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Gender Dimorphic ACL Strain in Response to Combined Dynamic 3D Knee Joint Loading: Implications for ACL Injury Risk

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Gender dimorphic ACL strain in response to combined dynamic 3D knee joint loading: Implications for ACL injury risk

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1. Introduction

The deleterious impact of non-contact ACL injuries, presenting with substantial short and long term consequences, remains a serious and largely unsolved clinical dilemma [1,2]. Adding to this concern is the unexplained gender-based disparity that exists in injury rates [1,3,4]. It is thus plausible within the coming decades that a significant number of relatively young and otherwise healthy females will undergo substantial and potentially life altering knee joint debilitation. Hence, elucidating the underlying mechanisms of non-contact ACL injury and the potential for gender-dimorphic contributions to this mechanism appears paramount. The potential for ligament injury is ultimately governed by the load or strain experienced within the tissue [5]. Understanding the strain response of the ACL to dynamic joint loading conditions synonymous with sports, and how this may vary across gender will thus provide substantial insights into injury causality. This information is also critical to the design and development of injury prevention modalities that can cater to individual joint vulnerabilities.

Current research geared towards ACL injury prevention remains focused primarily on gender-based neuromechanical differences elicited during high-risk sports postures, as such factors are modifiable, and hence, amenable to targeted interventions [6–8]. Females for instance tend to land with their knee in a more extended posture [9,10], and demonstrate increased knee abduction throughout stance compared to males [11–13], culminating in knee load states touted as more high risk [1,14] Despite the ever-increasing number of ACL injury prevention programs that have evolved in parallel with these tenets however, and reported early success in clinical trials [15–17], high ACL injury rates with large gender-disparity have persisted [4]. A number of potential factors, such as poor athlete compliance, inter-program variations, poor athlete follow-up and limited training resources are

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currently proposed to account for this discrepancy [7,17,18]. It seems equally plausible that current prevention methods may additionally be based on an incomplete understanding of the injury mechanism.

Non-contact ACL injury risk has been linked prospectively to specific structural and/or laxity factors [19]. Interestingly, gender-based differences also exist in many of these factors [20–24], suggesting that concomitant differences in the ensuing joint mechanics are possible. Currently, however, the potential for gender-dimorphic joint mechanical and resultant ACL strain behaviors to exist has not been examined. Considering that prevention methods continue to adopt a largely homogeneous, and what is considered a “safer” male-based movement strategy [7,16], failure to cater to gender-specific contributions to the injury mechanism may have catastrophic consequences. Hence, investigating the potential for gender-specific joint mechanical contributions to ACL strain in response to dynamic 3D knee loading appears paramount.

Relationships between knee joint and ACL load have been quantified previously in cadaver models for isolated and relatively simple load cases, such as anterior shear force [25], valgus torque [26], and combined internal–external rotation torque and anterior shear force [27]. Research has shown however, that multiple load variables and combinations similarly influence ACL loading [28,29] and that their contributions are neither linear nor additive [30]. Extrapolation of current data to the more general load case therefore is not feasible. Further, ACL load and/or strain responses are currently only known for relatively low, clinical exam loading levels, being well below those evident during sports maneuvers in which injury is common [12,31,32]. Such information is not only critical in terms of elucidating injury causality, but would also significantly enhance current injury prevention methods which rely on reducing ACL loads. Hence, this study used a combined cadaveric and analytical approach to develop and verify gender-specific generalized mathematical models of ACL strain as a function of any combined 6 DOF knee joint load state. Using these models, we subsequently examined the potential for gender-dimorphic ACL strain for combined 6 DOF knee load states consistent with both a clinical exam and a dynamic high-risk sports landing. To achieve these aims, we tested the following specific hypotheses:

1. Specimen and ultimately gender-specific generalized mathematical models of ACL strain can be developed capable of predicting the ligament strain response for any combined 6 DOF knee load state.
2. The female ACL undergoes larger relative strains compared to the male ACL under application of both clinically relevant of sports specific 6 DOF knee load.

2. Methods

2.1. Specimen preparation, instrumentation and fixation

To achieve the purposes of this study, we undertook a descriptive laboratory study comparing two discrete (gender) groups within a cadaveric experimental model. Data were collected from five male (mean age $= 57.5 \pm 9.4$ yrs) and five female (mean age $= 58.2 \pm 9.8$ yrs) fresh-frozen human cadaveric knee joints. All experimenters were

