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Activities of daily living influence tibial cartilage T1rho relaxation times

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ABSTRACT

Quantitative T1rho magnetic resonance imaging (MRI) can potentially help identify early-stage osteoarthritis (OA) by non-invasively assessing proteoglycan concentration in articular cartilage. T1rho relaxation times are negatively correlated with proteoglycan concentration. Cartilage compresses in response to load, resulting in water exudation, a relative increase in proteoglycan concentration, and a decrease in the corresponding T1rho relaxation times. To date, there is limited information on changes in cartilage composition resulting from daily activity. Therefore, the objective of this study was to quantify changes in tibial cartilage T1rho relaxation times in healthy human subjects following activities of daily living. It was hypothesized that water exudation throughout the day would lead to decreased T1rho relaxation times. Subjects underwent MR imaging in the morning and afternoon on the same day and were free to go about their normal activities between scans. Our findings confirmed the hypothesis that tibial cartilage T1rho relaxation times significantly decreased (by 7%) over the course of the day with loading, which is indicative of a relative increase in proteoglycan concentration. Additionally, baseline T1rho values varied with position within the cartilage, supporting a need for site-specific measurements of T1rho relaxation times. Understanding how loading alters the proteoglycan concentration in healthy cartilage may hold clinical significance pertaining to cartilage homeostasis and potentially help to elucidate a mechanism for OA development. These results also indicate that future studies using T1rho relaxation times as an indicator of cartilage health should control the loading history prior to image acquisition to ensure the appropriate interpretation of the data.

1. Introduction

Osteoarthritis (OA), a degenerative joint disease affecting articular cartilage, is a leading cause of disability and morbidity worldwide, impacting an estimated 27 million adults in the United States (Lawrence et al., 2008). However, there are limited treatment options for OA, making preventative measures of utmost importance. One factor that may play an important role in the initiation and progression of OA is aberrant mechanical loading (Coleman et al., 2016; Griffin and Guilak, 2005). For example, normal physiological mechanical loading potentially leads to a lower incidence of OA, an increase in cartilage thickness, and protection of the structural integrity of cartilage (Bader et al., 2011; Fransen et al., 2002; Jordan et al., 2003). In contrast, abnormal cartilage loading has been shown to be detrimental to cartilage health (Bader et al., 2011). Specifically, both sustained under-loading and overloading of cartilage can lead to altered mechanical properties, reduced proteoglycan content, fibrillation, ulceration, and erosion (Copray et al., 1985; Jurvelin et al., 1986; Muehleman et al., 1997; Palmoski et al., 1979; Radin et al., 1978). However, while these results suggest that normal cartilage loading is vital for maintaining cartilage health, many of these investigations have been performed in animal models. Therefore, limited information is available regarding appropriate loading guidelines in humans. A thorough understanding of the behavior and compositional changes of healthy articular cartilage in response to *in vivo* loading conditions in humans may help to elucidate the etiology of OA and can enhance disease prevention efforts.

Previous work in our laboratory has quantified cartilage thickness changes following a variety of activities, which is likely the result of water exudation from the extracellular matrix (ECM) (Cher et al., 2016; Coleman et al., 2013; Lad et al., 2016;

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Widmyer et al., 2013). This decreased water content results in a relative increase in proteoglycan concentration in the tissue (Mow et al., 1980). Specifically, Coleman et al. (2013) and Widmyer et al. (2013) demonstrated that cartilage thickness varies diurnally in response to activities of daily living. Thus, significant variations in proteoglycan concentration may occur throughout the day. These proteoglycan concentration fluctuations potentially cause changes in the fixed charge density and extracellular osmolarity of the cartilage (Guilak, 2011; Guilak et al., 1995), which subsequently affect chondrocyte cellular function and metabolism (Browning et al., 2004). Importantly, proteoglycan loss has been identified as a potential early change associated with OA development (Gray et al., 2004; Guilak, 2011). Thus, understanding proteoglycan concentration fluctuations provides a unique opportunity to gauge important biophysical changes in articular cartilage.

