Covariation between shape and bone microstructure in the proximal tibia in humans

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Abstract

Prosthetic knee replacement is a surgical procedure designed to restore knee joint function in cases of advanced osteoarthritis and fracture. Since tibial morphology and microstructure vary among different individuals, the surgeon’s anatomical expertise and knowledge of various implant designs is essential. In order to contribute to the pre-surgical diagnosis of bone degradation, we investigate patterns of variation and covariation between the shape of the proximal tibia and its microstructure. The general objective of this pilot study is the prediction of bone microstructure in relation to the shape of the proximal tibia, thereby delivering an estimation of bone microstructure based on the geometry of the knee. Our sample comprises dried bone samples of 20 human tibiae including cases of osteoarthritis. The shape of the tibia is represented by anatomical landmarks as well as curve and surface semilandmarks. Microstructural parameters are relative bone volume, trabecular thickness, number, and spacing obtained from high resolution X-ray computed tomography (XCT) images with an isometric voxel size of 50 µm. Geometric Morphometric techniques are used to study the covariation between proximal tibial shape and structural parameters using partial least squares analysis. Our results indicate that a decrease in bone volume fraction, as seen in older individuals, is moderately correlated (>0.6) with a flattening and broadening of the tibial plateau. Using this approach it is possible to estimate structural parameters in the knee according to its shape, allowing the three-dimensional visualization of covariation patterns in relation to aging. This method can potentially function as an aid in the clinical diagnosis of tibial bone degradation and delivers anatomical information that may be valuable in the design of custom knee implant components.

Keywords: XCT, knee joint, bone microstructure, tibial shape, Geometric Morphometrics, covariation

1 Introduction

The investigation of anatomical changes in the aging population is of particular interest in the healthcare sector - for diagnostic reasons as well as for the improvement of treatment strategies of degenerative bone diseases like osteoporosis and osteoarthritis (OA). OA involves degradation of joints including articular cartilage and subchondral bone, resulting in reduced mobility in affected patients. It is one of the most common forms of musculoskeletal disorders and substantially raises economic costs [1]. Due to increasing life spans, the frequency of OA is also on the increase and becoming a leading cause of chronic disability in the elderly, mostly involving the knee and hip [2]. In cases of advanced osteoarthritis and rheumatoid arthritis, but also in the treatment of fractures and dysplasia, knee replacement surgery (knee arthroplasty) is the most common surgical procedure to
restore the function of the knee joint. It consists of replacing the affected or damaged joint surfaces of the knee with a combination of various components such as metal alloys, ceramic material, and plastic material [3]. In both total and partial knee replacements, the prostheses are shaped to endure dynamic knee loads during bipedal movement. Total knee arthroplasty is characterized by the replacement of all three aspects of the knee (medial, lateral, and patellofemoral). In contrast, a partial knee replacement only involves the affected compartment of the knee. Since tibial morphology varies among different individuals each surgical intervention in partial knee arthroplasties has to be customized, placing high demands on the surgeon’s expertise and knowledge of various implant designs [4].

By quantifying shape and microstructural variation in the human tibia that may be accompanied by bone degradation, the Geometric Morphometric (GMM) toolbox will provide valuable support for orthopaedic specialists and surgeons in the absence of high-resolution peripheral quantitative computed tomography (HR-pQCT). We hypothesize that tibial shape and trabecular microstructure covary to a certain degree, reflecting subchondral bone remodelling due to aging or OA [5, 6] associated with shape changes of the tibial plateau. However, little empirical evidence exists for such a relationship. In this analysis we introduce a new 3D method for delineating the covariation between proximal tibial shape and microstructure. The combination of shape analysis and non-destructive testing will provide new insights in the relationship between shape and bone microstructure by estimating microstructural parameters according to the geometric properties of bones in the lower extremity.

