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Editorial

Compositional changes predict morphologic cartilage lesion development – are we one step closer to clinical translation of quantitative MRI?

Osteoarthritis (OA) affects multiple tissues in the joint and cartilage degeneration is one of the hallmarks of the disease. Magnetic resonance (MR) techniques that quantify cartilage matrix changes have become more accessible, with the rationale that detecting early and subtle cartilage degeneration would be critical for monitoring treatment efficacy of disease-modifying approaches and developing prevention strategies for OA[1,2]. Among quantitative MRI techniques for evaluating cartilage matrix composition, T_2 relaxometry ('mapping') has the longest history and has been applied the most widely as it neither requires contrast agent administration nor special hardware and can be feasibly performed in a clinical setting. In particular, the application of T_2 mapping in the Osteoarthritis Initiative (OAI) has provided the community a valuable dataset with large sample size and up to 10 years follow up for gaining knowledge and insights of the natural history of OA development and progression, particularly in its earliest phases[3].

Histologically, T_2 values of cartilage have been correlated with hydration, collagen content and organization[4,5]. Some studies have suggested that T_2 values are elevated in OA cartilage[6], while others could not confirm such results[7]. In more advanced stages of disease decreased T_2 values have been reported that are likely reflecting dehydration[8]. Elevated and more heterogeneous cartilage T_2 values have been observed in patients with risk factors for OA compared to healthy controls, whereas no significant difference has been observed between these groups regarding the prevalence of MRI morphologic abnormalities[9]. The addition of T_2 mapping to a routine MR protocol at 3T has been reported to significantly improve sensitivity for the detection of cartilage lesions (from 74.6% to 88.9%), and particularly in the identification of early cartilage degeneration[10]. Given that T_2 mapping is capable of showing intrachondral matrix alterations prior the appearance of visually detectable surface damage, one of the most intriguing questions in this context has been whether T_2 is able to predict disease onset and progression of OA.

To answer this question, a few studies have been performed demonstrating that cartilage T_2 and potentially also its heterogeneity may predict morphologic tissue degeneration and radiographic OA development[11,12]. However, one study found that cartilage T_2 is not a strong prognostic factor for cartilage loss as measured by MRI cartilage thickness and radiographic joint space width, although T_2 changes in the medial compartment did occur concurrently with medial femorotibial progression[13]. The reasons for such observed differences are multifold and may include different samples and outcomes that define progression or disease onset. Furthermore, all of these studies were limited to the mean T_2 values averaged over an entire compartment. Despite these studies, it is still largely unknown if focal T_2 alterations, likely reflecting early focal cartilage matrix changes, can predict disease onset, or more specifically, are able to predict focal cartilage morphologic lesion development. This question is particularly relevant because it is well recognized that once cartilage lesions are macroscopically detectable there is a high probability of further progression over time. To identify specific regions of cartilage with a high risk of subsequently developing focal surface lesions will potentially help in defining individuals that are likely to benefit from preventive interventions before the onset of macroscopic lesions.

The study performed by Kretzschmar *et al.* published in this issue of *Osteoarthritis & Cartilage* provides compelling data to fill this knowledge gap[14]. The authors asked whether newly appearing focal cartilage lesions are preceded by changes in T_2 at the site of lesion development and its surrounding and whether differences in heterogeneity and rate of change exist for plates that develop lesions vs those that do not. The authors used a case–control design including 57 cartilage plates with newly appearing cartilage lesions from 45 knees (cases) that were matched with 52 plates from 26 control knees without cartilage lesions from the OAI cohort (controls). The cartilage lesion regions of interest (ROIs) were defined semi-automatically by experienced musculoskeletal radiologists, which were then overlaid to preceding MRIs without focal lesions. T_2 values of local (the site of future lesions) and surrounding cartilage (remainder of the cartilage plate) was assessed 1–4 years prior to lesion onset.

