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EFFECT OF NORMAL GAIT ON *IN VIVO* TIBIOFEMORAL CARTILAGE STRAINS

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Abstract

Altered cartilage loading is believed to be associated with osteoarthritis development. However, there are limited data regarding the influence of normal gait, an essential daily loading activity, on cartilage strains. In this study, 8 healthy subjects with no history of knee surgery or injury underwent magnetic resonance imaging of a single knee prior to and following a 20-minute walking activity at approximately 1.1 m/s. Bone and cartilage surfaces were segmented from these images and compiled into 3-dimensional models of the tibia, femur, and associated cartilage. Thickness changes were measured across a grid of evenly spaced points spanning the models of the articular surfaces. Average compartmental strains and local strains were then calculated. Overall compartmental strains after the walking activity were found to be significantly different from zero in all four tibiofemoral compartments, with tibial cartilage strain being significantly larger than femoral cartilage strain. These results provide baseline data regarding the normal tibiofemoral cartilage strain response to gait. Additionally, the technique employed in this study has potential to be used as a “stress test” to understand how factors including age, weight, and injury influence tibiofemoral cartilage strain response, essential information in the development of potential treatment strategies for the prevention of osteoarthritis.

Keywords

Biomechanics; Osteoarthritis; Joint Loading; Knee; Deformation

Introduction

Articular cartilage, an avascular and aneural connective tissue (Griffin and Guilak, 2005; Mow et al., 1980), provides a low friction surface for joint motion (Burstein et al., 2000;

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Conflict of interest statement

The authors have no conflicts of interest to report.

Mow et al., 1992; Phan et al., 2009; Waterton et al., 2000). It is primarily composed of water (Burstein et al., 2000; Mow et al., 1992; Torzilli et al., 1983), such that chondrocytes, the cells responsible for metabolic activity in cartilage (Griffin and Guilak, 2005; Guilak, 2011; Mow et al., 1992), may respond to fluid flow caused by compressive strains (Kim et al., 1995) as well as subsequent changes in the osmotic environment (Erickson et al., 2001; Guilak, 2011; Phan et al., 2009).

Under compression, cartilage behaves as a biphasic material (Mow et al., 1984; Mow et al., 1980; Mow et al., 1992; Setton et al., 1993; Torzilli et al., 1983). When cartilage is compressed, fluid redistributes within or exudes out of cartilage (Eckstein et al., 2006a; Eckstein et al., 1999; Herberhold et al., 1999; Kim et al., 1995; Mosher et al., 2005; Mow et al., 1984; Mow et al., 1980; Mow et al., 1992; Setton et al., 1993; Torzilli et al., 1983; Waterton et al., 2000). Once the load is removed, due to the low permeability of the cartilage matrix (Arokoski et al., 2000; Eckstein et al., 1999; Herberhold et al., 1999; Mow et al., 1992; Setton et al., 1993), the fluid is reabsorbed over time (Eckstein et al., 1999; Herberhold et al., 1999; Torzilli et al., 1983). This results in a time-dependent recovery of deformation that can be measured using magnetic resonance (MR) imaging (Eckstein et al., 2006a; Eckstein et al., 2000).

