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Dynamic compression of human and ovine meniscal tissue compared to a potential thermoplastic elastomer hydrogel replacement

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Abstract

Understanding how human meniscal tissue responds to loading regimes mimetic of daily life as well as how it compares to larger animal models is critical in the development of a functionally accurate synthetic surrogate. Seven human and 8 ovine cadaveric meniscal specimens were regionally sectioned into cylinders 5mm in diameter and 3 mm thick along with 10 polystyrene-*b*-polyethylene oxide block copolymer-based thermoplastic elastomer (TPE) hydrogels. Samples were compressed to 12% strain at 1 Hz for 5000 cycles, unloaded for 24 hours, and then retested. No differences were found within each group between test one and test two. Human and ovine tissue exhibited no regional dependency ($p < 0.05$). Human samples relaxed quicker than ovine tissue or the TPE hydrogel with modulus values at cycle 50 not significantly different from cycle 5000. Ovine menisci were found to be similar to human menisci in relaxation profile but had significantly higher modulus values (3.44MPa instantaneous and 0.61MPa after 5000 cycles compared to 1.97MPa and 0.11MPa found for human tissue) and significantly different power law fit coefficients. The TPE hydrogel had an initial modulus of 0.58MPa and experienced less than a 20% total relaxation over the 5000. Significant differences in the magnitude of compressive modulus between human and ovine menisci were observed, however the relaxation profiles were similar. Although statistically different than the native tissues, modulus values of the TPE hydrogel material were similar to those of the human and ovine menisci, making it a material worth further investigation for use as a synthetic replacement.

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Conflict of Interest

No benefit of any kind will be received either directly or indirectly by the author(s)

Keywords

meniscus mechanics; human; ovine; TPE hydrogel; meniscus replacement

Introduction

The menisci are wedged fibrocartilaginous tissues housed within the knee joint located between the femoral condyle and the tibial plateau. The structure of the menisci allows for stabilization of the knee and load distribution within the joint^{(1),(2)}. The menisci are biphasic tissues composed of approximately 75% interstitial fluid and a ground matrix composed of predominantly circumferential collagen fibers and glycosaminoglycan rich proteoglycans^{(3)–(5)}. A number of studies have investigated the compressive mechanical properties of human menisci under confined^{(6),(7)} and unconfined environments^{(8)–(13)} as well as indentation relaxation^{(11),(12),(14)}. Little investigation of the dynamic properties of the tissue has been performed, and that which has been done has assessed the tissue under a limited number of cycles⁽¹⁵⁾. Understanding how the tissue responds to loading regimes more mimetic of daily life is necessary if we wish to succeed in ultimately replicating the meniscus with a functionally accurate synthetic surrogate or scaffold.

Meniscal tissue is primarily avascular in nature⁽³⁾ limiting its ability to heal when damaged, which is common as a result of both athletic injuries as well as degenerative changes⁽¹⁶⁾. The National Survey of Ambulatory Surgery in 2006 identified more than 364,000 knee arthroscopies performed due to a diagnosis of a tear to the medial cartilage or meniscus⁽¹⁷⁾, and meniscal arthroscopic treatment is one of the most common orthopaedic surgical procedures accounting for up to 20% of all surgeries⁽¹⁸⁾. Currently, there are few technologies to replace damaged menisci, and standard treatment is to leave asymptomatic damage alone or perform partial meniscectomies⁽¹⁹⁾. However, both of these solutions lead to an increased risk of osteoarthritis (OA) development^{(20)–(22)}.

Ultimately, the functionality of both the material used as a replacement or scaffold, as well as the large animal model used for in vivo testing should be considered carefully. A number of synthetic materials have been investigated for meniscal replacements^{(23)–(29)}. Limitations with previously reported materials include poor durability, mechanics, and biocompatibility^{(30)–(32)}. Degradable scaffolds have also been investigated to serve as temporary meniscal replacements but have been shown to have limited mechanical integrity and lead to cartilage damage once tested *in vivo*^{(33)–(37)}. Large animal models, such as the ovine model, are often used for in vivo studies of potential meniscal replacements^{(27),(36),(38),(39)} for their similarity to human menisci both with respect to size⁽⁴⁰⁾, single compression mechanical data⁽⁶⁾ and structural composition⁽⁴¹⁾. However, while these tissues are very similar in many aspects, comparisons thus far are limited and their differences are important to consider when designing a translational implant.

