Vol. 37 No. 2, March/April 2000
Pages 163–170

Methods for evaluating the progression of osteoarthritis

Thomas P. Andriacchi, PhD; Philipp L. Lang, MD; Eugene J. Alexander, PhD; Debra E. Hurwitz, PhD
Stanford University, Departments of Mechanical Engineering and Functional Restoration, Division of Biomechanical Engineering, Stanford, CA 94301; Rush-Presbyterian St. Luke's Medical Center, Department of Orthopaedic Surgery, Chicago, IL 60612

Abstract— This article discusses methods for evaluating the progression of osteoarthritis through dynamic functional imaging as opposed to current static techniques. Comparison is made between static and dynamic methods of evaluating knee alignment. The correlation between dynamic knee moments during gait and bone mineral content is discussed. Knee loading is considered in terms of high tibial osteotomy, knee braces, pain, and non-steroidal anti-inflammatory drugs. New image-processing techniques for quantitating cartilage loss are described, and computational methods for generating true three-dimensional (3-D) maps of cartilage thickness are developed. Finally, new approaches to cross-correlate magnetic resonance images with kinematic measurements are described. These new techniques promise to become powerful diagnostic tools to detect and characterize pathological load distributions across articular cartilage.

Key words: *dynamic functional imaging, dynamic knee loads, gait analysis, MRI, osteoarthritis.*

Address all correspondence and requests for reprints to: Thomas P. Andriacchi, PhD, Division of Biomechanical Engineering, MC: 3030, Stanford University, Stanford, CA 94301; email: Tandriac@leland.Stanford.edu

INTRODUCTION

The factors that influence the initiation and progression of osteoarthritis (OA) are not well understood. The knee is the most frequently involved joint site associated with disability in OA (1), and while that joint is affected in a substantial portion of the population over the age of fifty, there is a paucity of information on the underlying causes for this disease to progress more rapidly in some individuals and not in others. The development of new methods for prevention and treatment of OA requires an improved understanding of the factors that influence progression of the disease. The ability to quantitatively assess the progression of the disease is a necessary first step in understanding factors that influence the disease process.

Currently, assessment of OA is based on clinical examination, symptoms, and radiographic assessment, techniques based on information taken under static conditions and from images representing only a portion of the joint. Knee malalignment as a prognostic factor has been evaluated more often for surgical outcomes (2–6). Dougados et al. (7) found, however, that the presence of "varus/valgus deformity" did not differ between those who progressed and those who did not.

Dynamic measurements of loading during gait have been shown to have better predictive value of clinical outcome than static measurements. Dynamically, the adduction moment at the knee during gait has been shown to influence the outcome of high tibial osteotomy (HTO) for varus gonarthrosis (8,9). Subjects with a low preoperative adduction moment had a lower adduction moment following HTO, and better functional and radiographic outcome, including a greater likelihood of increased minimum medial joint space. These results could not be predicted from pre- or post-operative static alignment (mechanical axis) measurements, thereby confirming that individual variations in dynamic loading during gait strongly influenced the clinical outcome of a treatment for medial compartment OA. While clinical assessment of knee OA is based on radiographic assessment (10), there is no agreement on how to define progression. Joint space width obtained from radiographs has been used to quantitatively assess knee OA. This measure is subject to inter-reader variations and requires precise joint positioning as well as strict radiographic protocol to obtain meaningful measurements that can be compared over time (11–13). As new treatment modalities emerge, the current methods for the assessment of OA will likely not have sufficient sensitivity.

Previously considered a "wear and tear" degenerative disease with little opportunity for therapeutic intervention, OA is now increasingly viewed as a dynamic process with exciting potential for new pharmacologic and surgical treatment modalities such as cartilage transplantation (14), osteochondral allo- (15,16) or autografting (17), osteotomies (18), and tibial corticotomies with angular distraction (19). The appropriate deployment and selection of newer treatment interventions for OA is dependent on the development of better methods for the assessment of the disease process. Degenerative changes to articular cartilage can be described in biological, mechanical, and morphological terms. From a morphological viewpoint, there has been substantial progress in our ability to study cartilage using magnetic resonance imaging (MRI). MRI, with its superior soft tissue contrast, is the best technique available for assessment of normal articular cartilage and cartilage lesions (20) and can provide morphologic information about the area of damage. Specifically, changes such as fissuring, partial or full thickness cartilage loss, and signal changes within residual cartilage can be detected. The ideal MRI technique for cartilage will provide accurate assessment of cartilage thickness, demonstrate internal cartilage signal changes, evaluate the subchondral bone for signal abnormalities, and demonstrate morphologic changes of the cartilage surface (21). From a mechanical viewpoint, recent studies have demonstrated a relationship between the dynamic loads at the knee during gait and progression of knee OA. The combination of imaging methods with functional kinematic information obtained during walking could greatly enhance our ability to study OA.

