Quantitative magnetic resonance imaging of osteoarthritis

Felix Eckstein
Institute of Anatomy & Musculoskeletal Research, Paracelsus Medical University (PMU), Strubergasse 21, A5020 Salzburg Austria,
and,
Chondrometrics GmbH, Ulrichshöglerstr. 23, 83404 Ainring, Germany
Tel.: +43 662 442 002 ext. 1240;
Fax: + 43 662 442 002 ext. 1249;
felix.eckstein@pmu.ac.at

The advent of magnetic resonance imaging has revolutionized the field of musculoskeletal research. In osteoarthritis (OA), articular cartilage can be visualized directly, its dimensions can be accurately quantified in 3D and its composition can be interrogated. The high demand for (quantitative) imaging in OA originates from two sources. First, OA pathobiology is poorly understood; although it is known that structural/compositional changes occur in almost all tissues that make up diarthrodial joints, it is currently unclear which of these changes are clinically important. Second, there is currently a lack of effective therapy, with traditional symptomatic therapies being unable to stop or slow down the structural progression of OA that may eventually lead to joint replacement. Quantitative imaging of osteoarthritis represents a highly promising tool for studying OA epidemiology and disease-modifying OA drug development.

A substantial proportion of people above 65 years of age and, thus, millions of people worldwide, are affected by osteoarthritis (OA) [1–3]. With the number of people of advanced age rising steadily, the demand for effective clinical management is enormous. Symptomatic treatment of OA is available, but cannot stop the structural progression of the disease. No structure- or disease-modifying drug for OA (S/DMOAD) has been approved by regulatory agencies to date [4,5]. Symptomatic treatment can be directly monitored by clinical outcomes such as pain and function, but it is currently difficult to evaluate the clinical benefits that result from structure modification (rather than symptomatic treatment) within similar timeframes. It has been demonstrated that OA is a slowly progressing disease, with cartilage loss of 0–7% per year having been reported in various studies [6–16]. These studies have examined patients who are likely to progress, and, therefore, the true progression in the general patient population can be assumed to be slower. Since there is little hope that the structural progression of disease can be completely stopped by medication, it is likely that the potential structure-modifying effect of a putative drug translates into a clinical benefit only after several years, if not decades. For initial proof-of-concept studies of S/DMOADs, surrogate end points are therefore required that can measure the potential (long-term) beneficial effect much earlier than the desired clinical benefit occurs. Since novel therapies cannot initially be administered over years and decades before the safety and effectiveness of a drug has been evaluated, the ability to demonstrate structural benefits using surrogate markers is of great importance [17–20]. Amongst those surrogate measures, imaging is particularly promising because it can visualize joint structure directly. Magnetic resonance imaging (MRI) has great promise in this regard because all tissues that compose diarthrodial joints can be delineated in 3D, and many structural pathological processes associated with OA can be visualized, including morphological and compositional changes of articular cartilage [17,18,20–24].

Limitations of current techniques for OA imaging

An important question is which imaging technique is optimal for measuring OA status and progression? Although many advances have been made with x-ray over the last few years [25–30], and although it is the technique currently accepted by regulatory agencies, it has well-known limitations: it is projectional and therefore prone to measurement error if the position of the joint relative to the x-ray film is not controlled very carefully [22,31]. These positioning errors make it difficult and challenging to maintain a high standard of imaging quality, particularly in larger multicenter, multinational clinical trials [32]. In addition, there is a current lack of consensus on the appropriate positioning and acquisition protocol. Protocols that employ fluoroscopy to position the joint appropriately in between the x-ray source and the film involve substantial radiation exposure and are, in addition, burdensome for the patient, the technician and the reader performing quality control. Since cartilage is not visualized directly with x-rays, information on cartilage status must be

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future medicine

estimated from indirect measures, such a the width of the joint space between the femoral and tibial subchondral bone in femorotibial OA [33]. This 1D measure, which is usually taken in a central location of the compartment, cannot differentiate between the specific loss occurring in the femoral or tibial cartilage [33], and has also been shown to be affected by meniscal status (extrusion) [34,35] and joint laxity [36], independent of cartilage status. Therefore, joint-space narrowing provides a composite measure of structural change in the joint that is not specific to a single tissue and may be confounded by artifacts.

Further important issues with this technology are the floor and ceiling effects. That is, the measure is insensitive to early changes in the disease process that may occur early in parts of the joints that are not in a central location (where the measurement is taken). In addition, the measure has little dynamic range with a ceiling effect, because once the joint space width is obliterated centrally, further progression of cartilage loss (e.g., an increase in the denuded cartilage area) cannot be documented. Given these technical limitations, it is not surprising that x-rays have been unable to measure structural progression in large cohorts over periods of less than approximately 1 year [31,37]. Despite large efforts, these limitations have not yet been overcome, and thus radiography is presumably already at the limit of its technical capability. However, MRI is at its infancy where substantial further technical developments can be expected over the coming decades.

Whole-organ assessment of joints with MRI

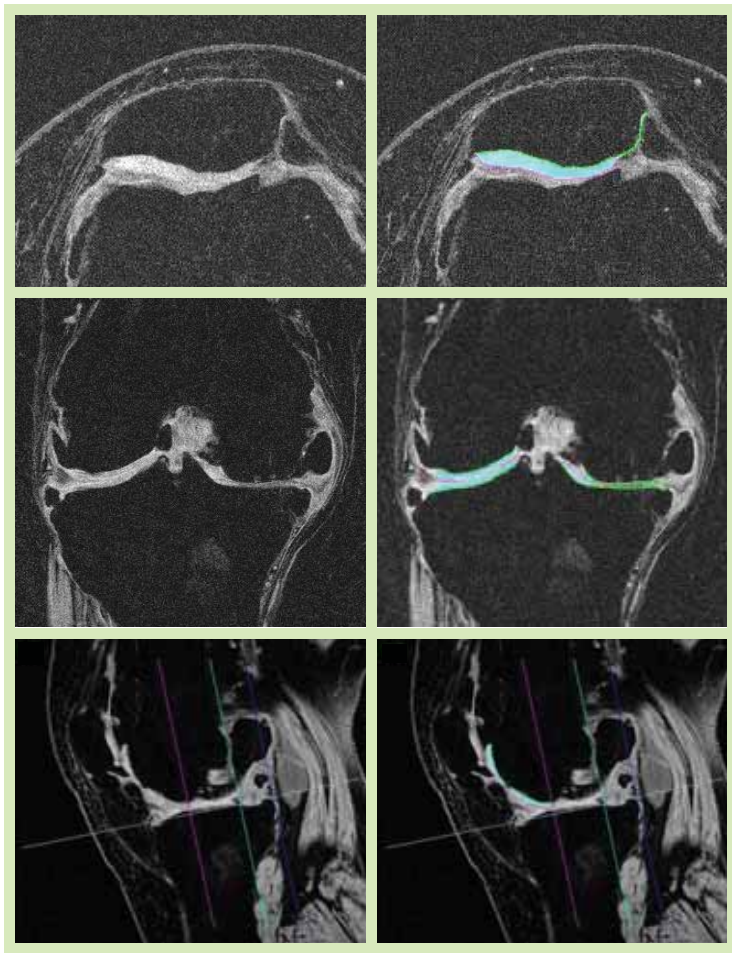
Many features of joint structural progression can be reliably visualized and graded with MRI, such as cartilage status, osteophytes, bone marrow abnormalities, synovitis, meniscal and ligament abnormalities, and effusion [14,24,38–45]. This approach provides a more holistic view of joint status. Describing (and eventually discriminating) different patterns of involvement of particular tissues in knee OA could potentially elucidate different causes of the disease and make it possible to adjust specific therapeutic strategies to the individual pattern of joint pathology. Moreover, whole-organ assessment of joints may enable early (preclinical) detection of the disease process, in which treatment may be most promising. Several scoring systems for whole-organ MRI have recently been presented [39,43,44]. However, in a recent clinical trial, no change has been documented over a period of 6 months [46] and, generally, few data on the sensitivity to change of these scores (and the underlying imaging features) are currently available [16,46]. However, over the next few years, these scoring systems will provide a wealth of information regarding the extent to which various tissues and structures of the joint are affected by the OA process in various subpopulations of patients, and to what extent these changes will progress along various timescales. These studies should also elucidate how these structural changes are related to future symptoms of the patient.

