

Mechanical and Architectural Bone Adaptation in Early Stage Experimental Osteoarthritis

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ABSTRACT

The purpose of this study was to quantify mechanical and architectural changes to knee joint periarticular subchondral cancellous bone in early stage experimental osteoarthritis (OA). Unilateral anterior cruciate ligament transection (ACLX) was performed on 10 dogs that were assigned randomly to two groups: 3 weeks or 12 weeks post-ACLX. Cylindrical bone cores excised from the medial condyle of the distal femur after death were scanned using high-resolution microcomputed tomography (μ CT) and subsequently failed under unconstrained uniaxial compression. The apparent-level elastic modulus was less in the ACLX femur compared with the contralateral control, and the decrease was significant (-45% ; $p < 0.05$) by 12-weeks post-ACLX. A finite element (FE) analysis based on μ CT data simulated the uniaxial compression tests on a specimen-by-specimen basis to determine tissue modulus. No change in tissue modulus was detected, and a single tissue modulus of 5100 MPa (95% CI, ± 600 MPa) explained the apparent-level modulus changes observed in the disease-related bone adaptation. The three-dimensional (3D) connectivity was evaluated from the original μ CT data to quantify architectural alterations in contrast to tissue alterations. Significantly increased connectivity (through plate perforations) occurred as early as 3 weeks post-ACLX and was as high as 127% by 12 weeks post-ACLX in the distal femur. These measured changes indicated that architectural adaptation predominated over tissue modulus changes affecting apparent-level elastic modulus in the early stage of experimental OA and suggests that to maintain normal cancellous bone after a traumatic injury, early intervention should focus on preventing the substantial architectural alterations. (J Bone Miner Res 2002;17: 687–694)

Key words: osteoarthritis, bone architecture, knee, finite element analysis, mechanical testing

INTRODUCTION

A KNEE INJURY involving tearing of the anterior cruciate ligament (ACL) increases the likelihood of developing post-traumatic osteoarthritis (OA)⁽¹⁾—a disease that can afflict all the joint tissues including the ligament, cartilage,

and bone. Subchondral bone changes very early in the disease pathogenesis,^(2–4) and those changes have been reported for both humans⁽⁵⁾ and experimental animal models.⁽⁶⁾ After ACL transection (ACLX), the periarticular cancellous bone mineral density (BMD) changes in experimental OA⁽⁷⁾ and the subchondral plate thickens.⁽⁸⁾ Although plate thickening occurs between 3 and 18 months post-ACLX,⁽⁸⁾ significant architectural changes to the can-

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cellous bone happens as early as 3 weeks post-ACLX.⁽⁹⁾ The architectural changes by 12 weeks post-ACLX include reduced trabecular thickness (Tb.Th) and bone volume density (BV/TV) of -31% and -35% , respectively, and greater bone surface-to-volume ratio (BS/BV) of $+74\%$.⁽⁹⁾ These morphological changes presumably affect the mechanical integrity of the bone.

Two factors influencing the mechanical properties of cancellous bone are trabecular architecture and trabecular material properties.⁽¹⁰⁾ The substantial architectural changes may adversely affect the apparent-level mechanical properties,⁽¹¹⁾ but it is not known if the trabecular tissue is altered also. Potentially, tissue modulus may be altered in experimental OA because trabecular tissue changes have been reported in later-stage idiopathic OA.^(12,13) A change in tissue modulus can influence the apparent-level strength of the cancellous bone, as well the tissue-level stress and strain distribution that influences further bone remodeling. Understanding the architectural and tissue modulus adaptation on the mechanical properties of the periarticular cancellous bone may be revealing for understanding the early stage pathogenesis of post-traumatic OA.

Another important factor associated with the architectural changes is the three-dimensional (3D) connectivity. Connectivity change has been proposed as a mechanism resulting in a loss of bone strength⁽¹⁴⁾ and is a potentially irreversible adaptation of the cancellous structure.⁽¹⁵⁾ Detection of connectivity changes in early stage OA may suggest that a permanent change to the cancellous structure and strength is occurring or, minimally, that its reversal is difficult.⁽¹⁵⁾ Preventing early changes to the tissues involved in OA may be important for treating the disease, and, therefore, fully understanding the post-traumatic adaptation of cancellous bone is an important aspect of its natural pathogenesis.

