Individual and cumulative measures of knee joint load associate with T2 relaxation times of knee cartilage in young, uninjured individuals: A pilot study

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ABSTRACT

Background: Articular cartilage structure and chondrocyte health are sensitive and reliant on dynamic joint loading during activities. The purpose of this pilot study was to determine the association between measures of individual and cumulative knee joint loading with T2 relaxation times in the knee cartilage of young individuals without knee injury.
Methods: Twelve participants (17–30 years old) without history of knee injury or surgery completed MRI, physical activity (PA), and biomechanical gait testing. T2 relaxation times were calculated in the cartilage within the patella and lateral and medial compartments. Accelerometry was used to measure mean daily step counts, minutes of PA, and % sedentary time over 7 days. Vertical ground reaction force, external knee joint moments and peak knee flexion angle were measured during stance phase of gait using three-dimensional motion capture. Cumulative knee joint loading was calculated as daily step count by external knee joint moment impulse. The relationship between measures of knee joint loading and T2 relaxation times was assessed using Pearson correlations.
Results: Higher T2 relaxation times in the femoral and tibial cartilage were consistently correlated to greater body mass, daily step counts, moderate and vigorous PA, and peak knee joint moments ($r = 0.10–0.84$). Greater cumulative knee flexion and adduction loading was associated with higher T2 relaxation times in the femoral and tibial cartilage ($r = 0.16–0.65$).
Conclusion: Preliminary findings suggest that individual loading factors and cumulative knee joint loading are associated with higher T2 relaxation times in the articular cartilage of young, healthy knees.

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1. Introduction

Osteoarthritis (OA) is a degenerative joint disease that is the leading sources of chronic pain and disability in the United States and many other countries [1,2]. The knee joint accounts for over 80% of the total burden due to OA [2]. Further, post-traumatic knee OA that results from joint injury or trauma accounts for 13% of the OA prevalence in the United States [3]. OA is a disease that is characterized by deterioration of articular cartilage. Articular cartilage is composed mostly of water, collagen, proteoglycans and chondrocytes, and provides a smooth, low-friction surface between joints to allow for transmission of load to underlying subchondral bone [4]. Due to the limited healing capacity of articular cartilage [4], early detection of damage is necessary for implementing strategies to prevent its progressive deterioration.

Radiography and magnetic resonance imaging (MRI) are commonly used to detect features indicative of OA. Radiographic changes of osteophyte formation, subchondral cysts, subchondral sclerosis, and joint space narrowing are most commonly used to diagnose structural OA, but these are late stage manifestations of the disease [5]. Thus, changes detected on radiographs are likely an indication of irreversible damage and loss of greater than 10% of total cartilage volume [6]. T2 relaxation time is a quantitative MRI measure that can assess articular cartilage structure and matrix organization [5,7,8]. It is dependent on water and collagen architecture as well as collagen organization [9]. Increases in T2 relaxation times have been used to measure cartilage degeneration after knee injuries including anterior cruciate ligament (ACL) injury, meniscus repair, meniscectomy, and cartilage repair [10–13]. T1rho and dGMERIC are other quantitative measures of cartilage quality that evaluate proteoglycan content [7]. dGEMRIC studies require intravenous injection of a contrast agent such as gadolinium and time for its diffusion into articular cartilage, making it less frequently studied compared to T2 and T1rho relaxation studies. Understanding factors that influence quantitative MRI markers of cartilage quality such as T2 relaxation time will inform interventions to prevent OA both within and outside of the context of joint injury.

In a healthy knee, dynamic mechanical loading during activities such as walking is protective to articular cartilage by facilitating joint metabolism and synthesis of proteoglycans and collagen within its extracellular matrix [14]. In uninjured individuals, greater medial knee joint loading, as estimated by a higher external knee adduction moment during walking, is associated with thicker articular cartilage in the medial tibiofemoral compartment [15–17]. Knee flexion angle at initial contact during the stance phase of gait is correlated to the locations of thickest cartilage in the medial tibiofemoral compartment [18]. Levels of physical activity (PA) have also been shown to affect cartilage structure. Middle-aged adults without knee OA who report moderate PA levels demonstrate smaller increases in T2 relaxation times than those participating in the highest and lowest levels of PA [19]. A lack of mechanical stimulation results in articular cartilage that is thinner and softer and may be more susceptible to damage [20,21]. This combined evidence suggests articular cartilage structure is influenced by cumulative joint loading, which integrates both magnitude and frequency of knee joint loading. Cumulative joint loading has been used by Maly and colleagues using the product of knee adduction moment impulse and steps per day to differentiate individuals with and without knee OA [22]. Voinier et al. used combinations of daily step counts with body mass index (BMI) to examine correlation of cumulative load and cartilage damage on MRI in middle-aged and older adults [23]. However, the relationship between measures of cumulative knee joint loading with articular cartilage structure in young, uninjured individuals is unknown. An understanding of the relationship between joint loading and uninjured articular cartilage quality will provide insight into factors potentially responsible for cartilage breakdown and OA development after knee joint injury. Because knee joint loading can be modified, these factors may serve as interventional targets to delay or prevent OA in young individuals after knee injury.