The objective of this study was to test human meniscal tissue across 5000 compressive cycles and compare findings to ovine menisci and a recently developed thermoplastic elastomer (TPE) hydrogel⁽⁴²⁾ engineered for its potential as a meniscal replacement. The TPE hydrogel evaluated in this study has been previously shown to possess high elasticity,

fatigue resistance, and compressive moduli tunable within the range of that exhibited by native meniscal tissue. This study will be one of the first to evaluate native meniscal tissue across a high number of compressive cycles. Previous work has only assessed strain rate dependency at low frequencies and a limited number of cycles⁽¹⁵⁾. Modulus values will be compared as well as a model fit of the modulus vs cycle data. It is hypothesized that the human and ovine modulus values, and cyclic relaxation profile will be similar given the physiological and compositional similarity between these tissues⁽⁶⁾. Preliminary work suggests the TPE hydrogel material will exhibit modulus values within the range of the native tissues, but is not expected to have the same magnitude of cycle to cycle relaxation due to its much faster fluid transfer and limited hysteresis compared to native menisci.

Materials and Methods

Sample Harvesting

Human specimens were de-identified and obtained from a tissue bank (National Disease Research Interchange, Philadelphia, PA, USA), and ovine knees were collected from other terminal studies. NIH guidelines for the care and use of laboratory animals (NIH publication #85-23 Rev. 1985) have been observed. Menisci, identified as healthy, from a total of seven human cadaveric specimens (ages 60±21) and 8 mature ovine (*Ovis aris* Rambouillet X Columbia breed) cadaveric specimens were sectioned into medial and lateral, anterior and posterior segments and slow thawed in 1× phosphate buffer saline (PBS) solution. Samples were created using a five millimeter diameter biopsy punch taken from the proximal to distal ends with the number of samples dictated by the tissue available; usually 4 samples were taken from each meniscus but individual meniscus shapes and thicknesses sometimes limited sample collection. Samples were then stored at 1.6°C in 1× PBS for 24 hours to allow equilibrium swelling to occur. A sizing apparatus was used to cut the samples 3 mm thick from the mid-belly of the biopsy (Figure 1). A total of 10 samples for all regions were tested for both human and ovine groups with the exception of the medial posterior region in human where only 9 samples were tested due to tissue availability.

TPE Hydrogels were created using custom aluminum cylindrical molds. A blend of polystyrene polyethylene oxide (PS-PEO) and polystyrene polyethylene oxide polystyrene (PS-PEO-PS) were synthesized as previously described⁽⁴²⁾, packed between two Kapton sheets, melt pressed in a Carver Press (150°C, 500psi, 10 minutes), allowed to cool to room temperature, and then swollen in 1× PBS for 24 hours prior to testing. Mold dimensions were created such that the swollen cylindrical samples were 3 mm thick and 5mm in diameter. A total of 10 TPE hydrogel samples were used for testing.

Testing Protocol

Samples were mounted with the femoral aspect of the plug exposed using a cyanoacrylate glue between two polished aluminum platens in a heated 1× PBS bath (96–99°F) and tested using a servo hydraulic testing system (Bionic Model 370.02 MTS) equipped with a 2lb load cell (Futek LSB200) for measuring axial force. The average thickness was measured using calipers, and following a 200mN preload, samples were compressed to 12% strain in a sinusoidal waveform for 5000 cycles at 1 Hz representing physiological strains, frequency,

and the average daily steps taken by Americans^{(43),(44)}. After initial testing, all samples were again stored at 1.6°C in 1× PBS for 24 hours after which the testing protocol was repeated resulting in two tests for each sample.

Data Analysis

A customized MATLAB (Mathworks, Natick, MA) script was used to analyze the data. Modulus values were determined from a linear fit of the 2–10% stress-strain data of each loading cycle. This portion of the data was found to be linear and avoided inconsistencies in data points resulting from change of direction in loading. A second order power law fit of the modulus vs cycle graph was used to fit the relaxation curve, as has been previously done for biological tissues^{(45)–(47)}. A one way analysis of variance (ANOVA) with a post hoc Tukey's test was used to assess differences between the two tests across all regions of interest. If no differences between the two tests were found, samples were averaged. A one way ANOVA was also used to assess differences between regions with values of interest including cycle 1, cycle 10, cycle 25, cycle 50, and the final 5000th cycle as well as the three coefficients from the power law fit (coefficients A, B, and C from Equation 1 where x is equal to the cycle and y is equal to the modulus). If no statistical differences were observed across regions, all regions were averaged. Once averaged an ANOVA was used to determine differences across cycles of interest within groups (human, ovine, and TPE hydrogel) as well as differences across groups for both modulus values and coefficients of the power law fit. Significance was set at $p < 0.05$.