It has been hypothesized that the substantial architectural changes in experimental OA are associated with alterations to periarticular cancellous strength, trabecular tissue modulus, and 3D connectivity. The purpose of this study was to use a canine ACLX model to quantify the pathogenesis of early stage experimental OA in periarticular cancellous bone. The aims were to (i) measure apparent-level mechanical properties of the periarticular cancellous bone, (ii) use those experimental results in combination with large-scale finite element (FE) models to determine if trabecular tissue modulus is altered, (iii) assess tissue-level stress and strain distributions, and (iv) quantify potential changes in cancellous bone 3D connectivity.

MATERIALS AND METHODS

Specimen preparation

Skeletally mature mixed-breed dogs were assigned randomly to one of two experimental groups: 3 weeks ($n = 5$) and 12 weeks ($n = 5$) post-unilateral ACLX. Both limbs of two additional nonoperated control animals (randomly selected from the same pool of animals) were used ($n = 4$) as a baseline comparison with the contralateral limbs of the experimental groups. Animal body masses ranged from 16 to 34 kg (mean, 23.5 kg), and ages ranged from 1.5 to 3 years (mean, 2.5 years). Unilateral ACLX was

performed by lateral arthrotomy^(16–18) after which the animals were housed in pens ($1.5 \times 2 \times 2 \text{ m}^3$) for the first 2 weeks postsurgery and then allowed to ambulate freely in large pens ($9 \times 8.5 \times 2 \text{ m}^3$). All procedures were approved by the University of Calgary Animal Care Committee. The animals were observed to return rapidly to their preinjury levels of activity. At death, the femora and tibia were cleaned of all soft tissues and stored (-80°C) in saline-soaked gauze. Subsequently, cylindrical bone cores (6-mm-diameter) were excised from the central weight-bearing region of the medial femoral condyles and medial tibial plateaus using a hollow coring bit while applying physiological saline. The cylindrical core included the cortical bone (1–2 mm) near the articular surface and the underlying periarticular cancellous bone (10–12 mm).

Microtomographic scanning

The bone cores were scanned using a high-resolution microtomographic (μCT) scanner ($\mu\text{CT} 20$; Scanco Medical, Bassersdorf, Switzerland),⁽¹⁹⁾ providing a nominal resolution of $34 \mu\text{m}$ (isotropic voxel dimension). A constrained Gaussian filter ($\sigma = 1.2$, finite support of 2) was used to suppress partly the noise in the original volume data, and the data were globally thresholded (10.2% of maximal possible gray value) to extract the mineralized bone phase.⁽²⁰⁾ The final 3D μCT scan was purified to remove artificial fragments.

Mechanical testing

Femoral cores were cut using a rotating diamond blade saw (Isomet Low Speed Saw, Buehler, Lake Bluff, IL, USA) to remove the cortical bone and cut to a length of 11 mm before compression testing to determine the apparent-level elastic modulus. The location of the cuts were measured precisely ($\pm 10 \mu\text{m}$) so the resulting test core could be related to the μCT scan. For each core, destructive unconfined compression testing (Instron 1122; Instron Corp., Canton, MA, USA) was performed (0.001/s strain rate) with lubrication between the specimen and the platens. Strain was measured using a novel extensometer⁽²¹⁾ that allows reduction of end artifacts and provides suitable boundary conditions for FE analysis. The position of the extensometer arms on the testing specimen was related to each original μCT scan so the appropriate portion of that scan could be extracted for a specimen-specific FE analysis (Fig. 1). From the mechanical tests, the linear portion of the stress-strain curve was analyzed to determine the experimental apparent-level elastic modulus (E_e^a).

FE modeling

Digital-based FE meshes using hexahedron elements were generated automatically from the μCT data describing the region delineated by the extensometer arms (cylinder of length 4.9 mm and diameter of 5.0 mm; Fig. 1). The boundary conditions given for uniaxial compression included a fixed Z and free X–Y displacement of the top and bottom nodes and no side constraints. The FE tissue material properties were given an arbitrary isotropic homoge-