There is substantial evidence for a need for improved methods to assess the progression of OA, the progression of which is multifactoral. The disease can be examined at many levels, from the biology of the cell to the dynamics of whole body movement. Changes in any of these factors can modulate the disease process and influence the way other factors impact the progression of the disease.

The purpose of this article is to describe new methods for the assessment of the dynamics of human movement relative to the progression of OA of the knee joint. In addition, new methods based on MRI are discussed in the context of describing changes in morphology associated with progression of the disease. While this article focuses on the knee joint, the general methods discussed apply to OA in general.

Dynamic Knee Loads during Gait

Directly measuring joint loads is not feasible on a large scale in humans due to the invasive nature of the method. However, gait analysis can be used to calculate the external joint loading parameters directly related to the internal joint loads. Using gait analysis and a statically determinate muscle model, it has been shown that the peak force on the medial compartment of the knee is almost 2.5 times that of the lateral compartment (22). The knee adduction moment (**Figure 1a**) has been shown to be a major determinate of not just the total load across the knee joint, but also its distribution between the medial and lateral plateaus (23). Variations in the adduction moment have been associated with variations in the distribution of bone between the medial and lateral plateau (24). In that study, the hypothesis that the external knee adduction moment during gait was correlated with the distribution of medial and lateral tibial bone mineral content (BMC) was tested. Twenty-six normal subjects (18 males, 8 females; 32±12 years) were measured with gait analysis and dual energy x-ray absorptiometry (DXA). The BMC of two proximal tibial regions, one medial and one lateral, were measured with DXA scans (DPX-L, Lunar). The best single predictor of the medial-to-lateral ratio of proximal BMC was the adduction moment

(R=0.56, p<.003) (**Figure 1b**).

The higher the adduction moment, the greater the load on the medial plateau relative to that of the lateral plateau, and the higher the bone mineral content in the proximal tibia under the medial plateau (**Figure 1b**) as compared to that under the lateral plateau (24). An increased adduction moment may be associated with a higher prevalence of medial compartment OA or a faster rate of disease progression.

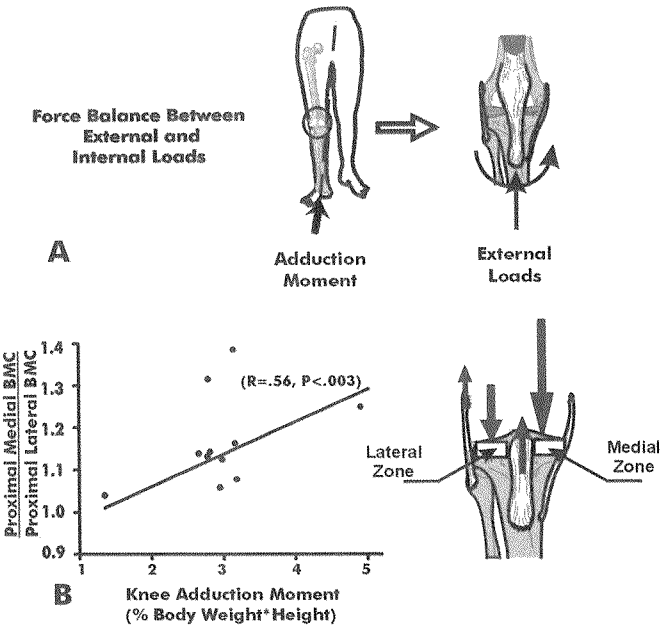

Figure 1.

A. The relationship between external loads at the knee during walking and internal forces acting on the tibiofemoral articular surfaces. **B.** The ratio of the proximal tibial bone mineral density (BMC) beneath the lateral and medial articular surfaces was correlated with the peak magnitude of the adduction moment during walking.

Surgical Outcome from High Tibial Osteotomy and Dynamic Knee Loads

The relationship (**Figure 1**) between the external dynamic loads during walking and the internal load distribution at the knee is consistent with an earlier study that demonstrated that individual variations in the preoperative adduction moment during gait related to the radiographic and clinical outcome from an HTO (8,9). The objective of an HTO is to realign the tibia and femur so that some of the load on the medial arthritic compartment is transferred to the more normal lateral compartment. Twenty-four subjects with 3 to 9 years' follow-up were tested with gait analysis prior to surgery. Surgical candidates with a lower preoperative adduction moment during gait had better long-term radiographic and clinical outcome than those candidates with a higher preoperative adduction moment during gait. The postoperative adduction moment has also been shown to be a better predictor of the postoperative clinical outcome than the postoperative mechanical axis (25).