Biomechanical factors are believed to play a significant role (Andriacchi et al., 2009; Andriacchi and Mundermann, 2006; Andriacchi et al., 2004; Arokoski et al., 2000; Griffin and Guilak, 2005; Guilak, 1995, 2011; Liu et al., 2010; Mow et al., 1992) in maintaining cartilage health. Altered cartilage loading may result in the degradation and loss of cartilage, which is characteristic of a debilitating disease, osteoarthritis (OA) (Arokoski et al., 2000; Guilak, 2011). While abnormal loading may be an important factor in OA development (Guilak, 2011; Kumar et al., 2013), the precise mechanisms are not well understood. Thus, some recent studies have focused on characterizing tibiofemoral cartilage deformation in response to *in vivo* loading conditions (Bingham et al., 2008; Chan et al., 2016; Coleman et al., 2013; Eckstein et al., 2006b; Eckstein et al., 1999; Horng et al., 2015; Liu et al., 2010; Sutter et al., 2015; Wang et al., 2015). Because of the time-dependent response of cartilage to loading, MR imaging can be used to measure cartilage volume (Eckstein et al., 2006b; Eckstein et al., 1999) and site specific strains (Coleman et al., 2013; Sutter et al., 2015; Widmyer et al., 2013) before and after various dynamic activities. Other studies have used a combination of MR imaging and biplanar fluoroscopy to assess *in vivo* cartilage deformation during weight-bearing loading conditions (Bingham et al., 2008; Carter et al., 2015; Liu et al., 2010). Finally, some investigators measured intratissue strains while compressive loads are applied to the foot during MR imaging (Chan et al., 2016). However, *in vivo* data describing the effects of a normal walking activity on tibiofemoral cartilage strains remain limited (Liu et al., 2010).

Given the evidence that abnormal loads influence cartilage quality and structure (Guilak, 2011), a better understanding of how normal gait, an essential activity of daily living, affects tibiofemoral cartilage may provide insight into the mechanisms by which the joint is predisposed to OA development as well as elucidate treatment strategies. Thus, the purpose of the present study was to measure normal gait-induced compressive strains in tibiofemoral cartilage in healthy knees using a combination of MR imaging and 3-dimensional (3D)

modeling techniques. Our hypothesis was that 20 minutes of treadmill gait at a comfortable walking speed would result in significant compressive strains in both medial and lateral compartments of the tibial plateau and femoral condyles.

Materials and Methods

Subjects

Eight healthy adult subjects (4 males, 4 females) were recruited for this Institutional Review Board-approved study. Mean age was 25.4 years with a range of 22–30 years; mean body mass index (BMI) was 22.3 with a range of 20.2–25.1. Subjects had no history of injury or surgery in either knee. Informed consent was obtained prior to participation.

Protocol and Imaging Analysis

To ensure minimal baseline cartilage compression, the study was conducted in the morning and participants were instructed to minimize load-bearing activity prior to testing (Coleman et al., 2013; Sutter et al., 2015; Widmyer et al., 2013). Subjects first lay supine for 45 minutes to allow for cartilage equilibration (Sutter et al., 2015). One knee from each subject (4 right knees, 4 left knees) was imaged using a 3.0 T MR scanner (Trio Tim; Siemens Medical Solutions USA, Inc.) with an 8-channel knee coil while subjects lay supine and relaxed. Sagittal plane images (field of view: 16cm×16cm; resolution: 512×512 pixels; thickness: 1 mm) were generated using a double-echo steady state (DESS) sequence (flip angle: 25°; TR: 17 ms; TE: 6 ms). Subjects subsequently walked on a level treadmill (F80; Sole Fitness Equipment) for 20 minutes at approximately 1.1 m/s, in a room adjacent to the MR scanner. We chose a walking speed of 1.1 m/s so the walking activity would be at a comfortable pace for most subjects (Fritz and Lusardi, 2009). After the walking activity, each subject was transported back to the MR suite to undergo a post-activity MR scan of their previously selected knee. Total time from completion of the activity to the initiation of the DESS scan was under 4 minutes. Each DESS scan took approximately 9 minutes to complete.

Using solid modeling software (Rhinoceros; Robert McNeel & Associates), the outer margins of the tibia and femur as well as their corresponding articular cartilage surfaces were manually segmented from the MR images and converted into 3D surface mesh models (Bischof et al., 2010 ; Coleman et al., 2013; Okafor et al., 2014; Widmyer et al., 2013) (Geomagic Studio; Geomagic, Inc.; Figure 1). This method has been shown to reliably recreate tibiofemoral cartilage thickness to within 1% (Coleman et al., 2013; Van de Velde et al., 2009).

