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TIBIAL CARTILAGE, SUBCHONDRAL BONE PLATE AND TRABECULAR BONE MICROARCHITECTURE IN VARUS- AND VALGUS-OSTEOARTHRITIS VS. CONTROLS

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AUTHOR CONTRIBUTION STATEMENT

SR contributed to data acquisition, study design, data analysis and interpretation, graphical representation, manuscript drafting. BCR, LBS, DT and EP contributed to the study design, data acquisition and interpretation, manuscript drafting, critical revision of this manuscript and sourced funding for this project. KJR was involved in study design, interpretation of data and critical revision of this manuscript and sourced funding for this project. All authors have read and approved the final submitted manuscript.

ABSTRACT

This preliminary study quantified tibia cartilage thickness (Cart.Th), subchondral bone plate thickness (SBPl.Th) and subchondral trabecular bone (STB) microarchitecture in subjects with varus- or valgus- mal-aligned knees diagnosed with end-stage knee osteoarthritis (OA) and compared them to controls (non-OA). Tibial plateaus from 25 subjects with knee-OA (undergoing knee arthroplasty) and 15 cadavers (controls) were micro-CT scanned (17 μ m/voxel). Joint alignment was classified radiographically for OA subjects (varus-aligned n=18, valgus-aligned n=7). Cart.Th, SBPl.Th, STB bone volume fraction (BV/TV) and their medial-to-lateral ratios were analysed in anteromedial, anterolateral, posteromedial and posterolateral subregions. Varus-OA and valgus-OA were compared to controls. Compared to controls (1.19-1.54mm), Cart.Th in varus-OA was significantly lower anteromedially (0.58mm, -59%) and higher laterally (2.19-2.47mm, +60-63%); in valgus-OA, Cart.Th was significantly higher posteromedially (1.86mm, +56%). Control medial-to-lateral Cart.Th ratios were around unity (0.8-1.1), in varus-OA significantly below (0.2-0.6) and in valgus-OA slightly above (1.0-1.3) controls. SBPl.Th and BV/TV were significantly higher medially in varus-OA (0.58-0.72mm and 37-44%, respectively) and laterally in valgus-OA (0.60-0.61mm and 32-37%), compared to controls (0.26-0.47mm and 18-37%). In varus-OA, the medial-to-lateral SBPl.Th and BV/TV ratios were above unity (1.4-2.4) and controls (0.8-2.1); and closer to unity and below controls in valgus-OA (0.8-1.1). Varus- and valgus-OA tibia differ significantly from controls in Cart.Th, SBPl.Th and STB microarchitecture depending on joint alignment, suggesting structural changes in OA may reflect differences in medial-to-lateral load distribution upon the tibial plateau. Here we identified an inverse relationship between cartilage thickness and underlying subchondral bone suggesting a whole-joint response in OA to daily stimuli.

Graphical Abstract

Micro-CT enables the non-destructive ex-vivo assessment of gross cartilage morphology and bone micro-architecture. Osteoarthritic (OA) tibias differ significantly from controls in cartilage thickness, subchondral cortical bone thickness and subchondral trabecular bone volume fraction depending on joint alignment, suggesting structural changes in osteoarthritis may reflect differences in medial-to-lateral load distribution upon the tibial plateau. Here we found an inverse relationship between cartilage thickness and underlying subchondral bone suggesting a whole-joint response in osteoarthritis to daily stimuli, involving both cartilage and bone.

Keywords – Knee osteoarthritis, micro-CT, cartilage, bone microarchitecture, tibial plateau

INTRODUCTION

Osteoarthritis (OA) is a debilitating joint disease that can affect all articular structures, but is most characteristically defined by the degradation of cartilage and alteration of subchondral bone.^{1,2} The knee is the most commonly affected joint³ and, according to national joint replacement registries, is the most common joint to undergo replacement^{4,5} with a reported 38% increase in total knee arthroplasty (TKA) due to knee OA from 2006 to 2016 in Australia.⁶ However, with TKA being the final treatment option for OA, there is a need for development of effective treatment strategies to delay and ideally prevent the progression of the disease. This may be achieved by firstly improving our understanding of relationships between independent

risk factors associated with OA, such as joint mechanics and alignment⁷⁻⁹, and the joint tissues.