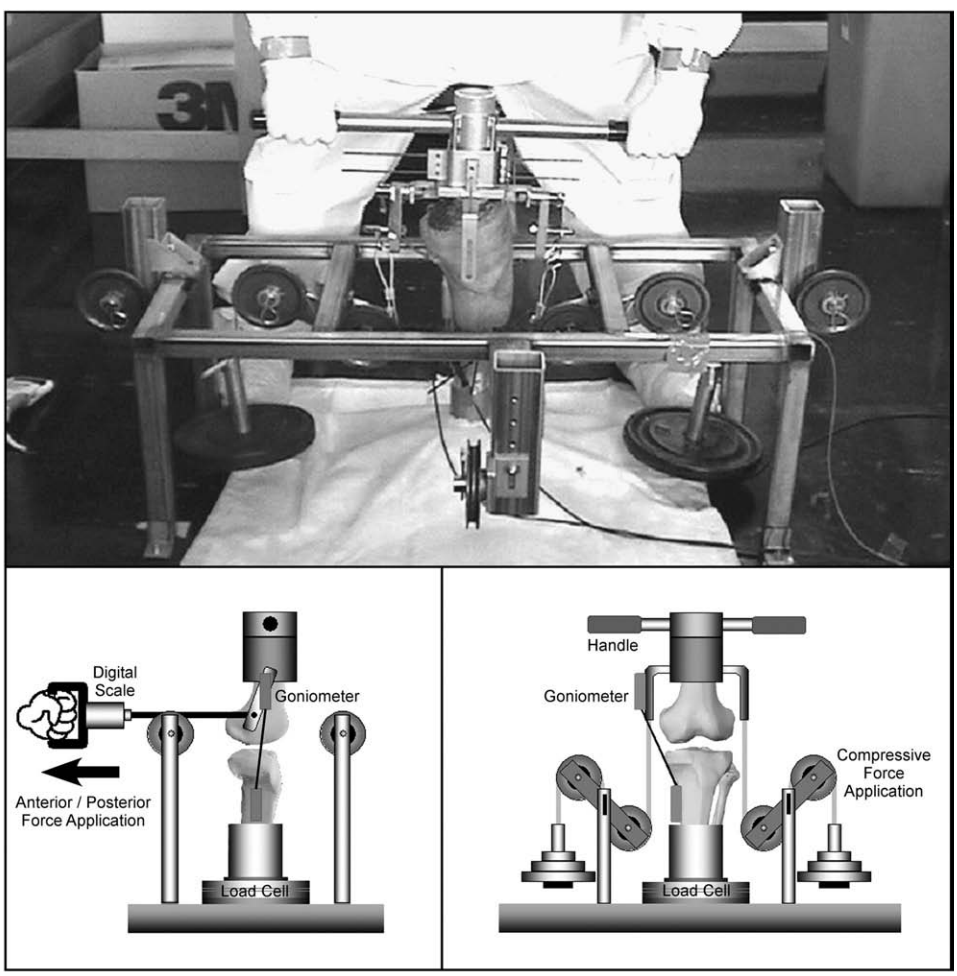

Fig. 1. Illustration of manual-loading device used to apply combined 3D knee load states to the knee joint. This device enabled external torques to be applied manually to the joint through a set of “handlebars” in combination with 3D static forces applied via a cable system.

blinded to specimen gender until the final data processing. Prior to testing, all joints were visually screened for any extreme joint damage or degeneration by an experienced orthopaedic surgeon (KM). Specimens were kept at −20 °C until 72 h prior to testing, at which time they were thawed at 4 °C [33]. Following thawing, specimens were amputated transtibially and transfemorally, approximately 30 cm from the joint line. The distal fibula (below the fibular neck) was cut, with the remaining portion fixed to the tibia via a bicortical screw. The skin, subcutaneous fat and musculature was then removed from the distal portions of the bones, exposing the femoral and tibial shaft, while leaving the knee joint capsule and collateral ligaments intact. The femur and tibia were then potted with polymethylmethacrylate in aluminum cylinders of height 15 cm.

Following specimen preparation, the tibial cylinder was attached to a universal force sensor (UFS; Theta 190 #S1-2500N-400Nm, ATI Industrial Automation, Apex NC), which in turn was firmly secured to a concrete floor. The femoral cylinder was then secured to a custom designed femoral load application mechanism via three 30 cm carbide-tipped high-speed steel aircraft extension drill bits (#2951A16; McMaster-Carr, Atlanta, USA), which similarly passed through the bone of interest. The load application mechanism allowed torques to be applied manually through a set of "handlebars", combined with static forces applied via cables along the three anatomical axes (Fig. 1).

Following specimen fixation, a flexible 2 DOF electro-goniometer (Model SG150; Biometrics Ltd, UK) was secured across the joint in order to continually measure knee flexion angle throughout the testing phase. The two endpoints of the goniometer were attached to the femur and tibia such that they coincided as close as possible with the longitudinal axis of each segment [34,35], as viewed in the sagittal plane (see Fig. 1). The anterior–medial bundle (AMB) of the ACL was instrumented with an ultra-microminiature (2.0 mm stroke) differential variable reluctance transducer (DVRT; MicroStrain, Inc., Burlington VT) to quantify ligament strain. Specifically, a vertical 3 cm incision was first made on the anterior–medial aspect of the knee joint, at the level of the joint space. The DVRT was then secured to the inferior portion of the anterior–medial bundle (AMB) midsubstance, via a 30 cm gauge insertion tool (MicroStrain, Inc., Burlington VT). This location was chosen for instrumentation to minimize the risk of gauge impingement when the knee joint was moved into full extension [36]. A minor femoral notchplasty (~1 cm) was performed to further reduce this risk.

