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Location-independent analysis of structural progression of osteoarthritis—Taking it all apart, and putting the puzzle back together makes the difference

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ABSTRACT

Objective: The metric accepted by regulatory bodies for determining structural progression in clinical trials of knee osteoarthritis (OA) remains change in radiographic joint space width in the medial femorotibial compartment. However, magnetic resonance imaging has revealed that cartilage loss is spatially heterogeneous, and that it is enigmatic which knee will lose cartilage at which location. Whereas previous reviews have focused on imaging in general, the purpose of this particular perspective is to highlight availability and applications of location-independent analysis methodology in measuring structural progression in epidemiological and interventional clinical trials, and to highlight its specific advantages over existing methodologies.

Methods: Narrative review/perspective based on a Pubmed search of original articles from 2009 to current.

Results: Ordering longitudinal change in subregion cartilage thickness by magnitude and direction, and averaging such ordered values or sums of negative and positive changes across knees is shown to be superior in detecting risk factors and interventional effects on structural progression of knee OA. Further, the methodology permits exploration of cartilage loss and gain simultaneously, phenomena that are missed when measurements are confined to cartilage volume or thickness loss in plates or compartments.

Conclusions: Given spatial heterogeneity of cartilage loss in knee OA, location-independent analysis by MRI may provide opportunity for a paradigm shift. The authors recommend use of a location-independent metrices as the structural endpoints in epidemiological and intervention trials, particularly when examining anabolic and catabolic drug effects. Location-independent methods may be translated to analysis of cartilage composition and other articular tissues.

Background and purpose of this perspective

Knee osteoarthritis (OA) substantially reduces the quality of life [1] and increases the demand for health care utilization, including necessity of knee replacement surgery [2,3]. Current treatment for OA is focused on controlling symptoms and replacing damaged joints, as no interventions have yet been approved for modifying the structural progression of the disease. Estimates suggest that the number of annual knee replacements (KRs) in the United States has doubled in the last decade, with a disproportionate increase amongst younger adults. The frequency of KRs now is considerably greater than that of rheumatoid arthritis [4] and is projected to increase to over 3 million annually in the United States by 2030 [3]. Developing effective therapy to halt or slow structural progression of OA thus represents a staggering unmet medical need, and a great challenge in rheumatology research and clinical management.

Whereas previous reviews have focused on imaging in general, the purpose of this particular perspective is to highlight availability and applications of location-independent analysis methodology in measuring structural progression in epidemiological and interventional clinical trials, and to highlight its specific advantages over existing methodologies. To this end, we reviewed the literature on location-independent MRI-based measurement technology of cartilage loss based on a Pubmed search of original articles from 2009 to current.

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Current analytic approaches

Imaging directly delineates articular tissues and hence represents an ideal analysis approach for evaluating disease modifying osteoarthritis drug (DMOAD) efficacy on articular tissues in clinical trials. The most widely used imaging techniques currently are plain radiography and magnetic resonance imaging (MRI) [5–15]. Current regulatory guidance for DMOAD approval recommends the measurement of minimum radiographic joint space width (JSW) in the medial femorotibial compartment as the efficacy endpoint [16], with a large variety of radiographic acquisition techniques available [5]. However, sensitivity to change in JSW is chronically low in knee OA [17,18]; moreover, JSW is not specific to a particular tissue, but is associated with loss of cartilage thickness, meniscus extrusion, and radiographic positioning [13,15,19–21]. Further, minimum JSW measurement is specific to the (central) medial femorotibial compartment and cannot capture effects on cartilage in the lateral compartment, or in the periphery of the joint [15,15,22]. Hence, large numbers of participants are currently required in DMOAD trials, and it has been recently argued that clinical trials have failed to identify efficacious therapies, because traditional radiographic imaging outcome measures are inadequate [20].

Unlike radiography, MRI directly differentiates all articular tissues, and may be used to extract quantitative or semi-quantitative measures, such as volume, thickness, other geometric and compositional properties, and pathologic features of various tissues [6–15,15]. Yet, total medial compartment cartilage thickness loss with MRI has not demonstrated greater sensitivity to change than medial JSW in knee OA [9,15,23]. With this in mind, a few research groups have introduced subregional analysis of cartilage in specific locations of the medial and lateral femorotibial compartment (e.g., Fig. 1) [22,24,25]. However, whereas central femorotibial subregions displayed somewhat greater rates and sensitivity to change than peripheral ones, the sensitivity to progression in knee OA was not markedly improved by relying on location-specific regional or subregional analysis [26–28]. Further, a number of clinical trials that relied on MRI were inconclusive, because significant DMOAD effects were shown in the lateral femorotibial compartment, but failed to reach statistical significance in the medial one [29–32].