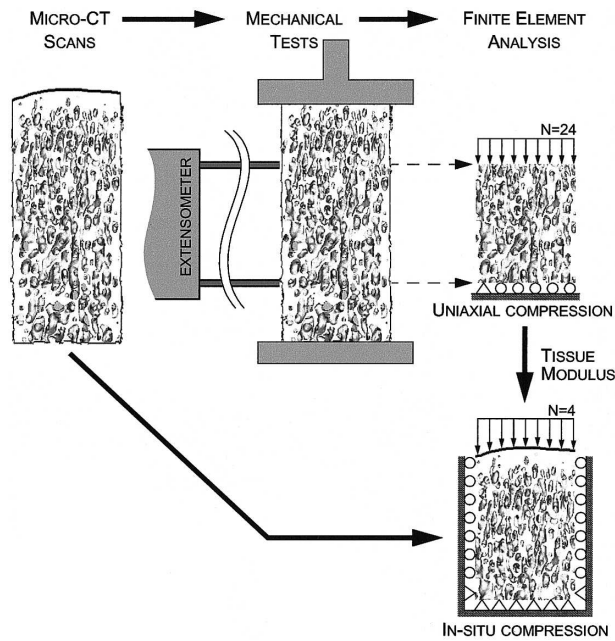


FIG. 1. The bone specimens were scanned using μ CT and then mechanically tested. FE models simulating uniaxial compression tests were based on the μ CT geometry within the region bounded by the extensometer arms to determine tissue modulus. FE models simulating in situ compression (confined compression) were created from the μ CT scans that included the subchondral plate and used the tissue modulus determined from the uniaxial compression tests.

neous linear elastic modulus of 5000 MPa and a 0.3 Poisson's ratio.⁽¹⁰⁾

Tissue modulus was calculated based on the proportional relation between tissue modulus and apparent modulus for the simulated FE results (denoted by subscript s , E_s^t , E_s^a , respectively) and the experimental results (denoted by subscript e , E_e^t , E_e^a , respectively)⁽¹⁰⁾:

$$E_e^t = \left(\frac{E_s^t}{E_s^a} \right) E_e^a. \quad (1)$$

The applied strain to the FE mesh was 1%, and the simulated apparent-level modulus (E_s^a) was calculated based on the reaction force in the FE model and used in Eq. (1) to determine tissue modulus (E_e^t).

In addition to the uniaxial compression models (a total of 24 models), confined compression models (a total of 4 models) also were developed (Figs. 1 and 2). One representative confined compression model was chosen from each experimental group and included the subchondral plate and cancellous bone to a depth of 5 mm. The criteria for selecting each representative sample was that it had the median structural measures (Tb.Th and BV/TV) within its respective group.⁽⁹⁾ The boundary conditions for the confined compression were the same as for the uniaxial, unconfined compression (Fig. 1), except the side nodes were confined in the X - Y directions. The material properties given for the subchondral plate were the same as the trabecular bone.⁽²²⁾

The FE problems were solved using custom in-house software that used the iterative method of the mesh-free element-

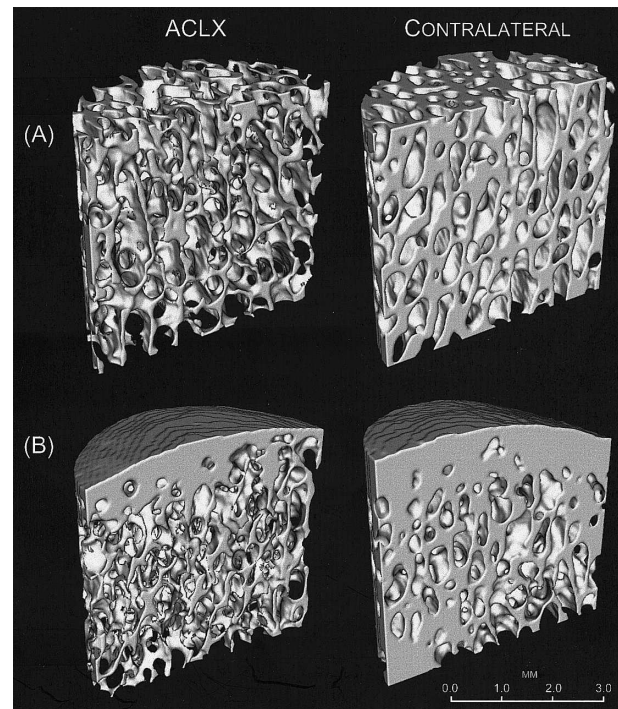


FIG. 2. The μ CT data were visualized showing data sets from 12-weeks post-ACLX and contralateral limb cancellous bone samples. (A) A sample data set used for the uniaxial compression FE models is shown and (B) the confined compression FE model data is shown.

by-element preconditioned conjugate gradient,^(23–25) and the convergence criteria were set to a nodal displacement tolerance of 10 nm. The distributions of the tissue stress and strain in the FE models are reported for the uniaxial unconfined and confined compression models.