The primary objective of this approach is to predict tibial bone microstructure in the elderly and its relationship to the shape of the knee joint. This will provide estimations of trabecular degradation based on tibial shape, possibly delivering an additional tool for diagnosing a decrease in bone mass and facilitating traditional methods like medical X-ray imaging and dual-energy X-ray absorptiometry. By quantifying age-related morphological variation of the tibia this analysis may finally contribute to the design and development of novel knee implant components.

2 Material and Methods

2.1 Specimens

Dried tibiae originating from a historical skeletal series stored at the State Collection for Anthropology and Palaeoanatomy in Munich (Germany) were divided into adult (n=8, biological age between 20 and 40 years), middle aged (n=4, between 40 and 60 years), and old (above 60 years old) age groups. Age and sex determination as well as the classification of bone pathologies for this archeological sample are based on the work of von Heyking [7]. Nine specimens show evidence of moderate osteoarthritis (OA) and one case exhibits severe signs of periostitis, a medical condition caused by inflammation of a layer of connective tissue that surrounds bone called the periosteum. Since only left tibiae were considered in the analysis, volume data of right specimens were mirrored for subsequent analysis.

2.2 High resolution XCT

The proximal part of each specimen was scanned at a resolution of 50 µm voxel size using a RayScan 250E cone beam XCT device equipped with a Perkin Elmer flat panel detector (2048x2048 pixels with a pixel size 200 µm) and a Viscom 225kV microfocus X-ray tube. The X-ray settings were standardized to 180 kV and 150 µA with an integration time of 1999 ms; a 0.5mm thick copper filter-plate was applied.

Images were thresholded to segment bone tissue from porosity via the (advanced) automatic surface determination function in Volume Graphics 2.2. In this analysis the outline of each region of interest (ROI) is defined by the curve that describes the outline of the articular surface of the medial and lateral
condyle respectively (see Figure 1 left; yellow landmarks). Three-dimensional ROIs for which the outline is defined by the edges of the articular surfaces were created in STL file format in Rapidform XOR (Inus Technology) and subsequently imported into VGStudio MAX 2.2 (Volume Graphics). The lower border of each ROI is defined by the epiphyseal line - the junction between epiphysis and metaphysis (see Figure 1 right). Morphometric indices are calculated in VGStudio MAX 2.2 using the surface determination and are based upon bone surface (BS), bone volume (BV) and total volume (TV). Trabecular bone morphology including bone volume fraction (BV/TV, bone volume/total volume), mean trabecular thickness (TbTh), mean trabecular number (TbN), and mean trabecular separation (TbSp) were determined separately for the medial and lateral condyle. The computation of these indices is implemented in VGStudio MAX 2.2 and based on the work of Günnewig [8].

Figure 1: Proximal tibia. Left: template of 316 anatomical landmarks (red), semilandmarks on curves (yellow), and the surface (green and blue). Right: regions of interest (green). Microstructural parameters (bone volume fraction, mean trabecular thickness, number and spacing) were extracted for the medial and lateral condyle, respectively.

2.3 Geometric Morphometrics and statistical analysis

In general, morphometrics represent the study of shape variation and its covariation with other variables. Geometric Morphometrics (GMM) techniques focus on coordinates of landmarks and preserve the geometric information about their relative positions [9]. Using the open-source software Edgewarp3D [10] along with AMIRA 5.3 (FEI), a template of 316 anatomical landmarks and semilandmarks on curves and the surface was created to capture tibial geometry in three dimensions (see Figure 1). Landmarks and semilandmarks are converted to shape coordinates by Generalized Procrustes Analysis (GPA). This involves translating, rescaling, and rotating the configurations relative to each other so as to minimize the overall sum of squared distances between corresponding (semi)landmarks [9].
GMM techniques are used to study the covariation between proximal tibial shape and microstructural parameters using a 2-block partial least squares (PLS) analysis. The application of PLS to Procrustes coordinates is also called singular warp analysis. It describes the multivariate relationship between tibial microstructure (BV/TV, TbTh, TbN, and TbSp; log transformed values for the medial and lateral condyle respectively) and the shape of the proximal tibia in terms of a pair of latent variables (one for microstructure and one for shape), which together have the highest possible covariance (predictive power). The loadings for these two linear combinations are contained in two particular singular vectors, and the corresponding singular value is the covariance between the two defined variables. The second pair of variables is (geometrically) orthogonal to the first pair and the successive pairs of variables are defined analogously [11].

