Dose and Recovery Response of Patellofemoral Cartilage Deformations to Running

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Investigation performed at Duke University, Durham, North Carolina, USA

Background: Running is a common recreational activity that provides many health benefits. However, it remains unclear how patellofemoral cartilage is affected by varied running distances and how long it takes the cartilage to recover to its baseline state after exercise.

Hypothesis: We hypothesized that patellofemoral cartilage thickness would decrease immediately after exercise and return to its baseline thickness by the following morning in asymptomatic male runners. We further hypothesized that we would observe a significant distance-related dose response, with larger compressive strains (defined here as the mean change in cartilage thickness measured immediately after exercise, divided by the pre-exercise cartilage thickness) observed immediately after 10-mile runs compared with 3-mile runs.

Study Design: Descriptive laboratory study.

Methods: Eight asymptomatic male participants underwent magnetic resonance imaging of their dominant knee before, immediately after, and 24 hours after running 3 and 10 miles at a self-selected pace (on separate visits).

Results: Mean patellar cartilage thicknesses measured before exercise and after the 24-hour recovery period were significantly greater than the thicknesses measured immediately after both the 3- and 10-mile runs ($P < .001$). This relationship was not observed in trochlear cartilage. Mean patellar cartilage compressive strains were significantly greater after 10-mile runs compared with 3-mile runs (8% vs 5%; $P = .01$).

Conclusion: Patellar cartilage thickness decreased immediately after running and returned to its baseline thickness within 24 hours of running up to 10 miles. Furthermore, patellar cartilage compressive strains were dose-dependent immediately after exercise.

Clinical Relevance: These findings provide critical baseline data for understanding patellofemoral cartilage biomechanics in asymptomatic male runners that may be used to optimize exercise protocols and investigations targeting those with running-induced patellofemoral pain.

Keywords: jogging; MRI; patella; trochlea; femoral groove; strain; exercise

About 56 million Americans recreationally run or jog each year.[15] Running provides many health benefits[10,12]; however, it is commonly linked to anterior knee pain, also known as patellofemoral pain or "runner's knee."[4] Runner's knee is a significant burden, affecting approximately 23% of the general population[18] and accounting for up to 17% of knee-related outpatient doctor visits.[4] Despite the prevalence of this condition, its cause is currently unknown.[4,18] Although some studies have hypothesized that patellofemoral cartilage loading contributes to anterior knee pain,[4,8,13] the response of patellofemoral cartilage to in vivo loading has yet to be fully characterized. Thus, it is critical to quantify how the tissue responds to running in individuals without patellofemoral pain, as this will ultimately serve as baseline data from which to frame future investigations targeting those with runner's knee.

It is possible to measure exercise-induced cartilage thickness changes by acquiring magnetic resonance imaging (MRI) scans before and immediately after loading (before fluid reentry into the cartilage is complete).[14,17,19,20] This information enables the calculation of cartilage strain, which we define here as the change in cartilage thickness after exercise divided by the baseline, pre-exercise cartilage thickness.[3,16,17,20,23] Although patellofemoral cartilage

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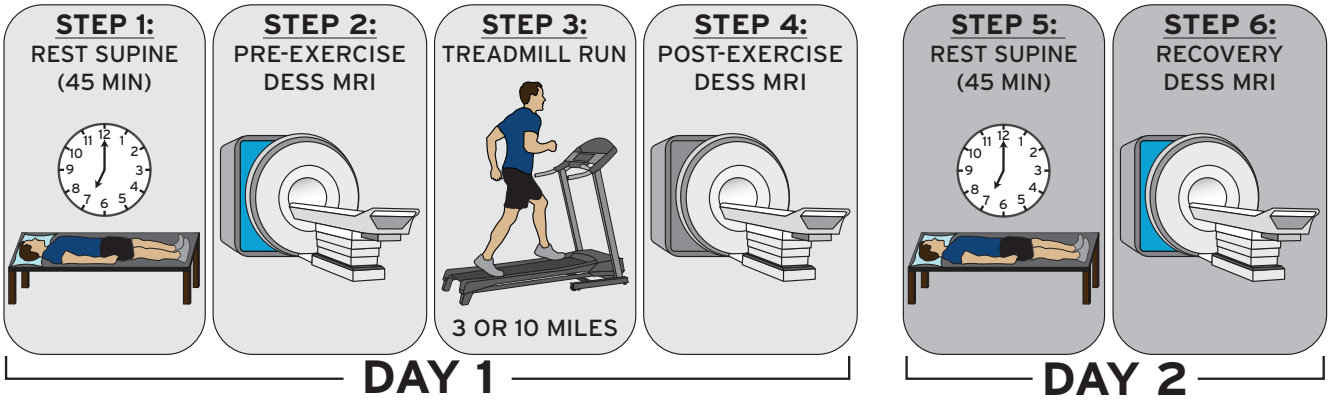