The literature appears contradictory with respect to current symptoms. Some studies have shown that bone marrow lesions are associated with the extent of pain in OA [47], other studies found this relationship to apply only for larger lesions [48], and other studies failed to demonstrate these relationships [38,45]. Conaghan and colleagues found synovitis and effusion to be related to pain [42]. In a small study on 50 subjects, Link and colleagues reported that cartilage lesions were better predictors of joint pain than other structural changes in MRI (including bone marrow lesions and osteophytes), despite cartilage being aneural [38]. However, Kornaat and colleagues only found synovial effusion and patellofemoral osteophytes to be related to pain, but not cartilage abnormalities, bone marrow lesions or other changes in a relatively large cohort of 368 participants [45]. This inconsistency may be partly due to the fact that different imaging and scoring methods have been used. Further work in larger samples with standardized and valid measures should help to clarify which of these structural abnormalities are actually associated with symptoms.

Quantitative MRI of cartilage

Since MRI is a 3D, multiplanar technique that provides serial, contiguous images, all structures that are visualized by this technology with adequate resolution are amendable to quantitative 3D analysis [23,24,49]. Although there are theoretical advantages to fully quantify structural changes by continuous variables, it should be kept in mind that grading is often faster and displays adequate agreement with fully dimensional measurements [50]. This is important because quantitative analysis on thin slices with high resolution often requires substantially more resources in terms of image processing and, as a result, personnel, time and financial costs.

Figure 1. Cartilage magnetic resonance imaging in a patient with osteoarthritis.



(Top row) axial, **(middle row)** coronal and **(bottom row)** sagittal images in a patient with knee osteoarthritis, without segmentation **(left)** and with segmentation of the cartilage **(right)**. Note that the total subchondral bone area (tAB) is also segmented in areas were the cartilage has been lost (green line). In this way, not only cartilage volume and thickness (ThC), but also denuded area (dAB) can be computed. Cartilage thickness should be computed both by including (ThCtAB) and by excluding denuded areas (ThCcAB) as 0 mm cartilage thickness.

To date, articular cartilage has created the greatest interest in terms of quantitative measurement of its morphology (geometric dimensions) and composition (biochemistry and internal structure) in OA [21,23,51,52]. It is generally thought (although not stringently proven) that articular cartilage is the most critical tissue in maintaining joint function. In a recent workshop on consensus on osteoarthritis imaging, held in Bethesda (MD, USA) in 2002, a survey of 64 workshop participants revealed that most experts ranked articular cartilage to be the most important MRI feature for evaluating OA severity and progression, followed by osteophytes, bone marrow lesions, synovitis, meniscal abnormality and synovial effusion [53]. Therefore, the remainder of this review will focus on past and current work on quantification of cartilage morphology (geometric extension) and composition (biochemistry and structural composition) as assessed by MRI. It must be noted that most advances described in this review are relevant to the knee, with some, but much less, work having been performed in other joints to date. In the text below, the following topics will be discussed:

- Cartilage imaging sequences
- Cartilage segmentation
- Computation of quantitative outcome measures
- Accuracy and precision of these measures
- Longitudinal change of these measures
- Software quality systems for quantitative imaging of OA

Cartilage imaging sequences

One of the requirements for reliable assessment of cartilage pathology is the use of MRI systems with 1.0-T or greater [54]. Conventional 1.5-T magnets [23,55,56], peripheral (extremity only) systems with 1.0-T [57,58] and, recently, 3.0-T whole-body magnets [59–64] have been successfully applied to quantitative cartilage imaging. MR sequences currently used for whole-organ assessment and semiquantitative scoring of cartilage lesions include fat-suppressed T2- or intermediate-weighted fast-spin echo [23,55,56] and, for the latter purpose, also T1-weighted spoiled gradient-recalled acquisition at steady state (SPGR) with fat suppression or water excitation [23,55,56]. These sequences are readily available on virtually all clinical scanners and, therefore, do not have particular hardware requirements.

For quantitative analysis of cartilage morphology, the aforementioned fat-suppressed or water-excitation T1-weighted SPGR sequences represent the current gold standard (Figure 1) [23]. Although there is no current consensus on the optimal resolution for imaging knees in OA, a 1.5-mm slice thickness and an isotropic 0.3-mm in-plane resolution have been commonly used at 1.5 T for morphological analysis of cartilage (volume and thickness measurement), and enable total coverage of the knee with a 10–12 min acquisition time [23,56]. Given the increased signal- and contrast-to-noise ratio, 1-mm thick slices are preferable at 3.0 T [63].

With regard to cartilage composition, current methodology has focused on measuring the architecture and concentration of collagen, and

the concentration of proteoglycans (PGs) and glycosaminoglycans (GAGs), which, together with the interstitial fluid, support the sophisticated properties and function of articular cartilage. Unlike the aforementioned sequences, compositional imaging requires substantial expertise at the site where the images are acquired. Collagen architecture has been studied by using transverse relaxation times (T2) [65], diffusion or diffusion-tensor imaging [66]. These techniques are sensitive to the molecular structure and concentration of collagen and GAG [67–72], but T2 is also sensitive to cartilage hydration [68,73]. The sensitivity of T2 to several tissue components makes its interpretation difficult, since competing effects may occur at the same time (partly or fully compensating each other). Owing to the magic angle effect (dependency of cartilage T2 on its orientation versus B0), the position of the joint in the scanner must be controlled very carefully, which is difficult to achieve under clinical imaging conditions.

