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Editorial
Another step towards the understanding of the earliest stages of osteoarthritis

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Improved diagnostic tools are being applied to understand the early pathologic changes in osteoarthritis (OA). In addition to providing information about early molecular events in the disease process, such methods are necessary to monitor the effects of therapeutic interventions, whether those are non-pharmacological[1], pharmacological or surgical. Traditionally, longitudinal OA changes have been assessed with radiography, which monitors the latter stages of OA[2]. Modern magnetic resonance imaging (MRI) techniques have improved our ability to directly detect cartilage lesions. By using a 3D imaging protocol, the knee cartilage thickness and volume can be analyzed accurately with a high reproducibility. For example, in patients with established OA, the annual loss of cartilage volume was approximately 1–3%[3]. Inherently, however, quantitative imaging still relies on changes in gross cartilage morphology, i.e., relatively late stage disease. This is an important limitation, because once macroscopic changes are present, the pathologic processes have probably passed the point of no return for reparative attempts given that the loss of hyaline cartilage is irreversible. With this perspective, other quantitative MRI methods have focused on the compositional integrity of cartilage, also referred to as molecular imaging of articular cartilage. These new MRI metrics include T2 mapping, T1rho mapping, and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC), all reflecting different aspects of the molecular integrity of articular cartilage[4,5]. In dGEMRIC, the negatively charged contrast agent Gd-DTPA2- is given intravenously and distributes in the cartilage in an inverse relationship to the negatively charged glycosaminoglycans (GAGs). As gadolinium has a shortening effect on T1 relaxation time, T1 measured in the presence of Gd-DTPA2- (usually referred to as the dGEMRIC index) provides a surrogate marker for the GAG content of articular cartilage. In several studies, a low dGEMRIC index has been demonstrated in radiographically normal compartments, both in the knee and in the hip[6–8]. Furthermore, a low dGEMRIC index seems to be a relevant measure of cartilage integrity because it also has a prognostic value in terms of disease progression. In patients with hip dysplasia, a low preoperative dGEMRIC index prior to a periacetabular osteotomy was associated with a worse outcome, i.e., radiographic OA progression 4 years after surgery[9]. Similarly, in patients with knee pain but no joint space narrowing on normal X-rays, a low dGEMRIC index was associated with increased risk of developing radiographic OA changes 6 years after the initial dGEMRIC investigation[10].

In this issue of the journal, Watanabe *et al.* present an important dGEMRIC study that brings us further in the understanding of early OA pathogenesis[11]. They have examined the patellar cartilage in 10 healthy volunteers and 25 patients with recurrent patellar dislocations, a risk factor for degenerative cartilage changes on the patella[12]. They report an ~17% lower dGEMRIC index of patellar cartilage in knees with recurrent patellar dislocations than in healthy controls, ~suggesting GAG loss and possibly early pathologic cartilage changes. Ten of the patients had bilateral dislocations whereas 15 patients had only unilateral recurrent dislocations. This excellent study design with inclusion of both asymptomatics and patients with asymmetric risk allowed the other, non-dislocated knee, to serve as a "normal" control. Interestingly, Watanabe *et al.* found a lower dGEMRIC index also in the non-dislocated knees compared to healthy controls, pointing out that contralateral limbs are not always appropriate controls. The low dGEMRIC index may be explained by a mild dysplasia in the contralateral knee, but could also be the result of a lower level of physical activity in patients with unilateral patellar dislocations. In this regard, it has been shown that healthy individuals with a sedentary life-style have a lower dGEMRIC index than those with a high level of regular physical activity[13]. Altogether, these findings further support that dGEMRIC is a sensitive measure of cartilage quality on the molecular level in cases where the gross cartilage morphology is still intact. Another strength in the study by Watanabe *et al.* is that they report the influence of duration from the initial dislocation to the dGEMRIC investigation, ranging from 6 to 60 months.

Dividing the patients into three groups (early, intermediate and late), the dGEMRIC index for both medial and lateral patellar facets was lower as the duration from the initial dislocation increased. This likely illustrates the initiation and progression of pathologic processes in patients with recurrent patellar dislocation that may lead to OA.

However, when interpreting the results by Watanabe *et al.*, as well as results from other clinical dGEMRIC studies, several issues need to be discussed. One example is the finding by Watanabe *et al.* that the dGEMRIC index was lower in the medial than the lateral patellar facet in healthy volunteers. Previously, a lower dGEMRIC index has been reported in medial vs lateral femoral cartilage in another group of healthy volunteers[13]. According to the principle behind dGEMRIC, this difference would reflect

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a higher GAG content laterally in both the patella and the femur. However, other explanations need to be ruled out. In order to evaluate cartilage GAG content using dGEMRIC, equilibrium in Gd-DTPA2- concentration throughout the cartilage is assumed. In the study by Watanabe *et al*., the cartilage was thicker on the lateral compared to the medial patellar facet. Furthermore, they found a trend towards higher dGEMRIC index with increasing cartilage thickness in healthy volunteers. These findings may be the result of incomplete contrast medium transport into the thicker lateral cartilage with a corresponding lower dGEMRIC index, instead of differences in GAG content[14].

Another limitation in the study by Watanabe *et al.* is that they analyzed only full thickness cartilage regions in one axial slice. A depth-wise analysis of the cartilage would provide more information about the influence of cartilage thickness. Furthermore, only one axial 2D slice was used for the dGEMRIC analysis. Multiple slices, or a 3D protocol, would add information about regional differences in the dGEMRIC index. Consequently, it was recently shown using 3D imaging that patients with femuroacetabular impingement (FAI) have different distribution patterns of dGEMRIC indices in the hip depending on the anatomical abnormality related to the FAI[15]. Clearly dGEMRIC provides important information about the structure of articular cartilage and may serve as a non-invasive diagnostic tool in early stage OA.

However, the results of Watanabe's study need to be replicated and several methodological issues remain to be addressed in future *in vivo* and *in vitro* studies. These include transport of the contrast medium into healthy and degenerated articular cartilage, as well as the sensitivity and specificity of a low dGEMRIC index regarding cartilage GAG content.

Furthermore, additional information about cartilage structure is likely gained if dGEMRIC is combined with other quantitative MRI techniques, such as T2 mapping[16]. In patients with autologous chondrocyte transplantation in the knee, the dGEMRIC index did not differ between repair cartilage and control cartilage, whereas T2 was longer in the repair tissue[17].

The longer T2 likely reflects increased water content and/or an abnormal organization of the collagen network.

Further from a predictive validity standpoint, we need to determine if these alterations in MRI metrics are of clinical relevance in predicting development of the OA clinical endpoint.

Irrespective, our best opportunity to intervene in OA is before gross structural alterations in joint morphology have occurred. Insights gained from both the research and clinical application of modern imaging techniques will allow us to determine structural changes at a point where these may be reversible.

Conflict of interest

The author has no financial interest, direct or indirect, in the work submitted.

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