Limitations of location-specific analysis of structural progression in OA

Analysis of subregional rates and sensitivity to change in a large subcohort of the Osteoarthritis initiative revealed that cartilage loss is spatially heterogeneous between patients and knees [27] (Figs. 1 and 2). Although patterns of subregional loss may be related to knee alignment [33], meniscus pathology, [34] and the location of radiographic JSN [35], it is currently impossible to reliably predict where in the knee cartilage will be lost, and by whom. Hence, if DMOAD efficacy is to be demonstrated by location-specific measurement, only very few patients/knees will actually contribute to an efficacy signal, whereas a great majority will provide only noise, because cartilage loss takes place at locations other than the one defined as the primary outcome (Fig 2). This approach may be compared to a fracture trial in osteoporosis focusing on just one vertebra, while ignoring fractures occurring in other vertebrae or other skeletal locations.

Cartilage thickening (swelling or hypertrophy) has been suspected to occur in the early phases of OA [36,37], particularly in peripheral subregions that are shielded from high mechanical loads. Hence, thinning and thickening may occur simultaneously in different joint regions, canceling each other out when measurements of the entire volume or total thickness are made [36] (e.g., Fig. 2). These phenomena may render global measurements at total plate or compartment level insensitive to detecting DMOAD effects that achieve reducing cartilage loss and thickening differently and/or at the same time.

Strenghts of location-independent analysis of cartilage loss in OA

To overcome these limitations, novel analytic methods for location-independent analysis was proposed [38], to more efficiently capture change in cartilage thickness in knee OA. Studying healthy reference subjects as well as participants with symptomatic knee OA, changes in 5 medial tibial, 3 medial femoral, 5 lateral tibial, and 3 lateral femoral subregions were ranked according to the direction and magnitude of change within each femorotibial compartment. These ranked values were termed ordered values (OVs; Fig. 1), with OV1 representing the individual subregion with the largest cartilage thickness loss or smallest gain, and OV8 the one with the largest cartilage thickness gain or smallest loss [38] (Fig. 2). Cartilage thinning after 24 months in knees with advanced radiographic OA significantly exceeded those in healthy knees in only 1 of 8 medial subregion ($P = 0.04$), whereas 4 of 8 medial OVs displayed significant differences ($P = 0.001$). Interestingly, in knees with early radiographic OA, medial femorotibial cartilage thickening occurred as frequently as cartilage thinning [36], and OVs were more sensitive in detecting thickening than subregions [38]. Wirth et al. ranked all 16 femorotibial subregions across the medial and lateral compartment (extended OV approach [39]; Fig. 2). Knees with baseline radiographic joint space narrowing (JSN) displayed greater magnitudes of cartilage thickness loss than those without JSN, with minimal P values of 0.008 for femorotibial subregions, $P = 0.0003$ for medial OV1, and $P = 0.0000005$ for extended OV1. In a subset of close to 300 participants with longitudinal radiographic analysis, minimum JSW did not discriminate between longitudinal rates of change in JSN vs. no-JSN knees, whereas medial OV1 ($P = 0.0005$) and extended OV1 did ($P = 0.00002$). The authors concluded that location-independent analysis approaches to cartilage change help overcome spatial heterogeneity of cartilage loss in knee OA are more sensitive in detecting cartilage thinning and thickening in osteoarthritic vs. healthy or knees with and without JSN than region-specific measurements approaches [38,39], and that the OV technique circumvents challenges of selecting a particular region “a priori” as the primary analytic endpoint in epidemiological or interventional clinical trials [36].

Not needing to define a specific region of interest is particularly useful when examining OA progression at the early stages, before radiographic JSN indicates which compartment is affected, or even before radiographic change has occurred, that is, stages at which no specific expectation exists as to where the initial changes may take place. Location-independent analysis methodology was then applied to explore changes in cartilage thickness over 5 years after anterior cruciate ligament rupture, a known risk factor of incident knee OA [40]. MRIs were acquired within 4 weeks of ACL rupture and at 2-year and 5-year follow-up. The rate of total feomorotibial cartilage volume and thickness change did not differ significantly between the baseline to 2-year vs. the 2–5-year follow-up period, whereas OV, that is themaximum subregional cartilage loss, and OV16, that is themaximal subregional cartilage gain were both substantially and significantly greater during the earlier interval [40]. To avoid issues of parallel statistical testing of multiple ordered values, and to potentially increase the robustness of the analysis, the author analyzed a total subregional change score, summarizing the magnitude of all subregional thickness changes