Correlation of damage score in PTOA with changes in stress on cartilage in an ovine model

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SUMMARY

Objective: There is a high risk of developing osteoarthritis (OA) following traumatic injury to the knee. Severe ligament injuries can disrupt the integrity of the multicomponent knee at both biological and biomechanical levels. We hypothesize changes in cartilages stresses could lead to tissue damage and development of OA.

Design: The in-vivo gait kinematics of the stifte (knee) joint of four adult female ovine subjects were recorded prior to and at ten-and-twenty weeks following partial ACL-MCL transection. The subjects were sacrificed and the experimental joint from each subject was mounted on a parallel robotic system programmed with the kinematic findings. Ten custom-built Fibre Bragg Grating optic sensors were arranged to measure contact stresses on the surface of the tibial plateau articular cartilage. These sensors provide the first accurate stress measurements in a joint during gait replication using the previously recorded in-vivo kinematics. The relationship between the results obtained and observed focal damage was assessed.

Results: The locations on the tibial plateaus that experienced the greatest change in contact stresses corresponded with the locations of focal damage development. No direct link was detected between individual animal differences in kinematics and variations in stress magnitudes or the development of focal cartilage damage.

Conclusions: The findings highlight the importance of mechanical stress determinants in the integrated set point for the knee (with individual variation), and how injury-related stress changes correlate with development of PTOA.

1. Introduction

Osteoarthritis (OA) is a very prevalent degenerative joint condition which affects more than 10% of the population over the age of 15 [1,2] with this percentage expected to rise. The term osteoarthritis should be considered an umbrella term, with a number of disease subsets based on initiating factors all culminating in loss of articular cartilage integrity. Some OA is associated with obesity [3] and may be labelled metabolic OA [4], while other forms appear to be associated with the post-menopausal state in females. The incidence of knee OA in males and females is ~1:1 prior to the age of menopause, but after menopause the incidence is reported to be considerably higher in females vs males [5,6]. While much of the OA in the remaining population is of unknown cause (i.e. idiopathic), ~12% of OA cases can be traced to an overt injury to a joint [7] - post-traumatic OA (PTOA). While in most types of OA, the time of disease initiation is unknown, in the case of PTOA the time of injury is likely known and thus has a frame of reference.

With the occurrence of a knee injury, there is increased risk of developing PTOA, but not all individuals with a similar injury develop OA [8]. In fact, the risk for development of OA after an ACL tear does not diminish even when the ACL is reconstructed to restore stability to the knee (~50% by 10–15 years post-injury) [8]. Thus, the response of
humans to a knee injury is quite variable, and the pattern of response very individualized.

While the development of PTOA is likely the most studied form of OA from both a preclinical and clinical perspective, with preclinical models ranging from small animals such as inbred mice to large outbred animals such as sheep, the answer to the question of how a knee injury contributes to development of PTOA remains unresolved. Some of the newer perspectives have focused on a change from viewing the condition as a cartilage disease in isolation, to viewing OA as a joint disease, with the joint considered an organ system [5,10]. Thus, at the time of skeletal maturity, this system has established a “set point” for the interactions of the various elements and tissues. The concept of a set point is based on the idea that a joint such as a knee functions as an integrated unit comprised of multiple tissues that develops during growth and maturation. The set point allows the joint to function within a physiologic “window” without damage to the individual components. Thus, it delineates and encompasses the biomechanical and biological boundary conditions under which the joint remains healthy. Disruption to this set point (structural, biological, or biomechanical) can result in a cascade of degenerative changes that affect one another, culminating in degenerative changes within the joint and leading to joint [9]. Likely such a set point is influenced by genetics, developmental and maturational variables, and use, leading to the individual nature of the set point.

Unfortunately, many of the methods that have been used to understand how such an injury would impact the biomechanical functioning of the joint, such as stress sensitive films have a number of important limitations [11,12]. The presence of the films within articular joints can alter joint biomechanics considerably [13,14]. To insert the films within articular joints a significant amount of dissection is typically required. Furthermore, there are significant errors associated with their use on curved surfaces, their elastic moduli, and other fundamental properties [14,15]. Consequently, newer methods are needed to provide improved assessment of stress changes on the cartilage of an injured joint such as a knee.