Singular warps of the shape block are linear combinations of the original shape coordinates and can be visualized either as scores (i.e., projections of the original variables onto these axes; see Figure 2) or as deformations (see Figure 3) [12]. We use the thin-plate spline algebra [9] to deform an extracted triangulated surface of a single specimen (see Figure 1). The landmarks and semilandmarks of this specimen are used to warp the surface points from the original configuration in Procrustes space into the same configuration after different multiples of the singular vectors are added. The visualization of the singular warps was rendered in Amira 5.3 (FEI). Data processing and analysis routines were written in R software (R development team) [13].

3 Results

In Table 1 the mean values for each microstructural parameter within the representative age class are summarized. On average, adult specimens have higher values for BV/TV, TbTh, and TbN, and lower values for TbSp. To assess the covariation of tibial shape and microstructure, we performed a PLS analysis of the Procrustes shape coordinates against microstructural parameters (BV/TV, TbTh, TbN, and TbSp; each one value for the lateral and medial condyle of each specimens, hence, eight variables in total).

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Table 1: Average values for microstructural parameters (bone volume fraction: BV/TV; mean trabecular thickness in mm: TbTh; mean trabecular number per unit length defined as 1/mm: TbN; mean distance between trabeculae in mm: TbSp) extracted from the lateral condyle and medial condyle for all age classes (adult, middle aged, old).

The first singular warp (the first dimension of the PLS analysis) accounts for 62.1% of the total squared covariance between the shape coordinates and the variables of microstructure. The first two singular warps span about 85% of the total squared covariance pattern. The correlation between the first pair of PLS scores (shape vs. microstructure) is 0.6 and between the second pair 0.71. BV/TV has the highest loading on the first singular vector. SW2 has high loadings on TbN. The score-plots for the PLS analysis of shape coordinates against all microstructural parameters show the moderate correlation between microstructural parameters and the shape of the proximal tibia (see Figure 2). Adult specimens tend to cluster on the right upper end of SW1 scores. Middle-aged and old specimens largely overlap and generally tend to show lower SW1 scores. The individual showing severe signs of
periostitis (marked by a crossed circle in Fig. 2) shows the highest SW1 score in relation to microstructural variables.

Figure 2: Singular warp scores (SW1, left; SW2 right) of the shape coordinate block plotted against the microstructural parameters. Pearson product-moment correlation coefficients for the correlation between the singular warp scores (SW1: $r = 0.6$, for SW1: $r = 0.7$). Adult specimens (circles) tend to cluster on the right upper end of SW1 scores. Middle-aged (triangles) and old individuals (squares) largely overlap and generally tend to show lower SW1 scores. Individuals with signs of osteoarthritis (OA) are highlighted in grey. The individual showing severe signs of periostitis is marked by a crossed circle.

Figure 3 illustrates the corresponding shape differences as predicted by the loadings of the first singular vector for the shape variables of the tibia. Shape features that are associated with high scores along the first singular warp, and thus tend to represent younger (adult) specimens, correspond to a high bone volume fraction, increased mean trabecular thickness, and a higher mean trabecular number. Shape changes associated with high SW1 scores include a proximal tibial plateau that is mediolaterally and anteroposteriorly narrower. Additionally, the articular surface area of the medial condyle is more concave while the distance between the medial and lateral intercondylar tubercles is larger leading to a broader intercondylar eminence. Finally the tibial tuberosity, which is the area of insertion for the patellar ligament, tends to be less pronounced in specimens that have high loadings on SW1 (see Figure 3). For lower SW1 scores, a mediolaterally and anteroposteriorly wider tibial plateau covaries with a decreased bone volume fraction, a higher level of mean trabecular spacing, and a decreased mean trabecular thickness and number. SW2 represents inter-individual shape differences concerning the shape and outline of the articular surfaces. Individuals with high SW2 scores show more convex lateral condyles and a narrower posterior intercondylar area, where part of the posterior cruciate ligament is attached. High scores along the second singular warp are associated with lower values of BV/TV, TbTh, and TbN – and a high value for TbSp.
4 Discussion