$$y = Ax^B + C \quad \text{Equation 1}$$

Results

The average thickness for the human, ovine, and TPE hydrogel samples was 3.02 ± 0.29 , 2.68 ± 1.38 , and 2.83 ± 0.06 respectively. The smaller meniscal size of the ovine samples resulted in a number of biopsies not producing a cylindrical sample with a thickness greater than 3mm. In this case samples were leveled on the proximal and distal aspects to create a uniform sample thickness and still tested to 12% strain accounting for the tissue height. Using a second order power law, the average curve fit had a R^2 value of 0.96 ± 0.04 , 0.87 ± 0.1 , and 0.99 ± 0.003 for human, ovine, and the TPE hydrogel respectively. No statistical differences were found between the test one and test two, so the two tests were averaged. After averaging the initial and repeat tests, statistical comparisons were performed to ascertain differences between regions for the human and ovine menisci. No statistical differences were found between regions, with respect to modulus (Figure 2), or the coefficients from the second order power law fit (Figure 3) for human and ovine tissue.

Since no regional differences were found in the native human or ovine meniscal tissue, all regions were combined for comparison with the TPE hydrogel samples (Figure 4). Rapid relaxation occurred in both the human and ovine menisci with equilibrium typically reached prior to 1000 cycles. With all regions averaged, statistical differences were assessed within groups (human, ovine, and TPE hydrogel) as well as across groups at specific cycles

including cycle 1, 10, 25, 50 and 5000. Significant differences were found, with the ovine meniscus having a higher modulus value than both human and the TPE hydrogel at all cycles of interest (Figure 5).

Discussion

This study is one of the first to investigate the mechanical response of multiple meniscal tissues as well as a potential replacement material under repeated cyclic compression similar to what is experienced *in vivo* over the course of multiple days. It was found that when allowed to rest for 24 hours between cyclic tests, no significant differences were seen in any of the samples with respect to the initial response, relaxation profile, and equilibrium response. Human and ovine menisci were found to be similar in response, but the magnitude of the modulus values for the ovine tissue was greater. The TPE hydrogel material, although often found to be statistically different, had a modulus value between that of the human and ovine for the majority of the 5000 cycle test. The greatest difference between the TPE hydrogel and the two native meniscal tissues was the limited relaxation observed in the TPE hydrogel.

Previous research has reported significant differences between the anterior and posterior regions of meniscal tissue⁽⁹⁾, which was not observed within this study. However, a previous report by Leslie et al. reported no significant differences between posterior and anterior values⁽⁸⁾, and although our data was not found to be statistically different, it does follow the trend of the anterior region being stiffer than the posterior region as others have shown^{(12),(48)}. In the current study, samples were sectioned into anterior and posterior regions, and when possible multiple samples were excised from a single region. While the biochemical constituents responsible for compressive and tensile mechanics have been suggested to be proteoglycans and collagen respectively, it is unclear how the tissue supports cyclic compressive loading.

Modulus values obtained in this study are similar to those previously reported for human and ovine meniscal tissue under alternative compressive testing methods. In a stepped relaxation followed by dynamic sweep study, instantaneous modulus values for human tissue was reported to be ~1MPa and equilibrium values ~0.2MPa with dynamic modulus values in the 0.7–0.8MPa range, all of which is in agreement with the current study⁽⁴⁸⁾. In a similar study by Bursac et al. the dynamic modulus at 0.2% strain and 1Hz was found to be 1.03MPa which is lower than that seen for the first few cycles in the current study, but can be attributed to the lower strain level. In a stress relaxation test of human tissue Chia et al. found instantaneous modulus values of approximately 0.7MPa and equilibrium values approximately 0.08MPa⁽⁹⁾ at 12% strain. Less work has been performed to characterize the instantaneous or dynamic response of ovine menisci, but the average 0.6MPa value reported here for the 5000th cycle (representing equilibrium) are similar to existing studies with aggregate moduli ranging 0.2–0.5MPa^{(6),(49)}. This leads the authors to believe that although continuous cyclic loading is important to understanding the temporal effects on the tissues and potential replacements, the more conventional single cycle compressive testing and relaxation testing could stand as a proxy for characterizing the initial and final cycles of such a test. These more conventional tests require far less time allowing for larger sample groups.

It has been well documented meniscal tissue has an initial response vastly different from the equilibrium response likely due to the fluid flow and/or inherent viscoelasticity within the tissue when compressed. It is unknown how much time the tissue requires to return to its fully hydrated, uncompressed state following a compressive cycle. In the current study a rest period of 24 hours was chosen and the meniscal tissue for both species was able to recover within this time frame. Additional work is necessary to determine the minimal time required and this time frame is likely dependent on the environment. Samples were tested and allowed to re-equilibrate in an unconfined and unpressurized environment which is not totally mimetic of the *in vivo* condition. Future work in this area would benefit from including histological analysis along with mechanical assessments. Comparisons between the relaxation profile of the tissue and the biochemical composition, specifically glycosaminoglycan (GAG) content, may provide a stronger correlation than purely comparing GAG content to the equilibrium response of the tissue as has been previously done⁽⁵⁰⁾.