One such technology is Fibre Bragg Grating (FBG) Sensors. FBGs are inscribed periodical variations in the refractive index of photosensitive optical fibres [16]. As light spanning a spectrum of wavelengths propagates through the core of an optical fibre reaching the FBG sensing segment, a portion of that light centered at the “Bragg wavelength” is reflected. The Bragg wavelength is a function of the spatial period of the change in the refractive index otherwise referred to as the “grating spacing”. Parameters such as load induced mechanical strain in the fibre, that cause a change in the grating spacing will create a measurable change in the Bragg wavelength [16].

FBG sensors offer a new approach to assessing cartilage stresses [11,12]. Their small size allows for easy insertion into tight joint spaces without the removal of biomechanically relevant structures. They are biocompatible, flexible, and mechanically compliant [13]. Furthermore, they exhibit excellent wavelength to strain linearity with sub-millisecond response time. The sensors used in this study are insensitive to orientation, axial strain, and limited changes in temperature [11,13].

The present study combined this novel FBG technology with our capability to measure, record and replicate accurately six degree of freedom joint motion, allowing us to measure changes in in-vivo stress levels within the knee following ligament injury. The chosen injury model involved a partial transection of the anterior cruciate ligament (ACL) performed arthroscopically and the complete transection of the medial collateral ligament (MCL). It was hypothesized that the inflicted ligament injuries would alter joint kinematics, creating a substantial change in the mechanical stress, culminating in the development of focal damage consistent with PTOA [8,17].

2. Methods

Four healthy mature female cross-Suffolk sheep were accepted into this study with an N-of-1 study design [18–20]. The subjects were similar in weight (75 ±5 kg) and age (3–5 years old). The sheep were trained to walk on a treadmill at a speed of 2 miles per hour. Following training, each subject underwent a plating surgery on the right limb where a stainless-steel fracture plate was implanted on the lateral side of the femur and a second fracture plate was implanted on the medial side of the tibia (Fig. 1). Each plate was firmly attached approximately 100 mm from the joint line using 2 to 3 stainless steel surgical screws (4.5 mm screws, Synthes, USA). The chosen locations for the plates ensures that the joint capsule remains intact while providing suitable flat surfaces on the bones for the plate. Each animal was allowed adequate healing time (a minimum of four weeks) such that they were visually walking normally again before undergoing a second surgery, where stainless-steel posts were screwed onto the implanted plates. Following the second surgery and once the sheep were visibly displaying normal gait each subject was guided onto a treadmill, the ISL was attached to the posts and used to record the six-degree-of-freedom kinematics of the right ovine stifle joint. Each subject walked on the treadmill, for a minimum of 100 natural strides. Following a second period of healing, each subject underwent a third surgery where a surgeon transected the MCL and part of the ACL in the right stifle joint arthroscopically. The ISL was then used to measure the six-degree of freedom kinematics of the right ovine stifle joint ten and twenty weeks after this surgery. Following the last gait kinematics recording, the subjects were euthanized, and the hind limbs were disarticulated. The skin, muscles, synovial sac, and tendons were removed. All procedures and surgeries were approved by the Animal Care Committee at the University of Calgary.

Each dissected right limb was digitized using a FaroArm coordinate measuring machine (FaroArm Platinum, Faro Technologies, Lake Mary, FL, USA; accuracy 0.025 mm). Two coordinate systems were defined, one on each of the femur and tibia. A MATLAB code was used to analyze the recorded gait kinematics and determine the motion of the tibia relative to the femur [19,20]. The joint was mounted on a 6 DOF parallel robot (R-2000, PRScO, Hampton, NH, USA; 0.05 mm accuracy). The parallel robot was used to replicate the median of the natural strides recorded for each of the three sets of recorded gait kinematics i.e. prior to injury and at ten and twenty weeks post pACL-MCL transection [21,22].