Quantitative magnetic resonance (MR) imaging provides non-invasive means for investigating articular cartilage composition *in vivo*. Specifically, T1rho imaging has been shown to be sensitive to proteoglycan concentration in cartilage (Akella et al., 2001; Borthakur et al., 2003; Hatcher et al., 2017; Regatte et al., 2002; Regatte et al., 2004; Souza et al., 2014). Negative correlations have been previously identified between T1rho relaxation times and proteoglycan concentration (Duvvuri et al., 2002; Hatcher et al., 2017). Additionally, while previous work has shown diurnal variations in tibial cartilage thickness (Coleman et al., 2013; Widmyer et al., 2013) due to water exudation from the tissue, there are limited studies investigating how these changes affect T1rho relaxation times (Li et al., 2014).

Variations in T1rho relaxation times over the course of a day due to joint loading are particularly important, as these fluctuations may influence the efficacy of using T1rho imaging as a quantitative tool for identifying early-stage OA. Additionally, variations in T1rho relaxation times may also provide important information on normal changes in the biophysical environment of cartilage. Thus, the objective of this study was to measure compositional changes in tibial articular cartilage in response to activities of daily living using T1rho quantitative MR imaging. Because Coleman et al. (2013) and Widmyer et al. (2013) previously demonstrated significant diurnal tibial cartilage strains, we hypothesized that T1rho relaxation times would decrease in tibial cartilage as a result of daily activities, corresponding to a relative increase in proteoglycan concentration in the tissue.

2. Materials and methods

2.1. Participants

Following Duke University Institutional Review Board approval, 7 healthy subjects (3M/4F; mean age = 27 years; age range = 24–30 years) were recruited to participate in this study. Each subject's weight (mean = 158 lb; range = 120–177 lb) and height (mean = 69 in; range = 64–72 in) were recorded to calculate body mass index (BMI; mean = 22.8 kg/m^2; range = 19.4–26.2 kg/m^2). Exclusion criteria included knee joint pain, stiffness, instability, or a history of knee injury or surgery at the time of the study.

2.2. MR imaging protocol

A randomly selected knee from each subject (2 left, 5 right) was imaged first thing in the morning (8 AM) and again in the afternoon (4 PM) (Coleman et al., 2013; Widmyer et al., 2013) using a 3.0T MR scanner (Trio Tim; Siemens Medical Solutions; Malvern, PA) and an eight-channel knee coil (Invivo; Gainesville, FL) (Carter et al., 2015; Taylor et al., 2013; Utturkar et al., 2013). Subjects were asked to refrain from any strenuous weight-bearing activities 12 h prior to the morning imaging session, and each subject rested supine for 45 min immediately before the baseline MR scan to enable cartilage equilibration (Eckstein et al., 1999; Owusu-Akyaw et al., 2018; Sutter et al., 2014). In order to most directly capture the effects of activities of daily living on T1rho relaxation times, no rest period was provided prior to the afternoon imaging session.

Sagittal T1rho-weighted MR images were acquired in the morning and afternoon using a 3D spin-lock preparatory pulse followed by a spoiled gradient recalled echo (SPGR) pulse sequence (matrix = 256 × 256, field of view (FOV) = 140 × 140 mm, repetition time (TR) = 3500 ms, echo time (TE) = 5.9 ms, spin-lock frequency = 500 Hz, slice thickness = 3 mm, spin-lock times (TSL) = 5, 10, 40, 80 ms) (Borthakur et al., 2003)(Collins et al., 2018b, Collins et al., 2018, Hatcher et al., 2017). The scan time for these images was 12 min, 30 sec, and all scans were reviewed by a fellowship-trained musculoskeletal radiologist with over 30 years of experience to ensure adequate quality for model creation and to confirm that patients should not be disqualified per the exclusion criteria.

Subjects were free to perform their normal daily activities between the morning and afternoon sessions. An electronic pedometer (Zip, FitBit, Inc.; San Francisco, CA) placed at the left hip of each participant was used to quantify the number of steps taken throughout the day.

2.3. Data analysis

The bone and cartilage surfaces of each tibia were manually segmented from the T1rho images using solid modeling software (Rhinoceros 4.0; Robert McNeel and Associates; Seattle, WA) (Bischof et al., 2010; Coleman et al., 2013). The AM and PM bone models were then co-registered using an iterative closest point technique (Abebe et al., 2009).