Figure 1. Each participant completed a multivisit magnetic resonance imaging (MRI) and exercise protocol. The first testing day consisted of a 45-minute rest period followed by a baseline (pre-exercise) double echo steady state (DESS) MRI, a 10-mile run on a treadmill at a self-selected pace, and a postexercise DESS MRI. The participants returned the following morning for an additional 45-minute rest period followed by a recovery DESS MRI. The entire protocol was repeated 2-3 weeks later, but each participant instead ran 3 miles at his mean mile pace from the 10-mile run.

strains resulting from a variety of activities have been previously quantified using MRI-based 3-dimensional (3D) solid modeling techniques,[3,16,23] limited information is available regarding how various running distances or durations affect patellofemoral cartilage deformations in vivo. Furthermore, the ability of patellofemoral cartilage to recover after running remains unclear. Thus, the purpose of this study was to investigate the biomechanical response of patellofemoral cartilage (composed of patellar and trochlear cartilage) to both 3- and 10-mile runs in a group of asymptomatic male runners. We hypothesized that patellofemoral cartilage thickness would decrease immediately after exercise and return to its baseline thickness within 24 hours of running. We further hypothesized that the cartilage would experience a dose-dependent response, with larger strains measured after 10-mile runs compared with 3-mile runs.

METHODS

Demographics

After Duke University Institutional Review Board approval was granted, we recruited and enrolled 8 male participants in this investigation; the participants had a mean age of 31 years (range, 27-40 years) and a mean body mass index (BMI) of 23 kg/m^2 (range, 18-25 kg/m^2).[9] Enrollment began on January 6, 2015, and concluded on June 29, 2016. Because sex differences in knee cartilage thickness have been previously identified,[11] we eliminated sex as a variable in this analysis by including only male participants in this cohort. Furthermore, individuals were excluded if they had any history of lower extremity pain, injury, or surgery, and all participants reported habitually running a minimum of 5 miles per week before this study.

MRI and Exercise Protocol

Participants were asked to avoid vigorous activity in the 24 hours before testing, and they were instructed to arrive at the MRI facility at 7 am on each testing day to minimize potential diurnal effects on baseline cartilage thickness measurements (Figure 1).[3,21,23] To further ensure that the cartilage equilibrated toward its unloaded state before testing, the individuals rested supine for 45 minutes before the baseline MRI was conducted.[5,9,20] Next, sagittal double echo steady state (DESS) images (field of view, 16 × 16 cm; matrix size, 512 × 512 pixels; resolution, 0.3 × 0.3 × 1 mm; flip angle, 25°; repetition time, 17 ms; echo time, 6 ms; acquisition time, 9 min, 49 s) were acquired of the knee on each participant's dominant leg (7 right; 1 left) using a 3.0-T MRI scanner (Trio Tim; Siemens Healthcare)

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Ethical approval for this study was obtained from Duke University (No. Pro00033254).

and an 8-channel knee coil (Invivo). The dominant side was defined as the leg with which each participant would choose to kick a ball.[22]

After the pre-exercise MRI scans were obtained, the participants were transported via wheelchair approximately 10 m into an adjacent, air-conditioned room, where they were instructed to run 10 miles on a level treadmill at a self-selected pace. Water was provided, as needed, during running. Once the participants completed their 10-mile run, they were transported back to the MRI scanner in a wheelchair for post-exercise MRI scanning. The post-exercise MRI protocol was identical to that performed before exercise. Next, the participants left the MRI facility and were asked to refrain from strenuous activity for the rest of the day. They returned the following morning at 7 am for another 45-minute rest period followed by a recovery MRI scan (identical to those obtained both before and after exercise) (Figure 1, day 2). This exercise and imaging protocol was repeated 2-3 weeks later, but each participant was instructed to run 3 miles at the recorded mean mile pace from his 10-mile run.