Prior to gait replication ten calibrated FBG sensors [12] were positioned on the articulating surface of the tibial plateau. The FBG sensors were along six optical fibres with four fibres containing two sensors each and two fibres containing one FBG sensor along its length. The approximate positioning of the sensors on the tibial plateau of each subject is shown in Fig. 2. During gait replication the sensors, along with an optical sensing interrogator (sm130, Micron Optics, Atlanta, GA, USA) and the compatible sensing analysis software (ENLIGHT, Micron Optics, Atlanta, GA, USA), were used to measure mechanical stress on the surface of the tibial plateau. Details regarding the design and use of the sensors are available in previous publications [11,12].

Previous studies in this model [23] have indicated that the responses to injury are individual in nature, similar to what has been observed in humans. Consequently, an N-of-1 experimental design was chosen [18–20], where each subject is serves as its own control with the kinematic assessments performed before and after the injury. Thus, comparisons and the detailed analyses are focused on the individual animal rather than group changes.

2.1. Scoring of joint damage

The damage to the articular cartilage in the stifle joints was morphologically graded by a minimum of two informed observers according to the grading system described by Cummings et al. [24]. The partial transection of the ACL and full transection of the MCL resulted in tissue alterations indicating the initiation of PTOA in the form of gross cartilage damage and osteophyte formation in all subjects. To only
consider the effects of the surgical intervention, the scores from the left limb (only minor morphological damage observed) were subtracted from the scores of the right (surgical) limb. The morphological grading of the articular cartilage was noted based on location of the damage.

3. Results

3.1. Six-degree of freedom gait kinematics

The analyzed results in terms of the six degree of freedom kinematics for the four ovine subjects are presented in Fig. 3. All four subjects exhibited an increase in the flexion angle at hoof strike at ten weeks post-injury as compared to intact kinematics. This remained the case for three of the four subjects at mid-stance and two of the four at hoof-off. During the swing phase the joints were considerably more extended at twenty weeks post-surgery compared to prior to surgery. In terms of the abduction-adduction and internal-external rotational degree of freedom, there was a large inter-subject variability both at ten- and twenty-weeks post injury, consistent with a disruption of integrity in an individual manner. Regarding the medial-lateral translation degree of freedom, three of the four subjects exhibited a medial shift at the hoof strike and mid-stance points for both ten- and twenty-weeks post injury. Considering the anterior-posterior translation degree, for three of the four subjects there was a statistically significant anterior shift for both time points. This was an expected outcome considering the role of the ACL in healthy joints in restraining the tibia from sliding anteriorly with respect to the femur. Lastly, considering the inferior-superior degree of freedom there was a general superior shift in all four subjects for both ten- and twenty-weeks post-injury.

Fig. 1. A surgical plate screwed onto the media side of the tibial providing an attachment site for the posts and the ISL (left). A schematic representation of the ISL used in the study. The ISL was attached to the plates on both the femur and tibia to record tibiofemoral kinematics of the ovine stifle joint as each subject walked on a treadmill at the predetermined speed of 2 miles/hr (right).

Fig. 2. The approximated positioning of the ten FBG sensors on the tibial plateau of each ovine stifle joint. The FBGs were placed on the articulating surface of the tibial plateau under the menisci. The dimensions shown in green represent the distance between the sensors along each fibre. All dimensions are in mm.
Fig. 3. The 6° of freedom in-vivo kinematics of the ovine stifle joint pre- and post partial ACL and MCL transection for subject 1 (a), subject 2 (b), subject 3(c) and subject 4(d). Including: degree of rotation in flexion-extension, abduction-adduction and internal-external direction and translations in mm for the medial-lateral, posterior-anterior and inferior-superior directions. Intact kinematics are shown in black, 10 weeks post injury in red and 20 weeks post surgery kinematics in blue. The solid line is representative of the mean recorded stride and the shaded areas denote mean ± one standard deviation for the recorded strides. The rotational degrees of freedom are in degrees and the translation degrees of freedom are shown in mm.
3.2. Morphological grading

The largest morphological changes on the tibial surfaces were observed on the anterior aspects of the medial and lateral compartments, with all four subjects exhibiting some degree of damage on the anterior side of each compartment. In contrast, there was no sign of damage for any of the subjects on the posterior side of the tibial plateau. Table 1 below shows the gross morphological grading for the tibial surfaces of each subject.

