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The Influence of Alignment on Physiological Performance, Cartilage T2 Relaxation Time and Subchondral Bone Architecture in Asymptomatic Knee Joints.

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I. Abbreviations

3D	Three dimensional
ANOVA	Analysis of variance
BMI	Body-Mass-Index
BMD	Bone mineral density
BV/TV	Bone volume over tissue volume
cLF	Centre of the lateral femur
cm	Centimeter
cMF	Centre of the medial femur
CVs	Coefficients of variation
DESS	Driven equilibrium in the steady state
dGEMRIC	Delayed Gadolinium enhanced magnetic resonance imaging of cartilage
Dr. med.	Doctor medicinae
DRIVE	Driven equilibrium pulse
ETL	Echo train length
et al.	et altera
FD	Fractal dimension
FOV	Field of view
FS	Fat saturation
FLASH	Fast low angle shot
HF	High frequency
HKA	Hip-knee-ankle alignment
Hz	Hertz
IDL	Interactive data language
JSN	Joint space narrowing
kg	Kilogram
LT	Laterale Tibia
m	Meter
MA-D	Digital-imaging based hip-knee-ankle alignment
MA-MR	MR based hip-knee-ankle alignment
MHz	Megahertz

min	Minute
mm	Millimeter
MR	Magnetic resonance
MRI	Magnetic resonance imaging
ms	Millisecond
MT	Medial tibia
n	Number (count)
OA	Osteoarthritis
P	Patella
PD	Protone density
pLF	Posterior lateral femur
pMF	Posterior medial femur
Prof.	Professor
ROI	Regions of interest
SD	Standard deviation
SE	Spin echo
T	Tesla
T1	Spin-lattice relaxation time
$T1_\rho$	Spin-lattice relaxation time in the rotating frame
T1w	T1 weighted
T2	Spin-spin relaxation time
T2w	T2 weighted
TbN	Trabecular number
TbSp	Trabecular separation
TbTh	Trabecular thickness
TE	Echo time
TR	Repetition time
TSE	Turbo spin echo
TrCF	Trochlea of the central femur
TrLF	Trochlea of the lateral femur
TrMF	Trochlea of the medial femur
TU	Technische Universität
U.S.A.	United States of America
WORMS	Whole organ magnetic resonance imaging score

II. Figures

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IV. Introduction

Definition and Prevalence of Osteoarthritis

Osteoarthritis (OA) is an increasingly common disease -in particular at the knee joint- and represents one of the leading causes of disability, especially in the elderly (16, 32). Approximately 15% of the western population is actually affected by OA, while the prevalence increases to 50% of those over 65 years of age and up to 85% of those aged 75 years or more (17, 22). As its predominant clinical symptoms, OA results in pain and is characterized by a progressive loss of hyaline articular cartilage, smouldering synovitis, osteophyte formation and finally, deterioration of subchondral bone architecture (10).

Malalignment and Osteoarthritis

A paucity of risk factors for OA has been identified already, while several causative pathomechanisms are still under extensive investigation. Alteration to frontal plane static knee alignment is regarded as one compound to be associated with developing OA at the lower limb (48). A recent systematic review provided the information that malalignment of the knee joint represents an independent risk factor for the progression of OA, while there remains controversy concerning malalignment and the risk of incident OA (52).

Janakiramanan and colleagues (31) reported that pathological changes to the mechanical axis are associated with the risk of compartment specific knee cartilage defects in both healthy and arthritic subjects. Chondral defects may progress (7, 8) and are known to predate further cartilage loss and possibly associated meniscus lesions. However, it still remains unclear whether asymptomatic malalignment results in cartilage and/or subchondral bone impairment or even alters the physiological performance of the knee joint. Changes within the subchondral bone architecture may be associated with knee malalignment as well, which has been shown to alter the load distribution across the knee joint (52). Adaption of subchondral bone structure to varying load is recently understood as a cell mediated process in which osteocytes play an important role as mechanical sensors in order to activate bone forming/resorbing cascades via miscellaneous biochemical pathways (28).