Connectivity

The 3D connectivity density (Conn.D) was determined for the original μ CT data. The Conn.D expresses the number of connections per cubic millimeter ($1/\text{mm}^3$) and was evaluated using the Euler-Poincaré formula⁽²⁶⁾ based on the Euler number (χ)⁽²⁷⁾ as follows: $\text{Conn.D} = (1 - \chi)/\text{TV}$. In cancellous bone, the Euler number is defined as $\chi = \beta_0 - \beta_1 + \beta_2$ where β_0 is the number of bone particles (traditionally assumed to be 1), β_1 is the connectivity, that is, the maximum number of connections that must be broken to split the structure into two parts, and β_2 is the number of marrow cavities fully surrounded by bone.

Statistics

Statistical tests (Systat v10; SPSS Science, Chicago IL, USA) for apparent modulus, tissue modulus, and 3D connectivity included a two-way analysis of variance (ANOVA; $p < 0.05$) with one factor being time (3 weeks and 12 weeks) and the other being operation (ACLX and contralateral). Subsequently, a post hoc analysis was run at each timepoint (3 weeks and 12 weeks) to test whether ACLX was significantly different from the contralateral side

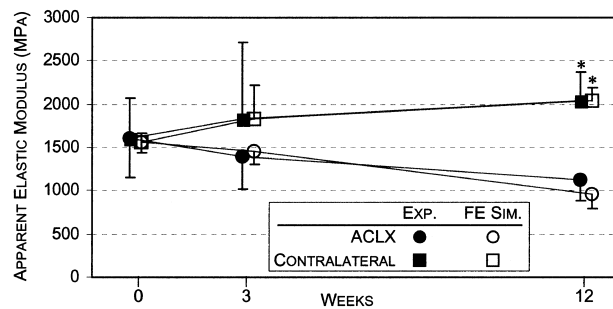


FIG. 3. Apparent elastic modulus of periarticular cancellous bone from the medial femoral condyle measured (i) experimentally with the extensometer and (ii) theoretically with FE analysis (given an arbitrarily selected 5000 MPa tissue modulus). Each point represents the group mean, and the error bars represent SDs. *Statistical significance ($p < 0.025$) by paired t -test is indicated with.

using a paired t -test with a Bonferroni adjustment for multiple comparisons ($p < 0.025$; i.e., $0.05/2$ groups). Linear regression analysis was performed including the unoperated controls to determine if there were significant trends with increasing time ($p < 0.05$).

RESULTS

Apparent-level elastic modulus of the ACLX periarticular medial femoral condyle was reduced at 3 weeks and 12 weeks post-ACLX, and the reduction was statistically significant at 12 weeks for both experimental and simulated FE compression testing ($p < 0.001$ each; Fig. 3). No significant change in the tissue-level elastic modulus was found ($p = 0.57$; Fig. 4), but the tissue-level stress and strain distributions were altered in the ACLX periarticular bone (Figs. 5 and 6). The connectivity of the trabecular core increased significantly at both 3 weeks and 12 weeks in the ACLX femora ($p < 0.001$ each; Fig. 7). Significant trends with time toward decreasing apparent modulus and increasing connectivity were found in the ACLX limbs (Figs. 3 and 7), and although there were signs of changes in the contralateral limb, the trend was only significant for the FE apparent modulus results ($p = 0.02$).

The mean and range of numbers of elements, nodes, iterations to solution, and reaction force at 1% strain are provided for the uniaxial compression FE models (Table 1). The time for solution ranged from 8 to 35 h (SGI Origin 2000; 195 MHz, Silicon Graphics, Inc., Santa Rosa, CA, USA).

The simulated FE apparent-level elastic modulus agreed closely with the experimental results (Fig. 3) for a given arbitrary tissue modulus (5000 MPa). Therefore, it follows that no significant differences in tissue modulus were detected ($p = 0.57$). The power of the tissue modulus test was $p = 0.31$, and based on the paired sample size at either 3 weeks or 12 weeks post-ACLX ($n = 5$, respectively) and variance for each group, the minimum detectable difference was 2500 MPa (power of 0.80). The tissue moduli determined were as follows: 3-weeks ACLX was 4800 ± 1400 MPa (mean $\pm$ SD), 3-weeks contralateral was 5000 ± 2500 MPa, 12-weeks ACLX was 6200 ± 2100

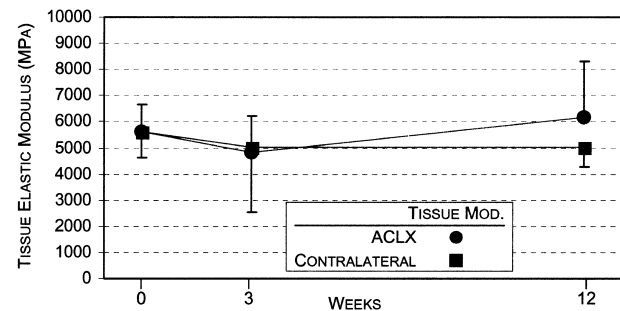


FIG. 4. The tissue modulus determined by combining experimental apparent-level results with FE simulations. Each point represents the group mean, and the error bars represent SDs.