On the femoral surface, the most damage was found on the anterior and posterior side of the lateral condyle, with one subject (Subject 2) showing no sign of damage in this section. There were no signs of damage observed on the distal patella in any of the four subjects and only minimal morphological change on the proximal aspect. The scores for cartilage damage were higher than gross osteophyte scores with the highest morphological change occurring on the lateral femoral condyles both in terms of gross cartilage score and gross osteophyte score (Fig. 4). Importantly, no correlations were found between alterations in the six degree of freedom joint kinematics and the gross morphological grading [25]. However, this may be due to the main limiting factor in this analysis - the small number of subjects considered in the study.

Table 1
Gross morphological grading of articular cartilage and osteophyte formations in four ovine stifle joints according to a grading system described by Cummings et al. [8].

| Subject  | Cartilage | Osteophytes | Cartilage | Osteophytes | Cartilage | Osteophytes | Cartilage | Osteophytes |
|----------|-----------|-------------|-----------|-------------|-----------|-------------|-----------|-------------|
| Subject 1| 2         | 0           | 0         | 3           | 0         | 0           | 2         | 0           |
| Subject 2| 3         | 0           | 0         | 0           | 0         | 2           | 2         | 0           |
| Subject 3| 3         | 0           | 0         | 0           | 0         | 2           | 2         | 0           |
| Subject 4| 3         | 0           | 0         | 3           | 2         | 0           | 0         | 0           |

3.3. Changes in stress magnitudes on the surface of cartilage

A key advantage of the described methodology is the simultaneous measurement and assessment of stress magnitudes at distinct positions on the surface of the tibial plateau at various stages of the gait cycle. Fig. 5 illustrates stress variations over the median stride for sensors located on the lateral tibial plateau of subject 3 and is provided as an example of the obtained data. Almost invariably, peak stress was achieved at approximately 8% gait corresponding to the point of “Hoof/foot flat”. “Hoof/foot flat” is the point in the gait cycle where the foot or hoof in question is in complete contact with the ground and the contralateral foot/hoof is lifted off the ground.

The data measurements obtained from a subset of sensors were deemed incomplete or unusable during analysis and omitted. This was due to blind sections in sensor data. Blind sections are indicative of the light not reaching the FBG sensing segment and can be indicative of high stresses, tight bends in the fibre, and/or damage to the fibre core.

The methodology described allows for analysis of stress magnitudes during the gait cycle including the calculation of peak and mean stress. These parameters are presented in Figs. 6 and 7 at the approximate position of each sensor, creating a map of the mean and maximum stress for each replicated gait cycle.
The present study follows the format of an N-of-1 study [18–20]. In this format, each subject is examined independently before and after a medical intervention or isolated event, enabling high resolution monitoring of individual subjects [20]. To investigate possible correlations between changes in stress magnitude and distribution patterns and the development of focal damage on the surface of articular cartilage, a qualitative comparison between the locations of observed focal damage and variation in stress magnitude following trauma was performed. Following the N-of-1 study design, each subject was considered independently.

3.4. Subject 1

On the lateral tibial plateau, the biggest change in both average and maximum magnitude of stress was at position L4 where the maximum stress value had an increase of approximate 40% at 10 weeks post trauma from 4.35 MPa to 6.07 MPa (Fig. 7).

The morphological change in the articular cartilage observed on the anterior aspect of the medial tibial plateau was located close to sensor positions M4 and M2 (very close to sensor position M4). Both sensor positions underwent significant increases in maximum stress magnitude after 20-weeks post trauma with the maximum stress magnitude at position M4 increasing by over 140%.

3.5. Subject 2

Considering the lateral tibial plateau, there were no large increases detected in peak stresses during the gait cycle after 20-weeks post-trauma. In terms of variations in average stress magnitudes during the gait cycle at 20-weeks post-trauma the biggest change occurred at position L5. The maximum stress magnitude at this point increased by approximately 2.33 MPa, an increase of over 138% compared to stress obtained when replicating intact kinematics. Interestingly, the only morphological change observed on the articular cartilage covering the lateral tibial plateau of this subject was located adjacent to this sensor position.