Strain Analysis

All DESS MRI scans were imported into solid modeling software (Rhinoceros; McNeel & Associates), where the bony cortices and cartilage surfaces of the patella and femoral trochlea were manually segmented in each image slice. The images were blinded during segmentation such that the rater was unaware of the distance and time point to which each scan corresponded. This segmentation technique has been previously validated to be repeatable to within 0.03 mm, or approximately 1% strain.[3] The segmentations were stacked to form wireframe models and then converted into 3D surface meshes (Geomagic Studio). All 3D bone models for each participant (6 per participant) were individually coregistered using an iterative closest point technique to enable site-specific comparisons of cartilage thickness across the joint. The trochlear cartilage was defined as all femoral cartilage mesh nodes anterior to the intercondylar notch and within the mediolateral boundaries of the patella (Figure 2).

Next, cartilage thickness was computed at each mesh node by finding the nearest vertex on the bony surface to each cartilage vertex (MATLAB; The MathWorks). The cartilage thicknesses at all nodes within a 2.5-mm radius of each mesh node were averaged. This value was used to compute the cartilage strain at each node, which was defined as the change in cartilage thickness immediately after exercise, normalized to the pre-exercise cartilage thickness (Figure 3B). By convention, postexercise decreases in cartilage thickness result in a negative strain magnitude and are subsequently referred to as compressive strains. To mitigate the effect of edge effects on boundary calculations, the convex hull of each cartilage mesh was computed, and the resulting convex hull coordinates were used to reduce the cartilage perimeter by 20%. All cartilage mesh nodes outside of this region were subsequently excluded from our analysis. Finally, the mean cartilage strain was defined as the mean strain at all remaining mesh nodes, whereas the peak compressive strain was defined as the maximum negative strain measured at a single remaining mesh node.

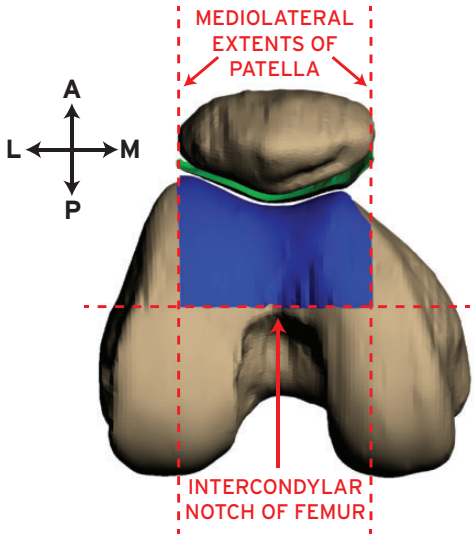

Figure 2. Trochlear cartilage (blue region) was defined as all femoral cartilage mesh nodes anterior to the intercondylar notch and within the mediolateral extents of the patella. Patellar cartilage is shown in green. A, anterior; L, lateral; M, medial; P, posterior.

Statistical Analysis

We determined our sample size a priori based on a previous investigation that quantified significant patellofemoral cartilage compressive strains in the intact knees of individuals with a unilateral anterior cruciate ligament deficiency immediately after a series of 60 single-leg hops (n = 8).[16] The normality assumption for parametric statistical analyses as well as the presence of outliers were tested via visual inspection of kernel density plots of the residuals and the inner and outer fences of the interquartile ranges of the residuals, respectively. Because 2 outliers were identified, a sensitivity analysis was performed to determine whether these data anomalies influenced the outcome of the statistical tests. As no statistical interpretations were altered by the presence of these outliers, these data points were included in all subsequent analyses.