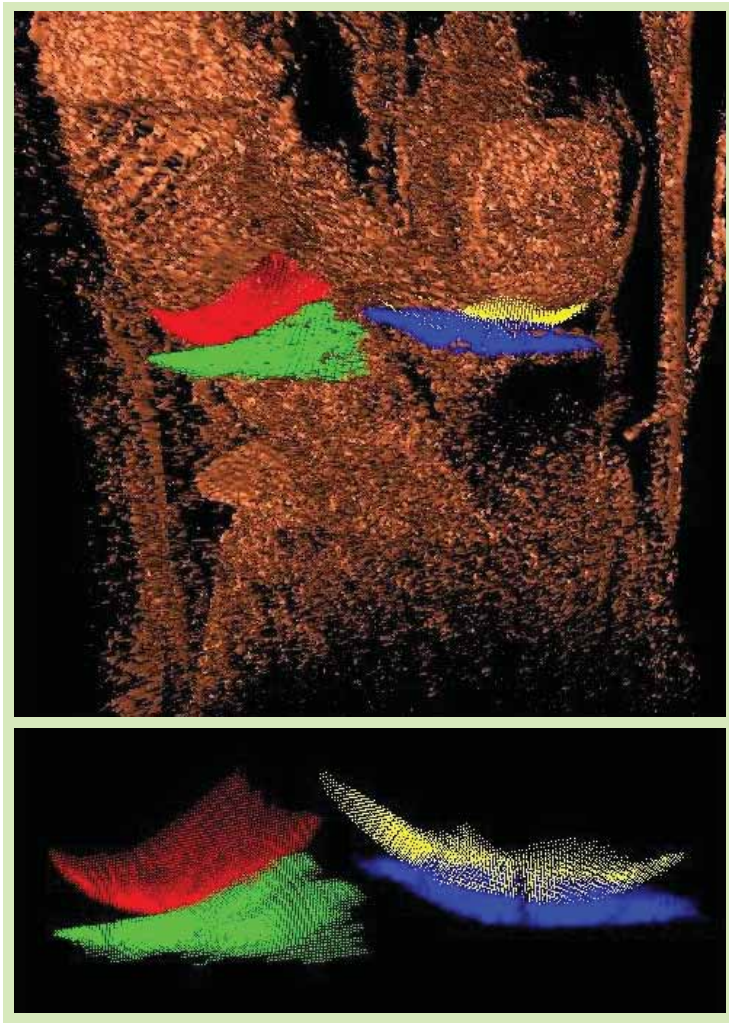
T1rho has been attributed to the PG/GAG concentration in cartilage [74–77], but has also been demonstrated to be sensitive to collagen [68]. Therefore, changes in T1rho might be due to changes in either component. In the absence of a contrast agent, T1 is relatively insensitive to cartilage composition [78]. However, T1 can become specific to molecular content if measured after penetration of a charged agent. delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) exploits these relationships and is based on the biophysical theory that $GdDTPA^{2-}$ (a clinically approved MRI contrast agent) distributes in a charged matrix. A T1 map, calculated from several images with different T1-weightings, which are acquired approximately 90 min after intravenous injection of $GdDTPA^{2-}$ ($T1_{Gd}$, dGEMRIC Index), has therefore been reported to be inversely related to the GAG content. The technique relies on the assumption that T1 is constant throughout the cartilage in the absence of $GdDTPA^{2}$, which has been shown to apply for natural, but not for tissue-engineered cartilage [79].

Segmentation of cartilage

The first step in the quantitative assessment of cartilage morphology and, to some extent, also of cartilage composition, is segmentation of the tissue (Figure 1). The segmentation process aims to distinguish all image elements (voxels) representing cartilage (of various cartilage plates in the joint) from its surrounding tissue. Given the relatively low contrast between cartilage and other tissues (e.g., synovial fluid, meniscus and bone) or the opposite cartilage layer (in the contact zone), and the various sources of artifacts that can occur with MRI, attempts to fully automate the segmentation process have failed [23]. Various semiautomated methods have been developed, but all of these require user interaction and verification by an expert on a section-by-section basis [23,80–84]. The time required for image preprocessing using various filters, algorithm verification and editing is often longer than that for manual segmentation, especially if performed by trained users who segment cartilage images on a regular basis. It is frequently assumed that automated or semiautomated segmentation algorithms provide more consistent and reproducible results than those obtained by manual segmentation; however, this is debatable because the actual interface of the cartilage with the surrounding tissues or the opposite cartilage is not always where the steepest gradient in signal intensity is located in the images. For this reason, considerable knowledge is required to identify the contour that represents the actual interface between the cartilage and other tissues, particularly in OA. More importantly, slight shifts in signal intensity that occur with repeat scans (particularly if the observation period is long in longitudinal studies) can lead to large differences in segmentation results with an automated or semiautomated algorithm, as with the contrast having shifted slightly, the algorithm may choose a different contour than in the partner data sets. Owing to the instability of the image contrast with MRI, most accurate results can be expected from either manual segmentation or carefully edited semi-automated segmentation, preferably by processing baseline and follow-up images of longitudinal studies in parallel.

A recent review from the OMERACT/OARSI workshop on imaging technologies in Bethesda summarizes the segmentation algorithms presented to date in the literature, and the extent to which they have been validated versus independent measures [23]. Other aspects that ensure the quality of segmentations have been discussed to a much lesser extent in the literature. These include formal training and continuous monitoring of expert personnel who perform cartilage segmentation [64,85,86]. This is of particular importance in large-scale cross-sectional or longitudinal studies, in which several users are required to perform the segmentation in a

Figure 2. 3D visualization of knee-joint cartilages.



3D visualization of the segmented weight-bearing femorotibial cartilage plates (Blue: medial tibia; green: lateral tibia; yellow: medial central femur; red: lateral central femur with **(top)** and without **(bottom)** surrounding tissues.

time-efficient manner. Under these circumstances, quality control of all segmentations by a single expert is recommended in order to minimize differences in segmentation strategies between different users, and to exclude performance drifts by the users throughout the study. The quality-control process of cartilage segmentation must ensure that slices that image the edges of the cartilage plate and show relevant partial volume effects are treated similarly (included or excluded) by the users; that cartilage contours are placed accurately (particularly in the contact zone of cartilage and in those slices that cut the cartilage layer obliquely and therefore display partial volume effects); that osteophyte cartilage is appropriately excluded from the segmentation of OA cartilage [49]; that areas of denuded and cartilage-covered subchondral bone are identified appropriately (Figure 1) and that all other criteria of the particular rule-based approach are met. One component to insure this is the structured training of all users, preferably using a standardized software program that guides them through the segmentation process and compares their segmentation with that of more experienced users. However, in addition, segmentation must be monitored continuously in ongoing studies, to exclude drifts in the performance or in the interpretation of the rule-based approach.

Segmentation of the cartilage (as previously described) can also be used to extract cartilage composition. Since the contrast in the relaxation-weighted images do not always produce good definition between cartilage and surrounding tissue, a secondary image set (e.g., SPGR) may be used to aid the segmentation, or to transform the coordinates of the segmentation (mask) into relaxation-weighted or other images that carry compositional information on the cartilage [87,88]. This can be achieved by spatially registering anatomical structures that can be clearly identified in both image data sets (e.g., the bone), or by transforming the coordinates of the segmentation masks relative to the MRI scanner coordinate system into another data set.