The purpose of this study was to determine the association between individual (i.e., knee joint moments, PA levels, body mass) and cumulative measures of knee joint loading with T2 relaxation times in the articular cartilage of the knee in young, uninjured individuals. We hypothesized that knee joint moments during walking, number of steps per day, total minutes of moderate and vigorous intensity PA, and body mass would be associated with T2 relaxation times throughout the knee's articular cartilage.

2. Methods

2.1. Participants

Young, healthy individuals with no previous history of lower extremity injury or surgery between the ages of 17–30 were eligible for this study. Older individuals were excluded due to higher baseline risk of early knee OA. Exclusion criteria included knee pain in the past 3 months, history of inflammatory disease, immune compromise, body mass index over 30 kg/m^2, chronic use of NSAIDS, history of cortisone injection during the prior 3 months, current pregnancy, or having contraindications to MRI. The University of Nebraska - Medical Center Institutional Review Board approved this study and all subjects provided written informed consent.

2.2. MRI acquisition & T2 relaxation time

MRI acquisition was performed at the University of Nebraska - Lincoln by a single technician. Due to acute effects of loading on T2 relaxation times, participants were in a non-weightbearing position (supine) for 30 minutes prior to the knee scan to unload the articular cartilage [24]. MRI data were acquired on a 3-Tesla Siemens Skyra MRI scanner using a 15 channel transmit /receive knee coil (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). A randomization table was used to determine if the left or right knee was scanned. Participants were positioned in a supine position with the knee in a minimally flexed position and neutral rotation. For T2 mapping, a spin echo (SE) sequence with multiple echoes was acquired with the parameters: TR = 2700 msec; 10 echoes with echo times $TE_i = i \times 11.1$ msec (i = 1, . . ., 10); FOV = 120 mm × 120 mm; acquisition matrix = 269 × 384; number of slices = 22; slice thickness = 3.0 mm; slice gap = 0.48 mm; pixel size = 0. 3125 mm × 0.3125 mm; echo train length = 10; number of averages = 1; scan duration = 12:11. In addition to T2 mapping sequence, MRI protocol also included a sagittal T1 weighted SE and fat suppressed proton density weighted SE sequence in axial, coronal, and sagittal orientations. The T2 mapping sequence was completed last for each participant.

T2 maps were generated by fitting the multi-echo MRI data at each pixel to the signal equation $S_i = S_0 \exp(-TE_i/T_2)$, using Levenberg-Marquardt nonlinear least squares algorithm. Here S_i is the signal at echo time $TE_{i,}$ and S_0 is the signal at TE = 0. Data corresponding to the first echo were not used in the fitting procedure to minimize the errors due to stimulated echoes [25]. The computer programs were written in Interactive Data Language (IDL; Harris Geospatial Solutions Inc., Broomfield, CO, USA).

Cartilage masks of the femoral, tibial and patellar articular cartilage were manually segmented using open source ITK-SNAP software [26] on images corresponding to TE = 44.4 ms from multi-echo data used for generating T2 maps. Thus, the segmented masks exactly matched the T2 maps for T2 relaxation time extraction from each region of interest. The 22 sagittal images were subdivided into medial and lateral compartments for both the femur (MFC and LFC, respectively) and the tibia (MTC and LTC, respectively) according to the center of the intercondylar notch. The femoral and tibial cartilage masks in each tibiofemoral compartment (LFC, MFC, LTC, MTC) were divided into anterior, weightbearing, and posterior regions as defined by the location of the meniscus horns in the sagittal plane (Figure 1). Axial and coronal MRIs were used to assist in identification of anterior and posterior meniscus horns. Anterior and posterior regions of the tibial cartilage contained very few pixels and thus were not included in this analysis. The patellar cartilage was not subdivided into smaller regions of interest. A board-certified, fellowship-trained musculoskeletal radiologist who was blinded to all other participant data confirmed accurate location of segmentation masks on each slice as well as region of interest boundaries. Our lab has demonstrated reliable segmentation of both the femoral and tibial articular cartilage (intrarater intraclass correlation coefficients [ICC] [n = 12]: femoral: 0.759; tibial: 0.775; interrater ICC [n = 12]: femoral: 0.949; tibial: 0.930). The labeled cartilage masks were then applied to the corresponding T2 maps to extract mean T2 relaxation times within all 9 regions of interest using in-house computer software. Only pixels with T2 relaxation times between 10 and 90 msec were included in this analysis to remove any outliers due to fitting errors [27].

2.3. Gait biomechanics

Biomechanical gait analysis was performed at the Nebraska Athletic Performance Laboratory (NAPL) at the University of Nebraska – Lincoln. Passive, 14-millimeter retro-reflective markers were attached to bony landmarks of the bilateral lower extremities and trunk, including the first and fifth metatarsal heads (over their own shoes), superior and inferior posterior heel (over shoes), medial and lateral malleoli, medial and lateral femoral epicondyles, greater trochanters, anterior superior iliac spines (ASIS), iliac crests and acromion. Rigid shells each containing four markers were secured using elastic wraps and athletic tape to the lateral shanks, lateral thighs, and lower thoracic spine. A rigid shell containing three markers was secured to the posterior pelvis with the superior edge placed at the height of the posterior superior iliac spines (PSIS). This lower extremity marker set has previously been shown to be reliable in measuring knee flexion angles during standing activities [28].