It has also been shown that although the preoperative adduction moment is not correlated with the mechanical axis, the postoperative adduction is correlated with the postoperative mechanical axis, and the change in the adduction moment is correlated with the change in the mechanical axis (25). Preoperatively, greater pain levels may have caused subjects to modify their adduction moment to decrease the medial compartment load.

Bracing and Dynamic Knee Loads

Knee braces have been designed to unload the degenerative portion of the medial compartment of the knee joint and provide pain relief (26). Theoretically these braces provide the advantages of an HTO without the surgical risk or expense. Two studies done at one institution on two different brace designs both confirmed that the function and pain levels among compliant subjects improved following the use of a brace (27). However, in one study the adduction moment was decreased while the brace was worn, and in the other study the adduction moment was unchanged. Oddly enough, the mean adduction moment when either brace was worn was about the same in both studies (3.6±0.8 percent body weight × height and 3.5±0.8 percent body weight × height). The difference in the findings therefore resulted from the fact that the adduction moment when the brace was not worn was larger in one study (4.0±0.8 percent body weight × height) as compared to the other study (3.5±0.8 percent body weight × height). Possible differences in disease severity, pain, prior surgical procedures (meniscectomy, ligament reconstructions or arthroscopies), extent of meniscus or ligament damage, or use of analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) account for the difference in the adduction moments when the brace was not worn. In fact, the study group with the lower adduction moment without the brace did have a higher pain level. Therefore it is conceivable that this group was already compensating for pain by decreasing their adduction moment. However, the small sample size of each of the study groups (11 and 13 subjects, respectively) does not allow the determination of whether differences in pain or any of these other factors listed are responsible for the higher adduction moment.

Pain and Knee Joint Loading

NSAIDs are an accepted treatment of OA, offering the subject reductions in joint pain and inflammation with an improved ability to carry out the activities of daily living: significant improvements in walking speeds (18 percent) and in degree of pain (27 percent) have been found following treatment with them (28). Given their analgesic capabilities it is conceivable that decreases in pain levels are accompanied by an increased load on the joint due to the loss of a pain protective reflex. In a study of 18 subjects with radiographic evidence of grade II or III knee OA and a varus deformity, the use of an NSAID resulted in improvement in degree of pain and activity of daily living parameters, but also resulted in an increase in the knee joint loads during walking (29). The external knee adduction moment was increased by 10 percent and the external knee flexion moment by 20 percent. Some of the increase in joint loading may be a direct consequence of faster walking speeds following the use of the NSAIDs. Similar changes in knee loading after treatment with an NSAID have also been reported following the use of a pure analgesic agent (30).

To examine in greater detail the relationship between pain and knee joint loads, subjects with knee pain and radiographic evidence of medial compartment OA, who were part of a larger group enrolled in a double-blinded study, were taken off their NSAIDs or analgesics for 2 weeks (31). Following the 2-week washout period they underwent a clinical and gait evaluation. They were then given an analgesic, NSAID, or placebo, and a second gait and clinical evaluation was repeated 2 weeks later. An inverse relationship was found between level of pain and the external adduction moment. The subjects whose pain decreased had a significantly increased adduction moment (**Figure 2**) between the first and second gait evaluations ($p<0.001$). Conversely, those whose pain increased had a decreased adduction moment. In contrast to the previous study relating the use of NSAIDs to increased knee joint loads, the walking speeds in the trials analyzed were not significantly different between the evaluations. This suggests that subjects employ an additional mechanism besides reduction in walking speed to dynamically decrease the load on the medial compartment. Of particular concern is the fact that anti-inflammatory or analgesic therapy may actually be associated with an increase in joint forces. In an ideal situation one would like clinical interventions to provide pain relief without an increase in joint load. Therefore, care should be taken in the use of pharmaceuticals directed at reducing pain, as it appears that a reduction in pain can be directly related to increased loading of the degenerative portions of the joints. The possibility exists that changes in loading parameters may be different based on the class of analgesic agents or even among the different NSAIDs. It is also possible that there may be some threshold of drug concentration that allows for an analgesic effect without adversely altering the knee joint loading.