However, controversial findings have been reported concerning the association between knee malalignment and incident knee OA defined by deterioration of the complex interaction of cartilage, subchondral bone and the jointôs mechanobiology (5, 29).

Imaging Techniques

Conventional X-rays may identify established, but advanced, signs of clear OA manifestation such as joint space narrowing (JSN) as a surrogate of cartilage volume reduction and osteophyte formation. On the other hand, standard X-ray imaging delivers several limitations such as pseudo-widening of the joint space in the less-loaded compartment or a reduced joint space due to meniscus and not cartilage pathology (30).

Obliged to recent advances in non-radiant musculoskeletal imaging, novel quantitative magnetic resonance imaging (MRI) sequences such as dGEMRIC, T1ρ or T2 mapping (34) allow for non-invasive exploration of articular cartilage and a potential prevailing pathology, which may progress silently with increasing age (33). In particular, changes among T2 times of the articular cartilage are regarded as a prestructural indicator of OA since it is correlated to pathological changes at the cartilage water content and/or collagen architecture, which are changes not to be identified by conventional radiography or even current standard MRI (11).
Quantitative MRI based assessment of subchondral bone changes among patients occupied by knee OA has furthered our understanding of the named disease. Lo and colleagues reported that comparing the medial to the lateral tibial plateau the specific ratio of bone mineral density (BMD) was positively associated with medial JSN and negatively associated with lateral JSN (36).
However, OA related changes of the subchondral bone architecture are controversially discussed. Cross-sectional and longitudinal studies revealed trends to lower values of morphometric trabecular bone structure parameters including bone volume fraction and trabecular thickness in subjects with severe OA compared to subjects with mild OA and normal controls, respectively (3, 4). On the contrary, a recent study found a positive association between morphometric trabecular bone structure parameters measured in the proximal medial tibia and medial JSN (35).

Aims and Scope

It remains to be investigated whether knee malalignment among otherwise healthy subjects entails early changes within the realms of the subchondral bone architecture, causes alteration of the articular cartilage or even compromises the physiological performance of the affected joint.

The aim of the study presented here was to investigate on signs and symptoms of disease, knee joint cartilage ultrastructure and subchondral bone architecture among young, active and asymptomatic subjects that are occupied by a native lower limb axis disturbance utilizing clinical scores, novel MRI based analysis of trabecular bone as well as quantitative cartilage T2 mapping techniques.

This knowledge may influence future treatment algorithms for young, asymptomatic patients that happen to be occupied by genu varum/valgum deformities when early prevention is considered.

V. Participants and Methods

Participants

A total of 96 knee joints of 48 non-smoking, healthy volunteers (26 females, 22 males) without any history of significant trauma, rheumatic disease, surgical intervention or ligament instability in either knee joint or any other joint-related pathologies were subdivided into four groups according to the static mechanical axes (Line of Mikulicz) of both lower extremities. Group division (n=12 subjects per group; n=24 knees per group) according to alignment was:

Neutral group 0 (<1° varus/valgus deformity), mild varus group 1 (2-4° varus deformity), severe varus group 2 (>4° varus deformity) and valgus group 3 (2-4° valgus deformity).

Clinical evaluation, including BMI calculation, was captured using the modified Lysholm score (38) and Tegner activity rating scale (53).
Standardized weight-bearing frontal plane full-length digital photographs of both legs in bipedal stance (MA-D) for measurement of static knee joint alignment were captured in the first place as previously described (47). MA-D values were then reappraised via MRI techniques as described below.

The study was performed in accordance with the Declaration of Helsinki. Informed consent from each participant as well as approval from the local ethics committee was obtained prior to investigation.