Three-dimensional kinematic data were collected using a 12-camera motion capture system (Oqus Series 400, Qualisys AB, Sweden) sampled at 120 Hz. Kinetic data were collected using 2 embedded force plates (Bertec Corporation, Columbus, OH) sampled at 1080 Hz. A static trial was collected for one second with the participant standing in anatomical position. For gait trials, participants were asked to walk at a comfortable, self-selected walking speed across the embedded force plates. Gait speed was established during the first three trials and was maintained within 5% for all remaining walk trials using timing gates across a 5.4-meter walkway (Brower TCi System, Draper, UT). Participants completed eight trials for each limb with valid kinematic and kinetic data.

After completing marker labeling in Qualisys Track Manager, kinematic and kinetic data were imported into Visual3D software (C-Motion, Inc., Bethesda, MD). Custom, post-processing scripts were used to construct subject-specific models and calculate joint angles and external joint moments [29]. 3D marker trajectory and ground reaction force data were processed using a low-pass, fourth-order, bidirectional Butterworth filter with a cut-off frequency of 6 Hz. A subject-specific model was created from the static trial to determine segment lengths and joint centers. A threshold of 10 N was used to define the first and last frames of stance phase in each limb during walking trials. An inverse dynamics approach was used to calculate external knee joint moments in the sagittal and frontal planes during stance phase [30]. Vertical ground reaction force (vGRF) was normalized to bodyweight (BW). External knee moments were normalized to mass (kilograms) and height (meters). Bodyweight and mass were measured using the vGRF component during the 1-second static trial. Height was measured using a stadiometer. The vGRF and external knee flexion and adduction moments were integrated over stance phase using the trapezoidal rule to calculate joint moment impulses. The external knee joint moment impulse is directly proportional to the average knee joint moment and duration of stance phase. Biomechanical gait variables of interest were averaged

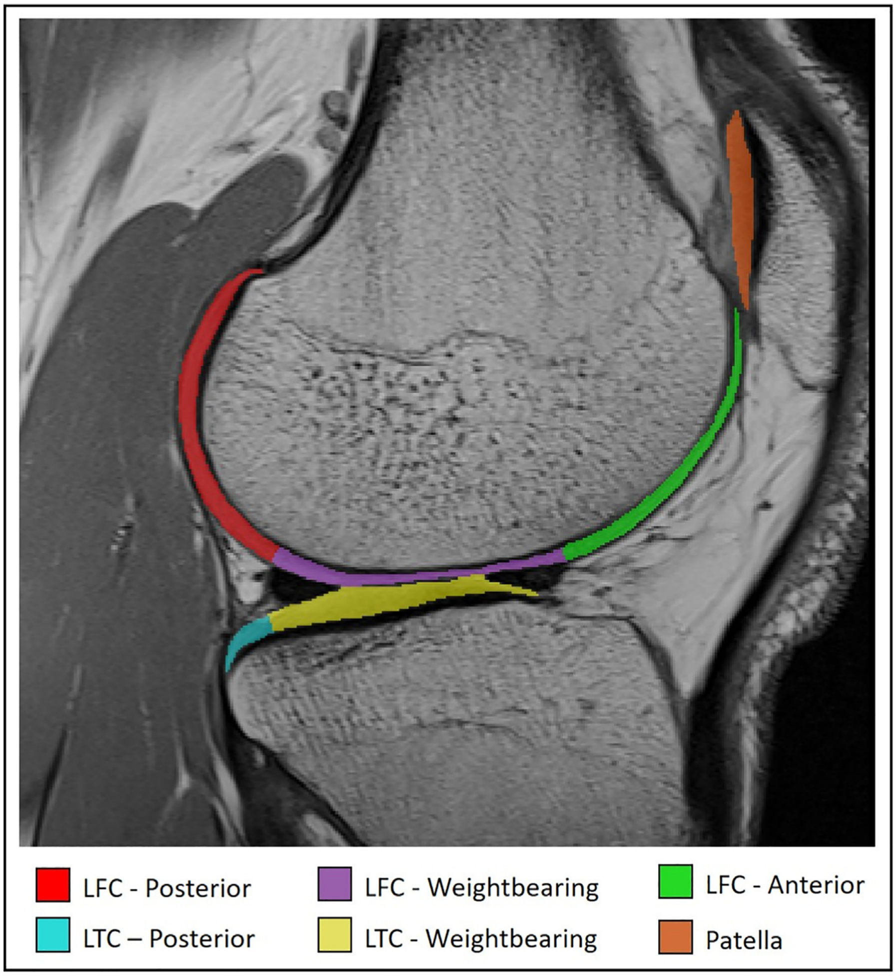

Figure 1. The femoral and tibial cartilage segmentation masks in each compartment (lateral compartment pictured above) were divided into anterior, weightbearing, and posterior regions as defined by the location of the meniscus horns in the sagittal plane. The anterior and posterior (not pictured) tibial cartilage was not used in analysis. The patellar cartilage comprised a single region.

over five gait trials across a 15-meter walkway and included mass as measured during the one-second static trial, peak vGRF during the first 50% of stance phase, impulse of vGRF during all of stance phase, peak knee flexion angle during weight acceptance of stance phase, peak external knee flexion moment, external knee flexion moment impulse during all of stance phase, peak external knee adduction moment during the first 50% of stance phase and external knee adduction moment during all of stance phase.