MPa, 12-weeks contralateral was 5000 ± 760 MPa, and nonoperated control was 5600 ± 1000 MPa. A linear regression of the tissue moduli across all four experimental groups and the nonoperated controls determined that a single tissue modulus of 5100 MPa (95% CI of 4500–5700 MPa; $R^2 = 0.93$) used in the FE simulations for all groups could explain the variation of apparent-level elastic moduli based on the extensometer measures (Fig. 3).

Although no change in tissue modulus could be detected, despite the large apparent modulus decreases, the tissue stress and strain distributions were altered post-ACLX. Average normalized distributions are presented from the FE models for the uniaxial compression tests (Fig. 5) and the confined compression tests (Fig. 6). Axial stress (σ_{33}) and strain distribution (ϵ_{33}) and the von Mises stress (σ_{VM}) distribution are shown because they illustrated the largest differences between ACLX and contralateral limbs. The range of the stress and strain distributions in the cancellous tissue increasingly widened between 3 and 12 weeks post-ACLX, whereas in the contralateral and nonoperated control it remained unchanged and consistently narrow. The increased distribution width was particularly evident in the von Mises stress where it was more than doubled in the ACLX cancellous bone compared with the contralateral. Von Mises stress often is used as a material failure criterion. The skewness of the distributions in the confined compression tests was increased (Fig. 6) because of the inclusion of the subchondral plate in those FE models, whereas the uniaxial compression FE models (Fig. 5) were pure cancellous bone.

The 3D connectivity of the trabecular structures was increased in both the femur and the tibia post-ACLX periarticular cancellous bone ($p < 0.001$ each), and those significant increases occurred as early as 3 weeks ($p = 0.016$ and $p < 0.001$, respectively) and were further increased at 12 weeks post-ACLX ($p < 0.001$ each; Fig. 7).

DISCUSSION

This study of early stage of experimental OA showed a large decrease in apparent-level modulus (i.e., modulus of the bone structure) of the periarticular cancellous bone in the ACLX limb, and although these changes were associated with increased connectivity and altered stress and strain

