Fabric-elasticity Relationships of Femoral Head Trabecular Bone are Similar in Type 2 Diabetes and Healthy Individuals

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ABSTRACT

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1. Introduction

Osteoporotic fractures
Type 2 diabetes (T2D)
Higher DXA value, not clinically recognised despite hier fracture risk
HR-pQCT
Homogenized FE
Homogenized QCT-based FEA used in clinical studies approved by FDA HR-pQCT-based hFE relies on fabric-elasticity relationships It was shown that these fabric-elasticity relationships hold even in case of osteogenesis imperfecta (OI) Thus the present study aims to compare trabecular bone microstructure of healthy and T2D bone samples and to test the hypothesis of similar fabric-elasticity relationships. Similar fabric-elasticity relationships will allow to further extend the application of HR-pQCT-based hFE of healthy bone to T2D bone at least in the linear elastic regime.

Abbreviations: ROI, region of interest; μCT, micro-computed tomography Type 2 diabetes, T2D

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2. Material and Methods

This technical note can be seen as an extension of the previously published work on OI bones [5]. Thus, most of the methods are similar and will be summarized here.

2.1. Participants, Samples, and Imaging

The control (Ctrl) and diabetic (T2D) groups consisted of 28 donors each. The control group was composed of 14 males and 14 females aged between 51 and 97 years old at death with a mean age of 73 ± 13 (mean ± standard deviation). The diabetic group also counted 14 males and 14 females aged between 54 and 97 years old at death with a mean age of 75 ± 13. A cylindrical sample of about 10 mm in diameter and 15 mm in height was collected from the femoral head (left or right) of each donor. After harvesting, samples were flushed with distilled water to remove excess marrow and embedded in polymethylmethacrylate (PMMA). The embedded samples were imaged by micro-computed tomography (μCT50, Scanco Medical AG) at an isotropic voxel size of 14.8 μm with standardized scanning settings (voltage of 60 kVp, 900 μA, 100 ms integration time).

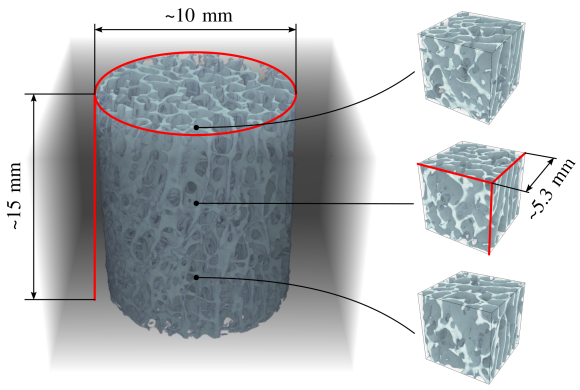

Figure 1: 3-dimensional rendering of a typical trabecular core sample

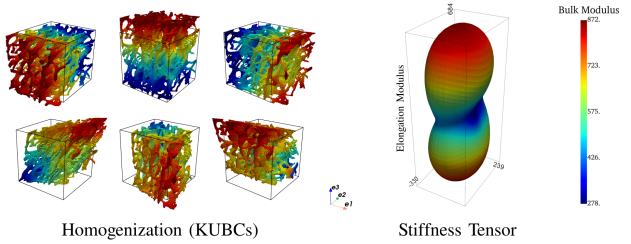

Figure 2: Schematic representation of the homogenization process leading the the ROI's stiffness tensor. Note that the deformation is amplified by multiple orders of magnitude in the illustration.

2.2. Region of Interest

In each scanned sample, three cubic region of interest (ROI) of about 5.3 mm were selected. For this, the image was divided in three stacks of 5.3 mm (top, center, and bottom) and a ROI was selected at the center of mass of the stack. A 3-dimensional rendering of a typical sample and its three cubic ROIs is shows in Figure 1.

2.3. Morphological Analysis

Image analysis was performed using medtool (v4.8; Dr. Pahr Ingenieurs e.U., Pfaffstätten, Austria) The pipeline was defined as: segmentation, cleaning, morphometry. The segmentation was performed using a single threshold based on the average Otsu threshold [3] of all the scans. The cleaning step consisted in removing isolated islands resulting from the single threshold segmentation. Then, standard trabecular morphometric parameters were computed. Namely, the bone volume fraction (ρ), trabecular thickness (Tb.Th.), trabecular spacing (Tb.Sp.), and trabecular number (Tb.N.). Additionally, the fabric tensor $\mathbf{M}$ was computed using the mean intercept length (MIL) method [2]. The degree of anisotropy (DA) of the ROI was computed by dividing the fabric tensor's highest eigenvalue by the lowest. A last morphological parameter, the coefficient of variation (CV), assessing the homogeneity of mass distribution within the ROI was computed as defined by Panyasantisuk et al. [4].

2.4. Numerical Analysis

After morphological analysis, each ROI underwent numerical homogenization. For this, µFE analyses were performed using ABAQUS 2023. The model was build using a direct voxel conversion approach to to a fully integrated linear brick elements (C3D8). Each element was assigned a Young's modulus of 10 GPa and a Poisson's ratio of 0.3. The homogenization scheme was composed of three uniaxial tests and three simple shear tests using kinematic uniform boundary conditions (KUBCs) [4]. Then, the ROI's homogenized stiffness tensor $\mathbb{S}$ was computed from these six independent loadcases. This step is illustrated in Figure 2. Finally, the resulting stiffness tensor was transformed into the fabric coordinate system and projected onto orthotropy, leading to nine different components.

