Clinical Biomechanics 41 (2017) 1–8

Contents lists available at ScienceDirect

Clinical Biomechanics

journal homepage: www.elsevier.com/locate/clinbiomech

Optimizing finite element predictions of local subchondral bone structural stiffness using neural network-derived density-modulus relationships for proximal tibial subchondral cortical and trabecular bone

S. Majid Nazemi [a,*], Morteza Amini [b], Saija A. Kontulainen [c], Jaques S. Milner [d], David W. Holdsworth [d], Bassam A. Masri [e], David R. Wilson [e], James D. Johnston [a,*]

[a] Department of Mechanical Engineering, University of Saskatchewan, Saskatoon, Canada
[b] Institute for Lightweight Design and Structural Biomechanics, Vienna University of Technology, Vienna, Austria
[c] College of Kinesiology, University of Saskatchewan, Saskatoon, Canada
[d] Robarts Research Institute, Western University, London, Canada
[e] Department of Orthopaedics, University of British Columbia, Centre for Hip Health and Mobility, Vancouver, Canada

ARTICLE INFO

Article history:
Received 19 October 2015
Accepted 25 October 2016

Keywords:
Finite element modeling
Density-modulus relationships for bone
Subchondral bone
Proximal tibia
Neural network

ABSTRACT

Background: Quantitative computed tomography based subject-specific finite element modeling has potential to clarify the role of subchondral bone alterations in knee osteoarthritis initiation, progression, and pain. However, it is unclear what density-modulus equation(s) should be applied with subchondral cortical and subchondral trabecular bone when constructing finite element models of the tibia. Using a novel approach applying neural networks, optimization, and back-calculation against in situ experimental testing results, the objective of this study was to identify subchondral-specific equations that optimized finite element predictions of local structural stiffness at the proximal tibial subchondral surface.

Methods: Thirteen proximal tibial compartments were imaged via quantitative computed tomography. Imaged bone mineral density was converted to elastic moduli using multiple density-modulus equations (93 total variations) then mapped to corresponding finite element models. For each variation, root mean squared error was calculated between finite element prediction and in situ measured stiffness at 47 indentation sites. Resulting errors were used to train an artificial neural network, which provided an unlimited number of model variations, with corresponding error, for predicting stiffness at the subchondral bone surface. Nelder-Mead optimization was used to identify optimum density-modulus equations for predicting stiffness.

Findings: Finite element modeling predicted 81% of experimental stiffness variance (with 10.5% error) using optimized equations for subchondral cortical and trabecular bone differentiated with a 0.5 g/cm^3 density.

Interpretation: In comparison with published density-modulus relationships, optimized equations offered improved predictions of local subchondral structural stiffness. Further research is needed with anisotropy inclusion, a smaller voxel size and de-blurring algorithms to improve predictions.

1. Introduction

The role of subchondral bone in the osteoarthritis (OA) disease process is a controversial and growing area of focus in OA research (Goldring and Goldring, 2010). OA-related subchondral bone alterations are believed to increase the local structural stiffness of subchondral bone (i.e., the stiffness directly at the subchondral bone surface), thereby altering load and stress distributions in cartilage, resulting in cartilage degeneration and OA progression (Radin et al., 1972; Radin et al., 1973; Radin and Rose, 1986). Variations in local subchondral bone structural stiffness will also create stiffness gradients, which will alter cartilage shear stresses, leading to further cartilage degeneration (Radin and Rose, 1986). Current theories regarding the role of subchondral bone in OA rely on evidence from animal studies (which may not be applicable to the human OA process) or ex vivo cadaveric studies (which are questionable, given that clinical OA status or pain symptoms are often unknown). To help clarify the role of subchondral bone in OA, in vivo methods based on finite element (FE) modeling are needed to monitor variations in subchondral bone mechanical properties in people living with OA.

We previously developed and validated a subject-specific finite element (FE) model of the proximal tibia to predict local proximal tibial subchondral bone structural stiffness (Nazemi et al., 2015). Validation

* Corresponding authors at: Department of Mechanical Engineering, University of Saskatchewan, 57 Campus Drive, Saskatoon, SK S7N 5A9, Canada.
E-mail addresses: majid.nazemi@gmail.com (S.M. Nazemi), jd.johnston@usask.ca (J.D. Johnston).

http://dx.doi.org/10.1016/j.clinbiomech.2016.10.012
0268-0033/

was based on comparisons of FE stiffness predictions with experimentally-derived stiffness obtained using in situ macro indentation testing. The FE model was based on quantitative computed tomography (QCT) images (often referred to as QCT-FE) to account for subject-specific variations in both bone geometry and material properties (elastic modulus, E). Isotropic material properties were defined by inputting QCT-imaged bone mineral density (ρ_{QCT}) into *published* density-modulus relationships derived from isolated compression testing or ultrasound of excised bone samples (Morgan et al., 2003; Anderson et al., 1992; Linde et al., 1992; Goulet et al., 1994; Hodgskinson and Currey, 1992; Snyder and Schneider, 1991; Keyak et al., 1994; Rho et al., 1995). These relationships were generally non-linear, power-law equations expressed as $E = a \times \rho^b$, with a and b constants and ρ being either ash or apparent density. Our results indicated that application of cortical-specific and trabecular-specific density-modulus equations (as opposed to a single density-modulus equation), separated using the literature-based cut-off apparent density of 1 g/cm^3 (Gray et al., 2008a; Rho, 1996) resulted in the most accurate estimation of local structural stiffness (Nazemi et al., 2015). However, the observed range in predictive ability (R^2 from 0.56 to 0.77) (Nazemi et al., 2015) and errors in stiffness predictions (root mean square error (RMSE), normalized in relation to maximum measured stiffness (RMSE%), ranged from 16.6% to 338%) (Nazemi et al., 2015), indicated that published equations may not be ideally suited for modeling local subchondral bone structural stiffness. This may be because previously evaluated density-modulus equations were obtained from epiphyseal and metaphyseal trabecular bone and cortical shaft regions (Morgan et al., 2003; Anderson et al., 1992; Linde et al., 1992; Goulet et al., 1994; Hodgskinson and Currey, 1992; Snyder and Schneider, 1991; Keyak et al., 1994; Rho et al., 1995) with different microarchitecture and tissue composition than bone from subchondral trabecular and cortical regions. Another possibility explaining moderate predictions could be the choice of density threshold (i.e. 1 g/cm^3) for differentiating trabecular and cortical bones, which may not be optimum.