UNCONFINED COMPRESSION

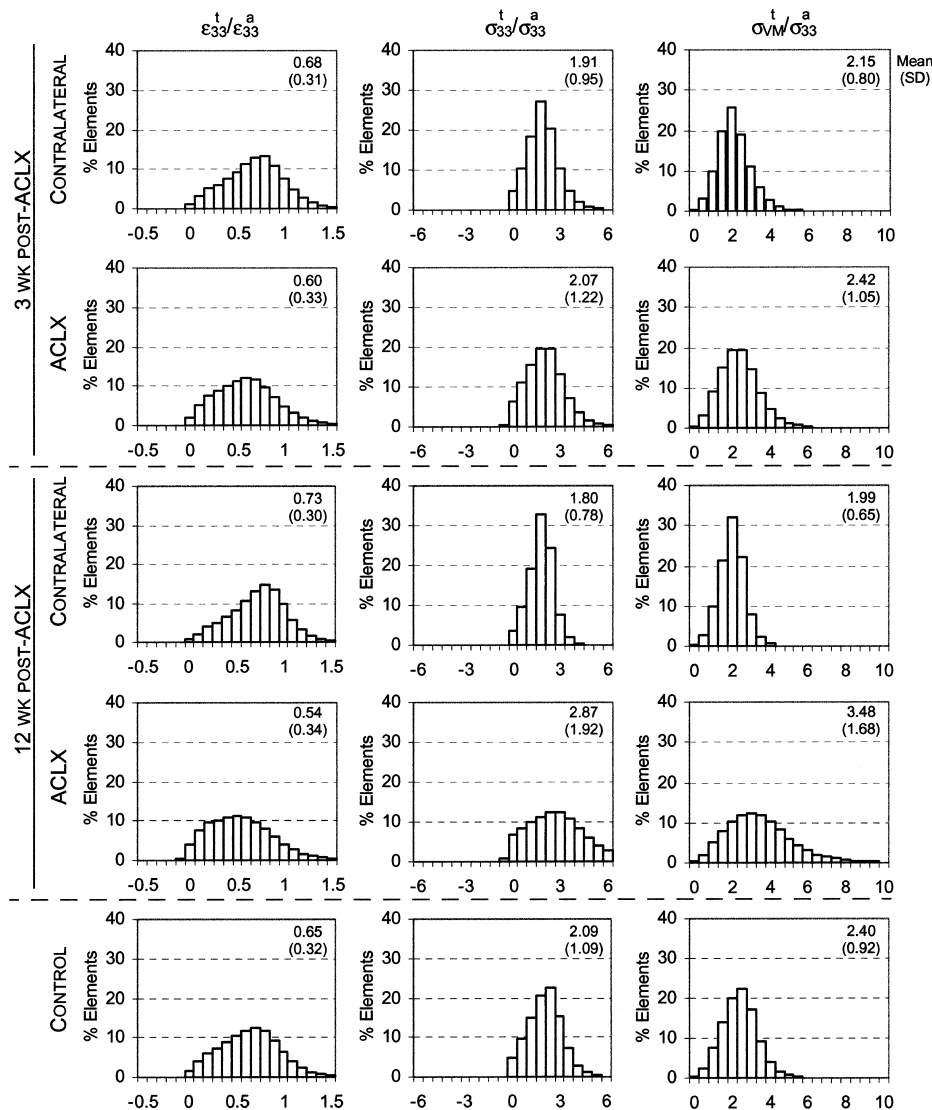


FIG. 5. Uniaxial compression FE histograms showing the variation in distribution of stresses and strains in the medial femoral condyle normalized by their respective apparent-level values. Mean and SDs for the distributions are shown in the top right corner. These results represent the average distributions from each group: 3-weeks and 12-weeks ACLX and contralateral limbs and controls.

distributions at the trabecular tissue level, there was no detectable change in the tissue modulus itself (i.e., modulus of the mineralized bone phase). Therefore, the primary mechanism for loss of cancellous bone strength in early stage experimental OA was a change in architecture rather than a change in the cancellous tissue modulus. The mechanism responsible for the architectural changes is not known, but the tissue stress and strain distribution are likely related to the adaptive bone remodeling that has occurred in the early stage and potentially play a role in further adaptive remodeling in late-stage OA.

The experimental apparent modulus and tissue modulus results were reasonable compared with past literature. The apparent modulus ranged between 1000 and 2000 MPa, depending on whether ACLX or contralateral bone was tested. In comparison, the canine forelimb cancellous bone has an apparent modulus of ~1500 MPa,⁽²⁸⁾ and equestrian cancellous bone falls into a range between 500 and 5000 MPa.⁽²⁹⁾ Also, the trend of decreasing apparent modulus

after ACLX is consistent with the findings of Wohl et al.,⁽³⁰⁾ who used a similar canine experimental OA model. Tissue modulus reports in the literature vary widely (between 400 and 25,000 MPa) because of differences in species, sample site, and measurement method (i.e., testing orientation of direct contact methods may correlate with tissue anisotropy).^(31,32) Although we are not aware of any canine tissue modulus data specifically, our current results fall within this broad range. In a previous study using the FE method to determine tissue modulus, van Rietbergen et al.⁽¹⁰⁾ found an average tissue modulus of 5910 MPa, with a possible variation from 2330 to 10,100 MPa. Their wide variation in tissue modulus estimates may be caused by species and site-specific differences, but it was also because the apparent modulus in that study was estimated from apparent density using logarithmic functions,⁽²⁹⁾ rather than the direct specimen-specific experimental compression tests.

The finding that there was no detectable change in tissue modulus despite the large apparent modulus changes in