2.4. Physical activity (PA)

PA data were collected using a 3-axis Actigraph accelerometer (wGT3X-BT; Actigraph Corporation, Pensacola, FL) that has previously been shown to reliably measure step counts across gait speeds [31]. Participants were instructed to wear the accelerometer on a provided elastic belt at the top of the right iliac crest in line with the axilla consecutively during all waking hours (except when in water) for 1 week following MRI and biomechanical gait analysis. Uniform instructions were provided in a handout detailing appropriate wear and positioning of the accelerometer. We used previously reported criteria established by Troiano and colleagues and the National Cancer Institute (NCI) to define valid accelerometer wear time [32]. Wear criteria consisted of at least 10 hours per day on at least four of the seven days, as this is the minimum time required to reliably estimate PA behaviors [32–34]. Non-wear days were excluded from analysis. Activity counts, which represent the weighted sum of the number of accelerations, were used as outputs over 1-minute intervals to identify accelerometer wear and PA intensity. Daily non-wear periods were defined as intervals of at least 90 minutes of zero activity counts that contained no more than two minutes of activity counts less than 100 [34]. Activity count outputs were used to define intensity levels of PA based on metabolic equivalents (METs) for each 1-minute of wear. Activity count cut points for each minute were 0–99 for sedentary activity, 100–2019 for light PA, 2020–5998 for moderate PA, and greater than or equal to 5999 for vigorous PA [32]. Variables of interest for this study were average steps per day, percentage of day during accelerometer wear in sedentary activity and average daily minutes of light, moderate, and vigorous PA. All PA activity was analyzed within Actilife 6 software (Actigraph Corporation, Pensacola, FL).

2.5. Cumulative knee joint loading

Daily cumulative knee joint loading was defined by the average daily step count (measured by accelerometry) multiplied by the average normalized (mass × height) external knee joint moment impulse (measured during one stance phase of gait). Thus, cumulative knee joint loading is an individual specific estimate of total knee joint loading based on individual characteristics of walking biomechanics and daily PA behavior. Cumulative knee flexion load was calculated as the product of mean daily step count and mean external knee flexion moment impulse. Cumulative knee adduction load was calculated as the product of mean daily step count and mean external knee adduction moment impulse. Cumulative knee flexion and adduction loads were examined because both knee flexion and adduction moments have been found to predict joint contact forces in the knee [35].

2.6. Statistical analysis

Continuous data were described using means, standard deviations and 95% confidence intervals. Nominal data were described using counts and proportions. Pearson correlation tests were used to identify associations between mass, height, PA levels, gait biomechanics, and cumulative knee joint loading with T2 relaxation times in each articular cartilage region of interest. Pearson correlation coefficient (r) of 0.1 to less than 0.3 and -0.1 to greater than -0.3 was categorized as weak association, 0.3 to less than 0.5 and -0.3 to greater than -0.5 as moderate association, and 0.5–1.0 and -0.5 to -1.0 as strong association (Cohen 1988, 1992). A p-value less than 0.05 was considered statistically significant.

3. Results

Of the 12 participants included in this study, 5 (41.7%) were female and 7 (58.3%) were male. Nine participants (75%) were white, one (8.3%) was Asian, one (8.3%) was Hispanic, Latino or Spanish, and one (8.3%) did not report race or ethnicity. Mean demographics, body size, sports activity levels, PA levels, gait biomechanics, and measures of cumulative knee joint loading are presented in Table 1. Mean T2 relaxation times in each articular cartilage region of interest are presented in Table 2.

3.1. Gait biomechanics

Greater knee joint moments and angles were consistently associated with greater articular cartilage T2 relaxation times. Associations with gait biomechanics were stronger in the weightbearing and posterior regions of femoral and tibial cartilage compared to the anterior femoral and patellar cartilage (Figure 2). Peak knee flexion angle demonstrated the strongest pos-

Table 1
Mean age, mass, height, physical activity levels, gait biomechanics, and measures of cumulative knee joint loading for all 12 participants. Abbreviations: SD, standard deviation; CI, confidence interval; yrs, years; kg, kilogram; m, meter; %, percentage; PA, physical activity; °, degree; BW, bodyweight; s, second; N, newton; KFA, knee flexion angle; KFM, knee flexion moment; KAM, knee adduction moment. vGRF, vertical ground reaction force.

