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Diurnal Variations in Articular Cartilage Thickness and Strain in the Human Knee

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Abstract

Due to the biphasic viscoelastic nature of cartilage, joint loading may result in deformations that require times on the order of hours to fully recover. Thus, cartilaginous tissues may exhibit cumulative strain over the course of each day. The goal of this study was to assess the magnitude and spatial distribution of strain in the articular cartilage of the knee with daily activity. Magnetic resonance (MR) images of ten asymptomatic subjects (six males, four females) with mean age of 29 years were obtained at 8:00AM and 4:00PM on the same day using a 3T magnet. These images were used to create 3D models of the femur, tibia, and patella from which cartilage thickness distributions were quantified. Cartilage thickness generally decreased from AM to PM in all areas except the patellofemoral groove and was associated with significant compressive strains in the medial condyle and tibial plateau. From AM to PM, cartilage of the medial tibial plateau exhibited a compressive strain of $-5.1 \pm 1.0\%$ (mean \pm SEM) averaged over all locations, while strains in the lateral plateau were slightly lower ($-3.1 \pm 0.6\%$). Femoral cartilage showed an average strain of $-1.9 \pm 0.6\%$. The findings of this study show that human knee cartilage undergoes diurnal changes in strain that vary with site in the joint. Since abnormal joint loading can be detrimental to cartilage homeostasis, these data provide a baseline for future studies investigating the effects of altered biomechanics on diurnal cartilage strains and cartilage physiology.

Keywords

Magnetic Resonance Imaging; Biomechanics; Cartilage deformation

1. Introduction

Articular cartilage is an avascular and aneural connective tissue that provides a nearly frictionless surface to distribute loads across diarthrodial joints (Mow et al., 1992). During activities of daily living, articular cartilage experiences numerous cycles of relatively high

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levels of load. For example, the knee joint transfers forces of several times body weight during activities such as gait and stair climbing (Kutzner et al., 2010). Due to the viscoelastic properties of cartilage (Mow et al., 1980), the resulting deformation may not completely recover following each cycle of loading (Eckstein et al., 2006). Thus, cartilaginous tissues may exhibit cumulative strain throughout the day that recovers with prolonged periods of unloading (Paajanen et al., 1994; Sitoci et al., 2012).

In vivo studies have demonstrated that repeated joint loading has been shown to cause reversible decreases in the thickness and volume of articular cartilage (Eckstein et al., 2006; Van Ginckel et al., 2011b). For example, Eckstein et al. reported decreases in patellar cartilage volumes after performing activities such as knee bends, running, squatting, and walking (Eckstein et al., 2005b). Other studies have reported decreases in ankle cartilage volumes after landing from a jump (Van Ginckel et al., 2011a; Van Ginckel et al., 2011b). Furthermore, activities of daily living have been shown to decrease femoral cartilage thickness by up to 0.6mm between morning and evening MR imaging scans (Waterton et al., 2000). Similarly, decreases in height of the intervertebral discs of the lumbar spine have been observed between morning and night, with changes in disc height of approximately 1mm (Paajanen et al., 1994).

These studies suggest that cartilage might experience significant strains due to diurnal changes in cartilage thickness. However, there is limited data on the diurnal strains induced by the thickness changes experienced in the femoral, patellar, and tibial cartilage. These diurnal strains potentially play an important role in understanding normal cartilage function, as mechanical strains affect the osmotic environment of chondrocytes (Guilak et al., 1995; Wang et al., 2002). Osmotic stresses, secondary to mechanical loading of the cartilage extracellular matrix, are believed to play an important role in regulating the metabolic activity of chondrocytes (Browning et al., 2004; Phan et al., 2009), and thus, in maintaining normal joint physiology (Guilak, 2011). Furthermore, quantifying diurnal strains in healthy subjects may provide baseline data for future studies evaluating potential alterations in cartilage loading in populations at high risk for the development of OA. For example, altered cartilage loading has been thought to play a role in the development of osteoarthritis in both obese patients and patients with knee ligament injuries (Andriacchi et al., 2004; Griffin and Guilak, 2005; Van de Velde et al., 2009). Thus, the objective of this study was to assess the magnitude and distribution of diurnal strains in the articular cartilage of the knee with daily activity using magnetic resonance (MR) imaging and 3D modeling techniques. Our hypothesis was that activities of daily living would result in significant diurnal compressive strains in the cartilage of all three compartments of the knee. We also examined how these parameters were correlated to body mass index (BMI) and daily activity level.

2. Methods

MR Imaging

Following Institutional Review Board approval, healthy volunteers were recruited to participate in the study, and informed consent was obtained. A total of ten subjects (six male and four female, mean age: 29 years, range: 22–46 years) with normal body mass index (BMI, mean: 22.6, range: 21.1–24.4) were included (Table I). All participants reported having asymptomatic knees at the time of the study and denied any history of musculoskeletal injury. The right knees of all subjects were imaged with a 3 Tesla MR scanner (Trio Tim, Siemens Medical Solutions USA, Malvern, Pennsylvania) at the Center for Advanced Magnetic Resonance Development at 8:00 AM. Subjects were instructed not to exercise or perform any strenuous activity prior to the AM scan. Subjects were scanned using an eight channel receive-only knee coil and a double106 echo steady state sequence (DESS, flip angle: 25°, TR: 17 ms, TE: 6 ms, field of view: 16 ×16 cm, resolution: 512 ×512

pixels, contiguous slice thickness:1 mm) (Taylor et al., 2011). Scan time was approximately 9 minutes. During the day, the subjects were asked to perform normal daily activities. All participants wore a pedometer to quantify the number of steps taken throughout the day. For the afternoon scan, patients returned to the same facility at 4:00 PM and were immediately imaged upon arrival.