A repeated-measures analysis of variance (ANOVA) was used to investigate how the independent variables time point (pre- vs post-exercise vs recovery) and distance (3 vs 10 miles) influenced mean patellar cartilage thicknesses. Similarly, an analogous repeated-measures ANOVA was used to test how these variables influenced mean trochlear cartilage thicknesses. Significant results were followed up with a Fisher's least significant difference (LSD) post hoc test. Additionally, paired *t* tests were used to compare mean and peak patellar cartilage strains immediately after both 3- and 10-mile runs. Finally, linear regressions were computed to assess the relationship between baseline (pre-

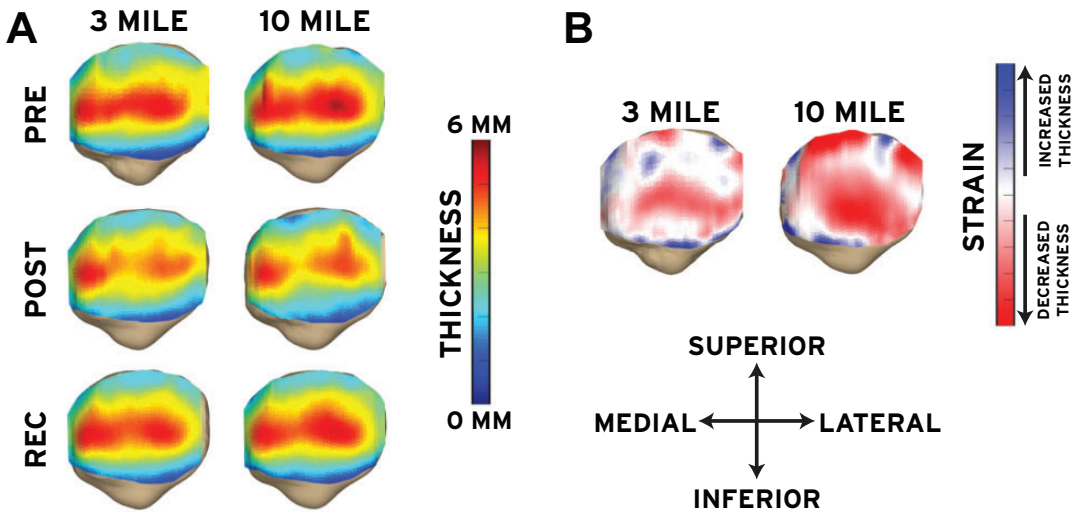

Figure 3. (A) Patellar cartilage thickness maps for a single participant generated from the pre-exercise (PRE), post-exercise (POST), and recovery (REC) magnetic resonance imaging scans for both the 3- and 10-mile runs. Red represents areas with thicker cartilage, whereas blue represents areas with thinner cartilage. (B) Patellar cartilage strain maps for a single participant, quantifying the immediate effect of the 3- and 10-mile runs. Red represents areas in which the cartilage thickness decreased (compressive strain), whereas blue represents areas where the cartilage thickness increased.

exercise) patellar cartilage thickness and immediate post-exercise strains. All results are reported as the mean ± SEM, and significance was defined where $\alpha < .05$. Bonferroni corrections were applied in order to account for multiple comparisons (Fisher's LSD: $\alpha_{new} = .05/6 = .008$; linear regressions: $\alpha_{new} = .05/2 = .025$); however, none of these corrections influenced the interpretation of the outcomes. Statistical analyses were performed using Statistica (TIBCO Software).

RESULTS

Running Exercise

Participants completed the 3- and 10-mile runs in a mean of 0:29:18 and 1:37:28 (h:mm:ss), respectively, corresponding to a mean mile pace of 0:09:45. A mean of 21 ± 2 days elapsed between visits in which the participants completed their 10- and 3-mile runs.

Cartilage Thickness

We observed a significant interaction between time point and distance on mean patellar cartilage thickness measurements ($P = .034$) (Table 1; Figures 3A and 4A). Specifically, mean ± SEM patellar cartilage thickness significantly decreased immediately after the 3-mile run (from 3.3 ± 0.1 mm to 3.2 ± 0.1 mm; $P < .001$) and the 10-mile run (from 3.4 ± 0.1 mm to 3.1 ± 0.1 mm; $P < .001$). These post-exercise thicknesses then significantly increased toward baseline after a 24-hour recovery period (3 miles, 3.3 ± 0.1 mm, $P < .001$; 10 miles, 3.4 ± 0.1 mm, $P < .001$). No significant differences were observed between the pre-exercise thicknesses and the corresponding recovery thicknesses (3 miles, $P = .42$; 10 miles, $P = .91$). Conversely, significant main effects or interactions were not observed for mean trochlear cartilage thicknesses (Table 1).