2.2. Loading protocol

All 6 DOF force and torque combinations were applied externally to knee joint specimens via the manual-loading device. Seven variables were chosen to represent the combined loading state of the joint: flexion angle, compression force, medial–lateral force, anterior–posterior force, flexion–extension torque, varus–valgus torque and internal–external axial torque. The force and torque variables were measured directly by the UFS and transformed to a tibial reference frame with origin at the knee center, defined in the transverse plane as the intersection of the transverse and anterior-posterior axes of the tibial plateau [35].

Prior to data testing, each specimen was taken through ten complete flexion–extension cycles to ensure that visco-elastic preconditioning had taken place [37]. Strain data were also monitored in real-time throughout these loading cycles to ensure that the DVRT was appropriately secured to the ligament and that there was no evidence of pre-test measurement artifact. DVRT length was then recorded at 20° of knee flexion while a 10.5 N anterior-directed tibial load was applied via a weight attached to the posterior aspect of the femur. This DVRT length was used to estimate a zero strain reference for the ACL. The relatively small 10.5 N anterior tibial load was applied to ensure adequate minimal tensioning to straighten the ligament for this zero train estimate [38].

The entire load application protocol for each specimen was intended to last approximately 15 min. The goal of the protocol was to generate a large number of combined 6 DOF joint loading conditions, with all possible combinations of the seven independent variables. To this end, three initial external compression loads of 0 N, 90 N, and 180 N were applied incrementally to the joint via weights attached by wire cables and pulleys to the femoral load application mechanism (see Fig. 1). Under each of the three compression load applications, one of seven anterior–posterior loads was simultaneously applied to the joint, namely 0 N, or an anterior or posterior load of approximately 44.5 N, 89 N and 133.5 N respectively. Specifically, the chosen anterior or posterior load was applied to the joint by the experimenter manually pulling on a wire cable attached to the femoral load application mechanism, using a digital scale for visual feedback. The design of the loading device meant that explicit load magnitudes experienced within the joint, and particularly the compressive loads, varied slightly as a function of knee flexion angle. Considering, however, that regression models were necessarily generated using data over the entire 6 DOF load space, constant external loads were not critical. During each of the 21 static loading conditions, combinations of varus–valgus and internal–external rotation torques were applied manually to the joint over a 40–60 s period via the handlebar mechanism, while at the same time, moving the joint continuously through a range of knee flexion angles (0° to 90°). "Safe" (non-injurious) torque application ranges were determined manually by the experimenter, with maximum values corresponding to the point where a definite "endpoint" was felt. Total joint load (from weights and manipulation) was monitored continuously via the UFS.

Analog signals from the UFS (3D force and moment), DVRT, and goniometer were recorded synchronously at 10 Hz, using custom software developed using the Matlab Data Acquisition Toolbox (Mathworks Inc., Natick, USA). This software included a real-time display of joint angle, varus–valgus moment and internal–external rotation moment to assist the experimenter in deciding when the entire space of possible loading states had been sufficiently explored. Prior to being displayed, joint moments were transformed to a reference frame with origin at the estimated center of the knee joint [35].

Following completion of all initial loading trials and a 5 min period where the specimen was completely unloaded, the entire protocol was repeated. This time, however, the torque variations were only applied over a 30 s period. These data were not used to generate the specimen-specific regression models. Rather, they were used purely to verify these models, which were generated with the original set of load data only. This second data set was also used to verify that the joint was intact following completion of testing.

After completion of the experiment, the femur was removed by transecting the joint capsule and ligaments, leaving only the tibia in place. The vertical distance (z) from the UFS origin to the knee joint center [35] defined above was subsequently measured with calipers. The x and y coordinates of the joint center relative to the UFS origin were obtained by taking two digital images from directly above the loading device, with and without the tibia in place. Specifically, both images were imported into Scion Image (Scion Corp, Maryland, USA) and the x and y distances from the UFS origin (image 2) to the joint center (image 1) were quantified.

2.3. Data reduction and processing and analysis

The raw data obtained from each specimen during the primary loading protocol consisted of more than 10,000 samples per data channel, with 8 channels in all being simultaneously recorded (3 DOF force, 3 DOF torque, DVRT length and knee flexion angle). DVRT analog data were converted to DVRT gauge length in mm using calibration information obtained immediately prior to each test session. Analog 6 DOF force and moment data obtained from the UFS were converted to a three dimensional force and moment vector acting at the knee joint center via standard coordinate transformations [39].

Following initial processing, the data from the primary loading protocol were submitted to a regression analysis to describe DVRT gauge length as a function of the seven loading variables defined above. A second-order polynomial regression model was used:

$$y = a_0 + \sum_{i=1}^{7} b_i x_i + \sum_{i=1}^{7}\sum_{j=1}^{i} c_{ij} x_i x_j \tag{1}$$

where y is DVRT gauge length and x_i is the ith independent loading variable. The 36 model coefficients a, b, and c that minimized the difference between left hand side (measured data) and right hand side (predicted data) were obtained using the linear least-squares function in Matlab (Mathworks Inc., Natick, MA). A step-wise approach was used to rank regression terms in Eq. (1) in order of decreasing contributions to the explained variance. The goodness of fit for the regression model was quantified by computing the root-mean-square (RMS) difference between measured and predicted gage lengths for the combined external load state inputs.

