New Quantitative Imaging Technologies in Osteoarthritis to Assess Disease Progression and Effects of Drug Treatment

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Knee osteoarthritis (OA) is a prevalent disease characterized mainly by cartilage degradation and which is reflected clinically by a gradual development of joint pain, stiffness, and loss of motion. Osteoarthritis frequently manifests in one or more of the three compartments of the knee (medial and lateral femorotibial and patellofemoral). Although this disease is often considered benign, severe degenerative changes may cause serious disability.

Several pharmacologic agents are under investigation to treat OA. Preclinical results are promising, demonstrating the possibility of retarding or inhibiting the progression of joint tissue structural changes. However, the tools to study such effects in the human population remain unsatisfactory. For many years, studies of drug interventions on symptomatic knee OA focused only on clinical parameters such as pain and joint function without assessing their impact on the structural change of the disease and the possible role of medication in preventing cartilage degradation. Sensitive and accurate methods for assessment of the progression of OA are key requirements in research efforts to find new ways of controlling the progression of arthritis.

The current gold standard for measuring cartilage thickness remains radiographic X-rays. Measurement of the JSW by standard radiography does not yield any information on the cartilage itself and gives only one measurement point; this practice considerably limits the statistical and clinical power of the technique in assessing cartilage degradation over time. Moreover, JSW, being a single-point evaluation of bone-to-bone distance, produces only an approximate measurement of the overall thickness of the articular cartilage and gives no indication of its volume or any other structural changes associated with the disease process.

Another recently described new technique, arthroscopy (chondroscopy), allows for assessment of the cartilage by direct visualization with the use of an arthroscope. Although this technique appears reliable and sensitive to morphologic change at one year, only the cartilage surface can be evaluated. Moreover, because this method is semiquantitative and invasive, large multicenter studies would be difficult to conduct.

Magnetic resonance imaging (MRI) allows for precise visualization of joint structures such as cartilage, bone, synovium, ligaments, and meniscus, and their pathological changes (1, 2). Recent advances in this technology have led to significant improvement in spatial resolution and contrast, enabling researchers to evaluate anatomical damage of all these joint structures across sagittal, coronal and axial planes (3-7). Although anatomical changes in the cartilage can be seen, quantification of these changes remains difficult. Initially, quantitative measurement of cartilage was studied in healthy subjects (8-10) or animal models (11). Early work on cartilage in OA patients was restricted to semi-quantitative methods (12, 13), with some of these measurements in OA patients correlating well with arthroscopy findings (14, 15) and histological specimens (16, 17). Recently, the quantitative assessment of OA cartilage volume has become possible (18-27).

To date, there are few in vivo methodologies that allow for sensitive, specific, valid, and reliable quantification of progression of OA of the knee. We have developed a method for the reliable evaluation of cartilage volume of the total knee (femur and tibia) using MRI sets acquired with fat-suppressed, gradient-echo

sequences (28). First, we evaluated the reliability of the novel imaging software system in normal and OA patients (29, 30). Second, we assessed the cartilage volume changes on patients with knee OA that had MRI acquisition at baseline and a 2-year follow-up (31). Finally, we determined whether other structural changes such as meniscal alteration could be associated as a risk factor for cartilage volume loss over time.

For the first part, 48 MRI examinations of the knee from normal subjects, from patients with different stages of symptomatic knee OA, and from a subset of duplicate images were independently and blindly quantified by three readers using our imaging system. The following cartilage areas were analyzed to compute volumes: global cartilage, medial and lateral compartments, and medial and lateral femoral condyles. The results of this study established the reliability of this MRI system. Indeed, test-retest reliability, between-reader agreement, and patient positioning reliability were excellent.

For the second and third parts, 32 patients meeting ACR criteria for knee OA were recruited from outpatient clinics. The mean age of the patients was 63.1 years, 74% were female, and the average body mass index (BMI) was 31. Grade IV radiographs were an exclusion criteria. MRI acquisition of the knee was done at baseline and 6, 12, 18 and 24 months of follow-up. For the second study, the images were randomized and the cartilage volumes of the total cartilage, as well as the medial and lateral compartments, were analyzed. The variables included the WOMAC, Visual Analog Scales of pain, global evaluation (patient and physician) of the disease, co-medication consumption and physical examination of the knee. The data on knee OA progression (cartilage volume losses in % from baseline) computed at all the time points of follow-up showed as early as 6 months a striking and statistically significant loss of cartilage (31). A higher loss was seen in the medial compartment. Interestingly, two populations described as “fast” and “slow” progressors were identified. These data support the strong advantage of quantitative MRI over existing techniques in that MRI is able to detect significant changes in knee OA cartilage volume as early as 6 months.

In the third study, the severity of OA changes in the medial and lateral menisci were evaluated using a semi-quantitative scale for degeneration, tear and extrusion. Data revealed a significant association between meniscal tear and extrusion at baseline ($r=0.59$, $p<0.01$) but not with meniscal degeneration. However, no significant change was seen in the three-parameter scores over the 2-year observation time. When comparing the meniscal alterations with the loss of cartilage volume over time, a statistically significant difference on global cartilage volume loss was observed between severe medial meniscal tear and no tear. There was an even greater difference between the medial meniscal changes on the medial compartment and the cartilage volume loss at the medial compartment. Similarly, a highly significant difference was found between the presence of a medial meniscal extrusion and the loss of cartilage volume at the medial compartment. A multi-linear regression analysis demonstrated that medial meniscal extrusion of the anterior horn was predictive of the global, medial compartment or lateral compartment cartilage volume loss. These data showed that meniscal tear and extrusion are key parameters that must be addressed when predicting the progression of knee OA.

In summary, the progression of cartilage degradation in knee OA is a key parameter that needs to be quantified in any study aiming at studying the efficacy of any therapeutic interventions for this disease in this context. The potential of the MRI approach is obvious as it provides a clear advantage over any of the other existing technologies. Moreover, our MRI quantification system makes a highly reliable quantification of cartilage volume possible. Furthermore, our technology enables us to assess the intra-individual variability of cartilage volume changes as well as meniscal structure modifications. Such technology will be critical for the analysis of disease progression over time and should hopefully reduce the number of patients needed in clinical trials, improve the retention of these patients, and reduce the overall costs and the length of clinical trials.

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