Knee joint malalignment has previously been linked to altered medial-to-lateral distribution of loads upon the joint^{10,11} and has been associated with regional changes in either subchondral bone^{10,12-16} or cartilage^{17,18} in OA. In our previous study, mapping of the 3D bone microarchitecture of end-stage knee OA tibial plateaus,¹⁰ joint alignment was suggested to be related to medial-to-lateral and within-condylar bone microarchitecture differences in OA groups. However, it is unknown whether similar variations also exist in non-pathological joints. Furthermore, those studies on bone did not consider cartilage thickness, which has also been shown to vary with joint alignment in a magnetic resonance imaging (MRI) study.¹⁷

Micro-CT enables the non-destructive 3D assessment of entire excised human tibial plateaus at high-resolutions.^{10,19-21} While historically used for the characterization of bone microarchitecture,²²⁻²⁵ there is growing interest in using micro-CT for the examination of human tibial articular cartilage with contrast agents^{20,21,26-28} and without.^{19,29,30} While studies have separately examined cartilage thickness, bone microarchitecture or joint alignment, to the best of our knowledge, these examinations have never been performed altogether in the same cohort. Moreover, comparisons with control subjects in the STB microarchitecture are conflicting and did not consider the influence of joint alignment.^{31,32} As cartilage and bone respond to every day mechanical loading as a single mechanical unit, they should be investigated concurrently.^{33,34}

The aim of this preliminary study was to quantify tibia cartilage thickness, cortical SBP thickness and STB bone volume fraction in subjects diagnosed with end-stage knee OA with varus- or valgus-aligned joints and compare them to control (non-OA) knees.

METHODS

Bone Specimens

OA group: Micro-CT scans of the human tibial plateaus generated in the previous study¹⁰ were used in this study. Briefly, twenty-five tibial plateaus were retrieved from end-stage knee-OA patients who underwent total knee arthroplasty surgery (Table 1). Approval to use these specimens for research purposes was granted by Southern Adelaide Clinical and Royal Adelaide Hospital Human Research Ethics Committees. All patients gave written informed consent.

Control group: Fifteen fresh-frozen, cadaveric tibial plateaus with no knee pathology were sourced for this purpose (Science Care, Inc. Phoenix, AZ). Approval to use these specimens was granted by the Southern Adelaide Clinical Human Research Ethics Committee.

All tibial plateaus were stored immersed (fixed) in 70% ethanol solution after retrieval.

Mechanical Joint Alignment from Radiographic Data

Prior to surgery, the degree of varus–valgus mechanical alignment was assessed in all patients by measure of the mechanical axis deviation (MAD), obtained on long leg weight-bearing radiographs by an experienced examiner (LBS). In the frontal plane, the mechanical axis of the lower limb is the line connecting the center of the femoral head to the center of the ankle plafond.³⁶ The MAD was defined as the perpendicular distance from the mechanical axis to the center of the knee joint.³⁶ A varus alignment was defined as a medial deviation greater than 15 mm and a valgus alignment was defined as a lateral deviation greater than 0 mm,^{10,36} though for operational purposes, any medial deviation (0–15mm deviation; i.e. neutral joints, n=3) was considered varus in this study.

Micro-CT imaging

Micro-CT examination of the tibial plateaus were performed using a desktop micro-CT scanner (Skyscan 1076, Skyscan-Bruker, Kontich, Belgium). Prior to scanning, the specimens were removed from the ethanol solution and individually wrapped in cling-film. Specimens were scanned in pairs, separated by a layer of polystyrene (along the resected surface) and secured in place with elastic bands, with the medial-lateral axis of each specimen aligned with the system's rotation axis (Fig. 1).¹⁰ Specimens were scanned at 17.4 μm isotropic voxel size, peak voltage 100 kVp, current 90 μA , rotation step 0.4° over 180° rotation, 590 ms exposure time and four frames averaging.

The cross-section images were then reconstructed using a filtered back-projection algorithm (NRecon software, v1.6.9.8, Skyscan-Bruker) and saved as 8-bit bitmap format images (256 gray-levels, bmp value of 0 = air, 255 = mineralized tissue). For each specimen pair, a stack of up to 4,997 consecutive cross-sections was reconstructed (corresponding to 86.9mm length), slice thickness of one pixel (17.4 μm) producing a dataset of 70 GB¹⁰. The reconstructed cross-section images were then rotated in 3D such that the anatomical superior-inferior axis of each plateau was aligned with the z-axis of the image stack.¹⁰

Image segmentation: Separation of Cartilage, Subchondral Bone Plate and Subchondral Trabecular Bone.

Cartilage (Cart)

A semi-automatic segmentation process was developed based on methods published in the literature.^{26,28,37,38} Firstly, on the coronal image stack of the specimen, a 3D median filter ($\sigma = 3$) was applied to minimize noise. A mask was then created, which included bone and marrow (“bone and marrow mask”), extending from the superior surface of the subchondral bone plate to the lower end of the tibial plateau, using a custom MATLAB script (2017b, The MathWorks, Inc., Massachusetts, USA). The inverse mask, containing only cartilage and air (= the image minus the “bone and marrow” mask) was then applied to the same coronal image stack (software CTAnalyser, Skyscan Bruker, Kontich, Belgium). Then, cartilage was segmented using a lower threshold of 18 and a higher threshold of 86 (“threshold window”, excluding air and potential bone debris, respectively), as defined from the gray-level

histograms over 5 representative specimens and applied consistently over all specimens (Fig. 2). The cartilage segmentation was verified manually every 15 slices (0.261 mm). Then, the “shrink-wrap” plug-in of CTAnalyser was applied, to conform the boundaries of the regions of interest (ROI) to the cartilage.