On the medial tibial plateau, the largest change in mean stresses occurred at positions M2 and M4. The average stress at position M4 increased by approximately 2.34 MPa (113% increase) at 20 weeks post-trauma as compared to preinjury levels. Moreover, the largest change in peak stress magnitudes during the gait cycle also occurred at position M4, reaching a magnitude of approximately 21.78 MPa (65% increase) at 20-
Fig. 6. Mean stress values over the gait cycle at approximate sensor positions of four ovine subjects. The sensors were placed under the menisci on the surface of articular cartilage covering the tibial plateau. The noted values to the right of each sensor denoted measured stress values in MPa. Stress values shown in black, red and blue denote measured stress values obtained during the replication of intact, 10- and 20-weeks post pACL-MCL transection respectively.

Fig. 7. Peak stress values over the gait cycle at approximate sensor positions of four ovine subjects. The sensors were placed under the menisci on the surface of articular cartilage covering the tibial plateau. The noted values to the right of each sensor denoted measured stress values in MPa. Stress values shown in black, red and blue denote measured stress values obtained during the replication of intact, 10- and 20-weeks post pACL-MCL transection respectively.
weeks post-trauma. The only morphological change observed on the articular cartilage covering the medial tibial plateau was located adjacent to this sensor position.

3.6. Subject 3

On the lateral tibial plateau, a grade 2 focal damage was observed spanning the anterior aspect of the plateau and extending to the lateral aspect. A grade 2 osteophyte formation was also found close to sensor position L2. Hence, large variations of stress were expected at sensor positions L2 and L4. Intact stress variations during gait for position L2 were unavailable due to blind segments in the data, but the peak stress at 10-weeks post-trauma was over 100% greater than that at 20-weeks post-trauma at this position. Considering changes in average stress magnitudes, the largest significant change occurred at position L4 where the average stress increased from 2.44 MPa to 8.24 MPa at 10-weeks post-trauma.

The focal damage observed on the medial tibial plateau consisted of a small grade 1 defect close to sensor position M5 and a larger grade two focal damage on the anterior aspect of the medial tibial plateau located between the two fibres containing sensors located at position M1-M4. However, the data obtained at sensor positions M1 and M2 were not suited for analysis In terms of average stress magnitudes during the gait cycle, there was an increase from 4.43 MPa for intact kinematics to 6.94 MPa for 20-weeks post-trauma kinematics at sensor position M5, representing an increase of >56%. While there was a similar increase at position M3 at 10-weeks post-trauma compared to intact kinematics, the difference was reduced by approximately 33% for 20-weeks post-trauma kinematics.

3.7. Subject 4

On the lateral tibial plateau, there were significant increases in peak stress magnitudes at positions L1, L2 and L4. In terms of variations in average stress magnitudes during the gait cycle, significant changes were apparent at positions L1 and L4. Average stress values also increased at position L2 by >100%. However, the average stress magnitude remained relatively low regardless of this increase.

Interestingly, there was a grade 3 morphological change observed on the anterior aspect of the lateral tibial plateau between sensor locations L1 and L4 and a grade 2 morphological change on the lateral aspect between sensors L1 and L2. These observations further support our initial hypothesis that the locations of morphological change in the knee joint following trauma are correlated to positions experiencing large changes in stress magnitude.

On the medial tibial plateau, where the data are incomplete due to issues regarding sensor sensitivity and sensor reliability, focal damage was observed on the anterior aspect of the medial tibial plateau between sensor positions M1 and M4 closer to sensor position M4. In addition, a grade 1 osteophyte formation was observed on the posterior aspect of the medial tibial plateau to the lateral side of sensor position M3. Due to the incomplete nature of stress measurements on the medial tibial plateau no further comments can be made regarding the correlation between changes in stress and the observed focal damage in this area for this subject.