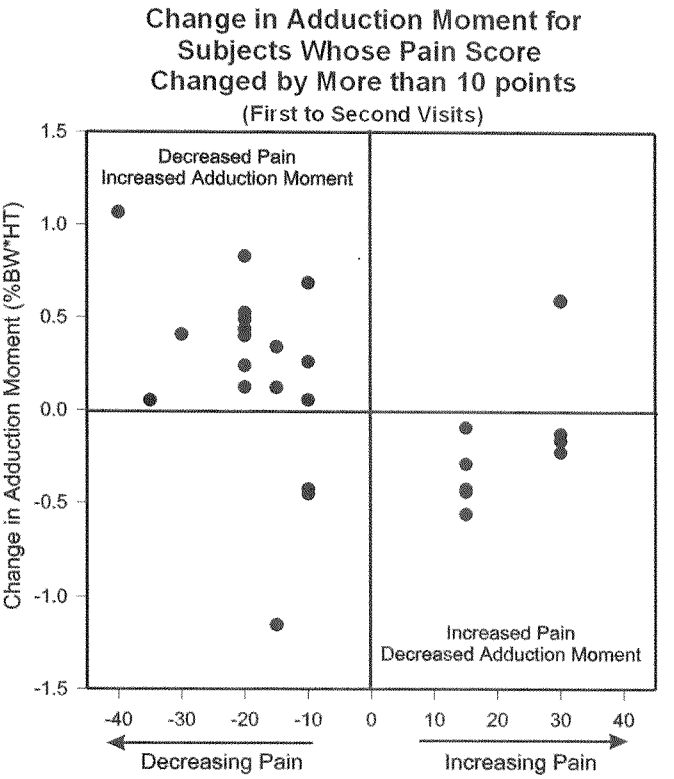

Figure 2.
The adduction moment increased when pain was reduced on the second visit. For patients with increased pain the adduction moment was reduced from the first to the second visit.

Image Processing Techniques for Quantifying Cartilage Loss and Osteoarthritis

Quantitative image processing and analysis techniques play an increasingly important role in evaluating cartilage loss and monitoring response to medical or surgical therapy (32–34). Several investigators (32–34) have reported the use of 3-D reconstruction of the articular cartilage with subsequent volumetric quantification of the entire cartilage surface. With this technique, cartilage is segmented from the surrounding tissues using a signal intensity based thresholding technique applied to a cartilage-sensitive MRI sequence (32). In the knee joint, intraobserver reproducibil-

ity error for measurement of 3-D cartilage volumes has been reported to range between 3.6 percent and 6.4 percent; interobserver error was 7.8 percent in the same study (32).

Unfortunately, all of these studies (32–34) are limited by the fact that global cartilage volume was measured, i.e., the entire cartilage covering the femoral condyles or the patella or the tibial plateau was measured, rather than only the cartilage defect. If the average reproducibility error of this technique is 5–10 percent based on these studies, and the total cartilage volume over the femoral condyles is approximately 20 cm^3, the volume of a new cartilage defect must be at least 1.0–2.0 cm^3 in order to be detectable. Cartilage defects are, however, often limited to a focal area with a volume less than 0.5 cm^3 (35). For this reason, other, more sensitive techniques are needed in order to detect subtle loss in articular cartilage volume between baseline and follow-up MRI studies.

A computational method for generating maps of cartilage thickness has been recently developed based on 3-D Fourier Transform spoiled GRASS images using a 3-D minimal distance algorithm that determines at each point the minimal distance from the articular surface to the bone-cartilage interface (36). Repeated measurements of patellar cartilage have been performed using this technique, and it has been reported that on average 75.1±4.1 percent of all test pixels could be attributed to the same cartilage thickness interval (0.5 mm) by image analysis; 14.8±2.4 percent deviated by one interval; 6.6±1.5 percent by two intervals; and 3.5±1.8 percent by more than two intervals, indicating that cartilage thickness can be determined with high precision *in vivo* (37). Similarly, a mean interscan deviation of the maximal cartilage thickness ranging from 0.1 to 0.3 cartilage thickness intervals (of 0.5 mm) has been reported by others using the same technique (38). Using this technique, it appears possible to achieve a sensitive and reproducible measurement of cartilage loss in a truly quantitative fashion. **Figure 3** shows an example of a 2-D map of cartilage thickness derived from the surface normals of the lateral femoral condyle. In another approach, calculation of the cartilage thickness is based on a 3-D Euclidian distance transformation (EDT; 39). For a given set of feature points in a binary volume, the EDT computes the distance to the closest feature point for each non-feature point of the volume. By using the points on the cartilage-bone interface (inner cartilage surface, ICS) as feature points, the EDT measures the distance to the closest voxel on the ICS for all other points, including points on the outer cartilage surface (OCS), resulting in a truly 3-D distance value determined normal to the ICS (**Figure 4**).