Subchondral bone plate (SBP)

The subchondral bone plate was segmented according our previous protocol.¹⁰ Briefly, a uniform threshold was applied to the coronal image stacks to segment the bone tissue from the background (air, marrow and cartilage). A lower threshold level (87) was defined from the gray-level histograms (256 gray-levels) over 5 representative specimens (Fig. 2). Pixels representing bone tissue (gray-level values between 87 and 255) were segmented as solid and those representing non-bone tissue (gray-level values from 0 to 86) as background. From the coronal binarized image stacks, the SBP was then manually contoured every 15 images (0.261 mm) removing trabecular struts adjoining the lower end of the SBP.¹⁰ Then the “ROI shrink-wrap” plug-in was applied, to conform the ROI boundaries to the plate border.

Subchondral trabecular bone (STB)

The STB had its superior boundary in common with the inferior boundary of the previously saved SBP ROI, extending distally towards the growth plate. Only STB within the first 5 mm below the inferior subchondral bone plate was considered, as microarchitectural and bone mineral density differences in tibial condyles are most prominent within this distance.^{12,32,39}

From the saved cartilage, SBP and STB datasets, subvolumes of interest (VOI) for morphometric analysis were then selected, as follows.

Volumes of interest (VOIs)

For each tibial plateau, four cylindrical VOIs (10 mm in diameter, total height of approximately 7-8 mm, depending on the specimen) were selected within regions of the tibial condyles indicated as high and low-load bearing in the literature,^{10,11} using CTAnalyser as shown previously by our group.¹⁰ The height of the VOI varied based on the specimen, with each VOI containing the cartilage (up to 2-3 mm), the adjacent cortical SBP and STB underneath (up to 1 mm and up to 5 mm, respectively, depending on the specimen) (Fig. 3), each previously segmented as detailed in the paragraph 2.4 “Image Segmentation”. These cylindrical VOIs were defined in our previous study¹² and were located at the center of the anterior or posterior halves of the medial and lateral condyles, which were defined by elliptical regions: anteromedial (AM), anterolateral (AL), posteromedial (PM) and posterolateral (PL) condyles (Fig. 3b).

Morphometric analysis

From the micro-CT images, cartilage thickness (Cart.Th; mm), cortical SBP thickness (SBPl.Th; mm) and the STB bone volume fraction (BV/TV; %) were analyzed in the four cylindrical VOIs. The medial (M) and lateral (L) condyle values were also computed, as the average of the anterior and posterior VOIs within the condyles.

The average cartilage thickness was calculated by dividing the volume of the voxels identified as cartilage (in mm³) by the circular cross-section area (in mm²) within the cylindrical VOI.⁴⁰ This method accounts also for VOIs containing partially denuded areas of cartilage, whereas plainly using a 3D sphere-fitting thickness algorithm in these areas would overestimate the thickness over the VOI. The 3D SBPl.Th was calculated using the sphere-fitting method in the corresponding SBP VOI, as done previously.^{10,41,42} The STB BV/TV was calculated as the percentage voxels segmented as bone divided by the voxels constituting the examined STB VOI.^{10,25}

Finally, the medial-to-lateral ratios in these parameters between cylindrical subregions within each condyle (AM:AL, AM:PL, PM:AL, PM:PL, M:L) were computed. Medial-to-lateral ratios, for example providing insight into the distribution of bone mass (SBPl.Th, STB BV/TV) between the condyles, may also provide insights into the intra-condyle distribution of loads across the tibial plateau.

Statistics

Morphometric parameters (Cart.Th, SBPl.Th, BV/TV) in the 4 tibial regions (AM, AL, PM and PL) and their regional ratios for the varus-OA and valgus-OA group, were compared to controls using a Kruskal-Wallis test, which if significant, was followed by post-hoc Mann-Whitney U-tests. To account for multiple testing, the false discovery rate (FDR) was controlled (FDR = 0.05) using a Benjamini-Hochberg adjustment.⁴³ Non-parametric tests were used in this study, rather than parametric tests, due to the small sample size of the valgus-OA group (n=7) and because the assumption of homogeneity of variance (Levene's test) and assumption of normality (Shapiro-Wilk's test) were not met in some comparisons. Statistical analysis was performed using SPSS Statistics 25 (IBM Corp., Armonk, NY).

RESULTS

Age and body mass were not significantly different between varus-OA, valgus-OA and controls groups. Body mass index (BMI) did not significantly differ between varus-OA and valgus-OA groups, whereas knee alignment did (Table 1).

Fig. 4 displays representative tibial plateaus from each group (control, varus-OA and valgus-OA), with photograph (top) and the 3D-distribution of cartilage thickness (middle) and of subchondral trabecular bone obtained by micro-CT (bottom), whereas coronal cross-sections for appreciation of also the subchondral bone plate thickness are shown in Fig. 5.