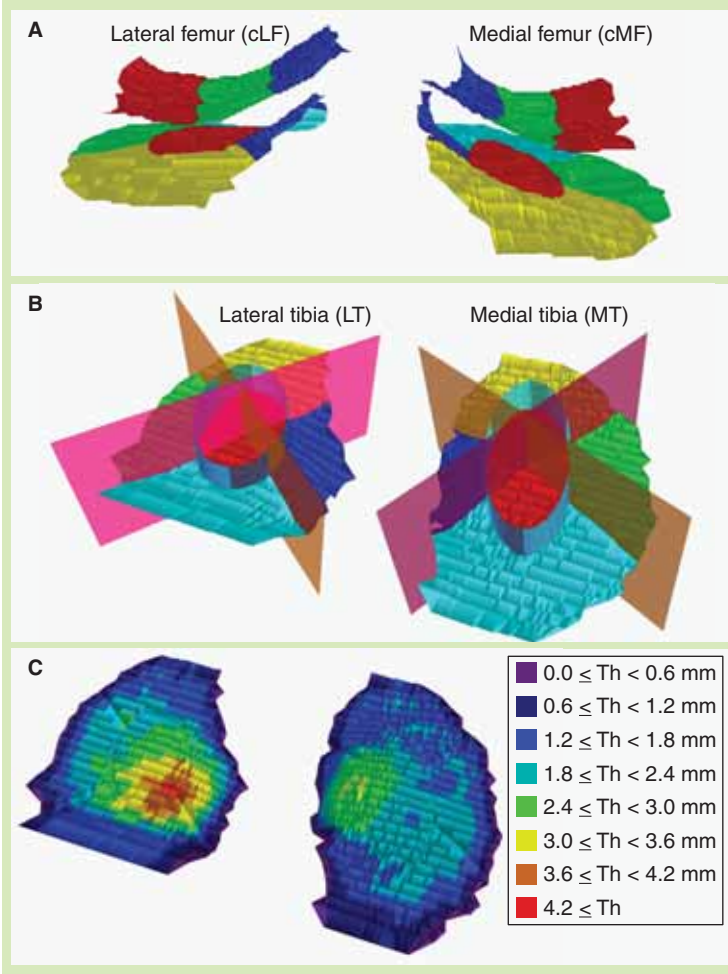
Computation of quantitative outcome measures

To date, most studies that look at cartilage morphology have focused on cartilage volume alone, since it is the most straightforward and the easiest parameter to measure. Cartilage volume can be computed simply by numerical integration of all segmented voxels and multiplication with their spatial resolution (Figure 2). Although differences in cartilage volume over time provide a direct measure of cartilage loss, the amount of information that can be drawn from it is limited. For instance, in cross-sectional studies, subjects with larger bones will have larger cartilage volume, and, in order to exclude this bias, either the cartilage thickness must be computed or the cartilage volume must be normalized to the size of the total area of subchondral bone. This has been demonstrated to substantially improve the discrimination of OA and non-OA patients by measurements of cartilage morphology [89,90]. In longitudinal studies, where the area of subchondral bone can be assumed to be relatively constant, the process of cartilage volume loss can be differentiated into loss of

cartilage thickness or increase in the denuded area (the area of subchondral bone no longer covered by cartilage).

In animal models of OA, cartilage volume can prove to be an insufficient outcome variable, because surgical challenge not only stimulates cartilage loss but also affects bone modeling in (growing) animals. For instance, in a meniscal tear rat model of OA, it was demonstrated that cartilage volume remained constant in comparison to nonoperated contralateral joint over time, whereas computation of more sophisticated parameters of cartilage morphology revealed that cartilage thickness decreased in the operated joint, this effect being masked by an increase in the total area of subchondral bone [91]. We therefore recommend exploiting the full capacity of quantitative MRI and determining the total area of subchondral bone (tAB), the part of the tAB that is covered by cartilage (cAB), the part of the tAB that is denuded. In addition we recommend that cartilage thickness be computed both in the regions that are covered with cartilage (ThC-cAB) and over the total area of bone, including denuded areas of bone as 0 mm cartilage thickness (ThCtAB), but excluding osteophyte cartilage (Figure 1) [49]. However, this requires more than one contour label to be used during the segmentation process (AC for articular surface, and tAB for total area of subcondral bone; Figure 1), and it demands greater expertise from the user because the subchondral bone also must be segmented where it is denuded and, therefore, where contrast is relatively low (Figure 1). Additionally, the maximal cartilage thickness and the thickness variation throughout the joint plate may be reported.

Figure 3. Regional analysis of femorotibial cartilage.



Regional analysis of cartilage morphology in the tibia (dark blue: internal; green: external subregion; light blue: posterior; red: central; yellow: anterior) and weight-bearing part of the femur (blue: internal; green: central; red: external subregion). **(A&B)** Anterior–posterior view of the knee with femur on top and tibia at bottom. **(C)** View from proximally onto the tibial cartilage surface.

Since relaxation times are extracted from a series of MR images with varying repetition time (TR) and echo time (TE) values, these must be computed by integrating information from several data sets. To extract T1, an equation must be fitted through the data points obtained from these acquisitions. This can either be done by averaging signal intensities for a given region of interest and fitting one curve through all data points (voxels) or, preferably, by fitting each voxel to the relevant equation and producing a relaxation time map [49]. If motion has occurred between acquisitions, registration algorithms must be used to spatially register the data before the fitting; for example, by using the bone contours [81], so that T1 values are computed from voxels that represent the identical anatomical location in the cartilage. This is relatively straightforward for 2D acquisitions, but when T1 maps are obtained in 3D, registration becomes more involved [87,88]. In addition, the accuracy of the registration is limited by the relatively coarse section thickness of these acquisitions (often >3 mm).

dGEMRIC displays relatively little heterogeneity across the cartilage and may thus be expressed as one composite value for one cartilage plate or region of interest. However, T2 demonstrates substantial heterogeneity across the zones of healthy cartilage and, therefore, should be analyzed in a depth-dependent manner [88,92–95]. In addition, the T2 of the cartilage (and in particular its zonal variation) depends on

the angle of the cartilage layer to the main magnetic field B_0 (magic angle effect at 55°); therefore, this angle must be controlled very carefully. Segmentation masks derived from morphological sequences (described previously) may help to determine relevant regions throughout the depth of the tissue, but this is challenging in osteoarthritic cartilage, where the zonal distribution may be less evident.

Recently, a proposal by an international group of experts has been published outlining how morphological and composition parameters of cartilage should be named and defined, in order to provide a uniform, clear and common nomenclature and to ease communication between researchers [49]. In addition, it would be beneficial to achieve consensus on processing and analytical methods as well as on the clinical validity of these measures once further work on their responsiveness becomes available.

Recent efforts have been directed at identifying reproducible subregions within the joint surface (e.g., central, anterior, posterior, internal and external) and to determine morphological parameters (thickness) within these subregion (Figure 3). This effort is driven by the observation that changes of cartilage morphology preferentially occur in certain areas of the joint surfaces (e.g., where weight-bearing predominates), but do not affect the entire cartilage plate homogeneously [96]. Regional approaches might substantially enhance the ability to measure change longitudinally during short time intervals (Figure 3), but larger longitudinal studies will be required to identify which subregions are best suited for this purpose, and whether these regions vary between different populations with different risk factors for OA.