Cartilage masks for each T1rho image were generated manually, and the raw signal intensity (S) from each masked voxel was tracked across spin-lock times (TSL). T1rho relaxation times ($T_{1\rho}$) and the initial signal intensity (S_0) were computed using image processing software (Mathematica 8.0; Wolfram Research; Champaign, IL) by fitting the data to the following equation using the Levenberg-Marquardt algorithm:

$$S(TSL) = S_0 e^{-TSL/T_{1\rho}}$$

T1rho relaxation times were sampled within 18 regions spanning the tibial cartilage (9 on each tibial plateau) (Fig. 1), as has been previously employed to investigate site-specific changes in cartilage thickness following various loading activities (Coleman et al., 2013; Lad et al., 2016; Widmyer et al., 2013). The T1rho values of all voxels within 2.5 mm of each of the 18 sampling regions were averaged to provide localized T1rho relaxation times and to allow for site-specific comparisons between the AM and PM imaging sessions. The overall T1rho relaxation times were computed by averaging the T1rho relaxation times across all 18 grid points, while the medial and lateral T1rho relaxation times were computed by averaging the T1rho relaxation times of the 9 grid points located within each respective region.

2.4. Statistical analyses

A repeated measures ANOVA was used to test for main effects of time (morning, AM vs. afternoon, PM), compartment (medial vs. lateral), and their interaction on T1rho relaxation times. Additionally, to test for site-specific differences in baseline T1rho values, a second repeated measures ANOVA was used to compare T1rho relaxation times based on cartilage location (grid point). To

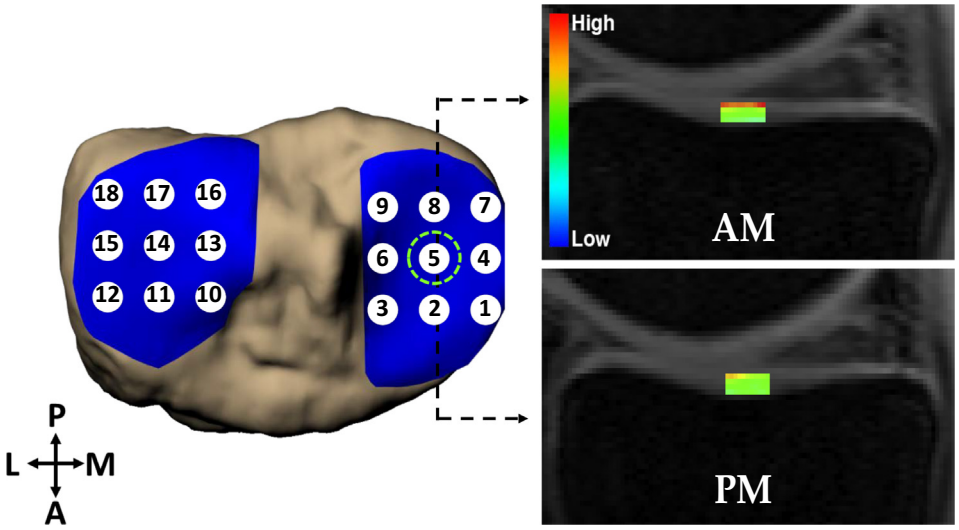

Fig. 1. Changes in T1rho relaxation times were observed following activities of daily living for a given sampling region within the tibial cartilage. Higher T1rho relaxation times, as illustrated in the morning (AM) model, are representative of a lower relative proteoglycan concentration in comparison to the afternoon (PM) model. (A = anterior, P = posterior, M = medial, L = lateral).