In this study we statistically quantified patterns of morphological associations between tibial shape and microstructure. The aim of our study was to investigate 3D patterns of covariation between tibial shape and cancellous bone microstructure to provide an additional tool in the clinical diagnosis of tibial bone degradation using low-resolution systems. It is the first time that patterns of covariation between shape and microstructure in the human knee are quantified and visualized.

Our findings point to a moderate correlation between shape and microstructure, showing that a decrease in bone volume fraction, as seen in older individuals, is moderately correlated (>0.6) with a flattening and broadening of the tibial plateau. This may reflect age-related functional and structural adaptations in the knee due to cartilage damage or thinning of cartilage in aged individuals – and may be the consequence of changes in the mechanical load transfer [14]. OA is a chronic joint degenerating disease characterized by the degeneration of articular cartilage, changes in subchondral bone, and ossification of calcified cartilage. Though it is still unknown which mechanisms cause these subchondral bone changes, van den Broek [6] showed that subchondral bone changes could be explained by changes in the local load distribution. The author concluded that changes in the loading regime “due to malalignment of the joint plays an important role in mechanically induced subchondral bone changes during osteoarthritis” (p19). In our analysis specimens exhibiting osteoarthritis cannot be clearly separated from those showing no external signs of joint degradation, although specimens with OA do tend to show smaller SW1 scores and therefore a decreased bone volume fraction. The adult individual showing severe signs of periostitis has the highest values for BV/TV and TbTh in the sample, possibly indicating structural modifications the may be due to extensive new periosteal lamellar bone formation. Our findings do not provide conclusive evidence regarding causative factors and effects that lead to the observed covariation patterns, however, they do help in visualizing changes in tibial shape from younger to aged individuals that are accompanied by a decrease of BV/TV, TbTh, and TbN, as well as an increase TbSp. This is in agreement with earlier studies that investigated the changes in tibial microstructure in humans [15, 16].

In order to prove the potential clinical applicability of this method, several shortcomings of this pilot study must first be resolved. Foremost, a recent sample of known sex and age has to be investigated to
circumvent effects of secular trends in growth and skeletal maturation that might influence the interpretation of the results. One of the major disadvantages is certainly the dependency on the determination of age, sex, and pathologies – even though the statistical analysis does not necessitate an a priori classification of groups. This estimation mainly introduces an uncertainty in the classification of OA, which is diagnosed in the clinical routine not only by radiographically visible osteophytes, but also by knee pain and the excessive formation of synovial fluid [17]. A further aspect of this approach that needs consideration is the differentiation between cortical and trabecular bone, instead of determining structural parameters of the whole ROI. Future analysis will take cortical thickness as a separate variable into account, delivering an additional structural parameter that might increase the power of prediction of this method. Above all, further analyses should also include information on anisotropy, bone mineral density, and femoral shape.

5. Conclusion

The unique combination of shape analysis and non-destructive testing delivers valuable information about the anatomical relationship between shape and microstructure in the human knee. Furthermore, it provides additional data for the interpretation of bone degradation due to aging or disease. By examining shape changes and its covariation with microstructural parameters this new approach has the potential to serve as an aid for orthopaedic specialists in the diagnosis and treatment of musculoskeletal disorders. Finally, by investigating the variation of shape and microstructure in normal and pathological knee joints this analysis provides anatomical information that may be beneficial in the design and development of age-dependent knee implant components.

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References


