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BONE REMODELING IS AN EARLY SIGN OF BIOMECHANICALLY INDUCED PRE-OSTEOARTHRITIS

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Purpose: Despite the degenerative nature of osteoarthritis (OA), early diagnosis of a so-called pre-osteoarthritis - prior to the onset of irreversible degradations – may enable to either treat or modify its progression. Therefore, detection of early stage OA has become very important nowadays. Among various risk factors, excessive mechanical loading has been recognized to be involved in OA. Response of cartilage and bone to loading reflects mechanosensitivity of both tissues as a reaction to deformation and whether the applied mechanical forces can induce pre-OA conditions. In this study, we aimed to design different running models proceeding to mild damage or pre-OA in rats. For this purpose, we applied treadmill-running exercise and performed several assays to elucidate the diminutive initial changes in the involved tissues.

Methods: Sixty male rats (Wistar; Charles River, 8 weeks old) were used in this study and divided into three groups of 10 animals each: an *adaptive running group* that runs for 8 weeks in daily sessions of gradually increasing running on a treatmill up to 1120 m per hour (*adaptive running regime*) followed by 6 weeks of one hour per day at 1120 m/h (constant running regime); a *non-adaptive (constant) running group* that has rest for 8 weeks followed by 6 weeks of constant running regime; and a *control group* without running (Fig. 1). At baseline and after 14 and 20 weeks (additional 6 weeks of rest), different joint analyses were performed: micro computed tomography (micro-CT) - in epiphysis, metaphysis, and diaphysis -, histology, HSP70 immunohistochemistry, and micro-indentation.

Results: MicroCT data showed that, after 6 weeks (at 14 weeks) bone parameters including subchondral bone tibia plateau thickness and trabecular bone thickness for both running groups decreased in the load bearing region of the medial knee joint (epiphysis) as compared to the control (non-running) group ($P \leq 0.005$). This is opposite of the cortical bone further away from the joint that increased. At 20 weeks, (after the 6 weeks rest) for the running groups the differences between running animals and control disappeared for the most part (Fig. 2). Safranin-O stained histological sections revealed a significant variation after 20 weeks between adaptive running and control groups ($P < 0.05$). The two running groups showed chondrocyte proliferation, colony formation and hypertrophy (Fig. 3A), more HSP70 expression (Fig. 3B) and a lower stiffness, in particular at the lateral side and more in the adaptive running group (Fig. 3C).

Conclusions: In summary, we investigated how bone morphological changes and cartilage responses within the joint region contribute to a premature stage of OA. As a result of loading that could be considered excessive for these rats, bone adaptation occurs indicating a situation of pre-OA. This seems to lead to abnormal stress stimuli in the chondrocytes, kicking them to proliferation and hypertrophy. Furthermore, bone and cartilage behave differently in biomechanically induced pre-OA. While changes in articular cartilage are mainly exposed at the end, at week 20 (after the 6 weeks rest), bone turnover started earlier during the running period at week 14. In addition, whereas cartilage tissue changes appeared not to recover from adaptive running exercise, the subchondral bone normalized after the sedentary period of 6 weeks (Fig. 2). In conclusion, overloading by running exercise can induce a mild or pre-OA status in the knee joint of the rats.

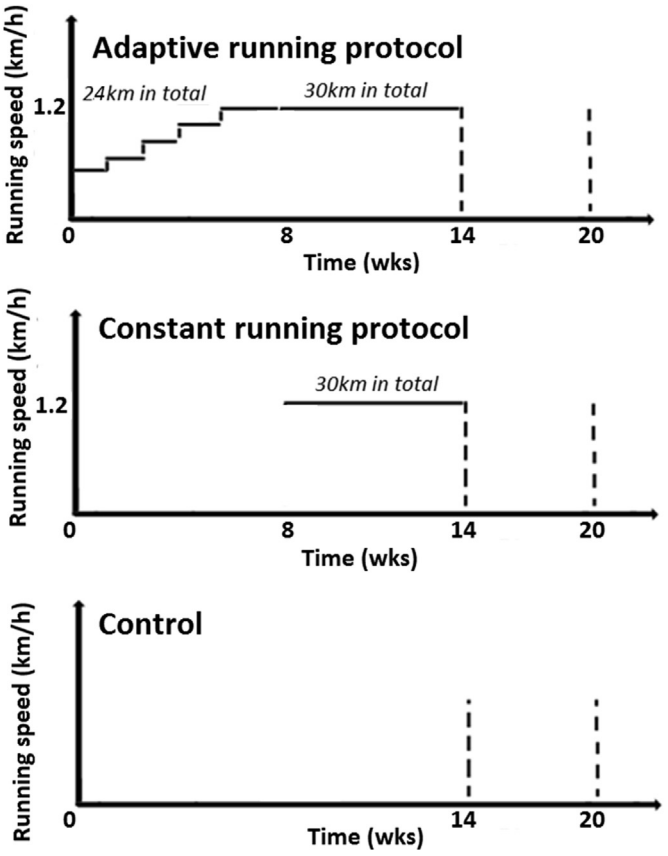

Figure 1. Exercise protocols of different experimental groups.