Cartilage

For the control group, the distribution of cartilage appears mostly uniform across the plateau (Fig. 4a), with an average thickness of approximately 1.4 mm in all 4 VOIs (1.19 – 1.54 mm; Fig. 6a, Table 2). In Varus-OA the average Cart.Th range was 0.58 – 2.47 mm and for valgus-OA 1.20 – 1.86 mm, depending on the region. Compared to controls (Fig. 4a), varus-OA exhibited a significantly thinner average Cart.Th in the AM ROI (0.58 mm, -59%, $p < 0.001$, Fig. 4b, 5b, 6a, Table 2) and thicker in the lateral regions (2.19 mm (AL) to 2.47 mm (PL); up to +63%, $p < 0.001$). For valgus-OA, whereas average Cart.Th was not different to controls laterally, it was significantly

thicker medially, ranging from 1.71 mm (AM) to 1.86 mm (PM) (+56% in PM ROI, $p<0.001$).

In controls the medial-to-lateral Cart.Th ratios were close to unity (range: 0.8-1.1, Fig. 6b, Table 2), in varus-OA they were all well below unity and below the values of controls (0.2-0.6, $p<0.025$); whereas in valgus-OA, they were similar to or higher than in controls (1.0-1.3).

Subchondral bone plate

For the controls, the average SBPl.Th range was 0.26 - 0.47 mm, for varus-OA 0.39 - 0.72 mm and for valgus-OA 0.43 - 0.61 mm (Fig. 5b, 6c, Table 2), depending on the region. SBPl.Th was significantly higher medially in varus-OA compared to controls (up to +107%, Fig. 5b, 6c, $p<0.001$), whereas it was significantly higher laterally in valgus-OA (up to +135%, $p<0.001$ in PM region, and $p=0.005$ in PL region).

In varus-OA, the medial-to-lateral SBPl.Th ratios (range 1.4-2.0) were above unity and higher than in controls (0.8-1.8, Fig. 6d, Table 2); in valgus-OA (0.8-1.0) they were closer to unity and lower than controls.

Subchondral trabecular bone

Average BV/TV ranged between 18% and 37% in controls, between 20% and 44% in varus-OA and between 23% and 37% in valgus, depending on the region (Fig. 5, 6e, Table 2).

The BV/TV in varus-OA was significantly higher medially (BV/TV= 44% AM ($p=0.022$) and 37% PM ($p=0.007$)) compared to controls (BV/TV= 37% AM and 24% PM, Fig. 5, 6e, Table 2), whereas in valgus-OA the BV/TV was significantly higher anterolaterally (BV/TV= 32% ($p=0.004$)) compared to controls (BV/TV= 18%).

Correspondingly, in varus-OA, the medial-to-lateral BV/TV ratios were above unity (1.6-2.4) and higher than controls (0.9-2.1, Fig. 6f, Table 2). In valgus-OA, they were closer to unity and lower (0.8-1.1; AM:AL ($p=0.004$) and PM:AL ($p=0.006$)) than in controls.

DISCUSSION

In this preliminary study, tibial cartilage morphology and bone microarchitecture of subjects diagnosed with end-stage knee OA were compared against non-osteoarthritic knees using high-resolution micro-CT imaging, while accounting for joint alignment.

Differences in cartilage thickness, underlying cortical plate thickness and trabecular bone volume fraction between OA and control joints were found when grouping the OA cohort by joint alignment. Medially, the varus-OA group had significantly lower Cart.Th compared to the controls (up to 59% lower) and significantly higher SBPl.Th and BV/TV underneath (up to 107% and 49% higher, respectively). Conversely, the valgus-OA group, laterally, had slightly thinner cartilage and significantly thicker SBP and BV/TV (up to 135% and 76%, respectively) compared to controls. Accordingly, in the varus-OA group, the medial-to-lateral Cart.Th ratios were lower

and the medial-to-lateral BV/TV (Fig. 6f) and SBPl.Th ratios (Fig. 6d) higher compared to controls; the opposite was seen in the valgus-OA group.

Knee joint malalignment has been previously linked to altered medial-to-lateral distribution of loads,¹¹ with joint contact forces higher medially than laterally in varus-alignments and the opposite for valgus-alignments. As cartilage is an avascular tissue with limited capacity for regeneration and repair,⁴⁴ whereas bone can adapt to everyday mechanical loading,⁴⁵ our findings might reflect the medial-to-lateral joint loading ratio that the joint has been subjected to in daily life.¹¹ In the present study, in the OA groups, regions of lower cartilage thickness (Fig. 6a) corresponded to regions of thicker cortical SBP (Fig. 6c) and higher BV/TV (Fig. 6e) underneath. Conversely, regions of thicker cartilage corresponded to regions of thinner cortical SBP and lower BV/TV. This suggests an interplay between cartilage and bone in OA, with an inverse relationship between cartilage thickness and bone volume. This is consistent with current literature on OA, with the response of the joint as a whole to daily stimuli, involving both cartilage and bone.^{34,46} However, whereas the present M:L cartilage thickness ratios (Fig. 6b) are consistent with previous MRI studies in OA, those studies did not consider the bone.¹⁷ Similarly, while the M:L BV/TV and SBPl.Th ratios are consistent with bone mineral density studies using dual X-ray absorptiometry (DEXA),^{47,48} DEXA cannot be used to assess cartilage, it is limited to 2D analysis and cannot separate the subchondral bone plate from the underlying trabecular bone. This study combines subregional assessment of the cartilage morphology and bone microarchitecture using high-resolution micro-CT in tibial plateaus from OA patients and controls, accounting for joint alignment.