Gage length data were converted to a measure of relative ACL strain to enable comparisons across specimens and with previous studies. Specifically, relative strain was calculated using the following equation:

$$\varepsilon_k = \frac{y_k - y_0}{y_0} \quad (\text{If } \varepsilon_k < 0 \text{ then } \varepsilon_k = 0) \tag{2}$$

where, y_k and ε_k corresponded to the length of the DVRT and the associated ACL strain estimate for the kth data sample respectively, and y_0 was the DVRT length at 10.5 N anterior drawer load, as described above. This procedure resulted in one regression model for each specimen, predicting ACL strain as a function of all knee joint loading parameters. A generalized model was then obtained for both males and females by averaging the coefficients of the five respective specimen-specific models.

2.4. Model verification

A within-specimen verification was initially performed on each specimen-specific regression model. Specifically, load and strain data recorded for each specimen during the secondary loading protocol (approximately 5000 samples) were input into their associated regression model, as defined above. The ensuing predicted strain values were then compared to the measured (secondary loading protocol) strain data and a prediction error was subsequently quantified as an RMS value. These results were also qualitatively examined for evidence of ligament creep, occurring if strains measured empirically during the second part of the experiment were consistently larger than the model-predicted values.

The performance of the gender-specific generalized regression models was evaluated by standard leave-one-out (LOO) cross-validation

Table 1
Mean (±SD) peak force and torque magnitudes applied to male and female cadaveric specimens.

Joint load[a]	Male	Female
Anterior force (N)	151.6±25.6	153.4±31.7
Posterior force (N)	180.4±8.5	178.8±26.3
Lateral force (N)	31.2±9.1	25.5±9.2
Medial force (N)	50.6±18.3	30.6±16.6
Compressive force (N)	410.8±26.3	397.0±38.8
Varus torque (Nm)	40.1±5.1	35.0±8.3
Valgus torque (Nm)	48.3±3.9	47.7±3.0
Int rotation torque (Nm)	24.4±5.2	22.1±3.2
Ext rotation torque (Nm)	18.0±4.0	15.9±2.8

[a] Loads above are defined within the tibial reference frame. That is, anterior force represents a force applied anteriorly to the tibia.

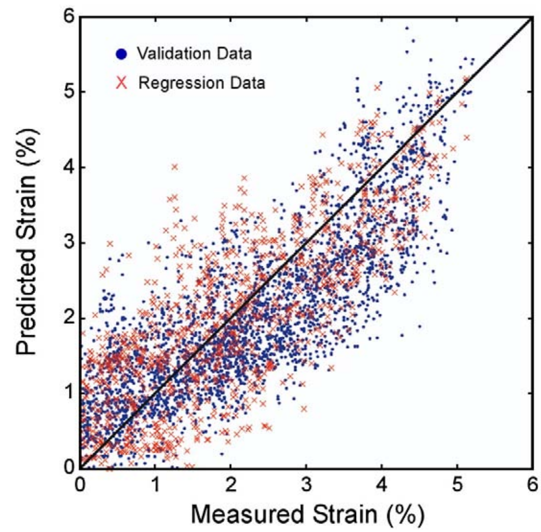

Fig. 2. Example correlation between measured and model-predicted ACL strain for a single (female) specimen. Male and female specimen-specific models were able to predict measured strain to within 0.51%±0.01% and 0.52%±0.06% of measured data, and within 0.61%±0.11% and 0.57%±0.05% of validation data respectively.

methods [40]. This treatment involves using a single observation or sample from the original data as the validation data, with the remaining observations being utilized as the training data. This process is then repeated such that each observation within the sample is treated once as the validation data [40]. Specifically for the current case, five generalized regression models were generated for each gender, obtained by averaging four of the five optimized specimen-specific models. In each instance, the load data measured for the fifth specimen, not used to formulate the generalized model, was then submitted to the generalized equation, and a mean RMS error between predicted and measured strain was calculated. A global gender-based mean RMS error was finally determined for all stain predictions, by averaging the mean RMS error terms calculated for these five generalized models.

2.5. Model predictions of ACL strain

Following verification, two generalized gender-specific regression models were defined by averaging the optimized model coefficients of all five (male or female) specimen-specific models. Two explicit 6 DOF knee joint loading combinations were subsequently submitted to these global male and female predictive models. First, a load combination consistent with standard clinical examination was utilized, where a combined valgus (10 Nm) and internal rotation (10 Nm) torque [29] was applied to the femur relative to the tibia at static knee flexion angles of 0°, 15°, 30°, 60° and 90°. Second, a load combination synonymous with a potentially high-risk dynamic sidestep cutting maneuver was adopted [13,31,32,41]. Specifically in this instance, valgus (45 Nm) and internal rotation (20 Nm) moments were applied in combination at a fixed knee flexion angle (40 deg), for a constant compressive load (300 N) and three discrete anterior tibial shear load magnitudes (50 N 100 N and 150 N). For each of the two pre-defined loading scenarios, model-predicted ACL strain data were obtained and submitted to one-way ANOVA's to test for the main effect of gender across the five flexion angles (clinical) and three anterior tibial shear loads (sidestep) respectively. An alpha level of 0.05 was adopted to denote statistical significance in each instance.