	Mean (SD)	95% CI
Age (yrs)	22.9 (3.3)	20.8–24.9
Mass (kg)	69.8 (14.0)	60.9–78.7
Height (m)	1.76 (0.07)	1.72–1.80
Tegner activity scale [36]	6.9 (1.2)	6.1–7.7
Steps per day	8187.7 (3595.5)	5903.2–10472.2
Sedentary time (daily %)	63.8 (11.4)	56.5–71.0
Light PA (daily minutes)	1512.3 (537.9)	1170.5–1854.1
Moderate PA (daily minutes)	178.4 (136.8)	91.5–265.4
Vigorous PA (daily minutes)	29.7 (39.1)	4.9–54.5
Peak KFA (°)	20.6 (6.0)	16.7–24.4
Peak vGRF (BW)	1.15 (0.10)	1.09–1.22
vGRF Impulse (BW·s)	0.53 (0.03)	0.52–0.55
Peak KFM (N·m/kg·m)	0.34 (0.16)	0.24–0.45
KFM Impulse (N·m·s/kg·m)	0.05 (0.03)	0.03–0.06
Cumulative KFM Load (daily N·m·s/kg·m)	393.7 (294.0)	206.9–580.5
Peak KAM (N·m/kg·m)	0.24 (0.09)	0.18–0.30
KAM Impulse (N·m·s/kg·m)	0.08 (0.02)	0.07–0.10
Cumulative KAM Load (daily N·m·s/kg·m)	650.2 (317.9)	448.2–858.1

Table 2
Mean T2 relaxation times (milliseconds) in each articular cartilage region of interest for all 12 participants. Abbreviations: SD, standard deviation; CI, confidence interval; LFC, lateral femoral condyle; MFC, medial femoral condyle; LTC, lateral tibial condyle; MTC, medial tibial condyle.

	Mean (SD)	95% CI
LFC – Anterior	54.3 (2.7)	52.6–56.0
LFC – Weightbearing	50.2 (2.7)	48.5–51.9
LFC – Posterior	49.8 (3.1)	47.9–51.8
LTC – Weightbearing	45.4 (4.0)	42.9–48.0
MFC – Anterior	55.0 (5.1)	51.8–58.3
MFC – Weightbearing	50.1 (3.8)	47.6–52.5
MFC – Posterior	46.8 (5.3)	43.4–50.1
MTC – Weightbearing	46.0 (3.8)	43.5–48.4
Patella	44.4 (2.2)	43.0–45.8

itive associations with T2 relaxation times in the medial femoral and tibial cartilage. Greater peak knee adduction moment and impulse, which are surrogate measures for higher medial compartment and lower lateral compartment loading, were moderately to strongly associated with higher T2 relaxation times in the medial tibiofemoral compartment and lower T2 relaxation times in the lateral tibiofemoral compartment.

3.2. Physical activity

All participants had a valid number of accelerometer days and wear time to be included in the analysis. Moderate and strong positive associations were consistently present between PA levels and T2 relaxation times in the femoral and tibial cartilage but not in the patellar cartilage (Figure 2). A higher daily step count and minutes of both moderate and vigorous PA was associated with higher T2 relaxation times in the weightbearing and posterior regions of bilateral femoral and tibial compartments. These relationships were not consistently present in the anterior femoral cartilage. A greater percentage of the day spent in sedentary activity was associated with lower T2 relaxation times in the medial and lateral tibiofemoral compartments.

3.3. Cumulative knee joint loading

Peak knee flexion moment and impulse did not demonstrate strong correlations with T2 relaxation times in any articular cartilage regions of interest (Figure 2). However, greater cumulative knee flexion load (steps per day × knee flexion moment impulse) was moderately to strongly associated with higher T2 relaxation times across weightbearing and posterior regions in the medial and lateral tibiofemoral compartment. Similarly, greater cumulative knee adduction load (steps per day × knee adduction moment impulse) was moderately to strongly associated with higher T2 relaxation times in all regions within the medial tibiofemoral compartment.

3.4. Body size and age

Individual characteristics also influenced T2 relaxation times in the articular cartilage of the knee (Figure 2). Greater body mass and height were associated with lower T2 relaxation times only in the anterior lateral femoral cartilage and with higher T2 relaxation times in most other regions of the tibiofemoral and patellar compartments. Greater age was weakly associated with lower T2 relaxation times in all weightbearing regions and posterior femoral cartilage while a moderate negative correlation was present with patellar cartilage.

4. Discussion

This pilot study aimed to determine associations between individual joint loading variables (knee joint moments, PA levels, body mass) and cumulative knee joint loading variables with T2 relaxation times in the articular cartilage of the knee in young, uninjured individuals. Our results support our hypotheses; greater T2 relaxation times were consistently correlated to measures that influence overall knee joint loads, including greater knee joint moments during gait, daily step counts, moderate and vigorous PA, and body mass. Cumulative knee flexion and adduction loading [measures that combine average steps per day with the magnitude of knee joint moments during each step of gait] was associated with greater T2 relaxation times in the femoral and tibial cartilage. The correlations between these variables were consistently positive relationships, indicating greater magnitudes and frequencies of knee joint loading were associated with higher T2 relaxation times. In addition to our hypotheses, greater height was associated with higher T2 relaxation times while a higher percentage of daily sedentary time correlated with lower T2 relaxation times.