As opposed to evaluating previously published density-modulus equations and thresholds, back-calculation is a promising means to derive optimum equations that best predict local proximal tibial structural stiffness (MacNeil and Boyd, 2008). Back-calculation involves iteratively adjusting different FE modeling parameters (e.g., a and b constants of $E = a \times \rho^b$ and cortical-trabecular threshold) to derive optimum equations, which best match in situ mechanical testing results. With this approach, the developed FE model should be optimized to accurately reflect subchondral bone structural stiffness. However, although back-calculation is an effective method to derive optimum density-modulus equations for FE modeling, the approach can be quite time consuming due to the incremental nature of the analysis, particularly for analyses investigating optimum equations for both cortical and trabecular bone with multiple parameters and parameter combinations.

Neural networks offer the potential to accelerate the back-calculation process for deriving optimal density-modulus equations for both cortical and trabecular bone, as well as threshold information. Using previously acquired QCT-FE and measured stiffness results, neural networks can be trained to forecast the approximate RMSE between QCT-FE predicted and measured stiffness corresponding to specific combinations of density-modulus equations and threshold density quite quickly (seconds). The trained network can then be linked with optimization methods to identify density-modulus equations and threshold information that best predict subchondral bone structural stiffness. In contrast, identifying optimal density-modulus equations using incremental methods (e.g., a and b terms varied in increments of 0.01) could take months or years to process depending upon incremental sizing.

Thus, the objective of this study was to integrate QCT-FE stiffness information with a neutral network to identify subchondral-specific density-modulus equations and the differentiating threshold density that optimized QCT-FE predictions of local structural stiffness at the proximal tibial subchondral surface.

2. Materials and methods

2.1. Specimens

Thirteen proximal tibial compartments (9 lateral, 4 medial) from an earlier experiment (Johnston et al., 2011) were used in this study. The specimens were excised from 11 intact fresh-frozen knee samples (3 bi-lateral and 5 mono-lateral) obtained from 8 donors (7 males and 1 female, ages ranging from 51 to 88 years). Details of the specimens and preparations are provided in Johnston et al. (2011). Briefly, each compartment was fixated in a potting system comprised of a PVC outer shell and support base made of gypsum potting material (Denstone, Modern Materials Inc., South Bend, IN) and polymethyacrylate bone cement (PMMA) (Fastray, Bosworth, Chicago, IL). Four stainless steel fiducial markers were inserted in the outer PVC shell for registration purposes.

2.2. QCT imaging

Each potted compartment, including fiducials, was imaged using a clinical CT scanner (64-slice helical Aquilion 64, Toshiba Medical Systems, Tokyo, Japan) (Johnston et al., 2011). Imaging parameters include: tube voltage: 120 kVp, tube current-time product: 150 mAs, bone standard reconstruction algorithm, 0.5 mm isotropic voxel size. A QCT phantom (Model 3T; Mindways Software Inc., Austin, TX) was used to map Hounsfield units (HU) to equivalent volumetric ρ_{QCT} (g/cm^3 K_2HPO_4).

2.3. Mechanical testing

In situ macro indentation testing was performed directly at the subchondral bone surface using a 3.5 mm diameter flat-ended nonporous indentor at a rate of 2 mm/min (Johnston et al., 2011). A total of 47 test sites from 13 specimens were included in this study. The slope of the most linear part of the load-displacement curve was determined and defined as structural stiffness for the corresponding indentation site.

2.4. Finite element modeling

2.4.1. Geometry generation

QCT images were segmented using commercial segmentation software (Analyze10; Mayo Foundation, Rochester, MN, USA). Details of the FE analysis are provided in Nazemi et al. (2015). Briefly, a marching-cubes algorithm was used to convert the segmented volume into a 3D polygonal surface mesh. The generated volumes were then imported in reverse engineering software (Geomagic Studio 12; Systems, Rock Hill, SC, USA) to heal the surfaces. While maintaining maximum geometric complexity, imported volumes were smoothed and converted to NURBS volumes, then exported to commercial FE software (ABAQUS; Providence, RI, USA) for volume meshing. To model the experimental test, cylindrical flat surfaces were generated at the subchondral surface for each indentation site.

2.4.2. Meshing and material properties

Geometries were meshed into quadratic tetrahedral elements. Based upon convergence studies, a global element size of 0.95 mm was used, resulting in 400,000–640,000 elements and 560,000–890,000 nodes. A custom algorithm (Matlab; MathWorks, Natick, MA, USA) mapped ρ_{QCT} into E, and a converging approach was used to map E to corresponding tetrahedral elements (discussed in more detail in Nazemi et al. (2015)). A global Poisson's ratio of 0.3 was assumed for all elements. Material behavior was treated as linearly elastic and isotropic.

2.4.3. Material mapping – published equations

For comparison purposes, the combination of Goulet et al. (1994) and Rho et al. (1995) equations ($E_{Trab} = 6310 \times (BV/TV)^{2.1}$, $E_{Cort} =$