Somewhat surprisingly, cartilage was thicker in some regions of the OA groups compared to controls (i.e. thicker laterally in varus-OA specimens and thicker medially in valgus-OA, Fig. 4 and Fig. 6a). A previous in vivo MRI study has reported regions of thicker cartilage in the femorotibial compartment of knee OA patients (with a Kellgren Lawrence grade of 2 (mild)) compared to controls.⁴⁹ The authors of that study speculated the thickening to be due to cartilage swelling in earlier stages of OA. We suggest that in the present study the regions of thicker cartilage in the malaligned OA specimens (laterally for varus-OA, medially for valgus-OA) may have been subjected to less local everyday loading than in controls and hence, the cartilage has eroded less compared to a non-OA joint.

The significant regional differences between OA and non-OA tibiae reported in this study may have been masked (“averaged out”) in previous studies,¹⁹ that did not consider joint alignment. Such “averaging out” becomes evident when combining the present varus-OA and valgus-OA groups (i.e. no subdivision based on joint alignment) and comparing them to controls (Fig. 7). While we have more varus-OA specimens (n=18) than valgus-OA (n=7), this distribution follows that of the alignment of knee OA subjects of the general population.⁵⁰ As such, the pattern in cartilage thickness, SBPl.Th and BV/TV of the combined OA group follows that of the varus-OA group, but to a lesser degree. For example, Cart.Th in AM for the varus-OA group was significantly thinner than in the control group by 59%; when combining the OA groups, this difference shrinks to only 35%, becoming not statistically significant. Similarly, the SBPl.Th differences diminish in the combined OA group compared to controls, although maintaining statistical significances, whereas the medial-to-lateral SBPl.Th ratios show almost no differences from the

controls anymore. Additionally, the BV/TV differences diminish (vanish) when comparing the combined OA group to controls. This is also the case for the medial-to-lateral ratios of Cart.Th and BV/TV (Fig. 7b,d,f), where the opposite distributions of Cart.Th, SBPL.Th and BV/TV across the medial and lateral condyles for the varus-OA and valgus-OA groups shown in Fig.4-6 almost vanish. Not taking account joint alignment may then explain why, for example, in a recent micro-CT study in OA and non-OA tibial plateaus, no significant differences in cartilage thickness and BV/TV in the lateral regions were found between the two groups,¹⁹ whereas differences found in the medial regions were similar to our varus-OA group, but to a lesser degree. However, in that study, the patient cohort was 30kg lighter compared to ours in body mass (60.3 ± 7.4 kg (OA group; no reported BMI) vs. 90 ± 17.6 kg (OA group)), which could also, in part, explain possible differences in findings between studies.

A limitation of this study is that we did not have joint alignment nor BMI data for our cadaveric non-OA tibial plateaus. The OA knees in this study were mostly varus-aligned or valgus-aligned. This is in agreement with data reported in the literature,⁵⁰ where in a study of over 5,000 OA and non-OA knees, OA joints ranged from extremely varus to extremely valgus, whereas non-OA joints were found to be mainly neutral-, if not slightly varus-aligned.⁵⁰ Our OA cohort is reflective of that reported OA-distribution and it can be assumed that the alignment of the cadaveric controls also follows that of the reported general population. Furthermore, literature reports about control knees having on average a neutral to slightly varus alignment are consistent with our medial-to-lateral ratios of subchondral bone plate thickness ratios and trabecular BV/TV, where the pattern of controls is similar to that of varus-OA but to a lesser severity (Fig. 6d and f). This possibly reflects similar joint loading in daily life, although to a lesser extent in people without knee OA.

Our controls had a cartilage thickness across all regions of 1.2-1.5 mm and medial-to-lateral thickness ratios of approximately 1, indicating a rather uniform distribution among the medial and lateral VOIs. This thickness is slightly lower than for non-OA tibial plateaus reported in some literature (1.7 - 2.5 mm on average).^{19,29} This could be due to the region selection,^{19,29} where both studies included regions close to the tibial plateau midline, whereas our anterior and posterior regions were further from the midline (closer to the anterior or posterior aspect, as these were the center of the anterior and posterior halves of the condyle, respectively) and hence at least partially covered by the meniscus. Regions covered by the menisci (i.e. further from the midline of the tibia) have been reported to contain thinner cartilage.^{51,52} Indeed, our cartilage thickness values in controls are comparable to those reported by Delecourt et al, with “2D measurements” of 1.7 mm in their more peripheral regions.²⁹ Another study reported tibial cartilage thickness of 1 - 4 mm in non-OA knees,⁵¹ however, that study was performed in a younger cohort (39.7 ± 12.5 years vs. 61.6 ± 12.9 years in the present study) and used clinical MRI, which has been found to overestimate cartilage thickness if under 2 mm.⁵³

