Does T1ρ Measure Proteoglycan Concentration in Cartilage?

Victor Casula, PhD,[1*] Jouni Karjalainen, PhD,[1] Vladimir Mlynarik, PhD,[2] Timo Liimatainen, PhD,[1,3] Matti Hanni, PhD,[1,3] Edwin H.G. Oei, PhD,[4] Mikko J. Nissi, PhD,[5] and Miika T. Nieminen, PhD[1,3]

To the Editor:

In their recent review, Zibetti et al. provide a comprehensive and insightful overview of various quantitative MRI methods for cartilage assessment.[1] While we fully endorse the authors' perspective that T1ρ mapping has proven its value as a noninvasive tool for assessing the structural integrity of the extracellular matrix, we wish to address a point of concern regarding the narrative of T1ρ as an indirect measure of glycosaminoglycan (GAG) content in cartilage.

Despite acknowledging that T1ρ is not exclusively specific to GAG, in Table 1 of the review, the authors refer to T1ρ as a measure for GAG and explicitly state that an increase in T1ρ should be interpreted as indicative of GAG loss. However, it is important to recognize that variations in T1ρ values can also reflect changes in other tissue components, including anisotropy of the collagen structure. The GAG-specific interpretation derives from seminal studies in which changes in T1ρ were correlated to trypsin-induced GAG depletion.[2,3] Nevertheless, trypsin is known to be nonspecific for GAG, and these studies neglected its potential impact on other biochemical components, such as alterations in content and structure of collagen, which led to an overemphasis of GAG-related changes.

T1ρ is sensitive to low-frequency macromolecular interactions, of the order of the spin-lock amplitude, and it has been speculated that the exchange of protons between hydroxyl and amide groups of the GAG chains and interstitial water might be the primary relaxation mechanism affecting T1ρ in cartilage. However, currently there is no evidence supporting exclusive attenuation of dipolar relaxation by spin-lock, while preserving the contribution of chemical exchange to the overall T1ρ relaxation in cartilage. Indeed, there is substantial evidence supporting the correlation of T1ρ with GAG loss. However, this correlation varies with the amplitude and type of spin-lock pulse, and T1ρ relaxation is also influenced by changes in water content and collagen composition and structure.[3–6] Some literature suggests a lack of correlation between T1ρ and GAG,[7] a study missing from the review in question.

The most commonly used T1ρ measurements (low spin-lock amplitude and continuous-wave preparation) demonstrate significant collagen-related anisotropy in cartilage, even higher than 50%, as demonstrated both at 3T and 9.4T.[6,8] T1ρ maps reveal typical