Creation of 3D joint models

In each image, the bony and articular cartilage surfaces were segmented (Figure 1) in solid modeling software (Rhinoceros 4.0, Robert McNeel and Associates, Seattle, WA) (Bischof et al., 2010). These lines were then used to create 3D polygonal mesh models of the femur, tibia, and patella as well as the corresponding articular surfaces of cartilage (Geomagic Studio, Geomagic Inc., Raleigh, NC). The AM and PM models of the femur, tibia, and patella were then individually aligned using the iterative closest point technique (Abebe et al., 2009) to compare thickness measurements on the same regions of the AM and PM models. A grid sampling system was created on each osseous surface to quantify the changes in cartilage thickness at each sampling site: each tibial plateau was covered by a 3×3 grid, the patella was covered by a grid of 11 points, and the femoral grid consisted of 6 equidistant points localized to the subpatellar region and a total of 36 points across the medial and lateral condyles (Figure 2). All vertices on the mesh model within a 2.5 mm radius of the grid sampling point were then averaged to calculate the mean thickness at each site. Cartilage thickness was measured as the distance from each vertex on the articular surface of the cartilage to the nearest point on the surface of the bone (Figure 3) (Van de Velde et al., 2009). For each grid sampling point, diurnal strain was calculated using the difference of AM and PM thickness divided by the AM thickness at the same location.

Repeatability Study

A number of previous studies have used MR imaging to measure articular cartilage volume and thickness in human subjects (Bowers et al., 2008a; Cohen et al., 1999; Eckstein et al., 2005a; Van Ginckel et al., 2011b; Waterton et al., 2000). The methodology used in the present study has been previously validated to measure cartilage thickness distributions in the tibiofemoral joint (Van de Velde et al., 2009). However, to assess the repeatability of the thickness measurements of the femoral, tibial, and patellar cartilage used in this study, the coefficient of repeatability (Bland and Altman, 1986) was calculated for four repeated trials of image segmentation at 11 different sites on the femoral, tibial, and patellar cartilage. The coefficient of repeatability was 0.03mm, which corresponds to a difference of 1.2% in cartilage thickness; thus differences less 0.03mm or 1.2% are within the noise of this technique and unlikely to represent meaningful changes in thickness.

Statistical Analysis

All analyses were performed with STATISTICA (StatSoft, Inc., Tulsa, Oklahoma). The effects of location and sex on AM cartilage thickness were tested with an ANOVA with LSD post-hoc tests. AM and PM thicknesses were compared with paired t-tests. Strains were assessed for difference from zero with t-tests. Strains were compared across compartments and sexes with an ANOVA with LSD post-hoc tests. Bonferroni corrections were applied as appropriate. Simple linear regressions were used to determine whether variation in BMI, number of steps taken, or age were significant explanatory variables in determining the amount of strain in each compartment.

3. Results

Subjects took an average of 8057 steps (Table 1) during the course of the day. AM cartilage thickness, which represents the undeformed (or minimally deformed) state, varied

significantly by location and by sex with no significant sex-location interaction (Figure 4, ANOVA, location $p < 0.00001$, sex $p < 0.00001$, location*sex $p = 0.79$). Cartilage was thickest on the patella, followed by the femoral groove and lateral tibia, which were thicker than the medial femur, lateral femur, and lateral tibia. Males had significantly thicker cartilage than females by an average of 28%. Cartilage thickness generally decreased from AM to PM in all areas except the patellofemoral groove and the lateral femoral condyle (Figure 5).

The tibial cartilage experienced significant compressive strains on both the lateral and medial sides (Figure 6). In the undeformed state (AM), the lateral plateau was significantly thicker than the medial (Figure 4). On the medial plateau, regions bordering the medial intercondylar tubercle were thickest, with the most anterior of these experiencing the greatest strain (site 3: -11.7%). However, on the lateral tibial plateau, greatest strain was experienced on the lateral border (site 18: -5.0% , site 12: -4.8%).

The undeformed patellar cartilage was thicker than any other location (Figure 4). Patellar cartilage also experienced significant compressive strain (Figure 6). The highest strain occurred in the antero-lateral corner of the patella (site 8: -4.2%). The cartilage in the patellofemoral groove did not significantly change thickness from AM to PM; nor did it undergo significant strain.

The cartilage in the medial femoral condyle also experienced significant compressive strains (Figure 6). The lateral femoral condyle cartilage, on the other hand, did not change thickness or experience significant strain from AM to PM. The highest diurnal strains in the medial condyle were seen in the anteromedial region (site 7: -8.5% , site 8: -9.2%).

The cartilage in the medial compartment, on both the tibia and condyle, experienced the largest compressive strains during the course of the day. These strains were significantly greater than the lateral condyle and the patellofemoral groove. The lateral tibia and patella experienced intermediate strains.

The number of steps was inversely correlated with the subject's BMI ($\#Steps = 47261 - 1733 * BMI$, $r^2 = 0.45$, $p = 0.03$). Compressive strain in the lateral and medial tibia significantly decreased with increasing number of steps taken (Lateral Tibia: strain = $-0.79 + 5.99 * 10^{-6} * \#steps$, $r^2 = 0.05$, $p = 0.03$; Medial Tibia: strain = $-0.18 + 1.65 * 10^{-5} * \#steps$, $r^2 = 0.17$, $p = 0.0005$), whereas compressive strain in the lateral femur and medial tibia significantly increased with increasing BMI (Lateral Femur: strain = $0.067 - 0.03 * BMI$, $r^2 = 0.05$, $p = 0.05$; Medial Tibia: strain = $0.66 - 0.031 * BMI$, $r^2 = 0.09$, $p = 0.003$). Age did not significantly correlate with any of the strains measured.