4. Discussion

The development of the unique FBG sensors used in this study together with our capability to replicate in-vivo joint motions accurately has produced the first direct measurement of stresses on the surface of cartilage using in-vivo gait kinematics. In comparison to other motion recording systems, the instrumented spatial linkage used to measure and record gait kinematics, possesses a higher dynamic accuracy (0.1 ± 0.1 mm, 0.1 ± 0.1 degrees).

The main finding of this study is the relationship between changes in stress and the development of focal damage on the cartilage surface in terms of location. The observations from each subject lend credibility to the hypothesis that large changes in stress magnitudes at each position on the surface of articular cartilage are correlated to the formation of focal damage at those positions. Importantly it is the change in stress following ligament injury that is correlated with the development of focal damage and not the magnitude (mean or Peak), highlighting the importance of determining the base level of stress in the healthy joint and the need to look at the data on an individual basis. The idiosyncratic nature of the development of OA is due to factors such as genetics, so while a change in stress is a critical factor, its impact is dependent on the quality of the cartilage in the individual subject.

Another interesting finding was that analysis of the kinematic results yields no direct correlation between changes in kinematics and the development of damage on the articular surface [25].

Considering the intricacies of stress distribution patterns across articular joints and the dependency of stress magnitudes on biological factors, material properties, small individualistic differences in gait kinematics and joint structures among other factors, this finding further illustrates thatkinematic measurements alone are not sufficient to form strong conclusions regarding joint kinetics and contact stresses, and their distribution in the knee [25,26].

The results of this study also illustrate that stress values on the surface of the tibial plateau are extremely position dependent with magnitudes varying significantly between points only a few mm apart.

By providing an overview of the perceived stresses at different locations on the tibial plateau, these findings show that the menisci certainly carry load and spread the load over a wider area than just cartilage-cartilage contact, but they do not do so uniformly. Consequently, this study also underscores the importance of experimental investigations in validating computer models that can be over simplified (e.g.: assuming axisymmetry), providing suboptimal or misleading findings and conclusions.

The FBG sensors used in this study possess unique advantages over previously available stress sensing technologies such as stress sensitive films and gauges. They are small enough to be inserted into articular joints without the removal of biomechanically relevant structures and provide continuous real time stress measurements. However, there are important limitations associated with the use of these sensors. Although data obtained using the sensors were highly repeatable, blind segments in data output and sensor fragility were observed. These issues resulted in a few sensors not yielding useable data and consequently an incomplete stress map for the medial plateaus of subjects 3 and 4. To address these limitations sensor data output should be monitored closely during the data acquisition phase. Sensors must be replaced when blind spots or irregular sensor data are observed. Further improvements to the available technology are also necessary to increase sensor durability and establish FBG sensors as the new gold standard in stress sensing technologies in biomechanical applications.

The main limitation of this study is the low number of subjects included in the study. The complex longitudinal nature of the study, high cost associated with the inclusion of each subject (training, housing, surgeries, etc.) and variables such as trainability were factors that influenced the number of subjects included in the study. While the results obtained from each subject, independent of the group, support our hypothesis it is important to note that any conclusions reached maybe affected by this limitation. Although it would be difficult to adapt the methodology used in this study for human subjects, various human studies have found a direct link between factors influencing mechanical stress magnitudes such as weight gain and certain types of physical activity and the development of OA [4]. Considering the main findings of this study, careful consideration must be given as to how to avoid such increases in stress after an injury. As such a major shift in stress magnitude, particularly an increase, would appear to be detrimental. In other words, some biological tissues (certainly articular cartilage with its hypocellularity and slow metabolic
The largest changes in stress (peak or average in the cycle) on the articular cartilage in the development of OA appear to be associated with the locations of focal damage seen during the life of the joint. Other biomechanical properties such as stiffness have also proven to change with age and stiffness of chondrocytes acquired from individuals older than 55 shown to be significantly greater than that of chondrocytes acquired from younger individuals [28]. Thus, it is likely that upon maturation of the individual, the tissues in the joint, especially the articular cartilage, reach a "set point" on mechanical stress tolerance and that this set point may slowly decline as the person ages. In other words, once an individual reaches late adulthood, they are no longer able to adapt quickly to a changing mechanical environment. This intrinsic biological/mechanical behaviour may provide an explanation for the adverse affects of increased stress on joint health and the increased likelihood of OA initiation with age.