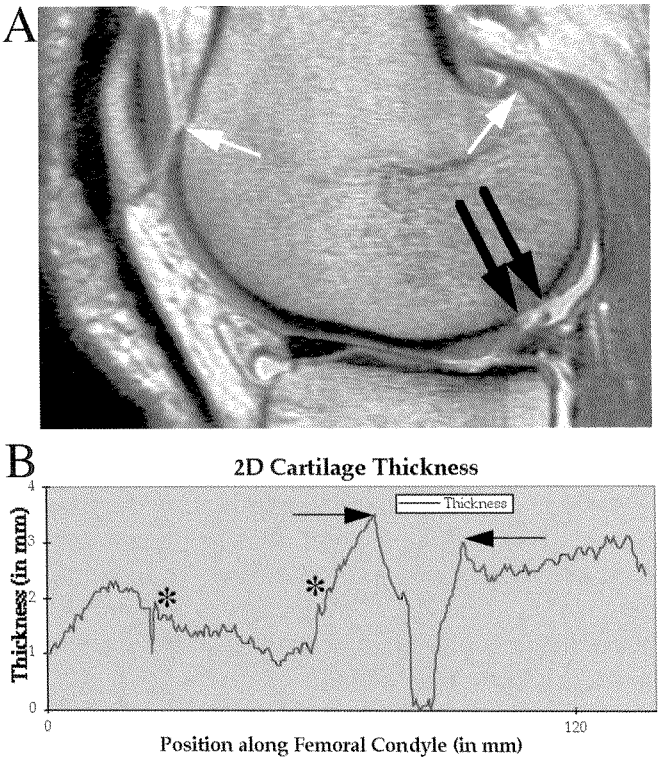

Figure 3.
Two-dimensional cartilage thickness map. A. A proton density fast spin-echo MR image demonstrates a focal cartilage defect in the posterior lateral femoral condyle (black arrows). White arrows indicate endpoints of thickness map. B. Two-dimensional cartilage thickness map demonstrates abrupt decrease in cartilage thickness in the area of the defect (arrows). The thickness between neighboring pixels can be used to define the borders of the cartilage defect. Note diffuse cartilage thinning in area enclosed by the asterisks (*).

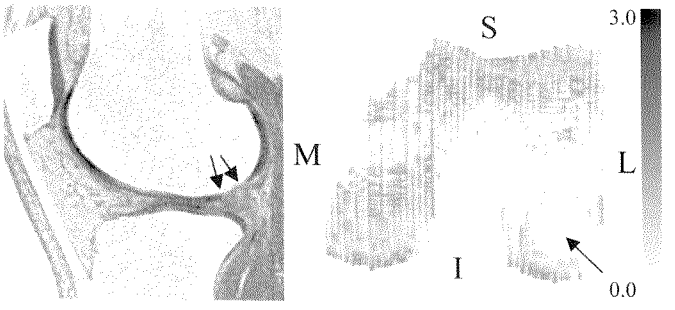

Figure 4.
Two-dimensional MRI (3-D SPGR) and 3-D cartilage thickness map. A. The 2D MRI demonstrates a full thickness cartilage defect in the posterior lateral femoral condyle (arrows). B. Three-dimensional cartilage thickness map generated using a EDT. The thickness of the articular cartilage is color encoded and displayed on a pixel-by-pixel basis along the 3-D surface of the articular cartilage. The cartilage defect is black, reflecting a thickness of zero (arrow) (M: medial, L: lateral, S: superior, I: inferior).

In a pilot study, we explored the possibilities of integrating high-resolution MRI of the articular cartilage with kinematic measurements in the Biomotion Laboratory. External markers filled with water doped with Gd-DTPA (Magnevist®, Berlex Inc., Wayne, NJ) were applied to the skin around the knee joint at the same positions used for gait analysis in the Biomotion Laboratory. Three volunteers underwent MRI of the knee joint in this fashion (GE Signa, 1.5T, 3-D SPGR, TR=60 msec, TE=5 msec, flip angle 40º, 1 excitation, matrix 256×160 elements, rectangular FOV 16×12 cm, slice thickness 1.3 mm, 128 slices, with fat saturation and repeated without fat saturation). After image acquisition, the MR images were transferred to an independent imaging workstation (Advantage Windows, General Electric, Madison, WI), and the femoral and tibial bones and cartilage were segmented using standard thresholding and seed-growing techniques. We generated 3-D reconstructions of the femoral and tibial cartilage and of the femoral and tibial bone in this fashion.