Pre- and post-activity bone models were then registered to each other using an iterative closest point technique (Abebe et al., 2011; Okafor et al., 2014). Next, a uniform grid system was designed to span the articulating surfaces of the tibia and femur. The medial and lateral compartments of the tibial plateau were each fixed with 9 grid points, totaling 18 grid points for the proximal tibial surface; the medial and lateral femoral condyles were each fixed with 18 grid points, totaling 36 points for the distal femoral surface (Figure 2). Grid points were spaced equidistantly in order to evenly sample cartilage thickness. Cartilage thickness for

each grid point was calculated as the average of cartilage thicknesses at all mesh nodes within a 2.5 mm radius of the grid point (Coleman et al., 2013; Sutter et al., 2015; Widmyer et al., 2013) (Figure 3). Strain was defined as the normalized post-activity change in cartilage thickness and was determined for each grid point. Compartmental strains were then calculated by averaging the strain values of the 9 grid points in each compartment of the tibial plateau and of the 18 grid points on each femoral condyle.

Statistical Analysis

The effects of sex and compartment on pre-activity cartilage thickness were tested with a Kruskal-Wallis ANOVA test and a Mann-Whitney U post-hoc test (STATISTICA version 7; StatSoft, Inc.). A Wilcoxon matched-pairs test was employed to determine whether cartilage thickness changed after walking. Compartmental strains were compared using a Kruskal-Wallis ANOVA, and strains in the tibia and femur were compared using a Mann-Whitney U post-hoc test. Differences were considered statistically significant where $p < 0.05$.

Results

Before participating in the 20-minute walking activity, subjects' cartilage thicknesses varied significantly by sex and by compartment (ANOVA; sex: $p < 0.0001$; compartment: $p < 0.0001$; Figure 4). Males demonstrated an average of 17% thicker cartilage than females. Lateral tibial plateau cartilage was significantly thicker than cartilage on the medial tibial plateau and both medial and lateral femoral condyles.

After the walking activity, tibiofemoral cartilage significantly decreased in thickness ($p = 0.003$; Figure 5). Overall tibial cartilage strain was found to be significantly greater than the overall compressive strain experienced by femoral cartilage ($p = 0.0006$; Figure 6).

Tibial cartilage experienced significant overall compressive strains in both medial and lateral compartments (Figure 6). In the medial compartment, there was an overall compressive strain of $3.5 \pm 0.6\%$ (mean $\pm$ standard error of the mean; $p = 0.0005$). Local compressive strains in the medial compartment reached a maximum of 8.4% at the center of the medial tibial plateau. In the lateral compartment, an overall compressive strain of $3.4 \pm 0.4\%$ was observed ($p < 0.0001$). The lateral compartment demonstrated local compressive strains that reached a maximum of 5.3% close to the center of the tibial spine.

Both medial and lateral compartments of the femoral condyles also experienced significant overall compressive strains (Figure 6). The medial femoral condyle cartilage experienced an overall compressive strain of $1.2 \pm 0.6\%$ ($p = 0.005$). The maximum local compressive strain was 7.3% in the anteromedial portion of the medial femoral condyle. In the cartilage of the lateral femoral condyle, an overall compressive strain of $1.3 \pm 0.4\%$ was observed ($p = 0.001$), with local compressive strains peaking at 3.3% in the central lateral portion of the condyle.

Discussion

Abnormal loading is considered to be a risk factor for cartilage degeneration (Andriacchi et al., 2009; Guilak, 2011; Haugom et al., 2012; Kumar et al., 2013; Scarvell et al., 2004). An improved understanding of how normal gait, an essential loading activity of daily living, affects tibiofemoral cartilage deformation may provide insight into normal joint biomechanics as well as how altered cartilage loading may predispose the joint to OA development. The present study used a novel methodology to measure *in vivo* tibiofemoral cartilage strains in normal, healthy knees in response to walking on a treadmill for 20 minutes. The results of this study confirm our hypothesis by demonstrating that cartilage in both medial and lateral compartments exhibit significant strains with tibial cartilage experiencing significantly higher overall strain than femoral cartilage.