4. Discussion

Mechanical stresses and strains alter the biophysical environment of cartilage and potentially play an important role in normal cartilage homeostasis (Guilak and Hung, 2005). Thus, an improved understanding of the effects of daily activity and joint loading on cartilage deformation is important to understanding normal cartilage function and may provide critical insights into the mechanisms leading to cartilage degeneration (Halloran et al., 2012). The findings of this study show that, with daily activity, human knee cartilage undergoes diurnal changes in thickness and significant compressive strains. The magnitude of compressive strain varied as a function of location within the joint, with average compressive strains reaching values as high as 5% in the medial compartment of the tibia.

The compressive strains observed in the present study are consistent with previous studies reporting changes in the diurnal thickness changes in knee cartilage (Waterton et al., 2000) and the intervertebral disc of the spine (Paajanen et al., 1994). These diurnal changes are

likely due in large part to fluid flow resulting from compressive loading of the cartilage (Roberts et al., 1998; Setton et al., 1993). While the individual components of cartilage are effectively incompressible (Bachrach et al., 1998), mechanical loading of cartilaginous tissues results in the time-dependent exudation of water (O'Connell et al., 2011; Torzilli et al., 1983), and, due to the low permeability of cartilage, recovery of water and thickness may require times on the order of hours (Eckstein et al., 2006; Mow and Guo, 2002). For example, a recent series of studies using MR imaging demonstrated that patellar cartilage volume decreases by 5% after performing 50 deep knee bends (Eckstein et al., 2006). After 45 minutes of rest, approximately 50% of the volume loss was recovered. In another study, more than 90 minutes was required for the patellar cartilage to fully recover from 100 knee bends (Eckstein et al., 1999). In the present study, a similar mechanism is likely causing the diurnal cartilage strains observed in response to daily activity. Although we asked subjects to refrain from exercising or performing any strenuous activity prior to the morning scan, their normal activity prior to the morning scan is likely to have resulted in some cartilage deformation that may not have been measured. Thus, the measurements reported in the present study may be an underestimate of the diurnal strains experienced throughout an entire day of activity.

MR imaging techniques have been widely used to measure cartilage volume and thickness in the knee (Bowers et al., 2008b; Cohen et al., 1999; Eckstein et al., 2001; Li et al., 2005; Raynauld et al., 2003). The images used in this study were acquired in approximately 9 minutes to minimize motion artifacts (Eckstein et al., 2006; Tieschky et al., 1997). In our study, the average morning thicknesses were 2.9mm for the tibia and 2.5mm for the femur. These data were similar to thickness measurements previously reported in the literature (Ateshian et al., 1991; Bingham et al., 2008; DeFrate et al., 2004; Liu et al., 2010). For example, Ateshian et al. reported average thickness measurements of 2.9mm for the tibia and 2.0mm for the femur. Since data in the present study were collected from selected sample locations, the thinner regions near the periphery of the cartilage were not included in this calculation. Thus, the numbers reported in this paper may be slightly higher than average thickness values obtained from volumetric measurements of cartilage. Furthermore, differences in cartilage thickness measurements between studies could also be related to variations in age (Hudelmaier et al., 2001), activity (Eckstein et al., 2006), BMI (Anandacoomarasamy et al., 2012), or, based on the findings of the present study, the time of day that the images were acquired. Thus, our findings emphasize the importance of precisely controlling the loading history of the joint in clinical trials utilizing measurements of cartilage thickness or joint space narrowing.

Our results demonstrated a statistically significant but relatively weak correlation between increasing compressive strain and BMI. These findings are consistent with the hypothesis that increased body weight, as represented by BMI, may result in higher loads at the knee joint (Aaboe et al., 2011; Messier et al., 2005), thus inducing greater cumulative deformation of the cartilage. However, as the BMIs of subjects in this study were selected within a narrow range of normal values, it is not possible to form strong conclusions about the role of BMI. Further study of individuals with BMIs covering a greater range may yield additional information in this regard.

Of interest was the finding that the number of steps taken correlated inversely (albeit weakly) with increasing compressive strain. Under physiologic loading rates, the mechanical response of cartilage is characterized by rapid pressurization of the interstitial fluid, which results in little tissue dilatation at short times (Ateshian, 2009), although instantaneous normal strains can exceed 10–15% (Guterl et al., 2009). However, sustained or static loading leads to increased cartilage deformation as fluid is exuded from the cartilage (Butz et al., 2011; Chan and Neu, 2012; Cotofana et al., 2011). Our findings suggest that cyclic daily

activity may in fact lead to decreased cartilage strains due to the continuous loading and unloading of the joint which allows repressurization, and therefore little deformation (Caligaris and Ateshian, 2008). More comprehensive measurements of joint motion and loading throughout the day (as opposed to the total number of steps taken) may provide additional insight into these relationships. In particular, measurements characterizing the time course of activity may be useful to the interpretation of this data, since activities performed immediately prior to the afternoon scan could have a greater effect on the deformation of the cartilage than activities performed earlier in the day.

Both the tibial and femoral cartilage showed significantly higher strain on the medial side. This observation is consistent with previous studies that have shown increased acute cartilage contact strain in the medial compartment during gait (Liu et al., 2010) or during a static lunge (Bingham et al., 2008). These data are also in agreement with predictions of higher medial compartment loads based on gait analysis techniques (Hurwitz et al., 1998; Schipplein and Andriacchi, 1991). In addition, a recent MR-based study demonstrated higher strains in the medial compartment, lower strains in the lateral tibial cartilage, and very small strains in the lateral femoral cartilage in response to compressive loads applied to the tibia (Cotofana et al., 2011). Thus, in healthy knees, the medial compartment appears to experience higher strains than the lateral compartment under different loading conditions, including gait, lunging, and compressive loading. These findings are consistent with our observations of greater diurnal strains in the medial compartment relative to the lateral compartment in response to activities of daily living.