CONFINED COMPRESSION

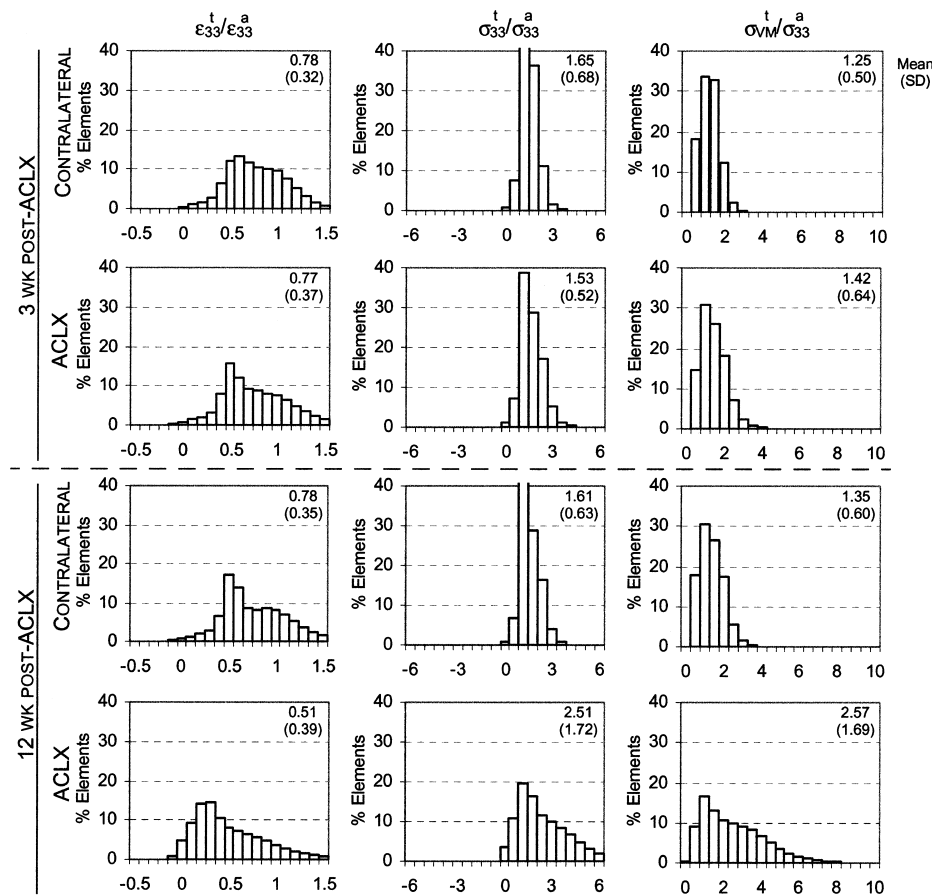


FIG. 6. Confined compression FE histograms showing the variation in distribution of stresses and strains in the medial femoral condyle normalized by their respective apparent-level values. Mean and SDs for the distributions are shown in the top right corner. These results represent an exemplar sample (selected based on median morphological properties) from each group: 3-weeks and 12-weeks ACLX and contralateral limb.

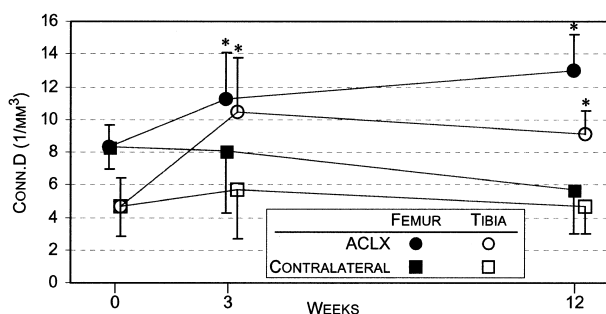


FIG. 7. The Conn.D ($1/\text{mm}^3$) for the femur and tibia periarticular cancellous bone. Each point represents average values with SD error bars. *Statistical significance ($p < 0.025$) by paired t -test is indicated.

early experimental OA is important. FE models based on geometric data from medical imaging tools (i.e., CT or magnetic resonance imaging) may be useful in the future to noninvasively predict bone strength in age- and disease-related processes. However, use of such a method to track changes currently depends on the assumption of tissue modulus remaining constant in these types of adaptive processes. In this experimental model of OA, the large apparent modulus changes could be predicted accurately based on

TABLE 1. A SUMMARY OF THE RANGE AND AVERAGE NUMBER OF ELEMENTS, NODES, ITERATIONS TO CONVERGENCE, AND REACTION FORCE FOR THE UNIAXIAL COMPRESSION FE SIMULATIONS (5.0-mm-DIAMETER, AND 4.9-mm-HEIGHT CYLINDERS)

	Elements	Nodes	Iterations	F_r (N)
Minimum	721,678	1,023,351	1349	144.9
Maximum	1,491,427	1,814,848	4408	456.5
Mean	1,174,694	1,508,589	2598	307.8

geometric information alone (Fig. 3), and the assumption of constant tissue modulus was valid in this early stage. Thus, the FE simulation appears to be a useful tool for determining mechanical strength, especially because it exhibits reduced variability compared with experimental mechanical testing (Fig. 3).