3. Results

Original loading protocols lasted 15.23±0.31 min and 15.35±0.24 min for male and female knee joint specimens respectively. Additionally, validation loading protocols lasted 10.11±0.14 min and 10.08±0.21 min for respective

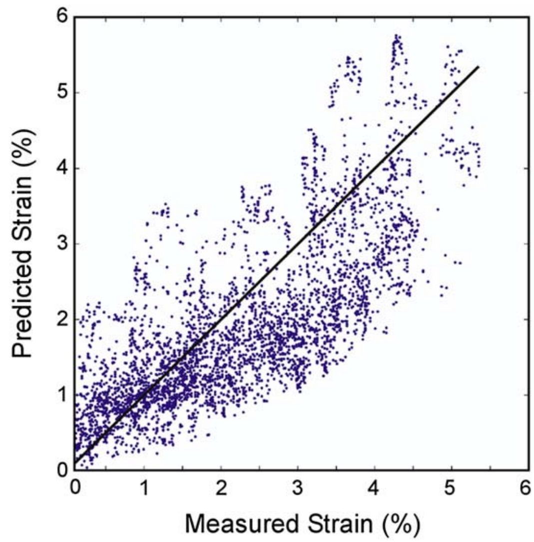

Fig. 3. Example correlation between generalized model predicted and measured ACL strain data, not used in the generalized model development. The five male and female generalized regression models produced mean validation errors of 0.90% ± 0.11% and 0.88% ± 0.15% and were able to explain 51.5% ± 8.8% and 60.7% ± 7.1% of the variance in measured ACL strain respectively.

male and female specimens. The mean maximum force and torque magnitudes applied to the five male and five female knee joint specimens during the complete series of loading protocols are presented in Table 1. Mean maximum strain recorded during the combined loading experiments was 5.1 ± 0.6% and 5.6 ± 0.5% for male and female specimens respectively. The five male and five female specimen-specific regression models were able to predict ACL strain within an average of 0.51% ± 0.01% and 0.52% ± 0.06% of the measured data and explain an average of 77.6% ± 6.0% and 82.7% ± 3.8% of the associated variance respectively (Fig. 2). Furthermore, submitting load data obtained from the secondary (verification) loading protocol to these models resulted in a mean RMS prediction errors of 0.61% ± 0.11% and 0.57% ± 0.05% for male and female specimens respectively.

Cross-verification errors remained below 1% strain for both the male and female specimens. Specifically, when ACL strain was predicted by averaging the regression models of four male specimens, measured strain in the 5th male specimen was predicted with an RMS error of 0.90% ± 0.11%, explaining 51.5% ± 8.8% of the associated variance. When ACL was predicted based on the average of four female specimen-specific models, measured strain in the 5th female specimen was predicted with an RMS error of 0.88% ± 0.15%, explaining 60.7% ± 7.1% of the variance (Fig. 3). Generalized gender-specific regression models, being the average of all five (male or female) specimen-specific models, were subsequently generated (Table 2).

Mean male and female model predictions of ACL strain in response to application of combined 10 Nm valgus and 10 Nm internal rotation torques were consistent with previously published experimental data over a similar range of knee flexion positions (Fig. 4) [29]. Furthermore, predicted female ACL strains were statistically significantly (p<0.05) larger than male strain values for this load combination at each knee flexion position, except for 90°. For the second, sports-relevant joint load case, predicted female ACL strains were again statistically significantly (p<0.01) larger than concomitant male strain predictions for each of the three anterior tibial shear load values (Fig. 5).

4. Discussion

In this paper, we have developed a generalized mathematical model that successfully predicts ACL strain from seven variables which describe the loading state of tibiofemoral joint without the associated loads produced by muscle contraction. This also appears to be the first time that gender-specific descriptions of ACL strain for combined 6 DOF external knee joint load states have been presented, and further, that a gender-dimorphic ACL strain response has been identified. We consider this last finding to be extremely important, as it will directly impact the way in which the gender-based disparity in sports related non-contact ACL injuries is investigated in the future. Methods currently exist that enable 6 DOF knee joint loading associated with dynamic sports postures to be estimated *in vivo* [32,42,43]. These resultant inter-segmental loads at the knee joint can be further processed into estimates of muscle forces [44–46]. Additionally, estimates of the total *in vivo* intrinsic loads placed upon the knee joint are possible by combining muscle and resultant knee load data [44]. The regression models presented in Table 2 provide the final step in the analysis, enabling resultant ACL loads to be estimated from these intrinsic load states. With this additional step, therefore, gender-specific estimates of ligament loading, and inferences regarding injury risk, can now be made for any high-risk sports landing posture. This in turn is critical to the ultimate elucidation of ACL injury mechanisms, and immediately improves the ability to screen at-risk populations and subsequently formulate successful prevention strategies aimed at reducing ACL loading. A general model for estimation of ACL strain from knee joint loading variables is also an important step in the interpretation of computer simulation experiments, a step which was until now not possible [43,47,48].