Accuracy & precision of quantitative cartilage parameters

Many studies have now verified the accuracy of morphological assessment of cartilage, some having been performed *in vivo* on total knee arthroplasty patients [23,97,98]. Precision errors have been shown to range from 1% (patella and axial orientation) to approximately 3–5% in other surfaces of the knee [23]. Precision errors are critically dependent on the section orientation chosen (axial vs coronal vs sagittal), the spatial resolution selected and the cartilage plate examined [23]. In the patella, for instance, axial protocols have been demonstrated to yield only half the precision error (1%) [86,99,100] of that observed with sagittal imaging [23,99,101]. With a sagittal imaging protocol of 1.5-mm section thickness and 0.3-mm in-plane resolution, precision errors are high in the femoral condyles, even in healthy subjects [101]. Sagittal image protocols have the advantage that they cover all cartilage plates of the knee in only one acquisition, but that is at the expense of larger partial volume effects and larger precision errors in the patella (compared with an axial protocol) and in the weight-bearing femorotibial joint (compared with a coronal imaging protocol) [97,102]. Therefore, if information on the femoral trochlea and the posterior femoral condyles is not desperately required, we recommend combined acquisition of an axial and coronal data set, rather than a sagittal acquisition.

Using 3.0-T MRI, it has recently been possible to reduce precision errors in the femorotibial joint (coronal protocol) when choosing 1-mm rather than a 1.5-mm slices [63]. Double-echo steady state sequence (DESS) at 3.0-T with sagittal orientation and 0.7-mm slice thickness have been demonstrated to provide adequate precision in the femoral condyles [64], but this comes at the expense of having to segment 50–100% more slices than usually acquired, which has implications for the time and cost required to process a study. By contrast, results for the femoro-patellar joint have been less promising with the sagittal DESS, due to the relatively high precision errors [64] compared with previous studies using SPGR sequences [23,101]. These examples demonstrate that the image acquisition protocol selected needs to be tailored specifically to the purpose of the study. A delicate compromise between anatomical coverage of various knee-joint surfaces, the spatial resolution required, precision errors, time for turn around of the analysis and financial cost must be achieved in order to guarantee the successful completion of the study.

With regard to the accuracy of relaxation time measurements, these have been mostly assessed *in vitro* [51,52,78,92]. *In vivo* validation is difficult, as no gold standard is readily available. Surprisingly, the *in vivo* reproducibility of compositional cartilage imaging in clinical studies on OA populations has not been reported to date.

Longitudinal change in OA

Several studies have shown that MRI has the ability to measure longitudinal changes in cartilage morphology (volume or thickness) [6–16,23]. However, the rate of these longitudinal changes

varies substantially (0–7% annually) between studies, and the standard deviations of these changes have also been found to be relatively high. Therefore, substantial sample sizes and/or relatively long durations of clinical trials will be required to demonstrate drug effects on these changes. To date, few studies have compared MRI with x-ray changes, and these found either no or only a weak correlation between the two modalities [6,13,16,103].

Data are emerging on the factors associated with cartilage loss, such as meniscal status [14,41], body mass index [13], malalignment [104,105] and others. Since many large epidomiological trials, including the OA Initiative [201], are now underway, a wealth of data on longitudinal change of knee-joint structure will become available in the next few years. The OA Initiative has recently released the first data, and these are now available to researchers for investigation [202].

There have been contradictory results regarding how cartilage loss is related to symptoms [13,106–108]. However, one study reported that the rate of volumetric cartilage loss is associated with the likelihood of having knee arthroplasty 2 years later [109]. This has been the first study to clearly demonstrate the correlation between a surrogate (imaging) end point and a clinical end point (a measure of how a patient feels and functions).

With regards to the changes of T2 in OA, some studies have shown very discrete differences between control and OA populations (but no differentiation of the severity of OA [110]), whereas others have found no difference between control and OA populations [111]. This may be because the mean T2 (rather than its spatial variation throughout the depth of the cartilage) was assessed, or because clinical OA involves competing factors on T2 changes. While the disruption in collagen architecture and the increased hydration might lead to increases in T2, the cleavage of collagen molecules and the resulting increased water interaction sites might lead to decreases in T2, with the effects potentially off-setting each other. The OA initiative, which also includes assessment of T2, may shed further light on these relationships in the near future.

Regarding T1rho, two trials have demonstrated differences between healthy and OA subjects, but neither study reported T1rho relative to OA grade [111,112]. To date, dGEMRIC represents the technology that has been most thoroughly assessed for compositional cartilage imaging, and this technique has been demonstrated to correlate with cartilage softening assessed by arthroscopy [113], the level of physical activity [114], malalignment [115] and cruciate ligament status [116,117]. It is currently being introduced to larger clinical and epidemiological trials and, thus, more data are expected to emerge in the near future. However, one limitation of dGEMRIC is the need for an intravenous injection of $GdDTPA^{2-}$ and the sequential 90-min lag time, until acquisition of the T1 maps can be acquired.

Software quality systems for quantitative imaging of OA

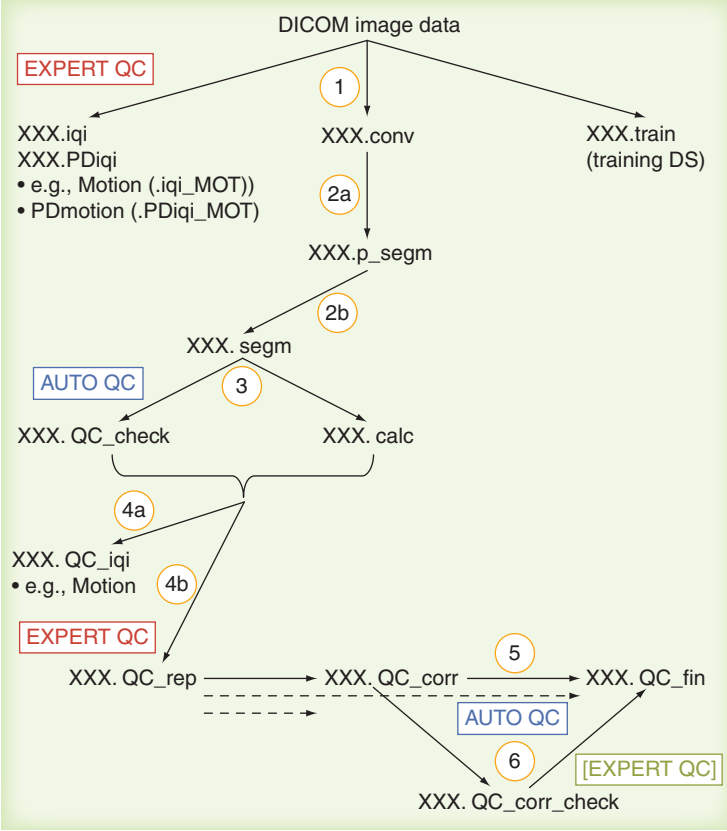
All aspects of a research or a clinical trial must be continuously controlled and monitored for quality. An important aspect of this is to ensure quality of the acquisition, since high quality data are required to guarantee satisfactory analysis. Therefore, measures must be implemented to ensure standardization of the image acquisition. Central review of the image data is necessary to warrant that all requirements are met at all imaging sites throughout the trial and to reduce measurement variability. This review should take place rapidly, so that a participant can be rescanned if the requirements (e.g., appropriate orientation of the images and complete anatomical coverage) are not met. The emphasis of this chapter will be on the analysis software quality system, with the understanding that standardization and a high quality of the image acquisition has been met.