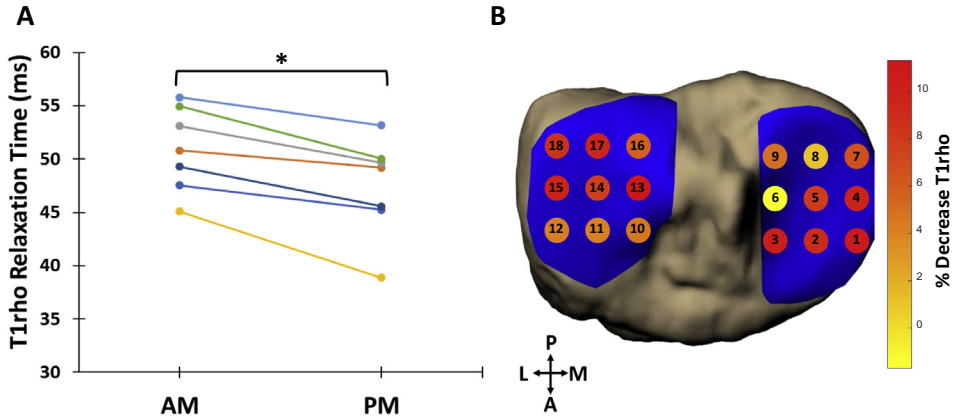

Fig. 2. A. T1rho relaxation times decreased in every subject (*p < 0.001) between the morning (AM) and afternoon (PM) measurements due to activities of daily living. B. Localized % decreases in T1rho relaxation times across all subjects are depicted for each of the 18 sampling grid points. (A = anterior, P = posterior, M = medial, L = lateral).

investigate the relationship between step count and percent changes in T1rho relaxation times (overall, medial, and lateral), linear regressions were performed. All analyses were performed in Statistica (StatSoft, Inc.; Tulsa, OK), and significance was determined where $p < 0.05$.

3. Results

Overall, a repeated measures ANOVA revealed that tibial cartilage T1rho relaxation times significantly decreased following normal activities of daily living (AM vs. PM, $p < 0.001$; Fig. 2A and B), with the overall (mean ± 95% confidence interval) T1rho relaxation time decreasing 7 ± 2% from 51 ± 3 ms in the morning to 47 ± 3 ms in the afternoon (Fig. 2A and B). Additionally, T1rho relaxation times decreased from AM to PM on both the medial (52 ± 3 ms to 48 ± 3 ms) and lateral (50 ± 3 ms to 47 ± 3 ms) plateaus. No significant compartment (medial vs. lateral, $p = 0.26$) or interaction ($p = 0.92$) effects were observed. A second repeated measures ANOVA showed localized variations in baseline T1rho relaxation times between grid points ($p < 0.001$; Fig. 3), with mean values ranging from 42 ms (grid point 6) to 57 ms (grid point 1) in

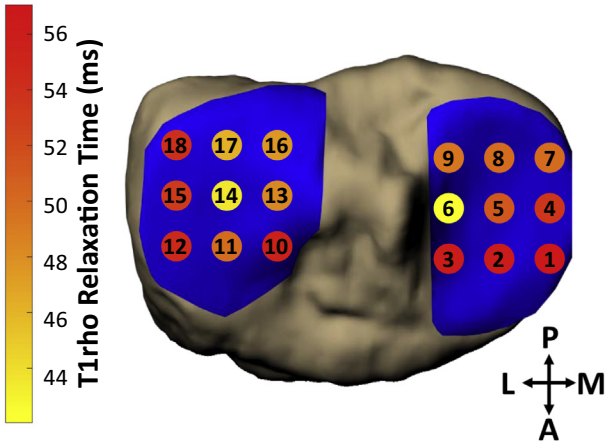

Fig. 3. Average localized baseline (AM) T1rho relaxation time within each sampling region by position ($p < 0.001$). Red represents high T1rho relaxation times, which are indicative of low proteoglycan concentrations. (A = anterior, P = posterior, M = medial, L = lateral). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the medial compartment and from 43 ms (grid point 14) to 55 ms (grid point 10) in the lateral compartment. Subjects took an average of 6684 ± 1953 steps between visits; however, we did not detect a significant correlation between the overall percent change in T1rho relaxation times and step count ($R = 0.56$, $p = 0.26$). Additionally, we did not detect significant correlations between step count and percent changes in T1rho relaxation times in either the medial ($R = 0.61$, $p = 0.20$) or the lateral ($R = 0.39$, $p = 0.44$) compartment.