Imaging Procedures

Both knee joints of every participant were assessed by standard MRI at 1.5 Tesla in the supine position (Siemens Avanto; Siemens Medical Solutions, Erlangen, Germany), equipped with 40 mT/m gradients, utilizing a dedicated 8-channel knee coil (Medical Advances, Milwaukee, WI, USA). An adapted knee protocol (46) was acquired in all participants consisting of a sagittal T1-weighted turbo spin echo (tse) sequence with a driven equilibrium (DRIVE) pulse, a field of view (FOV) of 16 cm, section thickness of 3 mm, an acquisition matrix of 384 x 384 and a bandwidth of 64 Hz/pixel. The T1-w sequence had a TE of 15, a TR of 647 and an ETL of 3. In average, 26 sections were obtained in 4:30 min.

Furthermore, a 3D T2-w fat set (fs) driven equilibrium in the steady state (DESS) sequence with a voxel size of 0.5 x 0.5 x 0.7 mm, (TE 6.9, TR 18.9) and a 3D T1-w gradient echo sequence (fast low-angle shot, FLASH) with a voxel size of 0.25 x 0.25 x 1.2 mm (TE 5.7, TR 11.7) were obtained each in 6 minutes. T2 relaxation time acquisition was accomplished by T2 mapping in the sagittal plane of all articulating joint surfaces. A multi-echo spin-echo acquisition was acquired with a TR of 1690 ms and 6 TEs (10, 20, 30, 40, 50 and 60 ms), a FOV of 17x13 cm, an acquisition matrix of 384 x 288 at a bandwidth of 64 Hz/pixel resulting in a time of acquisition of 6:04 min and an interpolated pixel size of 0.22 mm.

In addition, static frontal plane knee joint alignment of both lower extremities was determined using a previously established MRI-based measurement technique (25). In brief, coronal T1-weighted images centred to the ankle, knee and hip joint were acquired and full-leg images were obtained by image composition (Figure 1).

On the basis of these encoded images, MR-based hip-knee-ankle (HKA) alignment (MA-MR) of both lower extremities was measured and additionally compared to MA-D values. Groups were divided according to MA-MR data.