TABLE 1
Two-Way Repeated-Measures Analyses of Variance (Patellofemoral Cartilage Thickness)[a]

	Variables	*P* Value: Patellar Cartilage	*P* Value: Trochlear Cartilage
Main effects	Time point (pre-exercise/postexercise/recovery)	**<.001**	.076
	Distance (3 miles/10 miles)	.953	.676
Interaction	Time point × distance	**.034**	.166

[a]Bolded *P* values indicate statistical significance ($P < .05$).

Mean and Peak Patellar Cartilage Strain

Patellar cartilage experienced significantly larger mean compressive strains immediately after the 10-mile run (8% ± 2%) compared with the 3-mile run (5% ± 1%) ($P = .01$) (Figures 3B and 4B). Peak patellar cartilage compressive strains did not experience a significant dose effect ($P = .2$). No significant correlations were observed between baseline patellar cartilage thickness and the corresponding strain measured immediately after exercise, regardless of running distance ($P > .1$).

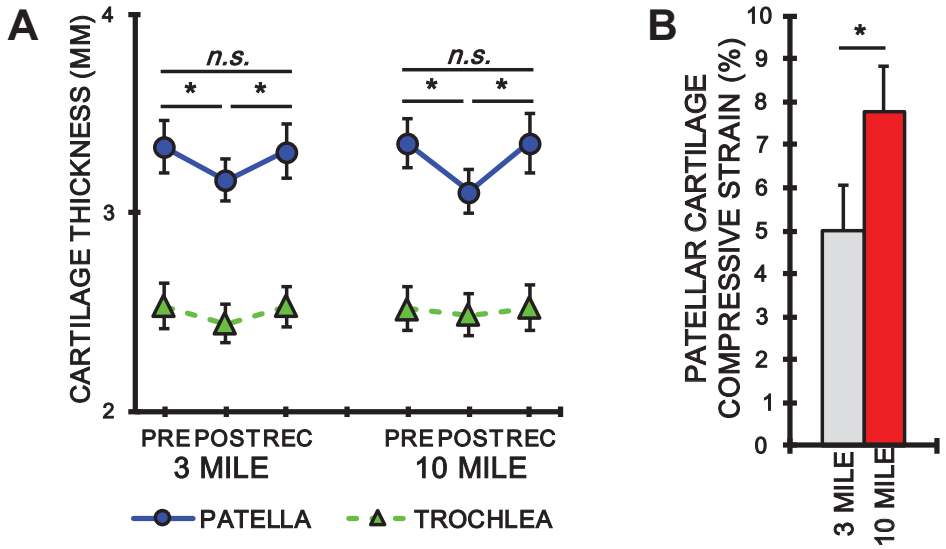

Figure 4. (A) Mean ± SEM patellar and trochlear cartilage thickness before (PRE), immediately after (POST), and 24 hours after (REC) 3- and 10-mile runs. Patellar cartilage thicknesses significantly decreased immediately after both 3- and 10-mile runs (*$P < .001$) before significantly increasing back toward baseline 24 hours later (*$P < .001$). No significant differences (n.s.) between baseline and recovery patellar cartilage thicknesses were observed for either running distance (3 miles, $P = .42$; 10 miles, $P = .91$). Similarly, no significant differences in trochlear cartilage thicknesses were observed. (B) Mean ± SEM patellar cartilage compressive strains immediately after 3- and 10-mile runs. The mean patellar cartilage compressive strain was significantly larger after the 10-mile run compared with the 3-mile run (*$P = .01$).

DISCUSSION

The purpose of this investigation was to quantify the response of patellofemoral cartilage to 3- and 10-mile treadmill runs, both immediately after exercise and after a 24-hour recovery period. We demonstrated that patellar cartilage thickness significantly decreased immediately after running and significantly increased toward its baseline thickness within 24 hours for both running distances. These relationships were not observed in the trochlear cartilage. Furthermore, we measured significantly larger mean patellar cartilage compressive strains after a 10-mile run compared with a 3-mile run, which is indicative of a dose response to loading.