While normal loading conditions do not necessarily lead to osteoarthritis, these regions of high strain coincide with regions where osteoarthritis lesions are likely to occur. For example, The National Health and Nutrition Examination Survey has shown a greater prevalence of osteophytic changes in the medial tibial and femoral cartilage (Dillon et al., 2006). Other epidemiologic studies have reported a higher prevalence of medial compartment osteoarthritis compared to lateral compartment osteoarthritis (McAlindon et al., 1992; Wise et al., 2012). Increases in loading in the medial compartment, as measured by the adduction moment using gait analysis techniques, are believed to be associated with a higher prevalence and a faster rate of progression of medial compartment osteoarthritis (Andriacchi et al., 2000; Vincent et al., 2012). Although many factors are likely to play a role in the development of osteoarthritis, the elevated medial compartment cartilage strains relative to the lateral side could potentially make the medial side more susceptible to degenerative changes.

An important consideration in the interpretation of these findings is that the mechanical properties of articular cartilage exhibits significant inhomogeneity with depth (Guilak et al., 1995; Wong and Sah, 2010), and thus strain measurements based on total change in thickness cannot account for zone-specific differences in strain at tissue and cellular levels. The difference in compressive modulus and local strain magnitude has been shown to vary up to an order of magnitude, potentially resulting in highly nonuniform strain fields under load (Choi et al., 2007; Guterl et al., 2009). The development of novel MR imaging modalities that allow for high-resolution imaging of cartilage strains may provide further insight into measurement of zone-specific changes in the mechanical environment of the tissue (Chan and Neu, 2012).

The observed diurnal strains reported in this study are likely due to water exudation from cartilage as a result of repeated loading throughout the day and are recovered overnight (Eckstein et al., 1999; Sitoci et al., 2012). This loss of water is associated with diurnal osmotic changes that may influence and potentially regulate chondrocyte biology (Browning et al., 2004; Peffers et al., 2010). Chondrocytes show high osmotic sensitivity to both hyper-

osmotic (Erickson et al., 2001) and hypo-osmotic (Erickson et al., 2003) conditions, and the sensitivity to these changes appears to depend on the initial osmotic stress (Leddy et al., 2010). Thus, diurnal cartilage strains would be expected to expose chondrocytes to daily cycles of hyper- and hypo-osmotic conditions that may be responsible for regulating cartilage metabolism and physiology (Chao et al., 2006; Clark et al., 2010). Similarly, in intervertebral disc cells, osmotic changes have been shown to not only affect gene expression (Boyd et al., 2005), but also to influence the response to mechanical loading (Wuertz et al., 2007). Therefore, alterations to normal patterns of joint loading, and therefore osmotic signaling, could potentially disrupt normal cartilage homeostasis.

In conclusion, we found that articular cartilage experiences significant compressive strain during the course of the day, presumably resulting from loss of interstitial water due to joint loading. This diurnal strain cycle may provide significant mechanoregulatory cues for chondrocytes, and changes to these normal strain distributions, such as those that may occur with weight gain or injury, may be detrimental to normal cartilage homeostasis. These novel data provide an important baseline for investigating the effects of altered biomechanics on diurnal cartilage strains.

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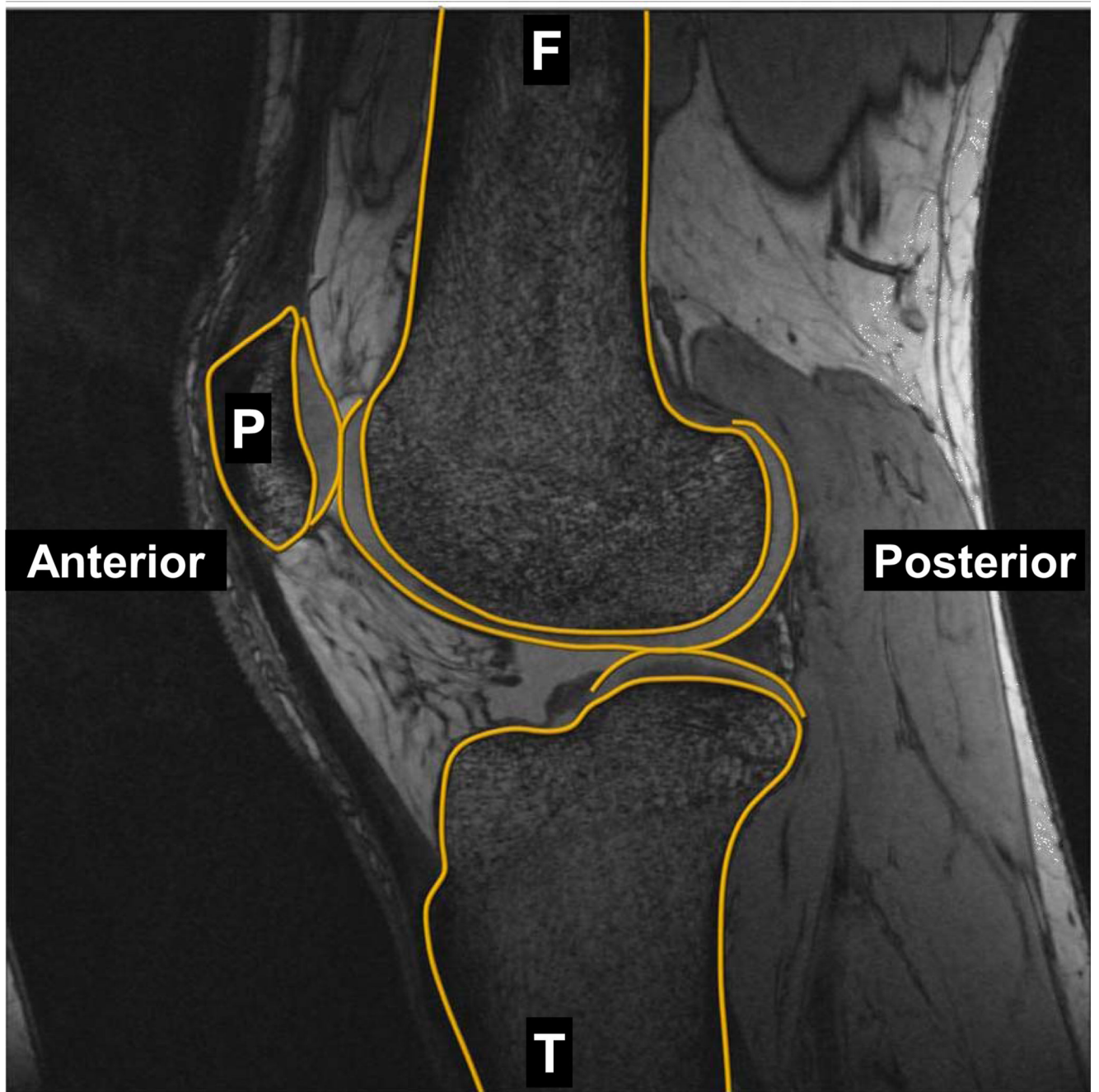