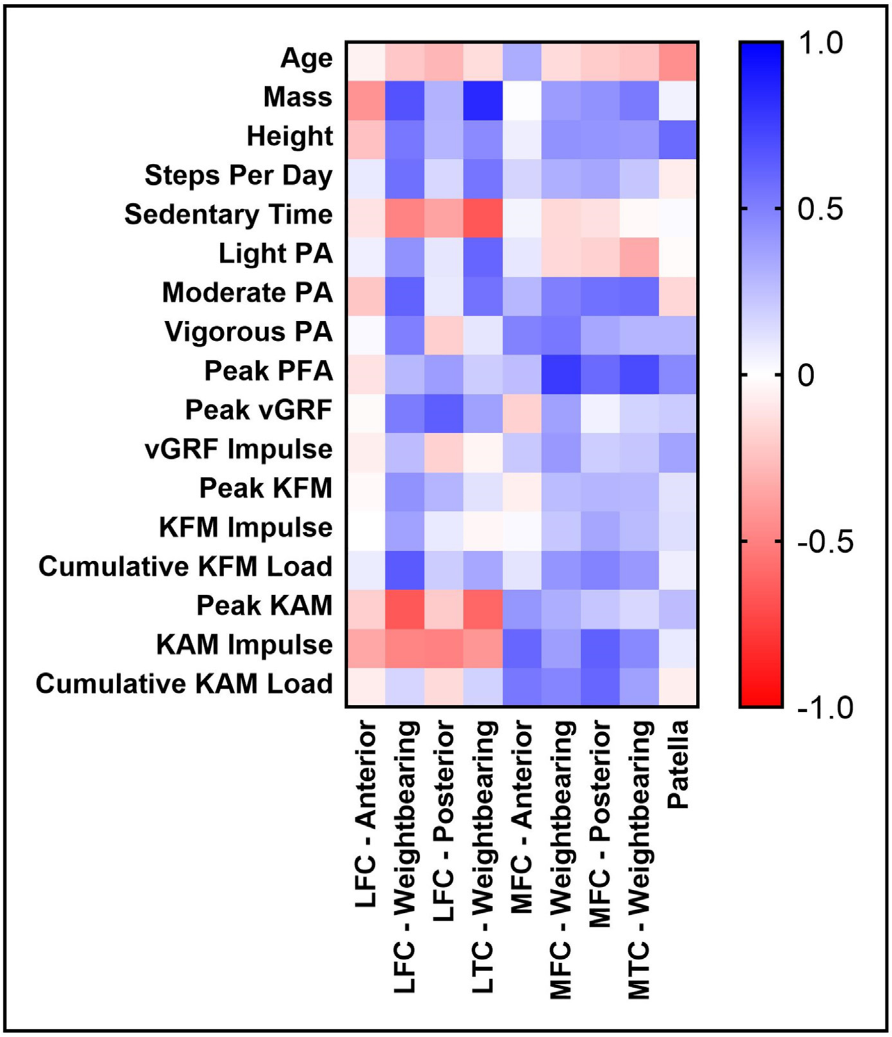

Figure 2. Generally, greater body size, higher physical activity levels, greater knee joint moments and angles, and greater cumulative knee joint loading (rows) were associated with higher T2 relaxation times throughout the femoral, tibial and patellar cartilage (columns). Pearson's correlation coefficients (r) are represented by blue and red shades, ranging from +1.0 to −1.0. Blue represents positive correlations. Red represents negative correlations. Darker shades of red and blue signify stronger correlations. Abbreviations: PA, physical activity; PFA, knee flexion angle; vGRF, vertical ground reaction force; KFM, knee flexion moment; KAM, knee adduction moment; LFC, lateral femoral condyle; LTC, lateral tibial condyle; MFC, medial femoral condyle; MTC, medial tibial condyle.

Articular cartilage structure and chondrocyte health are sensitive and reliant on dynamic joint loading [37]. Articular cartilage adapts to the repetitive loading patterns placed upon it such as during walking [38]. Frequency of walking, intensity of walking, and biomechanical movement patterns during walking all contribute to the cumulative load experienced by the knee. It is well established that periods of acute compressive loading in tibiofemoral joints without OA result in decreased T2 relaxation times that are most notable in the weightbearing regions [24,39,40]. The reduction in T2 relaxation times is likely the result of fluid moving out of the cartilage during periods of increased loading. However, less is known about the influence of cumulative knee joint loading patterns, particularly in young individuals. The results of this study suggest that higher sources of knee joint load, including greater body mass, PA, and knee joint moments are correlates of higher T2 relaxation times. Higher T2 relaxation times are thought to signal higher water content and poorer collagen matrix organization [41]. Thus, higher T2 relaxation times are frequently linked to signs of cartilage destruction and unhealthy tissue. However, the participants in this study had no risk factors for knee OA. Thus, higher T2 relaxation times in our study are likely not pathologically high. Further, systemic factors such as age, sex, race and genetics may establish an individual's baseline T2 relaxation profile [20]. It is possible that the higher T2 relaxation times in individuals with higher measures of knee joint loading are a normal, healthy response to the cumulative, daily loading withstood. Our findings that individual-specific profiles of body size, PA level, and knee joint loading patterns influence cartilage structure support the need for future studies to compare T2 relaxation times in a target knee (e.g. after joint injury) to the contralateral knee or as a percent change relative to baseline values to account for individual T2 differences.