Our study supports previous work showing that pre-activity cartilage on the lateral tibial plateau is thicker than on the medial tibial plateau (Cicuttini et al., 2002; Coleman et al., 2013; Cotofana et al., 2011; Eckstein et al., 2001; Jones et al., 2000; Widmyer et al., 2013) and on both medial and lateral femoral condyles (Coleman et al., 2013; Eckstein et al., 2001; Widmyer et al., 2013). Our observation that males have thicker cartilage than females is also consistent with previous studies (Cicuttini et al., 2002; Coleman et al., 2013; Eckstein et al., 2014; Jones et al., 2000; Otterness and Eckstein, 2007; Waterton et al., 2000). Even after measurements were adjusted for factors such as age, physical activity, BMI, bone size, height, and weight, several studies still observed sex differences in cartilage thickness of various compartments of the knee (Cicuttini et al., 2002; Jones et al., 2000; Otterness and Eckstein, 2007).

In accordance with the present study, other *in vivo* studies examining cartilage strains in response to daily and high-impact activities have also demonstrated that tibial cartilage experiences higher overall strain (Coleman et al., 2013; Sutter et al., 2015) and volumetric deformation (Eckstein et al., 2005) than femoral cartilage. This difference in strain magnitudes may be due to varying mechanical properties within cartilage (Treppo et al., 2000; Wong and Sah, 2010). Previous work has shown that femoral cartilage has significantly higher compressive moduli and lower hydraulic permeability compared to tibial cartilage (Treppo et al., 2000; Wong and Sah, 2010). As a result, higher overall strain may be observed in tibial cartilage relative to femoral cartilage with application of the same amount of compressive load. Furthermore, during dynamic flexion-extension movements such as the stance phase of gait, the femur may primarily have rolling contact with the tibia (Liu et al., 2010). This would increase the femoral cartilage contact area, while tibial cartilage would have a smaller area of contact that is more consistently loaded (Sutter et al., 2015). Increased contact area may allow for greater distribution of load, which may lead to lower overall cartilage strain in the femoral condyles when compared to the tibial plateau (Sutter et al., 2015).

In a study evaluating compressive strains in the tibiofemoral cartilage of normal subjects in response to single-legged hops, statistically significant overall strains in both medial and lateral compartments of the tibial plateau were also observed (Sutter et al., 2015). They also reported local maximum strain values around 8% and 7% in the medial and lateral tibial

plateau, respectively, and 6% and 3% in the medial and lateral femoral condyles, respectively (Sutter et al., 2015), values that are comparable to the local maximum strain values of around 8%, 5%, 7%, and 3% observed in corresponding compartments within the present study. The locations of maximum strain values determined by Sutter et al. (Sutter et al., 2015) and by the present study are also comparable. However, despite reporting similar magnitudes and locations of maximum strain values, Sutter et al. (Sutter et al., 2015) did not find overall medial or lateral femoral cartilage strain to be significant as the present study observed. This difference may be because the loading activity consisted of 60 hops, which likely resulted in a lower number of loading cycles compared to the 20 minutes of normal gait conducted in the present study. The longer activity period and the higher number of loading cycles in the present study may have resulted in an increased strain response.

Recently, Cotofana et al. (Cotofana et al., 2011) analyzed cartilage deformation in females, both healthy and with OA. Standing was simulated using a loading apparatus, within the MR scanner, designed to apply a load roughly 50% of the subject's body weight. In healthy subjects, only cartilage on the medial tibia and central medial femur experienced significant overall compressive strain (Cotofana et al., 2011), differing from data generated in the present study. These differences may be explained by differing loading mechanisms. During static activity, compression is continuous, while load varies with time during dynamic activities such as walking. Static and dynamic loading mechanisms may also differ in neuromuscular control patterns and in contact areas (Eckstein et al., 2000). Furthermore, the static load simulation conducted by Cotofana et al. (Cotofana et al., 2011) may not fully reproduce the biomechanical environment of dynamic activities of daily living such as walking, in which complex muscle loading patterns play an important role. Finally, methodological differences may have also contributed to the discrepancies in results. Cotofana et al. (Cotofana et al., 2011) used MR images taken during load application, which leads to the calculation of instantaneous cartilage strain. The present study instead used MR images taken prior to and following the walking activity to calculate the strain response.