Figure 1.

A sagittal view of an asymptomatic right human knee using a 3T MRI scanner. The cartilaginous and osseous boundaries of the femur (F), tibia (T), and patella (P) were segmented on each slice and stacked to create 3D models of the joint.

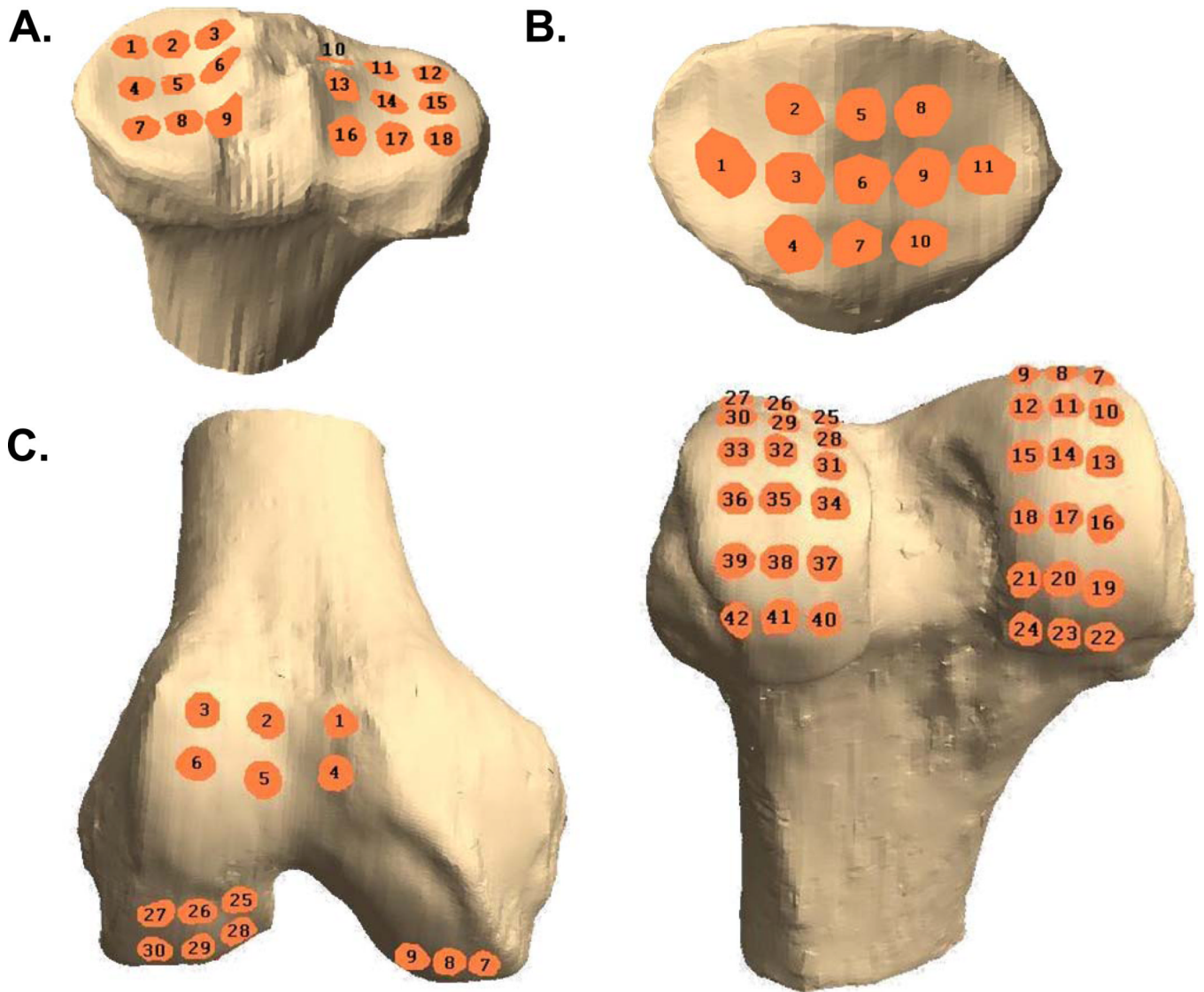


Figure 2. 3D models of the right tibia (A), patella (B), and femur (C) showing grid scheme for computing thickness changes and strains. The patella is shown from a posterior view. Right femur is shown from an inferior view (left) and a posterior view (right).

