Supplementary material:

**Machine learning model trained with finite element modeling can predict the risk of osteoarthritis*:* Data from the Osteoarthritis Initiative**

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# Material and Methods

* 1. **Atlas-based FEA method**

Due to the limitations of the X-ray images (only a 2D coronal view compared to the orthogonal 3D view provided by MRI and poor soft tissue contrast with no visible cartilage), the knee dimensions differed between these two modalities 1,2. The cartilage thicknesses from X-ray images were evaluated to be at the mid-point of the femoral medial and lateral condyles 1, whereas in MRI, cartilage thicknesses were measured from the central contact regions between femoral and tibial cartilage at medial and lateral compartments using coronal and sagittal views to evaluate the exact location.

Notably, since the knee dimensions were measured from 2D anteroposterior X-ray images, the maximum anterior-posterior dimensions at medial and lateral femoral condyles were approximated based on their relation to the medial-lateral width of the distal femur measured from X-ray images. We assumed that the full medial-lateral width of the distal femur (WXray) is linearly associated with the anterior-posterior dimensions of the medial and lateral condyles of the femur. Based on the average fraction between the anterior-posterior dimensions (obtained from MRI) and medial-lateral width of the distal femur (obtained from X-ray), the following equations were used to estimate anterior-posterior dimensions at the medial (APMED-Xray) and lateral (APLAT-Xray) femoral condyles for X-ray imaged knees 3:

, (1)

. (2)

After determining the anatomical dimensions from MRI or X-ray images as explained above, an existing atlas FE template was scaled separately for the medial and lateral compartments based on the fractional differences between dimensions measured from the template and the subject knee. It should be noted that the atlas model template is the same in both MRI and X-ray based approaches. Although the MRI and X-ray based measures differ, the scaling factors for atlas FE templates were similar 3. Finally, the generated FE models were simulated under generic gait loading conditions separately for the medial and lateral compartments 4. FEA simulations were run in Abaqus (Dassault Systèmes) using a previously verified homogenous transversely isotropic elastic (HTIPE, 5) material model for the femoral and tibial cartilages (Table S1).

Table S1: Material parameters of the HTIPE material model for the femoral and tibial cartilages 5.

|  |  |  |
| --- | --- | --- |
| **HTIPE material model** | **Femoral cartilage** | **Tibial cartilage** |
| Orientation of the plane of isotropy | Parallel to surface | Parallel to surface |
| = E22 (MPa) | 60 | 50 |
| (MPa) | 3 | 3 |
|  | 0.42 | 0.42 |
| = | 1.9 | 1.9 |
| (MPa) | 5.25 | 4.4 |
| = (MPa) | 7.9 | 6.4 |
| *k* (×10 -15 m4N-1s-1) | 6 | 18 |
| *nf* | 0.8 | 0.8 |

= = the in-plane Young’s modulus (representing primary collagen fibril orientation), = axial Young’s modulus (perpendicular to in-plane direction), *=* the Poisson’s ratio that characterize the transverse strain in the *j*-direction, when the tissue is stresses in the *i*-direction., = the shear modulus that characterize strain in i-plane in j-direction, k = the permeability and *nf* = the fluid fraction.

* 1. **Simulation of cartilage degeneration**

Cartilage degeneration was simulated by tensile stress levels that were above the tissue's failure limit 6. Similarly, as in a previous study 4, the age-dependent threshold tensile stress values () for initiating cartilage degeneration were determined using the following equations:

|  |  |
| --- | --- |
| , | if (), (3) |
| , | if (30 ≤ Age ≤ 45), (4) |
| , | if (45 < ), (5) |
| , | if (65 < ), (6) |
| , | if (). (7) |

The volumetric cartilage degeneration (DEG(age)) was calculated as the sum of the volumes of the elements where the threshold () was exceeded at any given time point during the gait loading. Given the baseline age of subject (b) and the desired simulated OA progression time (f = follow-up time = 8-years), the simulated tissue degeneration (D) can be formulated as follows:

|  |  |
| --- | --- |
| D=DEG(b+f). | (8) |

Cartilage degenerations for the medial and lateral compartments were simulated with atlas-based FEA workflow using both MRI and X-ray based input for model generation, and tibial and femoral cartilage degeneration were summed to obtain the total cartilage degeneration for lateral and medial compartments. KL grade is based on the compartment that is the most affected by the KOA 7,8, thus simulated cartilage degeneration was only considered in the compartment that measured thinner cartilage at baseline. The progression of degeneration was calculated using post-processing in Matlab (Mathworks) after simulating the tensile stresses during gait loading.

1. **Discussion**

Though the GPR1 models predicted the mechanical responses of cartilage on the medial compartment with excellent accuracy, their accuracy for the lateral compartment was lower. However, it should be considered that the mechanical responses were over the whole stance phase of gait, and the prediction accuracies between time point(s) may vary notably. The main reason may be related to the scaling of the model. As the template model was built from the medial side compartment, it had to be scaled more when generating FEA models for the lateral side compartments. Since the joint spaces in the lateral compartment are usually larger than the joint space in the medial compartment 5 and due to differences between MRI vs X-ray in JS measurements 1,2, training data might not have had enough data to provide a good model. Especially in cases where lateral JS dimensions obtained from X-ray were substantially higher/lower compared to training data based on the MRI measurements. However, the effect of the small differences in mechanical responses between atlas-based FEA workflow and GPR1 models did not affect the prediction accuracy of the onset and progression of KOA (cartilage degeneration) using the GPR1 model. This indicates that, in general, the distribution of tensile stresses above the tissue failure limits had an extremely high prediction accuracy.

**References**

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