In contrast to the reports here of no detectable change in tissue modulus in the early stage of this experimental model, there are studies indicating tissue modulus decreases in human idiopathic OA. The decrease was shown both indirectly,⁽¹²⁾ based on findings of hypomineralized tissue, and directly,⁽¹³⁾ using combined FE and mechanical testing. The discrepancy in tissue modulus may arise from a difference

in pathogenesis between post-traumatic OA and idiopathic OA (i.e., secondary versus primary OA). Also, possibly the early stage of post-traumatic OA (i.e., defined from time of initial injury) does not correspond to the early stage of idiopathic OA (i.e., defined from time of first clinical symptoms of OA). In this experimental model, the first 12-weeks post-ACLX may represent a transitory phase in the pathogenesis of post-traumatic OA, and that given more time, the 35% reduction in BV/TV may be compensated by the deposition of new, undermineralized bone on the remaining trabecular structure. Indeed, long-term studies in the canine experimental model have reported increased subchondral bone volume after 54 months,⁽⁶⁾ consistent with this hypothesis. Hence, the precedence of architectural changes before tissue modulus changes may represent a transitory phase in the pathogenesis of OA.

The increased tissue stress and strain distributions measured here in the post-ACLX cancellous bone were accompanied by significant architectural adaptation, and these two changes in the early stage of experimental OA are likely related. However, the exact relation to the mechanical stimulus for bone remodeling is not well understood (e.g., strain magnitude, strain rate, and strain gradient), and a causal relation cannot be established. Bone resorption dominated the early stage as evidenced by the architectural changes that occurred without tissue modulus adaptation, but tissue changes others have reported^(12,13) suggest that eventually new bone will be formed, possibly to counter the strength loss due to severely thinned trabeculae.⁽⁹⁾ The new bone formation may be a consequence of the increased stress and strain distributions observed at 12 weeks post-ACLX, and the methods based on μ CT geometry and large-scale FE models may be useful in the future for elucidating such causal relations.

There are some limitations of the study that should be discussed. First, the estimates of tissue modulus represent the average isotropic modulus as the methods used here cannot detect any variation within the trabeculae that may exist. Second, the determination of tissue modulus is related directly to the experimental mechanical testing results; therefore, variability in the tissue modulus can be influenced by errors in the compression technique as well as the interanimal variability within each experimental group. Generally, the statistical tests in this study should be regarded cautiously because of the small group sizes; nevertheless, statistically significant changes were detected. Third, the use of hexahedron elements in the FE model can cause stress raisers at the tissue level,⁽³³⁾ but this effect was minimized by using the maximal model resolution (34- μ m isotropic resolution) and resulted in acceptable fractal dimensions for all the ACLX and contralateral FE meshes and likely only affected the margins of the histograms (Figs. 5 and 6).

The mechanism responsible for apparent-level modulus decrease in early stage post-ACLX was architectural adaptation rather than tissue modulus change; thus, focus of the early natural pathogenesis should be on the architectural changes. Previously, it was shown that BV/TV and Tb.Th decrease by 12 weeks post-ACLX,⁽⁹⁾ but these types of changes potentially can be reversed.⁽³⁴⁾ Alternatively, 3D connectivity changes have been associated with irreversible

bone adaptation^(15,34); thus, the alteration in connectivity measured as early as 3 weeks post-ACLX (Fig. 7) may have serious consequences regarding the potential for return of normal periarticular cancellous bone. The reason the connectivity increased despite the decreased BV/TV (35%) was because the periarticular cancellous bone was primarily platelike,⁽⁹⁾ which when subjected to bone loss leads to plate fenestrations as noted by others.⁽³⁵⁾ In such cases, adding new bone may repair the plate fenestrations, but rod connections remain problematic⁽¹⁵⁾ and an overall permanent change in architecture would occur in spite of adding new bone.⁽³⁴⁾ In late-stage human OA, the thicker and more widely spaced trabeculae⁽³⁶⁾ may be related to an early loss of connectivity, followed by compensatory thickening of the remaining structure.

The contralateral cancellous bone appears to undergo some adaptation after surgery that is opposite to the changes seen in the ACLX limb, but this trend was only significant in the FE apparent modulus measures ($p = 0.02$). The compensatory response of the contralateral limb has been found to be negligible by others,⁽³⁷⁾ and although statistical significance was not found for all the parameters measured in this study, there is a recurring pattern of this trend (Figs. 3 and 7). The mechanical strength measures increased relative to the normal controls by $\sim 27\%$ and $\sim 31\%$, respectively, for experimental and FE apparent modulus. This indicates the possibility that increased loading on the contralateral limb has led to increased strength of that bone.

In summary, the apparent modulus alterations in the ACLX periarticular medial femoral condyle in the early stages of experimental OA were caused by changes in trabecular architecture, but not tissue. Therefore, interventions to arrest or slow the cancellous bone adaptive process should focus on maintaining normal trabecular architecture, and these interventions should be done early after the initial trauma to intervene in the natural pathogenesis of post-traumatic OA.

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