In this preliminary study, cartilage and bone morphometric parameters (Cart.Th, SBPL.Th, BV/TV) in the 4 tibial regions (AM, AL, PM and PL) and their regional ratios for the varus-OA and valgus-OA group were compared against the control group. However, one could have chosen a different approach to the comparison, that is, considering all possible combinations between groups and variables and including also within-group comparisons. This was not our goal and for such an approach, our

sample size would have been likely underpowered. This may be the goal for further studies.

Our analysis of articular cartilage did not use any contrast agents. Instead, cartilage was visualized by maximizing the signal-to-noise ratio (i.e. by increasing the exposure time and frame averaging and decreasing the rotation step). This method is similar to that of a previous study on tibial plateaus.¹⁹ This enables cartilage morphological parameters (e.g. thickness and volume) to be computed but cannot be used to derive proteoglycan content. Future studies might use contrast agents, such as Hexabrix, to derive proteoglycan content in the cartilage.²⁶ Furthermore, as our imaging method requires excised tibial plateaus, we were restricted to analyzing end-stage OA. However, monitoring the progression of OA in vivo may be possible by using a combination of MRI and high-resolution peripheral quantitative CT (HR-pQCT), or contrast-enhanced HR-pQCT²⁰ in future. The use of in vivo HR-pQCT could also allow for analysis of bone microarchitecture more distal to the first 5 mm of the tibial plateau investigated in this study as there may be value in looking deeper into the joint (near the epiphyseal line) where sclerosis may not occur.⁵⁴

CONCLUSIONS

Micro-CT enables the non-destructive assessment of gross cartilage morphology and bone micro-architecture. In this preliminary study, OA and non-OA tibias were found to differ significantly in Cart.Th, SBPl.Th and STB microarchitecture depending on joint alignment, suggesting that joint structural changes in OA may reflect differences in medial-to-lateral load distribution upon the tibial plateau. The inverse relationship between the cartilage thickness, the underlying subchondral bone plate thickness and subchondral trabecular bone volume suggests the response of the joint as a whole to daily stimuli involving both cartilage and bone. Detectable morphological differences between OA and non-OA joints depend on joint alignment and could become useful indicators of disease progression, warranting further exploration.

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FIGURES

Fig. 1. A photograph of two excised tibial plateaus, wrapped in plastic film and fixed on the carbon scanning bed of the micro-CT.

Fig. 2. a) Micro-CT cross-section images of an entire excised right tibial plateau, at 17.4 μm isotropic voxel size (bone in bright gray color, cartilage/marrow in dark gray). b) Example of a gray-level histogram (256 gray-levels) of a transaxial cross-section image. The threshold levels used to segment air, cartilage/marrow and bone are indicated by the dashed lines (values = 18 and 87). A: anterior, P: posterior, M: medial, L: lateral anatomical location.

Fig. 3. Varus-aligned osteoarthritic right tibial plateau: a) Photograph. b) Micro-CT 3D rendering of the same tibial plateau (17 μ m/pixel; superior view), showing cartilage thickness map and subchondral bone underneath (white color). The red colored circles are the 4 regions of interest investigated (10mm diameter cylinders): antero-medial (AM), antero-lateral (AL), postero-medial (PM) and postero-lateral (PL). c) coronal view of tibial plateau, showing cartilage (blue color), cortical subchondral bone plate (orange color) and subchondral trabecular bone (white color).

Fig. 4. Top row: Photographs of three representative excised right tibial plateaus, belonging to the a) control, b) varus-OA and c) valgus-OA group. Middle row: Micro-CT 3D rendering of the tibial plateaus showing cartilage thickness (Cart.Th) map. Noting the rather uniform distribution of cartilage thickness in control, compared to a more heterogeneous distribution in varus-OA and valgus-OA, depending on the joint alignment. Bottom row: Micro-CT 3D rendering of a slice of underlying subchondral trabecular bone (white color) for each specimen. MAD: mechanical axis deviation (mm), MA: mechanical axis ($^{\circ}$).

Fig. 5. Left column: Photographs of three representative excised tibial plateaus belonging to the a) control, b) varus-OA and c) valgus-OA group. Right column: Micro-CT 3D rendering of a coronal slice (1.31 mm thick) taken from the anterior region of each tibial plateau (see dashed green line in left column), showing cartilage in blue color, the subchondral bone plate in orange color and subchondral trabecular bone in white color. MAD: mechanical axis deviation (mm), MA: mechanical axis ($^{\circ}$).