The volunteers were studied in the Biomotion Laboratory using previously published techniques (40–45). Each subject was tested standing still, and during level walking, seated leg extension, standing leg flexion, and while ascending and descending stairs. The level walking measurements included six stride cycles over a range of walking speeds. The instrumentation included a four-camera, video-based, optoelectronic system for 3-D motion analysis, a multicomponent force plate for measurement of foot-ground reaction force, and a computer system for acquisition, processing, and analysis. The experimental model used for the functional evaluation study idealizes the lower limb as three segments with six degree-of-freedom (DOF) joints at the knee and ankle. External markers were located according to the standard point cluster technique (PCT) protocol, along with eight additional markers filled with gadolinium and covered with retro-reflective material. The data for each of the activities was reduced to six DOF motion of the thigh and shank segment, including application of the interval deformation correction technique to minimize the effects of segment deformation. An example of the resulting kinematic functional joint images is demonstrated in **Figure 5**.

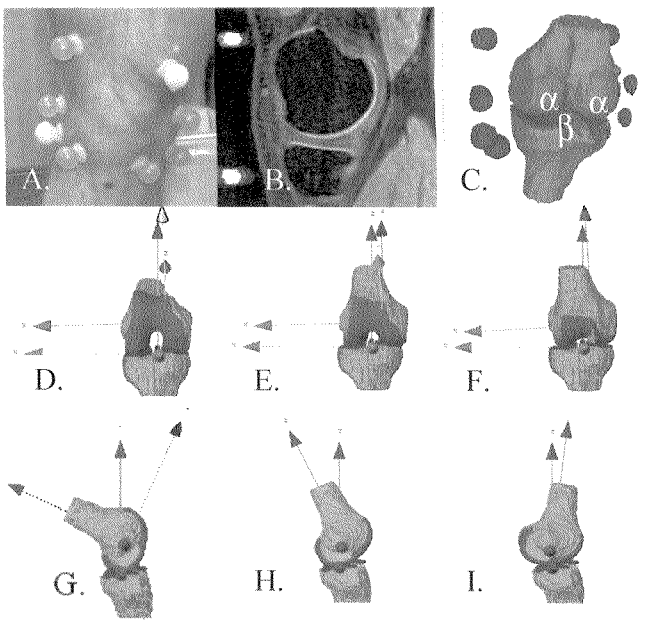

Figure 5.
Functional Joint Imaging. A. Photograph demonstrating the position of the external markers positioned around the knee joint. The markers are filled with dilute Gd-solution. B. Sagittal 3-D SPGR image through the medial femorotibial compartment. Two of the external markers are seen anteriorly as rounded structures with high signal intensity. C. Three-dimensional reconstruction of femoral and tibial bones (light gray), external markers (dark gray), femoral cartilage (red), and tibial cartilage (blue) based on the original SPGR MR images. **D–I.** Functional joint imaging sequence at selected phases of leg extension from a seated position. **D–F.** Anterior projection. The vectors represent the relative location and orientation of the femur with respect to the tibia. **G–I.** Lateral projection. These dynamic visualizations can be used to demonstrate tibiofemoral contact areas during various phases of gait or other physical activities.

DISCUSSION

Dynamic joint loading clearly influences the natural rate of disease progression in persons with knee OA (46). In addition, the dynamic loads during walking influence the outcome of certain treatment procedures. MRI techniques that provide 3-D thickness maps can provide objective assessment of morphological changes in cartilage over time. Combining the MRI information with dynamic loading measurements offers unique information that combines detailed images with functional loading.

This type of functional joint imaging (FJI) is a fundamentally new technique to assess the 3-D distribution of biomechanical loading forces applied to the articular cartilage, and to determine the position of areas of cartilage damage *in vivo* relative to load-bearing pathways. FJI integrates MRI with kinematic measurements in the Biomotion Laboratory. Unlike previous approaches employing only MRI or only gait analysis, FJI will provide a true 3-D map of the distribution of dynamic biomechan-

ical loads applied to the articular cartilage during all phases of gait and other daily activities, thereby providing unique insights into normal and pathologic joint function.

In the future, FJI will be a powerful diagnostic tool to detect and characterize pathologic load distributions across the articular cartilage in a variety of different knee disorders. This information, along with accurate localization of the position of cartilage defects relative to high-load areas, may help identify persons at risk for rapid progression of cartilage loss. FJI may aid clinicians in choosing the most beneficial pharmacological or surgical treatment modality in persons with OA and other disorders of the knee joint, and may help monitor the efficacy of therapeutic interventions.