The results in from this study highlight the importance of developing and applying novel and improved techniques in biomechanical studies as well as the importance of mechanical stress and stress on joint. Further studies are needed to provide a better understanding of the relationship between stresses and biological changes in the cartilage and menisci. The important finding of this study is that the locations of focal damage seen in the development of OA appear to be associated with the locations of the largest changes in stress (peak or average in the cycle) on the articular cartilage surface.

Contributions
- Dr. Paris Vakiel: Concept and design of the study, Data acquisition, analysis and interpretation of data, drafting the article, revising the article critically for important intellectual content, final approval of the article.
- Dr. Mehdi Shekarforoush: Data acquisition, revising the article critically for important intellectual content, final approval of the article.
- Dr. Christopher R. Dennison: Concept and design of the study, revising the article critically for important intellectual content, final approval of the article.
- Dr. Yamini Achari: Concept and design of the study, revising the article critically for important intellectual content, final approval of the article.
- Dr. Gregory Muench: Data acquisition, revising the article critically for important intellectual content, final approval of the article.
- Dr. Michael Scott: Data acquisition, revising the article critically for important intellectual content, final approval of the article.
- Dr. David A. Hart: Concept and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the article, obtaining of funding.
- Dr. Nigel G. Shrive: Concept and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the article, obtaining of funding.