Figure 1: MRI-based measurement of knee joint alignment

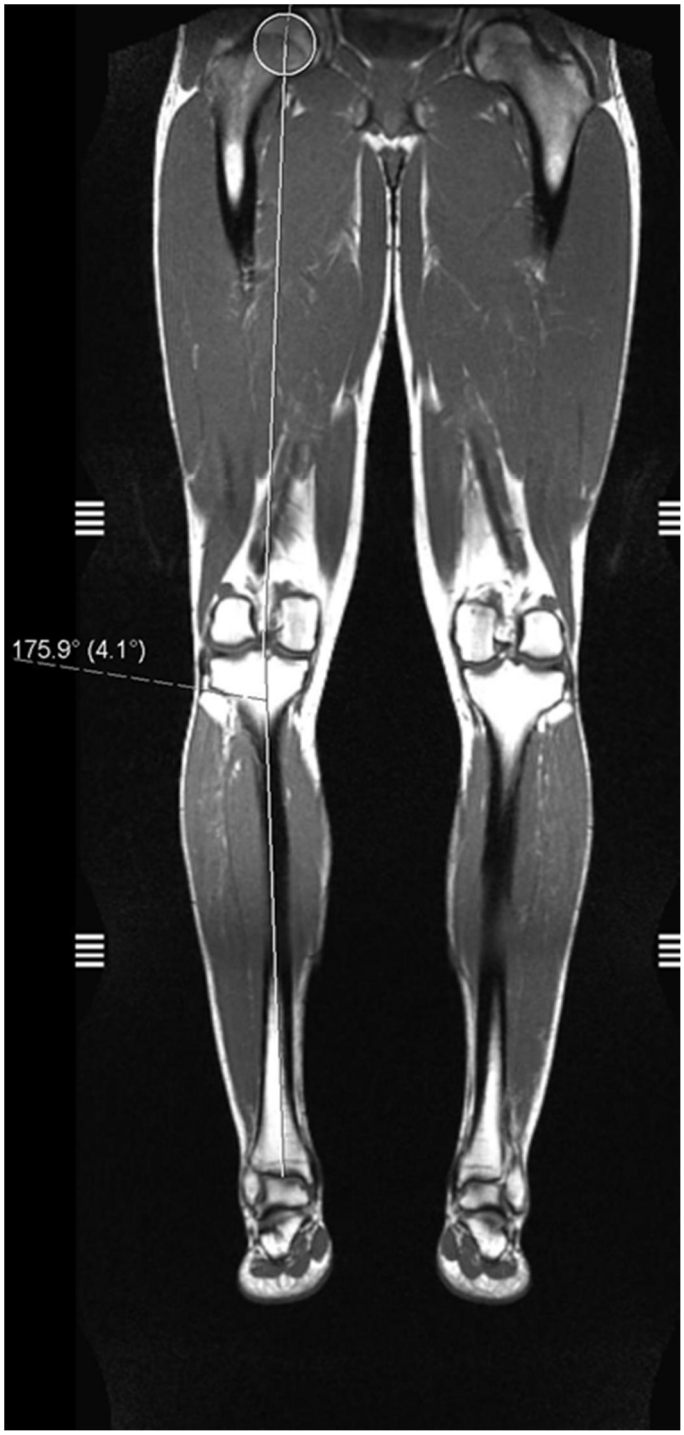

Figure 1: Static frontal plane knee joint alignment of both lower extremities obtained by image composition of coronal T1-weighted images centred to the ankle, knee and hip joint as described by Hinterwimmer et al. (25).

Evaluation of Images

All MR images were transferred to the institutional picture archiving communication system (PACS; Sectra AB, Linköping, Sweden) and reviewed to assess the presence and grade of focal knee lesions utilizing the whole organ MRI score (WORMS) (45).

Cartilage T2 Relaxation Time Mapping

In order to exclude the initially stimulated echo artefacts, T2 relaxation time maps were calculated pixelwise from five spin-echo images (echoes 2-6 from the stimulated echo) using a monoexponential nonnegative least squares fit analysis with a custom-built software (IDL, Creaso, Gilching, Germany) (9).

Regions of interest (ROI), with modifications, were suited to the realms of full thickness cartilage and subdivided in view of different levels of strain roughly based on the consensus recommendation for anatomically adapted labelling as described by Eckstein et al. (12). For that, the margins between trochlea, central and posterior femoral compartments were defined by a cutting line orthogonal to the cartilage surface and adjacent to the anterior and posterior horn of both menisci, respectively (Figure 2). Femoral (F) ROIs were stated as medial (MF) and lateral (LF) and subdivided into central (cMF, cLF) and posterior (pMF, pLF). Equally, tibial ROIs were set as medial tibia (MT) and lateral tibia (LT) and not further subdivided. The articulating surface of the patella (P) and the trochlea (Tr) was not further subdivided regarding the potentially shifting levels of strain at the patellofemoral joint in malaligned knees (14).