4. Discussion

Previous studies have identified proteoglycan loss and increased hydration in the ECM as two early changes that occur during OA development (Gray et al., 2004; Guilak, 2011; Souza et al., 2014). Recent advances in quantitative MR imaging have provided the means to study the compositional and structural properties of cartilage *in vivo* (Borthakur et al., 2003; Regatte et al., 2002; Souza et al., 2014), which may help to noninvasively detect early signs of OA development prior to typical radiographic changes associated with late stage osteoarthritis (Le et al., 2016; Tsushima et al., 2012). More specifically, T1rho imaging has been used to quantify the interactions between water molecules and the proteoglycan matrix of cartilage (Borthakur et al., 2003; Regatte et al., 2002; Souza et al., 2014), as T1rho relaxation times have been shown to have a strong negative correlation with the overall proteoglycan concentration in the tissue (Duvvuri et al., 2002; Hatcher et al., 2017). However, establishing changes incurred following normal activities of daily living in a healthy population would provide important information for understanding pathologic aberrations in T1rho relaxation times.

This study demonstrated that T1rho relaxation times significantly decrease over the course of the day, likely reflecting a relative increase in proteoglycan concentration (Regatte et al., 2002; Souza et al., 2014) due to water exudation caused by compressive loads sustained by the articular cartilage during activities of daily living (Coleman et al., 2013; Widmyer et al., 2013). Li et al. (2014) previously investigated diurnal changes in tibial cartilage T1rho relaxation times; however, they did not detect variations between their AM and PM measurements. Although their study did not record activity levels, they reported that their participants were mostly sedentary between testing sessions (Li et al., 2014). Our subjects took an average of 6684 steps between visits, which is above the average daily step count of 5117 steps taken by U.S. adults (Bassett et al., 2010). Due to a lack of quantitative data, it is difficult to compare studies; however, the differences between the current results and those seen previously may be related to the subjects' activity levels.

Previous studies quantifying variations in tibial cartilage T1rho relaxation times related to joint loading demonstrated between a 5% and 8% decrease in T1rho values compared to the baseline pre-load values in a healthy population (Hatcher et al., 2017; Souza et al., 2014; Souza et al., 2010). This percent change in T1rho relaxation times observed in response to loading is comparable to the 7% decrease in T1rho relaxation times demonstrated over the course of the day in the current study. Additionally, in studies investigating the effect of ACL deficiency on T1rho values, T1rho relaxation times in ACL intact knees were between 2% lower and 6% higher than their injured counterparts (Bolbos et al., 2008; Osaki et al., 2015; Su et al., 2013). Furthermore, other studies have shown that T1rho relaxation times in healthy cartilage is between 5% and 14% lower than OA cartilage (Li et al., 2007; Souza et al., 2014; Souza et al., 2010; Wang et al., 2012). Together, these findings emphasize the importance of controlling loading history in human subjects in clinical studies evaluating cartilage health, as the 7% change in T1rho relaxation times resulting from daily activity is comparable to those observed in relation to different loading, injury, and disease states. Therefore, it is important to note that if joint loading history is not appropriately controlled, differences in T1rho relaxation times caused by these variables may alter the interpretation of the findings.

This study detected statistically significant changes in tibial cartilage T1rho relaxation times in a young, healthy, active population following activities of daily living. These observed changes in cartilage composition may have been underestimated due to an inadequate recovery of the cartilage to its baseline state prior to the pre-exercise MR scan, or partial recovery prior to the post-exercise MR scan. Although subjects were asked to refrain from strenuous activity 12 h prior to the morning of testing and rested supine for 45 min before scanning to allow for cartilage to reach its baseline unloaded state prior to the AM scan, it is possible that the cartilage was not fully recovered. This could indicate that the results presented in the current study might underestimate the changes in tibial cartilage T1rho relaxation times that occur in response to activities of daily living, further emphasizing the need to control loading history when making T1rho measurements. Future investigations may seek to quantify the recovery time course of T1rho relaxation times during joint unloading.