4.1. Gait biomechanics

Knee joint angles and moments during gait were correlates of T2 relaxation in the weightbearing regions of the femoral and tibial cartilage. Peak knee flexion angle during stance phase strongly correlated with T2 relaxation in the weightbearing regions of the medial tibiofemoral compartment. Meanwhile, vGRF strongly correlated with T2 relaxation in the weightbearing area of the lateral femur. The external knee adduction moment was more strongly associated with T2 relaxation times than the external knee flexion moment. A higher peak knee adduction moment and impulse were correlated with higher T2 relaxation in the medial tibiofemoral compartment but lower T2 relaxation in the lateral tibiofemoral compartment. A higher external knee adduction moment is a surrogate measure for greater medial compartment joint loading relative to the lateral compartment. Therefore, these findings are consistent with our PA findings where higher loading (greater step counts, minutes of moderate and vigorous PA) was related to higher T2 relaxation times and lower loading (greater daily percentage of sedentary time) was related to lower T2 relaxation times.

The knee adduction moment has previously been shown to have a significant relationship with articular cartilage thickness in the medial compared to lateral tibiofemoral compartment [16,42]. Previous work detailing biomechanical movement patterns and T2 relaxation in the cartilage of the knee is limited. A small study by Souza et al. of 14 healthy participants with a similar age (22.7 ± 3.3 years) to the current study found that the peak knee adduction moment during a drop jump predicted higher overall T2 relaxation in the femoral, tibial and patellar cartilage [43]. However, this study also reported that a higher knee flexion moment during a single hop correlated to lower T2 relaxation times. Further work is needed to determine if joint loading patterns in young, uninjured individuals during less frequent movement patterns such as jumping are consistent with loading patterns exhibited during higher frequency daily activities such as walking. In contrast to our findings and those of Souza et al. [43], Van Rossom and colleagues reported that knee joint contact forces estimated through musculoskeletal modeling were negatively correlated to whole joint T2 relaxation times in 15 healthy individuals (age = 30.7 ± 5.8 years) without knee injury [44]. Further work is warranted to determine the role of movement patterns and knee joint loading in maintaining healthy articular cartilage in children and young adults.

Knee joint loading did not demonstrate significant relationships with T2 relaxation times in the anterior femoral and patellar cartilage. The trochlear and patellar surfaces within the patellofemoral joint are subjected to higher levels of shear stress in comparison to higher compressive stress experienced in the weightbearing regions of the femoral and tibial cartilage [20]. As a result, proteoglycan concentration and collagen orientation differ across articular cartilage within the knee. The current study focused on walking, which subjects the patellofemoral joint to relatively low levels of joint load and stress. Thus, our findings may not be generalizable to other movement patterns occurring at different angles and planes. For example, higher self-reported levels of knee-bending activity has been linked to higher T2 relaxation in the patella [45]. Teng and colleagues have reported associations between higher peak knee flexion moment, knee flexion moment impulse, and peak patellofemoral joint stress and greater T2 relaxation in the trochlear and patellar cartilage in individuals over 35 years old (mean = 52.5 years) both with and without patellofemoral joint OA [46,47]. The increased age of this population is a risk factor for cartilage breakdown and may explain the conflicting findings compared to the current study.

4.2. Physical activity

Daily step counts and minutes of moderate and vigorous PA were moderately to strongly correlated with T2 relaxation times in the tibiofemoral cartilage. This is the first study to investigate accelerometer-based measures of PA with T2 relaxation times in the articular cartilage of the knee in a young population (mean age = 23 ± 3.3 years). Kretzschmar and colleagues studied the association between PA levels and knee cartilage T2 relaxation time in 274 middle-aged adults (59.1 ± 5.5 years) at high risk for knee OA within the Osteoarthritis Initiative [48]. They found nonsignificant associations between moderate to vigorous PA and T2 relaxation in the medial and lateral tibiofemoral cartilage. However, it is known that regular PA positively relates to the maintenance of healthy cartilage. Weightbearing PA promotes a healthy body weight and lower extremity muscle strength, both of which decrease the risk of symptomatic knee OA [49,50]. Participation in vigorous sports activities results in thicker articular cartilage in children [51]. Even activities such as long distance recreational running that place repetitive cyclic loads through the knee do not result in a higher risk for OA development [52,53]. Two previous studies did not find that PA associated with T2 relaxation times in the cartilage of the knee. Stahl and colleagues reported that T2 relaxation was not different in the tibiofemoral or patellofemoral cartilage between healthy individuals who reported a Tegner score of 1–5 compared to those with a Tegner score of 6–10 [54]. Similarly, Hovis and colleagues reported that T2 times did not differ in the tibiofemoral or patellofemoral cartilage between healthy individuals who self-reported light or moderate-strenuous PA on the Physical Activity Scale for the Elderly (PASE) [45]. The differences in age across these studies (current = 23 ± 3.3 years; Stahl et al. = 33.7 ± 9.4 years; Hovis et al. 50.7 ± 2.7 years) as well as PA measurement methodology (current = accelerometry; Stahl et al. = Tegner score; Hovis et al. = PASE) may account for conflicting conclusions regarding the influence of PA on T2 relaxation times in the articular cartilage of the knee.