Figure 2: Regions of interest, cartilage T2

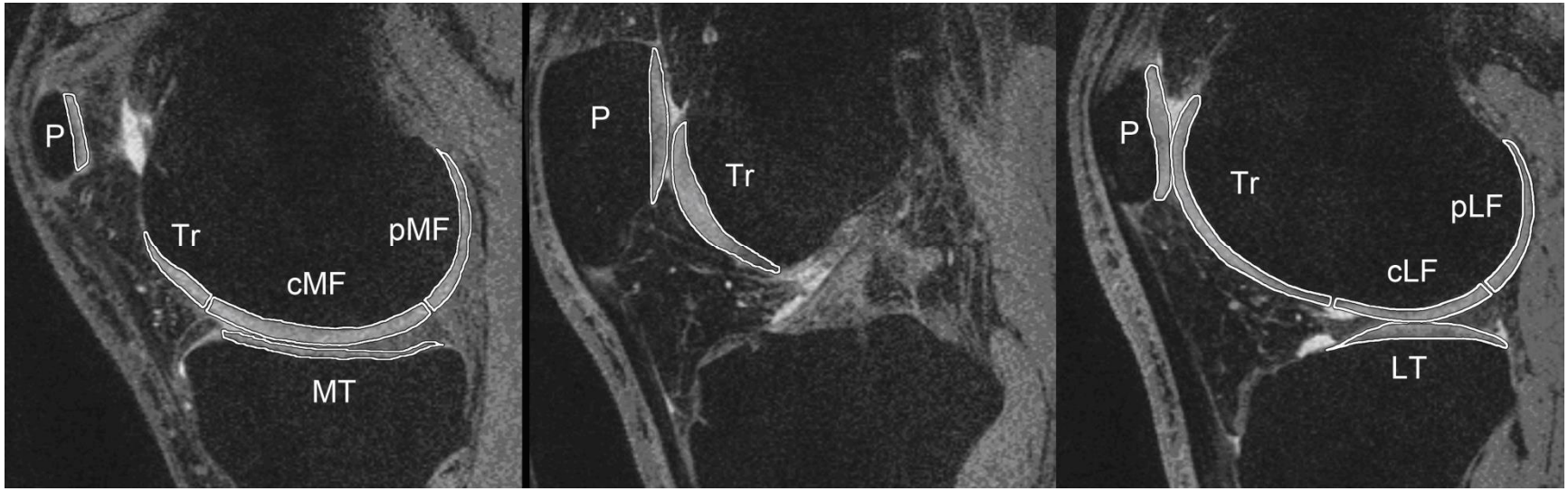

Figure 2: Division and nomenclature of the femoral, tibial and patellar cartilage segments respecting compartmental and functional knee joint anatomy with modifications according to the proposed nomenclature by Eckstein (12). Regions of interest: cMF, pMF and MT at the medial tibiofemoral compartment; P and Tr at the patellofemoral compartment; cLF, pLF and LT at the lateral tibiofemoral compartment.

Subchondral Bone Architecture

The axial images of the FLASH sequence were transferred to a remote LINUX workstation. Trabecular bone structure analysis was performed using an in-house developed program based on IDL (Interactive Data Language; Research Systems, Boulder, CO, USA).

Four compartments were manually segmented in the medial/lateral femur/tibia similar to previous studies (3, 4):

MF, medial femur, LF, lateral femur, MT, medial tibia, and LT, lateral tibia. The regions of interest (ROIs) of each compartment were drawn in eight consecutive slices. The first slice of each compartment was defined at the distal femur (proximal tibia) depicting the subchondral bone adjacent to the femorotibial joint line. The remaining seven slices were the consecutive slices located more proximal (MF and LF), respectively more distal (MT and LT) to the first slice (Figure 3).