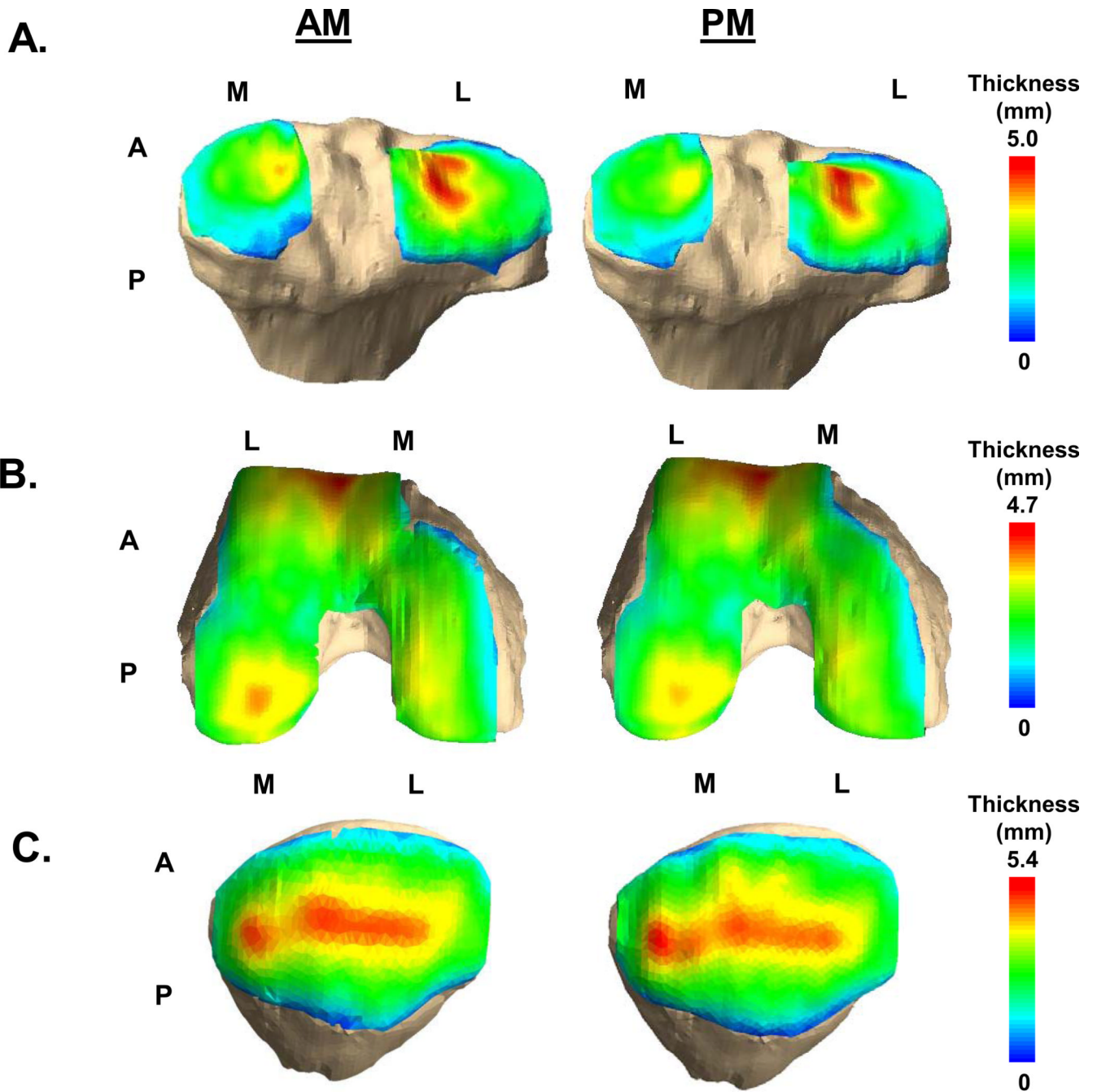


Figure 3. Cartilage thickness maps of the tibia (A), femur (B), and patella (C) measured in the AM (left) and PM (right). (M = Medial, L=Lateral, A=Anterior, P=Posterior)