Additionally, despite our significant findings, this study was not designed to investigate the effect of gender, age, BMI, or a variety of other factors that could influence these changes in T1rho relaxation times. Future work may focus on identifying how these factors alter the magnitude of the variations. Furthermore, cartilage responds differently when subjected to loads of varied magnitudes and frequencies (Coleman et al., 2013; Lad et al., 2016; Pfeiffer et al., 2017; Pietrosimone et al., 2015; Sutter et al., 2014; Widmyer et al., 2013), and it recovers over time as fluid re-enters the ECM (Eckstein et al., 1999). Thus, the magnitude, timing, and frequency of loading during the day could play an important role in influencing T1rho relaxation times, as these values are dependent on the proteoglycan concentration of the tissue at the time of the MR scans. While we observed changes in T1rho relaxation times as a result of daily activities, the precise cartilage loading incurred over the course of the day was unknown in this study. This may explain why we did not detect a correlation between step count and the percent change in T1rho relaxation times. In fact, previous investigations that have used step count to assess activity levels throughout the day have also been unable to strongly associate step count with MRI measurements of soft tissue strains (Coleman et al., 2013; Martin et al., 2018; Widmyer et al., 2013). These outcomes suggest that step count may not be able to fully characterize all types of joint loading performed throughout the day. Future investigations may also quantify changes in T1rho relaxation times following more controlled loading activities, such as treadmill walking (Hatcher et al., 2017), running (Subburaj et al., 2012), or hopping. Future studies may also aim to quantify how various injury or disease states impact side-to-side differences in T1rho relaxation times both at baseline and following loading.

Our site-specific technique was able to quantify localized changes in baseline T1rho relaxation times. This site-specific method may prove to be important in the future for identifying early changes in tissue health *in vivo*, as osteoarthritis potentially begins in localized regions before ultimately resulting in widespread cartilage loss (Collins and McElligott, 1960; DeFrate, 2017; Hatcher et al., 2017; Okafor et al., 2014). Furthermore, localized variations in cartilage composition (Stenhamre et al., 2008; Van Rossom et al., 2017; Van Rossom et al., 2018) and thickness (Koo et al., 2011; Liu et al., 2017; Okafor et al., 2014; Sutter et al., 2014; Van Rossom et al., 2017; Van Rossom et al., 2018; Widmyer et al., 2013) have been previously observed, even in healthy cartilage. These localized variations may be obscured when

averaging across an entire articular surface. Thus, the site-specific method employed in this study may be valuable when using T1rho relaxation times as quantitative diagnostic measures in the future. Additionally, this technique can be paired with our previously described site-specific assessment of cartilage thickness (Coleman et al., 2013; Lad et al., 2016; Sutter et al., 2014; Widmyer et al., 2013) to determine if there is a link between localized biochemical and biomechanical changes in cartilage.

Although a general trend of decreasing T1rho relaxation times over the course of a day was anticipated based on previously quantified diurnal tibial cartilage thickness changes (Coleman et al., 2013; Widmyer et al., 2013), the extent to which routine loading would alter proteoglycan concentration was less easily predicted. Accordingly, these outcomes may hold clinical significance regarding the degree of daily variation within proteoglycan concentration and how such changes affect cartilaginous tissue osmolarity, which is known to influence chondrocyte metabolism (Browning et al., 2004; Chao et al., 2006). Because routine loading is required for cartilage preservation and chondrocyte health (Bader et al., 2011; Fransen et al., 2002; Jordan et al., 2003; Leong et al., 2011), transient osmotic shifts in the pericellular local environment due to daily cumulative changes might be an important factor for chondrocyte sustainability (Clark et al., 2010; Wilusz et al., 2014). Therefore, understanding normal variations in tibial cartilage T1rho relaxation times could also help to determine mechanisms by which the cartilage maintains homeostasis.

In conclusion, this study demonstrated statistically significant changes in T1rho relaxation times as a result of activities of daily living. Furthermore, the results of the current study indicate that in order to utilize T1rho relaxation times as a quantitative imaging biomarker for clinical applications, it is necessary to carefully consider the loading history of the cartilage. Otherwise, variations in T1rho relaxation times caused by joint loading may influence the results of the analysis. The results of this investigation provide insight into the normal fluctuations of proteoglycan content in tibial cartilage *in vivo*. Identifying how routine loading contributes to changes in proteoglycan concentration in tibial cartilage may help to better understand normal cartilage homeostasis and provide insight on different disease states in the tissue.

Conflict of interest statement

The authors have no conflicts of interest to report.

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