Developing cutting edge imaging analysis techniques and applying them to small exploratory studies at a single site is one thing; applying them to large, multicenter (potentially multicontinental) trials in a time- and cost-effective manner is another. Data management, data integrity, data flow and quality assurance (QA) or control (QC) are an important challenge in large clinical trials. With the number and size of clinical trials in OA increasing, these aspects of successful implementation of quantitative imaging technology will become more and more important in the future [118]. As these aspects have rarely been addressed in the literature, a particular focus of this review will be on the application of software quality systems in the assessment of cartilage.

Development of an effective quality system requires planning (documentation), implementation and then verification. The image analysis tools must be resistant to human interaction error and easy to use, in order to provide quantitative data from large trials in real time (at the same pace at which patients are enrolled) and without error. This perspective provides some examples of

important components of such a quality system and will demonstrate some measures of how quality can be assured. The key components encompass quality QA at data entry and data conversion, standardized segmentation and test computations by expert users, QC of the segmentations by an expert and final computation at the batch level status (Figure 4).

Figure 4. Example of a software quality system requiring multiple defined QC steps for the data to achieve QC_fin status, combining automized and expert QC steps.



Note that only QC_fin data are ready for batch level computation. In a first step **(1)** DICOM image data sets are either converted for segmentation (XXX.conv), are rejected because the image quality is insufficient (iqi) or because the quality of the partner data set is insufficient (PD iqi), or are transformed into a training data set by an expert. In a next step, the segmentation is started **(2a)** and eventually completed **(2b)**. When a test computation (with auto QC) is performed after all activated labels have been segmented **(3)**, the data are advanced to XXX.calc status (no error detected during test computation) or to XXX.QC_check status (error detected that must be checked). During expert QC of the segmentation **(4)**, the data may then either be classified as QC-iqi to support the segmentation, or may be advanced to QC_rep level (expert QC to be repeated; **4b**, QC_corr level (corrections to be made, no second expert QC required) or QC_fin level. With a QC_corr status, another test computation (with auto QC) must be made, to rule-out that segmentation errors have been introduced during the correction. The test computation **(5)** advances the data set to either QC_fin or QC_corr_check status (error that must be checked by an expert; **6**).

Quality assurance at data entry & data conversion

Appropriate coverage of all anatomical structures that must be segmented, appropriate orientation of the images, adequacy of the signal-to-noise and contrast-to-noise ratio, and the absence of relevant artifacts must be verified by an expert before the segmentation process can start. This should preferably be performed by using an electronic checklist of a dedicated software module, and the step-wise verification should create an electronic signature as to when the QA was performed by whom at data entry. Only persons with the appropriate level of authorization should be able to complete these steps, and data conversion should depend on completion of this process. Consistency of the MR acquisition parameters (TR, TE, flip angle and resolution) need not be checked manually, but should preferably be automatically compared versus a defined study protocol, in order to rule-out inconsistencies of acquisition conditions. When naming individual data sets during the conversion process, all manual entries should be avoided or, at least, minimized at the image analysis center. An electronic protocol in the conversion software module can be used to compose the name automatically from various DICOM fields. In cross-sectional studies, this is straightforward, since an (anonymized) entry in the patient name or patient identification field of the MRI scanner can be used for naming the data set, and no other information is usually needed. However, if several data sets are acquired in each patient (test–retest acquisition with the same sequence, acquisition of the same sequence, but with different MRI parameters or resolutions, acquisition with different sequences or the same acquisition protocol at different time points [baseline and follow-up]), additional information must be used from the DICOM fields to create a unique name for each data set. Often, data from longitudinal studies are processed in parallel at one time point. Under these circumstances, care should be taken so that embedded strings, such as date of acquisition, do not unblind the users. Alternatively, the 'daytime' of acquisition (hour, minute, second), represented by another DICOM field, can be used to provide a unique identifier, without unblinding users as to the time point of acquisition.

Errors in which particular structures (e.g., cartilage plates) should be segmented in a particular study can be avoided, by either including the study standard operating procedure (SOP)

electronically with each data set, or, better still, by activating only the structural labels relevant to that particular study. These labels can be embedded in the electronic study protocol and automatically activated during data conversion, without manual intervention being required.

Standardized segmentation & test computations by expert users

As alluded to previously, segmentation is not trivial and users must therefore be trained, preferably using standardized software. When the actual process of segmentation starts, the software should be enabled to store electronic signatures (of the users) and to create audit trails that enable the process of segmentation to be reconstructed at any time point, in order to meet regulatory compliance. For time-efficient segmentation, the 'mouse' should preferably be used for segmentation only, whereas other commands (such as opening and closing data sets) may be supported by hotkeys. Additionally, it should be easy for the user to navigate through the data set, to zoom in and out, to change contour or plate labels, to display and hide previously segmented structures, to display and hide the current segmentation, to overlap segmentations from adjacent sections to check consistency, to open displays such as multiplanar reconstructions, 3D views or a previously segmented partner data set and others, since this can improve the quality of the segmentation. It is also useful if the software provides an image library of anatomical or histological sections of various joints and orientations. This is particularly important in the context of animal studies, where the anatomy of the cartilage plates may be somewhat different from what the users are acquainted with.

An important first step in the process is that the correct anatomical label is used for the appropriate structure and that, for instance, the medial tibia label is not accidently used for the lateral tibia and *vice versa*. Appropriate training of expert users and segmentation SOPs can be helpful in this context, but intrinsic checks that avoid mislabeling are superior. For instance, the software system may request the user to label the fibula in each data set, before any segmentation entries can be made. At later stages of the segmentation, when test computations are made, a distance vector from each anatomical structure can then be computed relative to the fibular marking, and the length of the vectors can be compared with a given matrix to ensure correct labeling (Figure 4). In this example, the vector of the medial tibia to the fibula must always be longer than that of the lateral tibia, and that of the medial femur longer than that of the medial tibia and so on. The same process can be used to ensure the tAB label is used to mark the subchondral bone, and the AC label for the area of the cartilage surface, but not *vice versa*. A series of other intrinsic checks can be made during these test computations, such as that the number of slices in paired data sets is equal and not different, that segmentations are not performed outside a defined region of interest (e.g., on the femoral condyles), that segmentations are completed within all slices in the region of interest and that AC contours do not penetrate tAB contours and do not overlap them. These measures can minimize the amount of error that occurs prior to expert QC, and it can facilitate but cannot replace the QC. To ensure that the test computation has been performed, a label attached to the data set name may verify whether test computations have been completed without errors, and only data sets with this particular label may be amendable to QC.