A unique aspect of this study was that we attempted to explore the entire six-dimensional space of tibiofemoral joint loading conditions, over a 15-minute protocol. Consequently, the loading states applied to knee joint specimens in this study were both of a greater magnitude and greater complexity than those typically adopted previously [26,27,29]. We of course remained well below

Table 2
Generalized regression model coefficients used in conjunction with a second-order polynomial regression model (Eq. (1)) to predict ACL strain (in %) for combined 3D knee load states, based on averaging the five male and five female subject-specific regression models.

Model term	Mean coefficient male (N = 5)	Mean coefficient female (N = 5)
A	1.15E+00	1.25E+00
B	1.38E−02	1.98E−02
$B*B$	2.92E−05	3.41E−05
C	1.37E−02	−2.19E−03
$C*B$	−1.39E−04	−7.84E−06
$C*C$	4.71E−04	3.82E−05
D	−2.98E−03	−5.62E−04
$D*B$	1.07E−05	8.51E−06
$D*C$	−1.31E−04	1.82E−05
$D*D$	8.25E−06	−2.54E−06
E	−1.04E−02	9.81E−03
$E*B$	1.30E−05	9.11E−05
$E*C$	−1.73E−04	−1.67E−04
$E*D$	−7.62E−05	−9.08E−05
$E*E$	4.06E−04	5.80E−04
F	9.91E−02	2.87E−01
$F*B$	2.41E−06	−1.49E−06
$F*C$	3.70E−03	1.49E−03
$F*D$	−1.94E−04	2.38E−04
$F*E$	4.78E−04	−3.59E−03
$F*F$	−6.91E−04	3.21E−03
G	−7.52E−03	−1.18E−02
$G*B$	−1.25E−04	−2.02E−04
$G*C$	−1.44E−04	−4.76E−05
$G*D$	1.21E−05	2.39E−05
$G*E$	3.52E−04	7.24E−06
$G*F$	−1.11E−03	−3.43E−03
$G*G$	−2.88E−05	−6.60E−05
H	4.76E−02	5.39E−02
$H*B$	1.78E−04	3.61E−04
$H*C$	1.67E−03	−1.25E−04
$H*D$	−2.23E−04	7.03E−05
$H*E$	−6.10E−04	−3.81E−03
$H*F$	1.95E−03	1.80E−02
$H*G$	3.70E−04	−2.83E−05
$H*H$	2.58E−03	5.88E−03

A = constant.
B = anterior–posterior force (N).
C = medial–lateral force (N).
D = compression–distraction force (N).
E = varus–valgus moment (N m).
F = internal–external rotation moment (N m).
G = flexion–extension angle (degrees).
H = flexion–extension moment (N m).

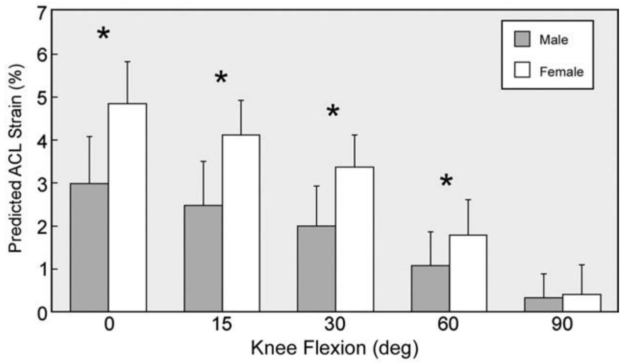

Fig. 4. Comparison of generalized male and female model predictions of ACL strain for a clinically relevant 3D joint load state [29]. Specifically, a combined valgus (10 Nm) and internal rotation (10 Nm) torque was applied to the femur relative to the tibia at static knee flexion angles of 0°, 15°, 30°, 60° and 90° respectively. Similar to the published data, ACL strains under the combined loading condition decreased with increasing knee flexion. Female ACL strain was statistically (* denotes $P<0.05$) significantly greater than male ACL strains for all knee flexion angles except 90°.

joint loads typical of ligament injury [49–51], since the experiment necessarily required an intact joint throughout. The manual application of internal–external and varus–valgus torques provided substantial assistance in maintaining joint integrity, as definite load endpoints could be "felt" in each case. By and large, we were also able to apply load scenarios consistent with those typical of sports maneuvers in which ACL injuries are common, such as sidestepping [14,31,32]. Knee joint compressive loads, however, did not reflect a true dynamic load state, being well below the equivalent of a weight bearing joint with quadriceps contraction. This limitation was due in part to the age range of the specimen donors, with substantial joint damage at higher compressive loads being a major concern. Compressive load states representative of sports movements could indeed be studied via the same methods, however, if younger specimens were used. Regardless, with compressive loads, as dictated by landing height, known to directly impact the resultant lower limb biomechanical profile, [52] current outcomes should necessarily be considered with this limitation in mind. We also note that these experiments were performed as slow, quasi-static, loading rates. Both the ACL tissue and the knee joint as a whole may introduce speed-dependent effects which were not investigated. With experimenters being blinded to specimen gender, however, it was unlikely that loading rates adversely impacted study outcomes.