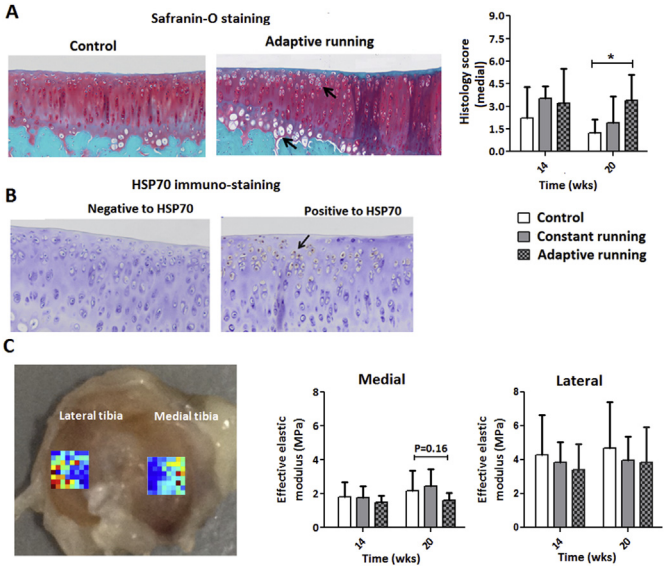

Figure 2. Micro-CT result on tibial epiphysis. Shubchondral bone thickness (Sb. Pl. Th.), shubchondral bone volume fraction (Sb. Pl. BV/TV), and trabecular bone thickness (Tb. Th.).

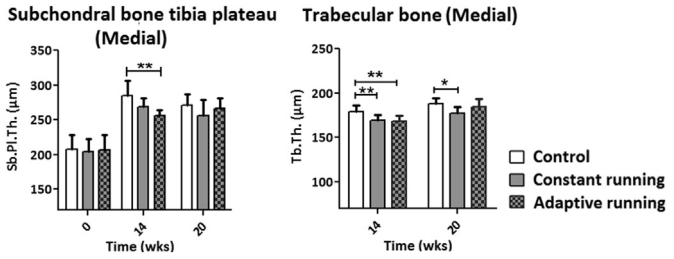

Figure 3. (A) Changes in the chondrocyte population and GAGs loss determined by Safranin-O histological staining on the rat knee joint for all three groups (B) HSP70 immunohistochemistry (Brown staining) (C) The effective elastic modulus measured from a 9×9 matrix of indentation on the center of both medial and lateral tibia plateaus of the rat knee joint.

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RACIAL DIFFERENCES IN MAGNETIC RESONANCE IMAGE-BASED THREE-DIMENSIONAL BONE SHAPE OF THE FEMUR VERSUS THE TIBIA AT THE KNEE: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: African Americans have higher prevalence and greater severity of knee osteoarthritis (OA) on radiographs compared with Caucasians, but why this may be is not clear. One possibility is racial differences in joint morphology. Joint morphology itself has been associated with differences in risk for knee OA, but its assessment is hampered by limitations of radiography. Magnetic resonance imaging (MRI)-based quantification of 3-dimensional (3D) anatomical changes of the knees may provide superior insights into potential racial differences in joint morphology compared with radiographs. Therefore, we applied this method to quantify 3D anatomical differences in the knees between African Americans and Caucasians as a potential mechanism for the racial difference in risk of knee OA.

Methods: We used data from the Osteoarthritis Initiative (OAI), a longitudinal cohort study designed to investigate the natural history of and risk factors for knee OA. Active appearance modelling, which has excellent reliability, was used to automatically segment the knee MRI (MAGNETOM Trio, Siemens) with sagittal 3D DESS-we sequence from each femur and tibia as principal components from a shape model. The OA bone shape vector is a line through the mean shape of OA and non-OA femurs and tibias, which were defined in a training set of a subset of subjects in the OAI who were Kellgren and Lawrence (KL) grade 0 at all time-points, and who were KL grade 2 or greater at all time-points up to 4 years. Individual bone shapes are projected orthogonally onto the OA bone shape vector. Zero in the bone shape vector is defined as the mean non-OA shape, and 1 unit is 1 SD of the non-OA shape distribution. Positive values indicate more of an OA shape. Separate vectors were obtained for males and females. We quantified the differences in 3D femur and tibia bone shapes between African Americans and Caucasians, stratified by sex, using linear regression, adjusting for KL grade, age, and body mass index (BMI), using generalized estimating equations to account for the correlation between knees within the same subject.