Quality control of the segmentations by an expert

Since cartilage segmentation in OA requires a high level of expertise and consistency, it is highly recommendable that one expert reviews all segmentations performed within one study (Figure 4). Even after appropriate training, users may undergo certain performance drifts, in that they tend to interpret certain image features or rule-based approaches differently than before over the course of a study. In order to rule-out these drifts, continuous monitoring of the consistency of the segmentation process within a study by a single expert is required. The software may help in this process, to support the QC reader by automatically loading the baseline and follow-up data set in parallel and by automatically displaying the slices that the user has identified as matching best in both data sets simultaneously for specific cartilage plates. The software system may allow the user to enter graphical or verbal comments (as chosen from a generic list or typed) into the data set. Additionally, the software should automatically alert the expert reader if she/he attempts to finish the QC process before all images with segmentations have been activated (looked at) by the QC reader, with the software specifying the

plates/slice numbers that have not yet been checked. QC entries made by the expert should be specific to slice number and to anatomical features (e.g., specific cartilage plate) and may be synthesized into a comprehensive 'to-do list' that the technician will have to complete after the QC. To facilitate this process, all slices with QC entries may be marked with a specific color in an overview display to permit efficient navigation of the data set.

If the QC entries are relatively minor and the data set does not need to be re-QCd by the expert, measures need to be taken to ensure that all corrections are made before the data set is entered into the database (Figure 4). For example, the data set may be blocked to convert into its final status (which is required to run a final batch computation) if single QC entries remain with 'to-do' rather than with 'done' status. Although the software cannot automatically check whether the corrections are made accurately, the software can prohibit accidental *en bloc* transformations of 'to-do' to 'done' entries, and it can verify whether or not changes have been made within that slice, using the relevant plate label. The software may refute converting an entry to 'done' status if no such change has been made. The software should also require that another test computation be made after the corrections have been completed, in which the intrinsic automated quantitative checks (mentioned previously) are repeated, to ensure that no errors are introduced during the corrections. If major edits are made, a label may be chosen that does not enable the user to advance the data set into a status that can be entered into the database, but must be re-evaluated by the expert (Figure 4).

These examples are not comprehensive, and represent relatively simple but effective measures which enhance the quality of the segmentation process, in particular in the context of processing multiple larger studies at the same time at an image analysis center.

Computation at batch-level status

At this level, all or several data sets of a study may be computed to export the relevant quantitative parameters. The procedures aforementioned ensure that no data set is entered into the batch which has not been QCd by an expert, and for which the required edits have not been completed (Figure 4). It is important that the computation of quantitative measures relies on the resolution specified (for each individual data set) in the DICOM header (slice thickness and in-plane resolution), and does not need to be entered manually by the user. However, if multiplanar reconstructions are processed, one must take into account that the DICOM header specifies the original resolution, but not that of the MPR. In this case, the resolution specified by the DICOM header must be over-ruled manually.

When running the batch, the quantitative data should be exported in conjunction with the data set name and all DICOM header information into text files or other files that can be easily imported into database systems, without the need to manually integrate the data and assign the outcome variables to either names or other DICOM header information.

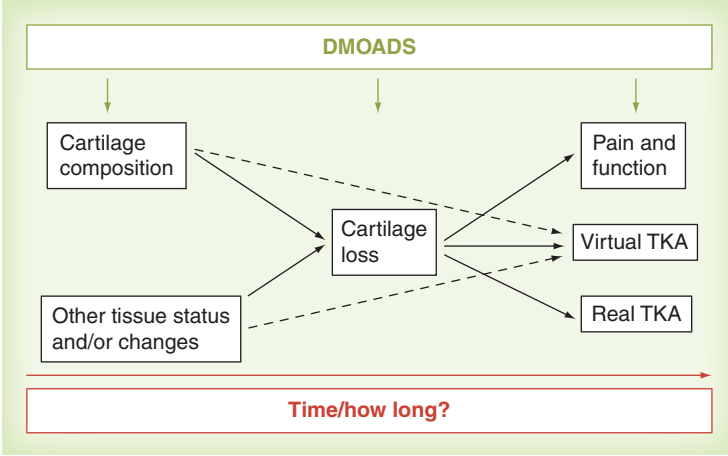
Conclusions

MRI and, in particular, morphological and compositional imaging of articular cartilage, hold considerable promise to become invaluable tools in epidemiological studies of OA and in the development of structure-modifying therapy. MRI sequences for whole-organ assessment of structural changes in joints and for quantitative assessment of cartilage morphology are readily available on state-of-the-art 1.5-T and 3.0-T clinical scanners and have been extensively validated. Sagittal imaging protocols have the advantage that they cover all cartilage plates of the knee in only one acquisition, but at the expense of larger partial volume effects and larger precision errors in the patella (compared with an axial protocol) and in the weight-bearing femoro–tibial joint (compared with a coronal imaging protocol). To date, segmentation has not been successfully automized and, for the time being, requires specific expertise, appropriate training of technical personnel and continuous monitoring using automated and expert QC readings. In this context, software quality systems are key to the successful application of this technology to larger clinical trials. Outcome measures of quantitative MRI are not limited to cartilage volume, but may include the area of denuded subchondral bone and regional cartilage thickness. However, whether regional analysis will enhance the sensitivity of MRI to longitudinal change in OA, and the relationship of imaging biomarkers with clinical end points, remains to be established.

Future perspective

The advent of quantitative MRI technology to OA epidemiology will provide a wealth of information on the risk factors for the onset

Figure 5. Perspective on future research work required in order to be able to test the efficacy of disease modifying osteoarthritis drugs in shorter timescales.



First, it should be confirmed whether cartilage loss as measured by magnetic resonance imaging predicts clinical end points (pain, function and TKA) several years later. In a second step, it must be elucidated whether changes in cartilage composition or changes in other articular tissues predict cartilage loss or clinical end points directly.
DMOADS: Disease-modifying osteoarthritic drugs; TKA: Total knee athroplasty.

and progression of OA over the next 5–10 years (Figure 5). One example of such a study is the OA Initiative. In this study, 5000 patients are monitored using 3-T MRI, radiography and biochemical biomarkers over a period of 5 years [201]. Given that MRI not only delineates cartilage, but also all other tissues that constitute the joint and undergo structural changes in osteoarthritis [24,39,43], these studies will also provide valuable insight into the pathobiology of the OA process.

The use of quantitative or semiquantitative end points in proof-of-concept studies for DMOADs may be less straightforward than it appears at first sight. Although the prevention of structural changes in OA is widely believed to be an important goal in drug development, it will have to be proven that structural changes predict clinical outcome (a measure of how a patient feels or functions or survives) and that the administration of the DMOAD has a clinical benefit (Figure 5). Since people do not die from OA, pain and function are the primary clinical outcomes, but these are subjective to some extent and not always easy to measure. However, the major obstacle is that clinical benefits of DMOADs cannot be expected to become apparent in the short term, but maybe only after a decade or longer (Figure 5). A more objective measure of clinical outcome may be total arthroplasty, but it is known that this outcome is influenced by other factors, such as patient comorbidity, social context, culture and the financial situation of the specific medical system (e.g., waiting lists). However, a concept of virtual knee arthroplasty that is currently being explored defines the need to undergo knee arthroplasty as a composite measure of pain, function and structure, independent of age, comorbidity and socioeconomic factors [119–121]. This clinical end point may potentially be used to measure the benefit of a DMOAD in the same way as fracture has been used to demonstrate the clinical benefits of antiosteoporotic drugs (Figure 5).