The efficacy of the current models suggests similar predictive success would be likely with larger 6 DOF load inputs. It is important to note, however, that results of the present study should not be extrapolated beyond the maximum loading conditions from which models were generated and verified. It would be ideal to include load states that induce ligament injury within the formulation of the regression models. This of course cannot be studied in cadaveric models, as irreversible tissue damage necessarily ends the experiment. There is thus a substantial need for validated computational models that can effectively overcome this problem [53]. Again, however, validation of these models under injurious conditions remains problematic. At best, validation against a single ACL injury within a cadaveric model may be possible.

Stepwise regression revealed that the most prominent model parameters were flexion angle, anterior force, and valgus and internal rotation torques. The three knee load parameters mentioned here are known in isolation to induce significant ACL strain [28,54,55], and are viewed in combination as one of the most hazardous joint loading scenarios in terms of non-contact ACL injury risk [1,28]. The relationship between ACL load/strain, external loads and flexion angle is also well documented, with ligament loading being most prominent between 0° and 20° knee flexion [36,38,56]. ACL strain predictions in the current study were similarly largest within this knee flexion range, further supporting model utility.

Specimen-specific regression models were able to predict ACL strain within 1% of measured values. Model-predicted ACL strains were also consistent with those reported previously for a prescribed 6 DOF joint load state reflective of a standard clinical exam [29]. Of course comparisons to an isolated relatively low loading case do not automatically infer global model efficacies. Model strain predictions were equally reliable, however, over a wide variety of explicit load prescriptions, with excellent accuracies similarly demonstrated when external load inputs not utilized within model generation were submitted (see Fig. 4). There is limited empirical data describing ACL strain for larger knee joint load magnitudes, such as those elicited during sports maneuvers linked to ACL injury. Cerulli et al. [57], observed peak *in vivo* ACL strain magnitudes during rapid deceleration tasks that were consistent with current model-predicted sports-relevant peak strains, with both being well below ultimate ligament failure strains [38,54]. Unfortunately, they did not record synchronous knee joint load data, making direct comparisons with our results impossible. Based on the joint kinetic profiles quantified previously for similar movements, however [41,58], concomitant dynamic joint states similarly appear feasible.

Model verifications revealed about 0.5% unexplained variation in strain within specimens (Fig. 3). The source of this variation is not immediately clear. If the passive knee joint is a perfectly elastic mechanism, ACL strain should only depend on the load applied to the joint. A second-order multivariate polynomial, however, may not be sufficient to successfully represent this relationship. A biomechanical [59], rather than the current statistical model, may fit better. It should be noted, however, that if the knee joint is not perfectly elastic, but undergoes creep, hysteresis, or other time-dependent phenomena, neither a statistical nor mathematical model will correctly predict ACL strain from forces and moments applied to the knee. Regardless, considering the relatively low amount of unexplained strain variation currently observed, our generalized models appear to be a reliable and potentially useful research tool.

Our results demonstrated that at both clinical exam and sports-relevant load magnitudes, the female ACL undergoes greater strain than the male ACL for precisely the same 6 DOF knee joint loads. We chose not to include medial–lateral joint loads within either of the simulated loading conditions. Load scenarios consistent with standard clinical examinations do not include medial–lateral joint loading [29], justifying their exclusion. For the sports-relevant loading condition, while medial–lateral knee loading is likely during the landing phase, empirical data outlining specific load profiles do not currently exist. Including these

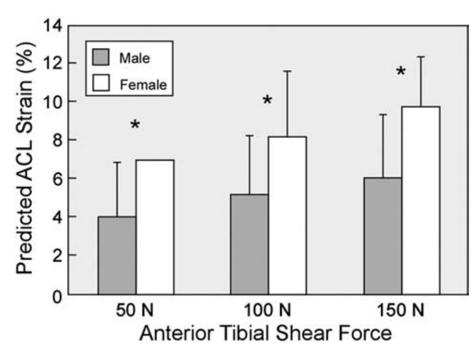

Fig. 5. Comparison of generalized male and female model predictions of ACL strain for a sports-relevant 3D joint load state [14,31,32]. Specifically, valgus (45 Nm) and internal rotation (20 Nm) moments were applied in combination at a fixed knee flexion angle (40°), for a constant compressive load (300 N) and three discrete anterior tibial shear load magnitudes (50 N 100 N and 150 N). Predicted female peak ACL strain magnitudes were statistically (* denotes $P<0.05$) significantly greater than predicted male values for the combined external load state under each of the three anterior tibial shear force conditions.

variables would have indeed influenced the modeled strain response [49]. There is no immediate reason to assume, however, that this altered response would differ across gender. With excessive strain directly related to tissue failure [60], current outcomes suggest the female ACL is thus likely to rupture in response to smaller inter-segmental knee joint load applications compared to the male ACL. Further, if the underlying mechanism of non-contact ACL injury is indeed influenced by gender as current results suggest, then it is reasonable to assume that a gender-dimorphic prevention strategy is also required. It may be for example, that females need to land such that they reduce inter-segmental knee loading, and in particular anterior tibial shear force and valgus and internal rotation moments to a greater extent than that required by males. Further, considering that muscles across the knee joint act to oppose extreme knee load states [44,61], and potentially hazardous muscle activation strategies are possible for females, [62] trained gender-specific neuromuscular control strategies may be necessary, with the successful female strategy being one which successfully counters out of plane knee loading. Hence, teaching females to adopt a male landing strategy, in which knee valgus and internal rotation loads are comparatively smaller [12,32], indeed appears critical in reducing female ACL injury rates. Additionally, current outcomes suggest that trained neuromuscular modifications aimed at reducing female knee loading even further may be necessary.