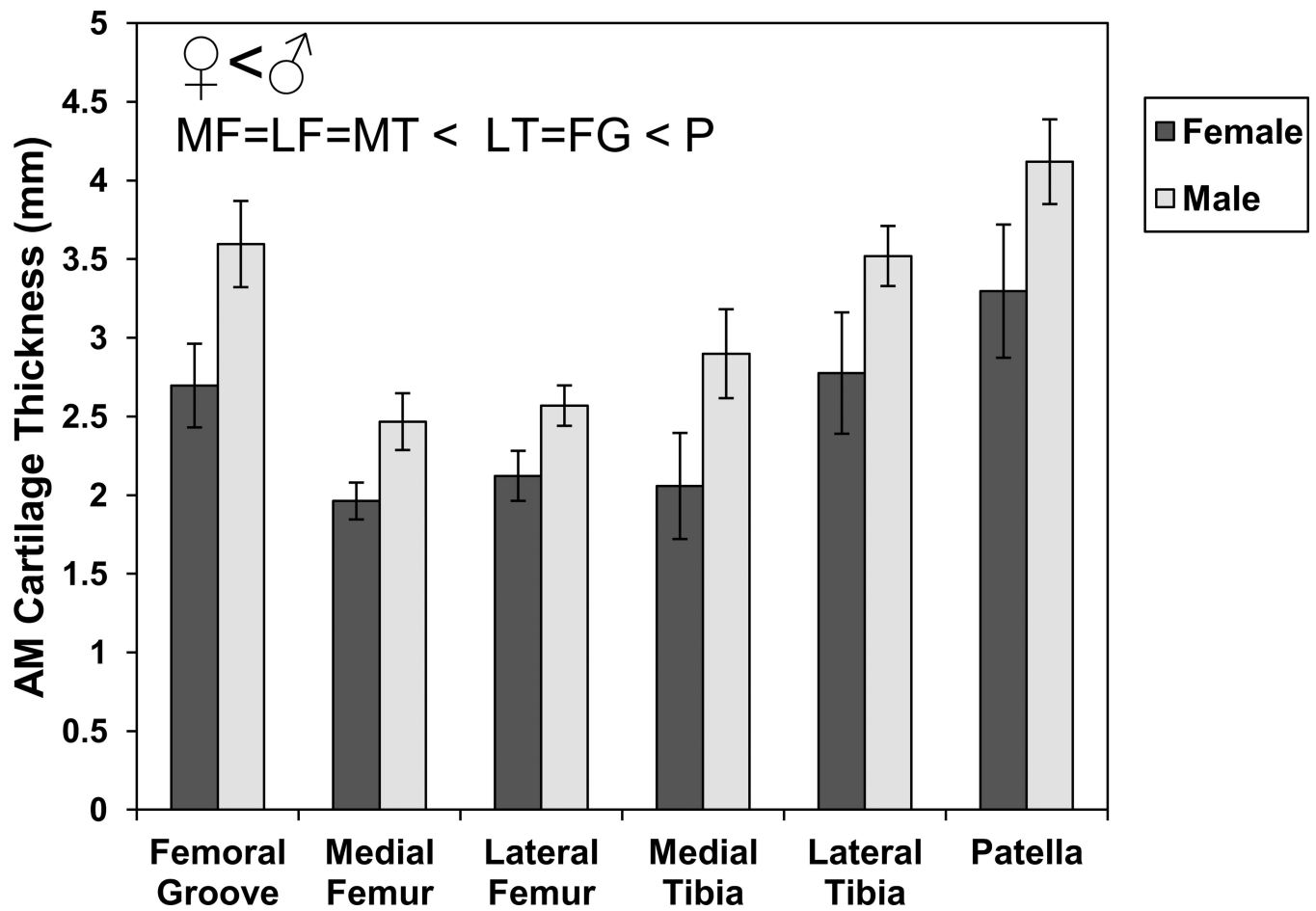


Figure 4. Mean (\pm sem) AM cartilage thickness varies significantly between compartments and with sex (ANOVA, location $p < 0.0001$, sex $p < 0.0001$, location*sex $p = 0.80$). Symbols show significant differences from post-hoc tests for each factor (sex, location) (LSD post-hoc test with Bonferroni correction, $p < 0.025$).