The authors observed that the mean local T_2-values were persistently elevated compared to the surrounding cartilage prior to lesion onset reaching significance 1 year prior (+2.94 ms, $P = 0.012$) in cases, but not in controls, suggesting focal T_2 elevation predicted cartilage lesion development at the same location. While authors mention that most lesions were found in the medial femoral condyle (MFC) compartment, no details on subregional analyses are provided. One may speculate that the observed locations may be relevant or indicative for associated risk of later lesion development with regions or locations exposed to higher mechanical stress like the medial weight bearing areas, and that initially lower values could be explained by adaptive compositional alternations or load induced dehydration in such regions.

The second important observation of this study was that T_2 values of the surrounding cartilage were also persistently higher in cases compared to controls, reaching significance 2 years prior

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to lesion onset (+3.61 ms, $P = 0.003$), suggesting both global (i.e., the entire plate) and focal regions of cartilage constitute high risk factors of cartilage lesion development and OA progression. Most interestingly, the sequence and time frame of the T_2 value elevation of global and local regions prompted the authors to propose a three-step model of early OA development: '1) early systemic compositional changes alter the cartilage quality in a diffuse generalized pattern; 2) further rapid degradation of already impaired cartilage composition in a focal pattern; 3) development of a macroscopic lesion within a mean time period of 1 year'.

The proposed model is intriguing. Although the exact mechanism by which OA develops is still poorly understood, it has been suggested that the formation of focal cartilage lesions may represent an early event in the disease process. Using human cadaver cartilage samples, Squires *et al.* demonstrated that cartilage from the lesion and adjacent area exhibited significantly more collagen cleavage by collagenase, elevated Type II collagen denaturation and synthesis, increased aggrecan turnover, and lower collagen and aggrecan contents, than did cartilage distant from the lesion[15]. There was also a clear gradient of histologic and molecular damage and altered synthesis from lesions adjacent to more remote areas, providing molecular evidence to suggest that the development of idiopathic OA involves the formation and growth of focal lesions. This current study by Kretzschmar *et al.* provided *in vivo* imaging data that is consistent with such models.

The authors proposed that the global changes of cartilage composition may be potentially caused by systematic risk factors including increased age, obesity, female sex, inflammation, metabolic or other systemic factors. For example in this study, cases had significantly higher BMI than controls. Thus, the elevation of cartilage T_2 in cases may partially be attributed to increased loading and biomechanical adaption of the joint. However, T_2 values were significantly higher in cases than controls 2-years before the onset of new lesions even after adjusting for BMI, suggesting impairment of cartilage health in cases during this time frame. The authors did not discuss potential risk factors for the second stage but one may speculate that these factors may include focal injury (meniscal tear for example) and loading alterations. It will be highly interesting to explore in future studies the interrelationship between changes of other tissues (e.g., menisci, bone marrow, synovium etc.), which may present changes before cartilage T_2 elevation (risk factors), concurrently with cartilage changes, or following cartilage changes.

This study presents the first imaging study in human subjects that elucidates the interrelationship between changes in cartilage matrix composition and subsequent focal cartilage lesion development at the same location. The demonstrated ability of T_2 values to predict cartilage lesion onset has potential clinical impact regarding patient management in OA, and potentially moved us one step further towards clinical translation of cartilage compositional MRI. Further work is needed for standardizing data acquisition and analysis methods (ideally automatic) of such compositional measures. Being non-invasive and highly reproducible, quantitative MRI will provide unprecedented specific and sensitive 3D information of tissue health that will develop further into a powerful tool for clinicians and researchers to gain more insight of the disease etiology and to eventually win the battle over OA.

Authors contributions

1. All authors were involved in the conception and design of this editorial.
2. All authors contributed to drafting the article or revising it critically for important intellectual content.
3. All authors gave their final approval of the manuscript to be submitted.

Additional contributions

- Analysis and interpretation of the data: XL, FWR
- Drafting of the article: XL, FWR
- Provision of study materials or patients: N/A
- Collection and assembly of data: N/A

Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by Xiaojuan Li, PhD (first author; lix6@ccf.org).

Competing interests

XL has no competing interests.

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