Fig. 6. (a) Cart.Th, (b) medial-to lateral Cart.Th ratios, (c) SBPl.Th, (d) medial-to-lateral SBPl.Th ratios, (e) BV/TV, (f) medial-to-lateral BV/TV ratios; average values and standard deviation (error bars) for the three groups examined (varus-OA n=18, valgus-OA n=7, controls n=15): dashed horizontal line indicates unity. A Kruskal-Wallis test followed by a Mann-Whitney U-test was performed to compare the varus-OA and valgus-OA groups against the control group; *Significant difference compared to control (Benjamini-Hochberg adjusted, false-discovery rate = 0.05). A: anterior, P: posterior, M: medial, L: lateral anatomical location.

Fig. 7. Same graphs as in Fig.6, but not accounting for joint alignment in OA (varus-OA and valgus-OA combined) (a) Cart.Th, (b) medial-to-lateral Cart.Th ratios, (c) SBPl.Th, (d) medial-to-lateral SBPl.Th ratios, (e) BV/TV, (f) medial-to-lateral BV/TV ratios; average values and standard deviation (error bars) for the two groups examined (OA n = 25, controls n=15): dashed horizontal line indicates unity. A Mann-Whitney U-test was used to compare between the OA-combined group and the control-group for each parameter; *Significant

difference compared to control (Benjamini-Hochberg adjusted, false-discovery rate = 0.05).

A: anterior, P: posterior, M: medial, L: lateral anatomical location.

TABLE 1

Summary of patient characteristics

Parameters	End stage knee OA subgroups		Controls	<i>p</i> value
	Varus-OA	Valgus-OA	Non-OA	
	(n = 18)	(n = 7)	(n = 15)	
Age (years)	66.9 ± 7.8	70.4 ± 6.0	61.6 ± 12.9	0.295
Mass (kg)	92.5 ± 17.7	84.1 ± 16.9	83.0 ± 15.6	0.234
BMI (kg/m ²)	32.5 ± 4.8	31.5 ± 4.7		0.657

Mechanical Axis Deviation* (mm)	29.4 ± 18.7	-34.4 ± 15.6	<0.001
Mechanical Axis** (°)	173.4 ± 4.2	188.2 ± 1.7	<0.001

Values reported as average ± standard deviation; A Kruskal-Wallis test was performed to compare between the varus-OA, valgus-OA and non-OA groups for age and body mass. A Mann-Whitney U-test was used to compare between the varus-OA and valgus-OA groups for BMI, Mechanical Axis Deviation and Mechanical Axis, significance denoted by p<0.05. *Knee alignment determined from mechanical axis deviation (MAD), where positive deviations are indicative of a medial deviation and negative values indicate a lateral deviation.¹⁰ **Mechanical axis (MA), defined as the medial hip-knee-ankle angle where an angle <178° was considered a varus alignment and an angle >182° was considered a valgus alignment.³⁵

TABLE 2

Mean ± standard deviation (SD) and Median [minimum, maximum] of subregional cartilage thickness, subchondral bone plate thickness and subchondral trabecular bone volume fraction and their medial-to-lateral ratios

Varus-OA			Valgus-OA		Controls	
Cartilage Thickness (mm)						
VOI	Mean ±SD	Median [min,max]	Mean ±SD	Median [min,max]	Mean ±SD	Median [min,max]
AM	0.58 ±0.58	0.40 [0.00,1.87]	1.71 ±0.76	1.94 [0.16,2.43]	1.41 ±0.27	1.38 [0.89,1.92]
AL	2.19 ±0.49	2.23 [1.34,3.56]	1.20 ±0.76	1.62 [0.06,1.90]	1.34 ±0.32	1.25 [0.85,1.99]
PM	1.42 ±0.72	1.75 [0.10,2.23]	1.86 ±0.37	1.92 [1.29,2.43]	1.19 ±0.14	1.23 [0.98,1.41]
PL	2.47 ±0.47	2.50 [1.84,3.24]	1.50 ±0.83	1.76 [0.00,2.28]	1.54 ±0.40	1.55 [0.95,2.39]
M	1.00 ±0.57	1.11 [0.05,1.93]	1.78 ±0.51	1.93 [0.94,2.43]	1.30 ±0.18	1.33 [0.97,1.60]
L	2.33 ±0.42	2.30 [1.66,3.35]	1.26 ±0.79	1.52 [0.03,1.95]	1.44 ±0.33	1.38 [1.06,2.19]
Ratio	Medial-to-Lateral Ratios					
AM:AL	0.25 ±0.24	0.20 [0.00,0.80]	1.12 ±0.85	1.10 [0.10,2.40]	1.10 ±0.33	0.99 [0.67,1.70]
AM:PL	0.24 ±0.23	0.20 [0.00,0.70]	1.00 ±0.67	0.90 [0.10,1.80]	0.95 ±0.22	0.94 [0.50,1.41]
PM:AL	0.63 ±0.33	0.70 [0.00,1.20]	1.28 ±0.65	1.10 [0.70,2.40]	0.93 ±0.23	0.90 [0.64,1.44]
PM:PL	0.58 ±0.29	0.70 [0.00,0.90]	1.12 ±0.50	0.80 [0.70,1.80]	0.82 ±0.19	0.85 [0.47,1.14]
M:L	0.43 ±0.23	0.44 [0.02,0.76]	1.09 ±0.52	1.05 [0.51,1.80]	0.94 ±0.20	0.90 [0.56,1.23]