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Declaration of competing interest
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References
[1] C. Bombardier, G. Hawker, D. Mosher, The Impact of Arthritis in Canada: Today and Over 30 Years, Arthritis Alliance of Canada, 2011. [2] Public Health Agency of Canada, Life with Arthritis in Canada: A Personal and Public Health Challenge, 2011. [3] T. Kelly, W. Yang, C.S. Chen, K. Reynolds, J. He, Global burden of obesity in 2005 and projections to 2030, Int. J. Obes. 32 (2006) 1431–1437. [4] A. Courties, J. Sellam, F. Berenbaum, Metabolic syndrome-associated osteoarthritis, Curr. Opin. Rheumatol. 29 (2017) 214–222. [5] V.L. Johnson, D.J. Hunter, The epidemiology of osteoarthritis, Best Pract. Res. Clin. Rheumatol. 28 (2014) 5–15. [6] V.K. Srikanth, J.L. Fryer, G. Zhai, T.M. Winzenberg, D. Hosmer, G. Jones, A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis, Osteoarthritis. Cartil. 13 (2005) 769–781. [7] T.D. Brown, R.C. Johnson, C.L. Saltzman, J.R. Marsh, J.A. Buckwalter, Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease, J. Orthop. Trauma 20 (2006) 739–744. [8] L.S. Lohmander, P.M. Englund, L.L. Dahl, E.M. Roos, The long-term consequence of anterior cruciate ligament and meniscus injuries, Am. J. Sports Med. 35 (2007) 1756–1769. [9] C.B. Frank, N.G. Shrive, R.S. Boorman, I.K.Y. Lo, D.A. Hart, New perspectives on bioengineering of joint tissues: joint adaptation creates a moving target for engineering replacement tissues, Ann. Biomed. Eng. 32 (2004) 458–465. [10] R.F. Loeser, S.R. Goldring, C.R. Scanzello, M.B. Goldring, Osteoarthritis: a disease of the joint as an organ, Arthritis Rheum. 64 (2012) 1697–1707. [11] P. Vakiel, M. Shekarforoush, C.R. Dennison, M. Scott, C.B. Frank, D.A. Hart, N.G. Shrive, Mapping stresses on the Tibial plateau cartilage in an ovine model using in-vivo kinematics, Ann. Biomed. Eng. (2020). [12] P. Vakiel, M. Shekarforoush, C.R. Dennison, M. Scott, C.B. Frank, D.A. Hart, N.G. Shrive, Stress measurements on the articular cartilage surface using fibre optic technology and in-vivo gait kinematics, Ann. Biomed. Eng. (2020). [13] C.R.S. Dennison, P.M. Wild, D.R. Wilson, M.K. Gilbart, An in-fibre Bragg grating sensor for contact force and stress measurements in articular joints, Meas. Sci. Technol. 21 (2010) 115803. [14] J.Z. Wu, W. Herzog, M. Epstein, Effects of inserting a presensor film into articular joints on the actual contact mechanics, J. Biomech. Eng. 120 (1998) 655–659. [15] P. Vakiel, Direct Measurement of the Change in In-vivo Stresses in Onine Stiffe Joints following Trauma Using Fibre Optic Sensors, 2019. [16] J. Hecht, Understanding Fiber Optics, fifth ed., N. J.:Pearson/Prentice Hall, Upper Saddle River, 2006. [17] T.P. Andriaccio, A. Mündermann, R.L. Smith, E.J. Alexander, C.O. Dyrb, S. Koo, A framework for the in vivo patehmechanics of osteoarthritis at the knee, Ann. Biomed. Eng. 32 (2004) 447–457. [18] L.M. Kronish, M. Hemyer, L. Falzon, B. Konrad, K.W. Davidson, Personalized (N-of-1) trials for depression: a systematic review, J Clin. Psychopharmacol. 38 (2018) 218–225. [19] R.D. Mirza, S. Punja, S. Vohra, G. Guyatt, The history and development of N-of-1 trials, J. R. Soc. Med. 110 (2017) 335–340. [20] B. Percha, E.B. Baskerville, M. Johnson, J.T. Dudley, N. Zimmerman, Designing robust N-of-1 studies for precision medicine: simulation study and design recommendations, J. Med. Internet Res. (2019), e12641. [21] M. Atarod, M.M. Ronvold, C.B. Frank, N.G. Shrive, A novel testing platform for assessing knee joint mechanics: a parallel robotic system combined with an instrumented spatial linkage, Ann. Biomed. Eng. 42 (2014) 1121–1132. [22] J.M. Rosvold, S.P. Darcy, R.C. Peterson, A. Achari, D.T. Corr, L.L. Marchuk, C.B. Frank, N.G. Shrive, Technical issues in using robots to reproduce joint specific gait, J. Biomech. Eng. 133 (2011) 054501.
[23] M. Shekarforoush, P. Vakiel, M. Scott, G. Muench, D.A. Hart, N.G. Shrive, Relative surface velocity of the tibiofemoral joint and its relation to the development of osteoarthritis after joint injury, Ann. Biomed. Eng. 48 (2020) 695–708.

[24] J.F. Cummings, E.S. Grood, M.S. Levy, D.L. Korvick, R. Wyatt, F.R. Noyes, The effects of graft width and graft laxity on the outcome of caprine anterior cruciate ligament reconstruction, J. Orthop. Res. 20 (2002) 338–345.

[25] M. Shekarforoush, J.E. Beveridge, D.A. Hart, C.B. Frank, N.G. Shrive, Correlation between translational and rotational kinematic abnormalities and osteoarthritis-like damage in two in vivo sheep injury models, J. Biomech. 75 (2018) 67–76.

[26] K.I. Barton, M. Shekarforoush, B.J. Heard, J.L. Sevick, C.R. Martin, C.B. Frank, D.A. Hart, N.G. Shrive, Three-dimensional in vivo kinematics and finite helical axis variables of the ovine stifle joint following partial anterior cruciate ligament transection, J. Biomech. 88 (2019) 78–87.

[27] N.O. Chahine, C. Blanchette, C.B. Thomas, J. Lu, D. Haudenschild, G.G. Loots, Effect of age and cytoskeletal elements on the indentation-dependent mechanical properties of chondrocytes, PloS One 8 (2013) e61651.

[28] N. Steklov, A. Srivastava, K.L. Sung, P.C. Chen, M.K. Lotz, D.D. D’Lima, Aging-related differences in chondrocyte viscoelastic properties, Mol. Cell. Biomech. 6 (2009) 113–119.