It is not currently clear whether comparatively larger female ACL strains stem from underlying gender-dimorphic joint and/or ligament characteristics. Gender differences in ligament ultrastructure [63], for example, may result in the female ACL undergoing larger strains that the male ACL for the same external force application [64]. Females also possess ACL's of smaller length, cross sectional area and volume [65], culminating in gender-specific ligament mechanical properties that are likely prominent during 3D knee joint loading [63,64]. Gender-based differences in knee joint geometry may similarly explain why the ACL in a female knee experiences larger forces than that within a male knee. Females for instance, have a less round and narrower intercondylar notch than males [24], which may increase the risk of ACL impingement in response to 6 DOF knee joint load applications [66]. Knee joint articular surfaces are also reported to be 20–35% smaller in females [67], possibly promoting a smaller lever arm between the tensile load on the ACL and compressive load on the lateral condyle during valgus loading compared to males [48]. The knee extensor moment arm is similarly reported to be smaller in females compared to males, resulting in comparatively higher knee joint forces for the same joint moment [68]. We did not explicitly measure ligament and/or joint structural characteristics within the current study and hence are unable to provide substantial insights here. Regardless, further research into the underlying causes of gender-dimorphic knee joint and ACL mechanical behaviors appears well warranted. Such research would further assist in developing neuromuscular prevention strategies that promote safe joint loading postures within the context of individual, rather than overly simplistic homologous joint vulnerabilities.

There are several methodological limitations that should be considered when evaluating the reliability of the model outputs. When applying the generalized regression model to a separate specimen, for example (see Fig. 5), a systematic overestimation or underestimation of approximately 1% strain was typically seen. This most likely stems from natural variation between the specimens used to develop the models, such as in geometry, alignment or tissue properties. There is no immediate reason to suggest that current specimens do not reflect joint variations evident within the extended population. Hence, this 1% error must be considered when applying the generalized regression model (Table 2) to predict *in vivo* ACL strains for other load scenarios and populations. We thus additionally suggest that absolute strain magnitudes cannot be predicted with this model. It can, however, successfully estimate within-subject changes in ACL strain, such as after neuromuscular training, which essentially modifies knee joint loading [7,15]. The 1% difference in strain observed between specimens of the same gender is similar to the difference between genders, which strongly suggests that some individuals are more vulnerable to ACL injury than others within the same gender. Hence, risk assessments that consider individual and not simply gender-based joint vulnerabilities, may improve ACL injury screening and prevention for both males and females. Non-invasive methods capable of successfully identifying all at-risk individuals, such as imaging or laxity evaluations, for example, should thus necessarily be explored.

Strain data were obtained, and hence strain predictions were based, on localized AMB measures only. It has been suggested previously that the strain behavior of the AMB provides a reasonable representation of the response of the entire ligament [36,38]. This is confirmed by the agreement between AMB strain and previously measured total ligament load under the same external load application [55]. Others have argued however, that the AMB and PLB may play reciprocative but equally important functional roles throughout knee motion [25,69]. It is possible therefore, that combined knee loading states typical of high-risk sports postures may cause non-uniform ACL bundle loads/strains, which may be extremely pertinent to initiation of ACL injury. Continued efforts to accurately quantify loading in both bundles within an intact knee joint are thus necessary and will be explored in future investigations.

A notchplasty was performed on all specimens to minimize the risk of gauge impingement on the intercondylar notch when the knee was moved into full extension. While the notchplasty was relatively small in size (1 cm), it did create the possibility of slightly altered strain measures when the knee joints were at or near full extension [28,66]. Nevertheless, we felt that inclusion of strain data obtained within this flexion range remained warranted. With the knee flexion postures associated with dynamic sports landings typically being outside of this range [1,11], however, the potential for erroneous ACL strain predictions for such tasks will likely remain small.

5. Conclusions

Based on the above research outcomes, the following conclusions can be drawn:

1. Mathematical regression models could successfully describe ACL strain in terms of seven specific 6 DOF knee joint loading variables: anterior–posterior, medial–lateral and compression force, varus–valgus, internal–external and flexion–extension rotation torques and knee flexion angle.
2. Results were consistent with previous data obtained for 6 DOF knee joint load states typical of standard clinical examinations.
3. A generalized model based on aggregate data from all specimens can, within verified limits, be used for prediction of *in vivo* ACL strain from combined 3D knee joint load states.
4. The female ACL undergoes greater strain than the male ACL in response to load applications consistent with clinical exam and dynamic sports landing load states.

Conflict of interest statement

None of the above authors demonstrate any financial and/or personal relationships with other people or organizations that could inappropriately influence (bias) the work presented within this manuscript.

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