In the present study, we measured mean patellar cartilage compressive strains of 5% and 8% immediately after 3- and 10-mile runs, respectively. Coleman et al[3] and Widmyer et al[23] reported a 2% patellar cartilage compressive strain in response to activities of daily living in individuals with normal BMI. Owusu-Akyaw et al[16] quantified a 3% compressive strain in patellar cartilage in response to 60 single-leg hops in the intact knee of individuals with a unilateral anterior cruciate ligament deficiency. In the current investigation, running induced larger patellar cartilage compressive strains than those reported previously,[3,16,23] which may be due to higher peak patellofemoral joint (PFJ) stresses during higher impact, dynamic exercise[24] compared with during lower impact, routine daily activities.[1,2] PFJ stresses during exercise have been previously quantified using motion capture systems, biomechanical modeling, and inverse dynamics.[1,2,24] Using these techniques, Wirtz et al[24] reported a peak PFJ stress of 8.5 MPa during running, whereas Brechter and Powers[1,2] reported peak PFJ stresses of 1.97 MPa during walking[2] and 7 MPa during both stair ascent and descent.[1] Higher peak PFJ stresses during dynamic exercise likely lead to greater water exudation from the cartilage, which contributes to the larger compressive strains measured in response to running compared with during lower impact activities.

Conversely, we observed smaller changes in trochlear cartilage thicknesses in response to running (2%) compared with the patellar cartilage changes (6%), which may be related to how the patella tracks along the trochlear groove.[13] Specifically, patellar cartilage articulates with different regions of the trochlear cartilage during knee flexion and extension.[6,7,13] This suggests that different regions of trochlear cartilage are cyclically loaded during running, which may lead to more uniform and overall lower magnitude thickness changes throughout the tissue in response to repeated loading cycles, compared with patellar cartilage. Additionally, patellar cartilage has a 30% lower aggregate modulus (H_A), or stiffness, than trochlear cartilage,[6] indicating that patellar cartilage is softer than trochlear cartilage and therefore more likely to deform under an applied load. This information further supports the smaller trochlear cartilage thickness changes quantified in the current study.

Here, we defined strain as the change in cartilage thickness immediately after exercise divided by the baseline, pre-exercise cartilage thickness. Importantly, these results may underestimate running-induced patellofemoral cartilage strains. Fluid reentry into the cartilage begins immediately after the cessation of loading[5]; therefore, the cartilage is

recovering in the short time before and during the 9-minute, 49-second DESS MRI scan. Furthermore, our participants self-selected their 10-mile pace, and they were later instructed to run 3 miles at that same pace to control for the cyclic loading rate across runs. This suggests that our participants may have completed their 3-mile run at a slower pace than they would have otherwise self-selected. As a previous study quantified increased tibial cartilage compressive strains as walking speed increased,[17] this slower pace may have resulted in lower measured patellofemoral cartilage deformations in the current investigation. Future studies may probe the effect of running speed on patellofemoral cartilage deformations. Furthermore, because sex differences in cartilage thickness have been previously observed,[11] we opted to include only male participants in our investigation. The effect of sex on running-induced patellofemoral strain may be investigated in the future. Notably, our cohort consisted of young, asymptomatic runners. Future studies may investigate how the presence of runner's knee influences running-induced patellofemoral cartilage strains.

CONCLUSION

This study provides baseline data for young, asymptomatic male runners without patellofemoral pain that may be used to inform exercise and recovery protocols. Specifically, we demonstrated that patellar cartilage thickness significantly decreased immediately after exercise and returned toward its baseline value within 24 hours of running up to 10 miles. This finding was not observed in trochlear cartilage. Although safe levels of exercise are currently unknown, these results may indicate that moderate running distances (up to 10 miles) do not have a lingering effect on patellar cartilage thickness. Further work is needed to probe this question to identify safe exercise and recovery regimens in terms of long-term cartilage health for both patellar and trochlear cartilage. We also observed a significant dose response on patellar cartilage, as significantly greater mean compressive strains were measured after 10-mile runs compared with 3-mile runs. Future studies may expand this method to investigate how other factors, including age and the presence of patellofemoral pain, may influence the current findings.

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