REFERENCES

1. Guccione A, Felson D, Anderson J, Anthony J, Zhang Y, Wilson P, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–7.
2. Allen P, Denham R, Swan A. Late degenerative changes after meniscectomy: factors affecting the knee after operations. J Bone Joint Surg Br 1984;66B:666–71.
3. Boe S, Hansen H. Arthroscopic partial meniscectomy in patients aged over 50. J Bone Joint Surg Br 1986;68B:707.
4. Ogilvie-Harris D, Fitsialos D. Arthroscopic management of the degenerative knee. Arthroscopy 1991;7:151–7.
5. Ritter M, Faris P, Keating E, Meding J. Postoperative alignment of total knee replacement. Clin Orthop 1994;299:153–6.
6. Yasuda K, Tsuchida T, Kameda K. A 10 to 15 year follow up observation of high tibial osteotomy in medial compartment osteoarthritis. Clin Orthop 1992;282:186–95.
7. Dougados M, Gueguen A, Nguyen M, Thiesce A, Listrat V, Jacob L, et al. Longitudinal radiologic evaluation of osteoarthritis of the knee. J Rheumatol 1992;19:378–84.
8. Prodromos C, Andriacchi T, Galante J. A relationship between gait and clinical changes following high tibial osteotomy. J Bone Joint Surg Am 1985;67A:1188–94.
9. Wang J, Kuo K, Andriacchi T, Galante J. The influence of walking mechanics and time on the results of proximal tibial osteotomy. J Bone Joint Surg Am 1990;72A:905–9.
10. Dieppe P, Altman RD, Buckwalter JA, Felson DT, Hascall V, Lohmander LS, et al. Standardization of methods used to assess the progression of osteoarthritis of the hip or knee joints. In: Kuettner KE, Goldberg VM, editors. Osteoarthritic disorders. Rosemont, Illinois: American Academy of Orthopaedic Surgeons; 1995. p. 481–96.
11. Buckland-Wright J, Macfarlane D, Lynch J, Jasani M, Bradshaw C. Joint space width measures cartilage thickness in osteoarthritis of the knee: high resolution plain film and double contrast macroradiographic investigation. Ann Rheum Dis 1995;54:263–8.
12. Altman RD, Fries JF, Bloch DA, Carstens J, Cooke TD, Genant H, et al. Radiographic assessment of progression in osteoarthritis. Arthritis Rheum 1987;30:1214–25.
13. Lequesne M, Brandt K, Bellamy N, Moskowitz R, Menkes C, Pelletier J-P. Guidelines for testing slow acting drugs in osteoarthritis. J Rheumatol 1994;(Suppl 41)21:65–73.
14. Brittberg M, Lindahl A, Homminga G, Nilsson A, Isaksson O, Peterson L. A critical analysis of cartilage repair. Acta Orthop Scand 1997;68(2):186–91.
15. Garrett JC. Osteochondral allografts for reconstruction of articular defects of the knee. Instr Course Lect 1998;47:517–22.
16. Stevenson S, Dannucci G, Sharkey N, Pool R. The fate of articular cartilage after transplantation of fresh and cryopreserved tissue-antigen-matched and mismatched osteochondral allografts in dogs. J Bone Joint Surg Am 1989;71 (9):1297–307.
17. Bobic V. Arthroscopic osteochondral autograft transplantation in anterior cruciate ligament reconstruction: a preliminary clinical study. Knee Surg Sports Traumatol Arthrosc 1996;3(4):262–4.
18. Nizard R. Role of tibial osteotomy in the treatment of medial femorotibial osteoarthritis. Rev Rhum Engl Ed 1998;65(7–9):443–6.
19. Mollica Q, Leonardi W, Longo G, Travaglianti G. Surgical treatment of arthritic varus knee by tibial corticotomy and angular distraction with an external fixator. Ital J Orthop Traumatol 1992;18(1):17–23.
20. Recht M, Resnick D. MR imaging of articular cartilage: current status and future directions. AJR Am J Roentgenol 1994;163:283–90.
21. Hayes C, Conway W. Evaluation of articular cartilage: radiographic and cross-sectional imaging techniques. Radiographics 1992;12:409–28.
22. Schipplein OD, Andriacchi TP. Factors influencing the distribution of knee joint reaction forces during level walking and jogging. In: Proceedings of the 12th Annual Meeting of the American Society of Biomechanics, 1988.
23. Schipplein O, Andriacchi, T. Interaction between active and passive knee stabilizers during level walking. J Orthop Res 1991;9:113–9.
24. Hurwitz D, Sumner D, Andriacchi T, Sugar A. Dynamic knee loads during gait predict proximal tibial bone distribution. J Biomech 1998;31:423–30.
25. Bryan J, Hurwitz D, Bach B, Bittar T, Andriacchi T. A predictive model of out come in high tibial osteotomy. Trans Orthop Res Soc 1997;718.
26. Matsuno H, Kadowaki K, Tsuji H. Generation II knee bracing for severe medial compartment osteoarthritis of the knee. Arch Phys Med Rehabil 1997;78:745–9.
27. Lindenfeld T, Hewett T, Andriacchi T. Joint loading with valgus bracing in patients with varus gonarthrosis. Clin Orthop 1997;344:290–7.
28. Blin O, Pailhous J, Lafforgue P, Serratice G. Quantitative analysis of walking in patients with knee osteoarthritis: a method of assessing the effectiveness of non-steroidal anti-inflammatory treatment. Ann Rheum Dis 1990;49(12):990–3.
29. Schnitzer T, Andriacchi T, Fedder D, Lindeman M. Effect of NSAIDs on knee loading in patients with osteoarthritis. Arthritis Rheum 1990;33:19:S92.
30. Schnitzer T, Popovich J, Anderson G, Andriacchi T. Effect of piroxicam on gait in patients with osteoarthritis of the knee. Arthritis Rheum 1993;36:1207–13.
31. Sum J, Hurwitz D, Janik R, Dressander J, Andriacchi T, Schnitzer T, et al. The impact of osteoarthritic knee pain on dynamic loads during gait. 2nd Annual Meeting North American Society of Gait and Clinical Movement Analysis Conference, Gait and Posture. 1997;5(2):173.