In investigations of volumetric cartilage deformation in response to running, two groups (Boockock et al., 2009; Kersting et al., 2005) observed significant post-activity cartilage deformation in lateral tibial cartilage and femoral cartilage. Notably, medial tibial cartilage deformation was not significant in either study (Boockock et al., 2009; Kersting et al., 2005). The discrepancy in results between these studies (Boockock et al., 2009; Kersting et al., 2005) and the present study may partially be attributed to differences between loading patterns in running and walking. However, the method used to quantify cartilage deformation may also play an important role. Both Boockock et al. (Boockock et al., 2009) and Kersting et al. (Kersting et al., 2005) measured cartilage deformation by calculating the change in cartilage volume. In contrast, the present study utilized site-specific measurements of cartilage thickness changes, which may be more sensitive to detecting local changes in morphology than volumetric measurements (Okafor et al., 2014; Sutter et al., 2015).

Using a combination of MR imaging and dual fluoroscopy, Liu et al. (Liu et al., 2010) evaluated instantaneous peak tibiofemoral cartilage deformation during the stance phase of gait. While our observation of higher local maximum compressive strains in the medial compartment of the knee relative to the lateral compartment is in agreement with the above

study, magnitudes of cartilage deformation were found to be lower in our study. This can be attributed to different types of strain measurements used between these two studies. Liu et al. evaluated the instantaneous strain response during the stance phase of gait. In contrast, the present study measured the strain response after completing multiple gait cycles, which includes the removal of the ground reaction force during the swing phase. Thus, lower magnitudes of strain would be expected compared to instantaneous strain measurements.

The results of the present study may also be compared to previous studies examining the effects of general diurnal activity on cartilage (Coleman et al., 2013; Widmyer et al., 2013). Coleman et al. (Coleman et al., 2013) reported statistically significant overall strains in both medial and lateral compartments of the tibial plateau as well as the medial femoral condyle in response to diurnal activity. Local maximum cartilage strains in these three regions were also comparable in magnitude to those detected in the present study (Coleman et al., 2013). In a study of the effects of diurnal activity in the tibiofemoral cartilage of normal BMI subjects, Widmyer et al. (Widmyer et al., 2013) found significant overall compressive strains in the medial tibial plateau and the medial and lateral femoral condyles. Similarities between these diurnal strain studies and the present study may be due to the fact that normal walking likely constitutes a large portion of diurnal activity.

However, while the present study found significant overall compressive cartilage strains in both medial and lateral compartments of the tibial plateau and femoral condyles, Coleman et al. (Coleman et al., 2013) found overall compressive strain to be insignificant in the lateral femoral condyle, and Widmyer et al. (Widmyer et al., 2013) found overall compressive strain to be insignificant in the lateral tibial plateau. One possible reason for this discrepancy is that the present study utilized a controlled walking activity, while the above studies assessed strains after general diurnal activity, an uncontrolled, though perhaps more realistic, combination of static and dynamic activities. Interindividual variability in diurnal activity may also be a reason for the difference in results between studies (Coleman et al., 2013; Widmyer et al., 2013).