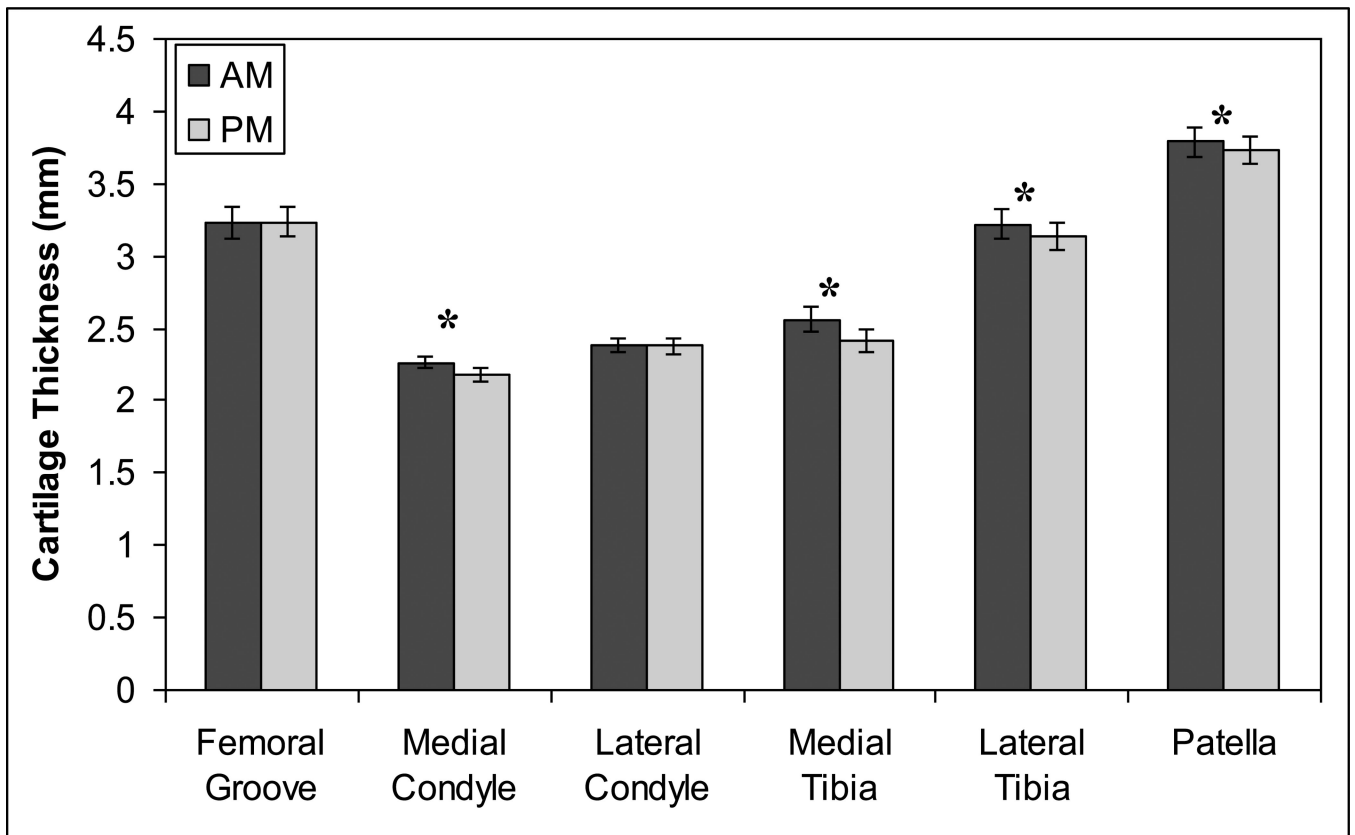


Figure 5. Mean (\pm sem) cartilage thickness decreases from AM to PM in most major knee compartments. *AM thickness significantly different from PM (paired t-test with Bonferroni correction, $p < 0.025$).

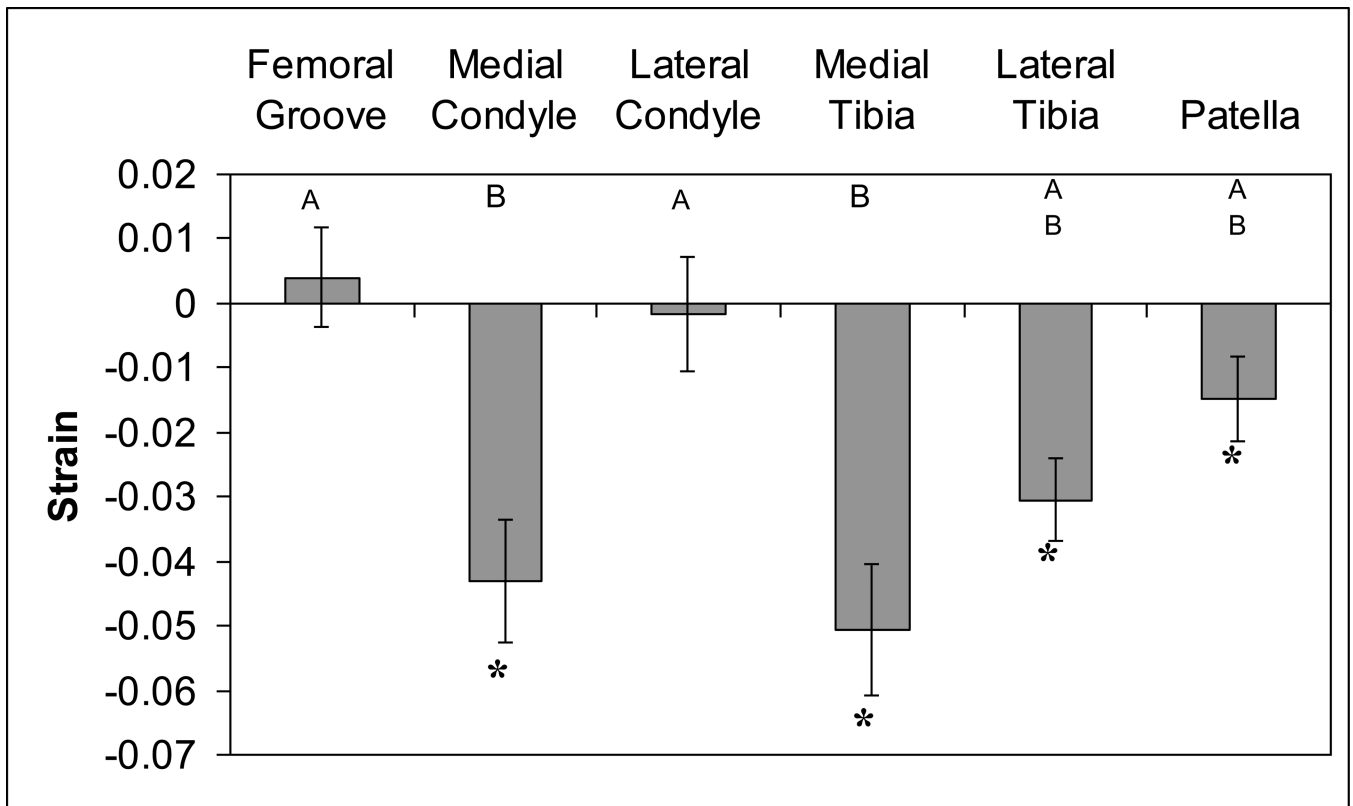


Figure 6. Cartilage in most knee compartments undergoes significant diurnal compressive strain. Bars are mean (\pm sem). *strains significantly different from zero (t-test with Bonferroni correction, $p < 0.025$). Bars with different letters are significantly different from one another (ANOVA, LSD post-hoc test with Bonferroni correction, $p < 0.025$).

Table 1

Sex	Age	Height (m)	BMI	Steps
F	25	1.65	21.6	10151
F	23	1.55	22.7	11005
F	22	1.73	22.8	8277
F	39	1.57	23.2	8525
M	24	1.85	21.1	12522
M	28	1.78	21.5	7067
M	24	1.93	22.5	5987
M	46	1.85	23.1	5668
M	25	1.65	23.3	6909
M	37	1.75	24.4	4460
Mean	29.3	1.73	22.6	8057
SEM	2.6	0.04	0.3	806