Results: We included 1534 African American (481 male, 1053 female) and 7139 Caucasian (3165 male, 3974 female) knees that had 3D bone shape measured at baseline. In both male and female knees, the crude mean distal femur bone shape vectors were higher for African Americans compared with Caucasians, even at KL grade 0, but the proximal tibia bone shape vectors were not significantly different between two races (Table 1). When stratified by sex and adjusting for age, BMI, and KL grade, significant differences in 3D bone shape were found between in African Americans and Caucasians in distal femur 3D bone shape vectors, but not in the proximal tibia (Table 2).

Table 1
Baseline demographics and crude mean 3D bone shape vectors.

	Male (N=3646 knees)		Female (N=5027 knees)	
	African American Mean (SD) (n =481)	Caucasians Mean (SD) (n=3165)	African American Mean (SD) (n=1053)	Caucasians Mean (SD) (n=3974)
Overall 3D bone shape vectors				
Distal femur	1.1 (1.5)	0.6 (1.4)	1.9 (1.8)	0.8 (1.5)
Proximal tibia	0.5 (1.2)	0.5 (1.1)	0.4 (1.2)	0.3 (1.1)
KL grade 0 3D bone shape vectors				
Distal femur	0.3 (1.0)	0.0 (1.0)	0.6 (1.3)	0.0 (1.0)
Proximal tibia	−0.1 (1.0)	0.1 (1.0)	0.0 (1.1)	0.0 (1.0)
Age, years	58.9 (9.2)	61.2 (9.5)	59.0 (8.2)	62.0 (9.1)
BMI, kg/m^2	30.2 (5.1)	28.6 (4.0)	31.5(5.0)	27.6 (5.1)

Table 2
Sex-specific differences in 3D bone shape between African American and Caucasian knees, adjusted for age, BML, and KL grade.

Femur bone shape vector	Male β (95% CI)	P value	Female β (95% CI)	P value
African American	0.29 (0.19−0.40)	<.0001	0.50 (0.41−0.58)	<.0001
Caucasian	0.00 (ref)		0.00 (ref)	
Age (per SD increase)	0.08 (0.04−0.11)	<.0001	0.13 (0.10−0.17)	<.0001
BMI (per SD increase)	0.05 (0.01−0.08)	<.0001	0.06 (0.03−0.09)	<.0001
Tibia bone shape vector	**Male β (95% CI)**	**P value**	**Female β (95% CI)**	**P value**
African American	−0.09 (−0.22−0.03)	0.145	−0.02 (−0.11−0.08)	0.680
Caucasian	0.00 (ref)		0.00 (ref)	
Age (per SD increase)	0.03 (−0.01−0.07)	0.093	−0.02 (−0.05−0.02)	0.398
BMI (per SD increase)	0.01 (−0.02−0.06)	0.422	0.01 (−0.02−0.05)	0.511

Conclusions: African Americans had more overall anatomical difference than Caucasians in MRI-based 3D femur bone shape, which were not due to differences in KL grade, age, or BMI. However, there was no significant racial difference in the proximal tibia. The greater anatomical femoral difference in African Americans may explain the higher prevalence of knee OA in African Americans. This finding of racial differences in 3D bone shape of the femur but not the tibia warrants further investigation to understand the underlying mechanisms causing these bone-specific differences to gain further insight into factors influencing the pathogenesis of OA.

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SUBCHONDRAL BONE PLATE SCLEROSIS DURING LATE OSTEOARTHRITIS IS MEDIATED BY LOADING-INDUCED DECREASE IN SCLEROSTIN AMOUNT

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Purpose: Subchondral sclerosis is a hallmark of late OA and previous studies attribute it to a high bone turnover. In late stage disease, the subchondral bone plate (SBP) thickens, but subchondral trabecular bone undergoes bone loss. The exact mechanism is still largely unknown. Using a unique genetic mouse model that we recently established for OA study and a computational finite elemental analysis (FEA), we discovered a novel mechanical and cellular mechanism to explain how cartilage depletion causes local subchondral sclerosis.