A greater daily percentage of sedentary activity was associated with lower T2 relaxation, most notably in the lateral tibiofemoral compartment. Regular dynamic loading of the joint enhances proteoglycan synthesis and chondrocyte function, whereas joint unloading leads to articular cartilage breakdown [20]. Previous studies have investigated periods of non-weightbearing activity on measures of cartilage structure in the knee. Souza et al. reported that T2 relaxation increases up to 12% in the weightbearing regions of the articular cartilage after 8 weeks of non-weightbearing resulting from distal lower extremity injury [55]. Vanwanseele et al. reported up to 13% thinning of the cartilage in the tibiofemoral and patellofemoral cartilage at 1 year following complete spinal cord injury [21]. Knee joint unloading was not as extreme in the current study compared to the non-weightbearing knee environments reported by Souza et al. and Vanwanseele et al. The average daily percentage of time spent in sedentary activity was 63.8 ± 11.4% (range = 41.2–81.3%). However, sedentary activity measured by actigraphy does not directly infer joint unloading (e.g. sedentary activity could include prolonged standing). Further, the negative correlation between sedentary activity and T2 relaxation times was observed in young healthy knees with no evidence of joint disease. Further study is warranted to determine if lower habitual PA in young, uninjured individuals negatively influences articular cartilage and increases risk for later OA development.

4.3. Cumulative knee joint loading

Cumulative knee joint loading has been shown to 1) differentiate individuals with and without knee OA using step counts and external knee adduction moment impulse and 2) identify at-risk individuals for greater progression of knee cartilage damage using steps counts and BMI [22,23]. These previous works highlight the absence of a standard definition for cumulative knee joint loading. We used a combination of daily step counts and average knee moment impulse during each step of gait to reflect dynamic knee loading patterns needed to maintain articular cartilage structure. Our findings demonstrated weak relationships between the external knee flexion moment during gait and T2 relaxation times throughout the knee cartilage. However, the relationship was strengthened when knee flexion moment was combined with daily step counts within the measure of cumulative knee flexion moment load. This early evidence supports further exploration into the role of cumulative knee joint loading on cartilage integrity and early OA development in young, active individuals.

4.4. Body size and age

Body mass and height were positively correlated to higher T2 relaxation times in the cartilage of the knee, but age was not. Not all participants in this study may have been fully physically mature. One individual in this study was less than 20 years old, while the remaining were 20–30 years old. Height typically plateaus by 20 years of age, but body mass typically increases throughout the second decade of life, indicating that participants in this study may not have reached musculoskeletal maturity [56,57]. In children, increases in height are associated with accrual of articular cartilage volume in the tibiofemoral joint [51]. T2 relaxation in the cartilage of the knee decreases with progressive maturation in children under 19 years of age [58]. Further, Wang and colleagues have demonstrated that increases in T2 relaxation times after a marathon are greater in runners with higher body weight and BMI but not correlated with age, height, or sex [59]. Taken together, these findings underscore the need to carefully consider the role of body size and maturation within compositional MRI analyses of cartilage in young, active populations.

There are several limitations to this study. Previous work has shown changes in quantitative MRI markers within the cartilage of the knee before and after a day of normal daily activities [60]. This study did not control for time of day of MRI testing which could have influenced T2 relaxation times. Further, PA was measured after completion of MRI assessment. PA behavior of participants before completion of the MRI could differ than the reported PA measurements in this study. Second, static knee joint alignment was not measured in this study but may be associated with T2 relaxation in knee cartilage [61]. Third, the sample size of this analysis was small, which limited multivariate regression modeling to identify the strongest loading predictors of T2 relaxation and prevents reported values to be used as normative values for uninjured, young individuals. It also limited our ability to compare T2 relaxation times by sex. Fourth, we only accounted for current PA levels and not lifelong PA levels that have chronically loaded the knee joint. Finally, the T2 relaxation times reported in this study represent a single time point and do not capture variations over time that can occur. Further, T2 relaxation times were not assessed between superficial and deep layers of cartilage, which have previously been shown to exhibit differences in young populations [62]. MRI methods that assess proteoglycan content such as T1rho and dGEMRIC may also yield results that differ from the current findings.

5. Conclusion

In this pilot study, individual loading factors of greater body size, PA and knee joint moments during gait as well as cumulative knee joint loading [integrating daily step counts and knee joint moments] were associated with higher T2 relaxation times in the femoral and tibial articular cartilage of young, healthy knees. Our findings provide insight into the potential role of modifiable joint loading factors that may influence early cartilage breakdown after knee injury. Future studies measuring T2 relaxation changes in knee cartilage of adolescents and young adults should use the contralateral limb or percent change relative to baseline values to account for individual T2 differences related to factors such as body size and PA patterns.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: No authors have financial disclosures. MAT is on the editorial board for *Current Reviews in Musculoskeletal Medicine*.

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