Underestimates in strain measured in the present study may have been introduced by inadequate cartilage recovery time prior to the walking activity. Though subjects were asked to refrain from any strenuous activity the morning of the study and 45 minutes of non-weight-bearing rest time were allocated (Cher et al., 2016; Sutter et al., 2015), lower baseline cartilage thickness resulting from insufficient recovery may have led to lower strain values in our results. Some cartilage recovery may have occurred during the time elapsed from the completion of the walking activity to the completion of the post-activity DESS scan (approximately 13 minutes), also resulting in underestimates of cartilage strain. To further address these effects, future studies might characterize the *in vivo* creep recovery of tibiofemoral cartilage strains at various time points after activities of daily living.

A variety of additional factors may have potentially influenced cartilage strain values in this study. For example, individually unique mechanics of walking may influence how loads and forces are distributed within the knee joint (Andriacchi et al., 2009; Taylor et al., 2004). Interindividual variation in baseline cartilage morphology (Cicuttini et al., 2002; Coleman et al., 2013; Eckstein et al., 2014; Eckstein et al., 2001; Jones et al., 2000; Otterness and

Eckstein, 2007; Waterton et al., 2000) may also influence the loading response of articular cartilage. Additionally, cartilage deformational behavior may be influenced by factors such as age and BMI (Hudelmaier et al., 2001; Widmyer et al., 2013). However, because the subjects of the present study were of relatively narrow age and BMI ranges, the influences of these factors are unlikely to have played a large role in our results. Future studies should explore how factors such as sex, age, BMI, and walking duration and speed may influence cartilage strain.

The results of this study provide important baseline data regarding compressive strains in healthy knees in response to normal gait. Establishing baseline data and identifying localized variations in the cartilage strain response to walking is critical to understanding the role of altered mechanical loading in the development of OA. In the future, differences in cartilage deformational behavior in those susceptible to OA development, such as injured (Buckwalter, 2003; Roos, 2005; Roos et al., 1995; Whittaker et al., 2015) and obese populations (Felson 2006; Gelber et al., 1999; Messier et al., 2000; Oliveria et al., 1999), may be compared to baseline data such as those reported in the present study. Identifying altered cartilage response to walking may allow this technique to be used as a “stress test” to understand how risk factors such as age, obesity, or joint injury affect tibiofemoral cartilage strain response (Sutter et al., 2015). An improved understanding of these mechanisms would be invaluable to the development of new interventions aimed at the prevention of OA.

In conclusion, the present study has found that normal walking causes significant compressive strains in the articular cartilage of both medial and lateral compartments of the tibial plateau and femoral condyles. By characterizing the effects of gait on cartilage strains, the present study provides a better understanding of how normal joint loading influences knee cartilage response. This knowledge may be used to better evaluate the relationship between altered joint loading and OA development and, in the long term, improve treatment approaches.

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Figure 1.

(a) Human knees were imaged in the sagittal plane using a 3.0 T MR scanner. The outer margins of the tibia and femur as well as the corresponding articular cartilage surfaces were segmented. (b) Segmented surfaces were stacked to form a wireframe model and were subsequently (c) converted into a 3D surface mesh model.

Figure 2. Tibiofemoral strain grid points consisted of 18 points on each femoral condyle and 9 points on each side of the tibial plateau.

Figure 3. Representative color thickness maps of pre- and post-activity tibial and femoral cartilage were generated with thicker cartilage in red and thinner cartilage in blue.

Figure 4.

Pre-activity cartilage thickness varied significantly by sex and by compartment (Kruskal-Wallis ANOVA test; sex: $p < 0.0001$; compartment: $p < 0.0001$). Symbols representing sex and compartment illustrate significant differences between groups (Mann-Whitney U post-hoc test). Error bars represent the standard error of the mean.

Figure 5. Post-activity cartilage thickness decreased significantly compared to pre-activity thickness (Wilcoxon matched-pairs test; * $p < 0.003$). Error bars represent the standard error of the mean.

Figure 6.

Cartilage strains differed significantly from zero in all four tibiofemoral compartments (Kruskal-Wallis ANOVA test; Mann-Whitney U post-hoc test; * $p < 0.005$). Bars with different letters are significantly different from one another. Error bars represent the standard error of the mean.