Figure 3: Regions of interest, subchondral bone

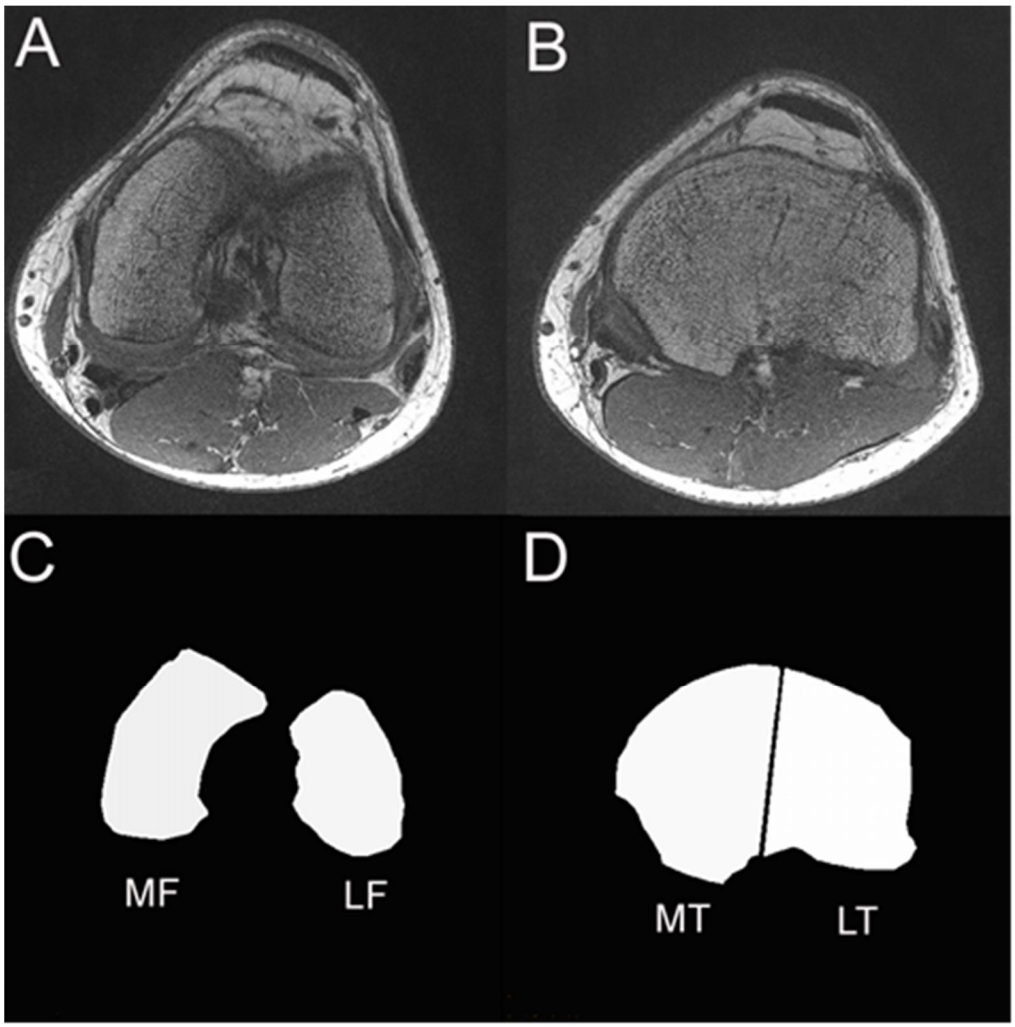

Figure 3: Representative MR images of the left knee of a subject with neutral knee alignment: distal femur (A), proximal tibia (B) and their correspondingly segmented compartments MF: medial femur and LF: lateral femur (C); MT: medial tibia and LT: lateral tibia (D).

After binarization, four morphometric parameters were calculated in analogy to standard histomorphometry using the mean intercept length method (44): bone volume divided by total volume (bone volume fraction, BV/TV), trabecular number (TbN), trabecular separation (TbSp), and trabecular thickness (TbTh). Parameters were labeled as apparent (app.) values, for they cannot depict the true trabecular structure due to the given limited spatial resolution.

Furthermore fractal dimension (FD) as texture measurement of the trabecular bone architecture was computed in the MR images using a box counting algorithm as previously described (39). Reproducibility errors of the trabecular bone structure analysis have already been reported in previous studies with coefficients of variations (CVs) ranging from 1.8% to 5.5% (3, 4).

Statistical Analysis

The major determinant for outcome comparison was the mechanical axis division according to the alignment groups described above. Statistical analysis was performed using the software package SPSS version 17 (SPSS Inc, Chicago, Illinois). All data were tested for normal distribution using the Kolmogorov-Smirnov test. Group data were compared using univariate ANOVA corrected for cofounding variables (age, gender, BMI). To control the family-wise error rate, the Bonferroni correction was applied. Unless otherwise stated, descriptive results were demonstrated as the mean ± standard deviation (SD). Significance was set at $P < .05$ for all tests.

VI. Results

Participant Characteristics and Clinical Findings

An overview of participant characteristics is given in Table 1. All patients were without knee complaints and clinical knee examination was without pathological findings. There was a significant overall group difference for weight, height, BMI ($P<.05$) as well as for axis deviation measured as MA-D ($P<.001$) and MA-MR ($P<.001$), respectively.