32. C, van Dijke C, Janzen D, Gluer CC, Namba R, Majumdar S, et al. Quantification of articular cartilage in the knee with pulsed saturation transfer subtraction and fat-suppressed MR imaging: optimization and validation. Radiology 1994;192:485–91.
33. Peterfy CG, van Dijke CF, Lu Y, Nguyen A, Connick TJ, Kneeland TB, et al. Quantification of the volume of articular cartilage in the metacarpophalangeal joints of the hand: accuracy and precision of three-dimensional MR imaging. AJR Am J Roentgenol 1995;165:371–5.
34. Piplani M, Disler D, McCauley T, Holmes T, Cousins J. Articular cartilage volume in the knee: semiautomated determination from three-dimensional reformations of MR images. Radiology 1996;198:855–9.
35. Disler D. Fat-suppressed three-dimensional spoiled gradient-recalled MR imaging: assessment of articular and physeal hyaline cartilage. AJR Am J Roentgenol 1997;169:1117–23.
36. Losch A, Eckstein F, Haubner M, Englmeier K. A non-invasive technique for 3-dimensional assessment of articular cartilage thickness based on MRI. Part 1: development of a computational method. Magn Reson Imaging 1997;15(7):795–804.
37. Tieschky M, Faber S, Haubner M, Kolem H, Schulte E, Englmeier KH, et al. Repeatability of patellar cartilage thickness patterns in the living, using a fat-suppressed magnetic resonance imaging sequence with short acquisition time and three-dimensional data processing. J Orthop Res 1997;15:808–13.
38. Eckstein F, Westhoff J, Sittek H, Maag KP, Haubner M, Faber S, et al. In vivo reproducibility of three-dimensional cartilage volume and thickness measurements with MR imaging. AJR Am J Roentgenol 1998;170:593–7.
39. Stammberger T, Eckstein F, Englmeier K, Reiser M. Determination of 3-D cartilage thickness data from MR imaging: computational method and reproducibility in the living. Magn Reson Med 1999;41:529–36.
40. Andriacchi T, Alexander E, Toney M, Dyrby C, Sum J. A point cluster method for in vivo motion analysis: applied to a study of knee kinematics. J Biomech Eng 1998;120(12):743–9.
41. Alexander EJ, Andriacchi TP. Correcting for deformation in skin-based marker systems. Proceedings of the 3rd Annual Gait and Clinical Movement Analysis Meeting; 1998, San Diego, CA.
42. Alexander EJ, Andriacchi TP. State estimation theory in human movement analysis. Proceedings of the 1998 ASME International Mechanical Engineering Congress; 1998, 39. p. 323–4.
43. Alexander EJ, Andriacchi TP. Internal to external correspondence in the analysis of lower limb bone motion. Proceedings of the 1999 Bioengineering Conference, ASME; 1999 Jun 16-20, Big Sky, MT; 1999. p. 415–6.
44. Alexander EJ, Andriacchi TP, Naylor DL. Optimization techniques for skin deformation correction. International Symposium on 3-D Human Movement Conference; 1998, Chattanooga, TN. p. 104–7.
45. Alexander EJ, Andriacchi TP, Lang PK. Dynamic functional imaging of the musculoskeletal system. Proceedings of the 1999 ASME Winter International Congress and Exposition; 1999 November 14–19, Nashville, TN. p. 297–8.
46. Sharma L, Hurwitz DE, Thonar EJ, Sum JA, Lenz ME, Dunlop DD, et al. Knee adduction moment, serum hyaluronic acid level, and disease severity in medial tibiofemoral osteoarthritis. Arthritis Rheum 1998;41(7):1233–40.