2.5. Group Comparison

The first comparison between the control and diabetic group was regarding their morphology. For this, Mann-Whitney test was performed on samples having a bone volume fraction lower that 0.5. Indeed, a bone volume fraction higher than 0.5 doesn't match the definition of trabecular bone. A p-value lower than 0.05 was considered meaning a significant difference between the groups.

The second comparison was regarding the components of the stiffness tensor after transformation into the fabric coordinate system and projection onto orthotropy. Mann-Whitney test was again used and a p-value lower than 0.05 was again considered significant. This comparison was performed on sample with a bone volume fraction lower than 0.5 and a CV lower than 0.263. Indeed, this CV threshold was determined by Panyasantisuk et al. [4] as a limit for the homogeneity assumption. A higher CV involve heterogeneous mass distribution which violate the representative volume element (RVE) homogeneity assumption [1].

The third comparison of the two groups was performed by fitting the orthotropic stiffness tensor to the Zysset-Curnier model [6] and comparing the resulting parameters and their 95% confidence interval (95% CI). Briefly, this model expresses the stiffness tensor $\mathbb{S}$ based on the bone volume fraction ρ, fabric tensor eigenvalues $m_1 < m_2 < m_3$, three stiffness constants λ_0, λ_0', and μ_0 and two exponents k and l. The fitting procedure consisted of a multiple linear regression which was performed on the logarithmic space as shown in Equation 1. However, as k and l are exponents, it is necessary to impose values for further fabric-elasticity relationships comparison. These imposed values can either be on the exponents (as dones in previous work [5]) or on the stiffness constants. In the present technical note, it was chosen to impose values for λ_0, λ_0', and μ_0 and compare the resulting k and l. The imposed values were determined by performing the fit on the control and diabetic group pooled together. The fit quality was assesed using the adjusted Pearson correlation coefficient squared (R^2_{adj}) and relative norm error of fourth-order tensors (NE). This relative norm error allows

to quantify the accuracy of the fit. Thus, the multiple linear regression was performed in three different steps.

1. Multiple linear regression with control and diabetic pooled together
2. Multiple linear regression with control group or diabetic group only allowing fit quality comparison
3. Multiple linear regression with control group or diabetic group only with λ_0, λ_0', and μ_0 from step 1, allowing exponents (k and l) comparison

$$\ln\begin{pmatrix} S_{11}\\ S_{12}\\ S_{13}\\ S_{21}\\ S_{22}\\ S_{23}\\ S_{31}\\ S_{32}\\ S_{33}\\ S_{44}\\ S_{55}\\ S_{66}\end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & \ln(\rho) & \ln(m_1^2)\\ 0 & 1 & 0 & \ln(\rho) & \ln(m_1m_2)\\ 0 & 1 & 0 & \ln(\rho) & \ln(m_1m_3)\\ 0 & 1 & 0 & \ln(\rho) & \ln(m_2m_1)\\ 1 & 0 & 0 & \ln(\rho) & \ln(m_2^2)\\ 0 & 1 & 0 & \ln(\rho) & \ln(m_2m_3)\\ 0 & 1 & 0 & \ln(\rho) & \ln(m_3m_1)\\ 0 & 1 & 0 & \ln(\rho) & \ln(m_3m_2)\\ 1 & 0 & 0 & \ln(\rho) & \ln(m_3^2)\\ 0 & 0 & 1 & \ln(\rho) & \ln(m_2m_3)\\ 0 & 0 & 1 & \ln(\rho) & \ln(m_3m_1)\\ 0 & 0 & 1 & \ln(\rho) & \ln(m_1m_2)\end{pmatrix} \begin{pmatrix} \ln(\lambda^*)\\ \ln(\lambda_0')\\ \ln(\mu_0)\\ k\\ l\end{pmatrix} + \begin{pmatrix} \epsilon_1\\ \epsilon_2\\ \epsilon_3\\ \epsilon_4\\ \epsilon_5\\ \epsilon_6\\ \epsilon_7\\ \epsilon_8\\ \epsilon_9\\ \epsilon_{10}\\ \epsilon_{11}\\ \epsilon_{12}\end{pmatrix} \tag{1}$$

Where S_{xx} are the components of the stiffness tensor and $\lambda^* = \lambda_0 + 2\mu_0$, and ϵ_i the residuals.

3. Results

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4. Discussion and Conclusion

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Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Data availability statement

The data that support the findings of this study are available on request. The data are not publicly available due to privacy/ethical restrictions. The scripts used for the analyses performed in the present study are available on Github: https://github.com/artorg-unibe-ch/FEXHIP-Histology

Research ethics

We further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

CRediT author statement

Mathieu Simon: Data Curation, Formal analysis, Investigation, Methodology, Software, Visualization, Writing - original draft. **Sasidhar Uppuganti:** Data Curation, Resources, Writing - review and editing. **Jeffry S Nyman:** Conceptualization, Funding acquisition, Project administration, Resources, Validation, Writing - review and editing. **Philippe Zysset:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing - review and editing.

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