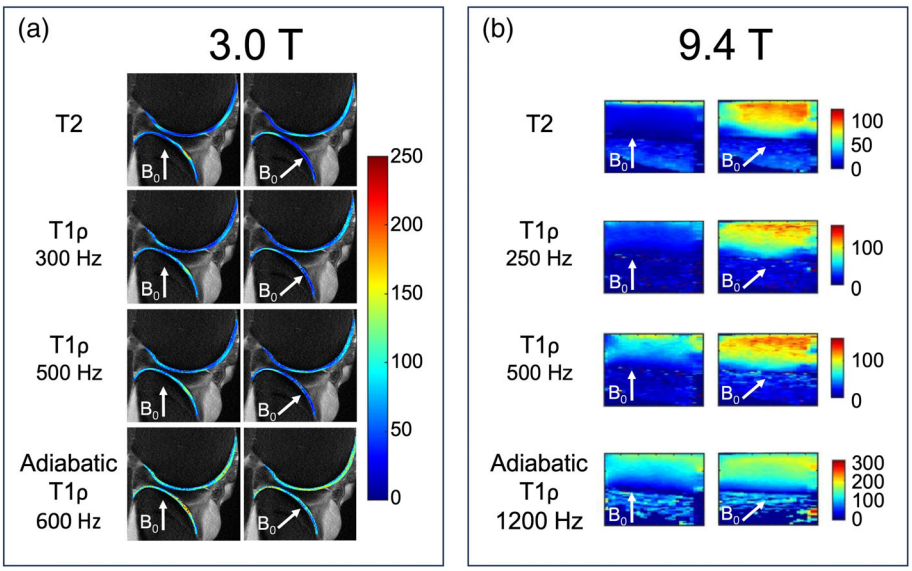

FIGURE 1: T2, T1ρ, and Adiabatic T1ρ maps for bovine knee cartilage measured ex vivo at 3.0 T (a), and a specimen measured at 9.4 T (b) at an orientation perpendicular to the main magnetic field and at the magic angle. Using continuous wave preparation and spin-lock amplitudes typically used in clinical studies (≤500 Hz), T1ρ maps clearly display a strong orientation dependence, resembling T2 maps, although to a lesser extent. T1ρ maps obtained with adiabatic preparation (trains of HS4 pulses) appear almost orientation independent. (a) Courtesy of Ville Kantola, University of Oulu[8]; (b) adapted under Creative Commons Attribution International License 4.0 from[6] http://creativecommons.org/licenses/by/4.0/.

laminar appearance and magic angle effect (Figure 1), and have been shown to correlate with T2.[9] Thus, the orientation-dependence observed in T1ρ relaxation cannot be explained by chemical composition alone. Since T1ρ approaches T2 with decreasing spin-lock amplitude and anisotropy of T1ρ decreases with increasing spin-lock amplitude, it is evident that contributions to T1ρ from different relaxation mechanisms vary continuously and include dipolar relaxation.[6,10]

Attributing T1ρ changes solely to GAG alterations implies a level of specificity that has not been established and could potentially misguide researchers and clinicians. It is advised to include collagen structure and water content as factors influencing T1ρ in Table 1. With this letter, we hope to encourage the community to examine the evidence and attain a more accurate view of the nuanced influences on T1ρ.

[1]*Research Unit of Health Sciences and Technology, Faculty of Medicine, University of Oulu, Oulu, Finland*
[2]*Institute for Clinical Molecular MR Imaging in the Musculoskeletal Area, Karl Landsteiner Society, Vienna, Austria*
[3]*Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland*
[4]*Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands*
[5]*Department of Technical Physics, University of Eastern Finland, Kuopio, Finland*

References

1. Zibetti MVW, Menon RG, de Moura HL, Zhang X, Kijowski R, Regatte RR. Updates on compositional MRI mapping of the cartilage: Emerging techniques and applications. J Magn Reson Imaging 2023; 58:44-60.
2. Akella SV, Regatte RR, Gougoutas AJ, et al. Proteoglycan-induced changes in T1 rho-relaxation of articular cartilage at 4T. Magn Reson Med 2001;46:419-423.
3. Duvvuri U, Reddy R, Patel SD, Kaufman JH, Kneeland JB, Leigh JS. T1ρ-relaxation in articular cartilage: Effects of enzymatic degradation. Magn Reson Med 1997;38:863-867.
4. Kajabi AW, Casula V, Sarin JK, et al. Evaluation of articular cartilage with quantitative MRI in an equine model of post-traumatic osteoarthritis. J Orthop Res 2021;39:63-73.
5. Menezes NM, Gray ML, Hartke JR, Burstein D. T2 and T1 rho MRI in articular cartilage systems. Magn Reson Med 2004;51:503-509.
6. Hänninen N, Rautiainen J, Rieppo L, Saarakkala S, Nissi MJ. Orientation anisotropy of quantitative MRI relaxation parameters in ordered tissue. Sci Rep 2017;7:9606.
7. van Tiel J, Kotek G, Reijman M, et al. Is T1ρ mapping an alternative to delayed gadolinium-enhanced MR imaging of cartilage in the assessment of Sulphated glycosaminoglycan content in human osteoarthritic knees? An in vivo validation study. Radiology 2016;279:523-531.
8. Kantola V, Karjalainen J, Jaakola T, et al. Anisotropy of T2 and T1ρ relaxation in bovine articular cartilage at 3 T. Proc Intl Soc Magn Reson Med 2022;31:2302.
9. Li X, Pai A, Blumenkrantz G, et al. Spatial distribution and relationship of $T_{1\rho}$ and T_2 relaxation times in knee cartilage with osteoarthritis. Magn Reson Med 2009;61:1310-1318.
10. Mlynárik V, Szomolányi P, Toffanin R, Vittur F, Trattnig S. Transverse relaxation mechanisms in articular cartilage. J Magn Reson 2004;169: 300-307.

DOI: 10.1002/jmri.28981

Level of Evidence: 5
Technical Efficacy: Stage 3