The current study shows that while ovine meniscal tissue under certain loading conditions is mimetic of human meniscal tissue, there is a statistically significant difference in the cyclic compressive load response. As shown in Figure 5 the human and ovine menisci were found to be significantly different in all areas assessed including modulus values at 5 different cycles throughout the 5000 cycle test as well as all three coefficients from the power law fit. From this data ovine menisci appear to be stiffer and relax slightly slower than human tissue. Nevertheless, the apparent response across all 5000 cycles shown in Figure 4 is comparable. For this reason the ovine model is still a valid animal model for meniscal work; however, researches should consider these stiffer properties when assessing translational therapies and replacements. In the case of a meniscal replacement restoring contact mechanics and pressure distribution is likely more vital than precisely mimicking the native tissue mechanics.

Our TPE hydrogel material did not achieve modulus values of the same magnitude as the initial few cycles of either native tissue, but relaxed much less than the native tissues as over 5000 cycles. The TPE hydrogel only lost 19% of the initial response compared to the human and ovine tissues which experienced a drop of 95% and 82% respectively. Compressive mechanical deterioration of the menisci has been shown to occur in patients with osteoarthritis and increase with the severity of osteoarthritis⁽⁵¹⁾. The pathogenesis of the disease and subsequent relationship to the mechanical integrity of the surrounding tissues is still not fully understood. It may be advantageous to design a replacement material that still exhibits some viscoelasticity but does not relax to the extent of the native tissue. The importance of the native tissue's vastly greater initial modulus compared to the equilibrium modulus as well as the rapid relaxation of the tissue has not been investigated. For this reason, the TPE hydrogel tested in this study may still be a viable material option for future meniscal replacements. The nature of this TPE hydrogel sets it apart from previous materials as it allows for long-term shape preservation and tunable swelling⁽⁴²⁾ while more closely matching native meniscal properties compared to other replacement technologies which often exceed the native tissues compressive mechanics^{(26),(30)}.

All TPE hydrogel samples used within the scope of this study were produced from a single batch polymerization and as such the variance from sample to sample was extremely low. In contrast, meniscal samples were taken from a range of donors leading to greater sample to sample variance. Ultimately, if this material is to be considered for potential meniscal replacement a more thorough assessment of mechanical properties should be conducted as well as an evaluation of batch to batch variance and cytocompatibility. Another limitation to the current study is human samples were healthy but were collected from a more elderly population. A clear link has yet to be discovered between tissue age and mechanics, as it is difficult to divorce joint changes resulting from age, genetics, obesity, and altered joint kinematics. However, increased severity of visual tissue degradation associated with OA has been shown to result in decreased compressive properties of human meniscal tissue ⁽¹⁴⁾, and tissue degradation along with OA prevalence is more common in elderly populations ⁽⁵²⁾.

In conclusion this study found that although ovine menisci are statistically different from human they do have similar relaxation trends when comparing cyclic compressive mechanic properties. This, in combination with previous literature, supports the use of ovine as a large animal model for the human meniscus condition. However, researches should bear in mind the modulus differences between the two species when choosing to use an ovine model for meniscal studies. The TPE hydrogel material tested had a similar average modulus to the human tissue and ovine tissue but did not experience the same rate or degree of relaxation across the 5000 cycles tested. Without a clear understanding of the importance of this relaxation phenomena, it is hard to conclude if the TPE hydrogels lack of relaxation would prove disadvantageous or not. Implanting the TPE hydrogel in the ovine joint and evaluating the long term effects of joint protection is necessary to determine its viability as a material option for meniscal replacement.

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Figure 1.
Meniscus harvesting and cutting

Figure 2.

Regional compressive modulus vs cycle for human (A, B) and ovine (C, D) meniscal tissue. B and D show compressive moduli (average $\pm$ std) after selected numbers of completed cycles (1, 10, 25, 50, and 5000) used for statistical analysis

Figure 3.
Coefficients of power law fit for all regions of human (A) and ovine (B) meniscal tissue.
Data shown as an average $\pm$ std

Figure 4.
Modulus values and relaxation profile across all 5000 cycles (average $\pm$ std)

Figure 5.

Modulus values (average $\pm$ std) for cycles of interest for human (A) ovine (B) and TPE hydrogel (C) as well as a comparison of all three groups (D). Coefficients from power law fit (average $\pm$ std) for all groups (E). Statistical significance denoted as the following: @ sig diff from cycle 10, # sig diff from 25, \$ sig diff from 50, % sig diff from 5000, ^ sig diff between human and ovine, & sig diff between ovine and TPE hydrogel, * sig diff between human and TPE hydrogel