However, the time that elapses between the indication for treatment and the indication for total knee arthroplasty is long, especially if a DMOAD is targeted to treat the early stages of the disease. Therefore, surrogate imaging markers will have to be used in short-term studies to demonstrate the effectiveness of a DMOAD (Figure 5). Quantitative MRI will play an important role in this context but, as has been described, the image analysis process should be governed by a thorough and stringent QC control process.

Current research must focus on the question of whether cartilage loss, or other structural measurements in joints, represent valid surrogate markers of clinical outcomes several years later, in particular whether or not a patient will require total knee arthroplasty (Figure 5). Once this relationship is more clearly established, investigators will be able to test DMOADs over 1- or 2-year periods (depending on cohort size and recruitment), to demonstrate a benefit based on the reduction of cartilage loss (Figure 5). However, even 1- or 2-year studies are relatively long if various drug candidates with unclear levels of safety and effectiveness are to be tested. Therefore, it will have to be investigated whether regional cartilage morphology (e.g., analysis of only a defined central part of a cartilage plate) is more sensitive to change than entire cartilage plates and can potentially reduce the period in which significant changes can be demonstrated.

Another focus of future research should be on addressing whether compositional markers of cartilage, bone marrow lesions or structural change in other joint tissues can reliably predict who will experience high or low rates of cartilage loss, respectively, or whether these markers are even better predictors of clinical outcome than cartilage loss (Figure 5). If clear relationships

can be established between these factors, this may enable the observation periods for DMOAD development to be reduced to several months (Figure 5).

Given the high number of studies underway, major progress should be made over the coming 5 or 10 years in determining how structural changes in various articular tissues and various anatomical compartments are related to each other, and how these are related to clinical outcomes such as pain, function or requirement for total knee arthroplasty. These observations should substantially improve our ability to evaluate and assess therapeutic interventions aimed at modifying the structural progression of this disease. Once DMOADs become available, there will be increasing demands for a more widespread application of quantitative MRI in the clinic, in order to monitor drug effect in individual patients. At this stage, a higher degree of automization of the above image analysis technologies will be critical, in order to serve the increasing demands for these diagnostic procedures.

Conflict of interest

Felix Eckstein is Chief Executive Officer of Chondrometrics GmbH (Ainring, Germany) a company providing consulting and centralized imaging services for research studies and clinical trials to other research groups and pharmaceutical companies. He currently provides consulting services to Virtualscopics, Pfizer and GlaxoSmithKline.

Executive summary

Why is quantitative imaging of osteoarthritis needed?

- A large proportion of people over the age of 65 years suffer from osteoarthritis (OA), with millions of people being affected worldwide.
- OA pathobiology is poorly understood: although it is known that structural changes occur in articular tissues, it is unclear which of these changes are clinically most important.
- Currently, there is a lack of effective therapy to combat the structural progression of OA.

Limitations of current techniques for osteoarthritis imaging

- Radiography, the currently accepted technique by regulatory agencies, is projectional and, thus, prone to measurement error. To keep these errors limited, fluoroscopic positioning is required, involving substantial radiation exposure.
- Information on cartilage status from radiography must be estimated from indirect measures, such as the width of the joint space, which is known to be influenced by other factors, such as meniscal extrusion and joint laxity.
- Radiography has a small dynamic range (floor and ceiling effects); that is, the measure is insensitive to early changes in noncentral locations of the joint, and is unable to monitor further progression once the joint-space width is obliterated.

Whole-organ assessment of joints with magnetic resonance imaging

- Magnetic resonance imaging (MRI) can delineate multiple features of joint structural progression directly, such as cartilage, osteophytes, bone marrow abnormalities, synovitis, meniscal and ligament abnormalities, effusion, and others.
- Several semiquantitative scoring systems for whole-organ MRI have recently been developed, based on fat-suppressed T2- or intermediate-weighted fast spin-echo sequences
- The sensitivity to change of these scoring systems (and the underlying structures that are being imaged), as well as their relationship with symptoms (pain) remains unclear.

Quantitative MRI of cartilage

- Imaging sequences for whole-organ assessment and for quantitative analysis of cartilage morphology (volume and thickness) are widely available on clinical scanners. By contrast, techniques for measuring cartilage composition, require longer imaging time, participant burden and considerable expertise at the imaging site
- Currently, cartilage segmentation cannot be automated and is a time-intensive procedure, that requires dedicated software and expert personnel. However, imaging analysis centers can provide centralized image analysis services.
- A nomenclature for quantitative outcome measures of cartilage morphology and composition has recently been proposed by an international group of experts.
- The accuracy and precision of morphological measurements of cartilage has been demonstrated under clinical conditions *in vivo*, but measures of cartilage composition have been less rigorously validated in a clinical setting.
- Morphological measurement of cartilage has demonstrated longitudinal change, with rates of change (volume loss) of 0–6% per annum reported in various studies.
- Amongst compositional techniques, good evidence exists that indicates changes in OA are measurable with proteoglycan-sensitive delayed gadolinium-enhanced MRI of cartilage imaging ($T1_{Gd}$), but further work is required to establish this for other techniques assessing collagen and hydration (e.g., T2 and T1rho)
- To warrant data integrity and efficient image analysis in clinical trials, software quality systems are required. The design of such a quality system and some of its key features are described in this article.

Executive summary

Conclusions & future perspective

- Although the prevention of structural changes in OA is widely believed to be an important goal in drug development, it must be proven that structural changes predict clinical outcome (a measure of how a patient feels, functions or can avoid joint replacement).
- In a next step, it must be demonstrated that the administration of disease-modifying drugs (DMOADs) has not only a structural, but also a clinical benefit. However, owing to the slow progression of OA, the clinical benefits of DMOADs may not become apparent immediately, but potentially, only after a decade or longer.
- Clinical outcomes are difficult to define in OA, and the field currently lacks a generally accepted clinical end point, such as fractures in osteoporosis.
- Current research should focus on establishing whether cartilage loss (or other structural measurements) as measured by MRI represent valid surrogate markers and have high predictive ability with regard to clinical outcomes several years later.
- In addition, it must be addressed whether compositional markers of cartilage, bone marrow lesions or structural change in other joint tissues (synovium, bone, meniscus and others) can reliably predict which patients will experience high or low rates of cartilage loss, respectively.
- If clear relationships can be firmly established between these factors, observation periods for DMOAD development trials may be substantially reduced. However, to demonstrate this it will require large and long-term observational studies, such as the OA Initiative.

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Websites

201. National Institute of Arthritis and Musculoskeletal and Skin diseases www.niams.nih.gov/ne/oi
202. Osteoarthritis Initiative www.oai.ucsf.edu./datarelease

Affiliation

- *Felix Eckstein, MD*
  Paracelsus Medical University (PMU), Institute of Anatomy & Musculoskeletal Research, Strubergasse 21, A5020 Salzburg Austria,
  and,
  Chondrometrics GmbH, Ulrichshölgerstr. 23, 83404 Ainring, Germany
  Tel.: +43 662 442 002 1249;
  Fax: + 43 662 442 002 1240;
  felix.eckstein@pmu.ac.at