VOI		Subchondral Bone Plate Thickness (mm)				
AM	0.72 ±0.17	0.68 [0.47,1.13]	0.49 ±0.08	0.48 [0.41,0.60]	0.47 ±0.07	0.45 [0.35,0.59]
AL	0.39 ±0.10	0.37 [0.22,0.61]	0.61 ±0.25	0.63 [0.29,0.97]	0.26 ±0.03	0.26 [0.20,0.31]
PM	0.58 ±0.18	0.60 [0.22,0.89]	0.43 ±0.13	0.41 [0.32,0.71]	0.28 ±0.05	0.28 [0.19,0.39]
PL	0.45 ±0.12	0.40 [0.32,0.70]	0.60 ±0.20	0.58 [0.38,0.91]	0.36 ±0.09	0.38 [0.22,0.49]
M	0.65 ±0.16	0.63 [0.37,1.01]	0.46 ±0.10	0.42 [0.37,0.64]	0.37 ±0.05	0.38 [0.28,0.47]
L	0.42 ±0.09	0.39 [0.29,0.56]	0.61 ±0.16	0.62 [0.37,0.77]	0.31 ±0.05	0.31 [0.25,0.39]
Ratio		Medial-to-Lateral Ratios				
AM:AL	1.97 ±0.65	1.95 [0.90,3.30]	0.96 ±0.48	0.70 [0.53,1.90]	1.81 ±0.39	1.70 [1.30,2.50]
AM:PL	1.69 ±0.58	1.65 [0.80,3.00]	0.93 ±0.36	0.90 [0.50,1.40]	1.35 ±0.38	1.30 [0.90,2.10]
PM:AL	1.61 ±0.60	1.70 [0.60,2.60]	0.88 ±0.70	0.60 [0.40,2.40]	1.09 ±0.29	1.00 [0.70,1.90]
PM:PL	1.38 ±0.55	1.20 [0.60,2.50]	0.83 ±0.45	0.70 [0.40,1.60]	0.80 ±0.16	0.80 [0.50,1.00]
M:L	1.64 ±0.53	1.60 [0.90,2.80]	0.82 ±0.45	0.70 [0.50,1.70]	1.21 ±0.20	1.20 [1.00,1.60]
VOI		Subchondral Trabecular Bone Volume Fraction (%)				
AM	44.3 ±8.80	43.0 [33.0,62.1]	30.4 ±6.83	30.5 [20.5,42.9]	36.6 ±8.71	36.5 [22.7,58.3]
AL	19.8 ±6.45	18.2 [11.6,36.5]	31.8 ±13.4	28.3 [18.7,54.0]	18.0 ±4.54	16.6 [9.85,24.8]
PM	36.5 ±14.8	31.5 [14.7,67.4]	22.8 ±7.32	21.3 [14.5,31.5]	24.5 ±8.22	24.4 [14.3,45.5]
PL	23.6 ±8.36	21.4 [12.9,46.5]	36.6 ±10.6	40.3 [19.9,49.1]	27.0 ±5.53	25.5 [17.6,36.8]
M	40.4 ±10.8	36.6 [25.9,64.8]	27.1 ±6.25	26.1 [20.2,37.2]	30.8 ±7.53	30.1 [21.1,45.5]
L	21.7 ±7.18	19.6 [13.3,41.5]	32.9 ±11.2	31.5 [18.7,51.6]	22.5 ±4.35	21.9 [13.7,29.2]
Ratio		Medial-to-Lateral Ratios				
AM:AL	2.41 ±0.80	2.19 [1.37,4.66]	1.14 ±0.56	1.08 [0.38,1.97]	2.14 ±0.72	1.92 [1.43,3.54]
AM:PL	2.03 ±0.62	1.72 [1.33,3.33]	0.94 ±0.50	0.75 [0.42,1.61]	1.41 ±0.27	1.41 [0.94,1.83]
PM:AL	1.91 ±0.64	1.89 [0.77,3.07]	0.80 ±0.38	0.78 [0.37,1.45]	1.40 ±0.48	1.23 [0.95,2.73]
PM:PL	1.60 ±0.52	1.58 [0.68,2.69]	0.81 ±0.52	0.56 [0.39,1.58]	0.90 ±0.20	0.89 [0.55,1.27]
M:L	1.95 ±0.50	1.99 [1.09,2.84]	0.93 ±0.39	0.89 [0.39,1.49]	1.38 ±0.27	1.36 [1.06,1.93]

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