Lysholm and Tegner scores for isolated (left, right) as well as for both knee joints/subject were each not different between groups. All MA-D and MA-MR (as well as the combined value per knee/subject) values were significantly different for every possible group comparison, respectively. Neither MA-D, nor MA-MR values (right versus left) were significantly different per knee/subject. There was no difference when comparing MA-D with MA-MR values and therefore, group division was performed according to the latter.

Table 1: Participant characteristics

	Gender	Age	Weight	Height	BMI	Tegner	Lysholm	Axis
Neutral	4/8	25.3±1.7	64.9±8.3	176±8	21.0±1.3	6.4±1.8	97.0±4.5	0.7±0.5
Mild Varus	10/2	25.7±1.2	72.1±8.6	179±9	22.5±1.5	7.8±1.7	96.6±4.9	3.0±0.6
Severe Varus	7/5	26.0±2.3	72.0±9.2	181±6	21.7±1.9	7.5±1.8	97.3±4.7	5.0±1.1
Valgus	1/11	24.5±1.3	61.5±6.5	170±5	21.4±2.0	6.2±1.4	96.5±5.7	-2.5±0.7

Table 1: Gender (male/female), age at time of examination, body weight in kg, height in cm, BMI, Tegner activity scale, both knee joints combined Lysholm score, both knee joints combined values in degree for mechanical axis (HKA-MRI) among subjects with neutral, mild varus, severe varus and valgus alignment of both lower extremities (n=12 subjects, n=24 knees/group), mean ± SD. Significance provided within results section.

MRI Outcome

There was no intraarticular, no ligamentous and particularly no meniscal or cartilage pathology (no focal lesions within cartilage and/or subchondral bone) in any knee joint, analysed in the standard morphological MRI protocol (WORMS). The soft tissue surrounding the knee joint was as well without pathological findings among all of the investigated joints.

Cartilage T2 Relaxation Time Mapping

An overview of the quantitative MR outcome is given in Table 2, Figure 4, Figure 5. Global T2 values (42.3 ± 2.3; 37.7-47.9 ms) of ROIs placed within every knee joint per subject were neither different between alignment groups nor between genders, respectively.

Comparing T2 values of the single anatomical regions, there was also no significant difference between all alignment groups. Highest global T2 value was found in Tr with 47.1 ± 3.1 ms while P produced the lowest global T2 with 38.7 ± 3.5 ms.

Regional T2 difference between right and left-sided knee joints never reached the level of significance. There were trends towards higher T2 values in MT than in LT and in cLF than in cMF among varus-aligned groups while the reverse holds true among valgus-aligned subjects.

Those findings never reached the level of significance.

Table 2: Global and knee joint region divided cartilage T2

	cMF	cLF	pMF	pLF	MT	LT	Tr	P
Neutral	42.0 ± 3.3	41.3 ± 2.9	41.5 ± 4.0	43.2 ± 2.8	40.8 ± 4.0	40.0 ± 3.7	45.8 ± 3.1	37.7 ± 3.1
Mild Varus	43.2 ± 3.4	43.6 ± 4.5	42.4 ± 4.1	43.9 ± 4.1	42.8 ± 2.7	41.5 ± 3.2	47.9 ± 3.2	39.7 ± 4.3
Severe Varus	42.3 ± 2.3	42.9 ± 2.6	42.3 ± 2.1	44.6 ± 3.6	42.4 ± 3.0	41.0 ± 3.4	47.8 ± 2.2	38.8 ± 3.0
Valgus	41.8 ± 3.1	41.0 ± 3.5	41.3 ± 3.4	42.8 ± 4.1	40.6 ± 3.0	41.0 ± 2.7	46.8 ± 3.6	38.8 ± 3.5
Global T2	42.3 ± 3.1	42.2 ± 3.6	41.9 ± 3.5	43.6 ± 3.7	41.7 ± 3.3	40.9 ± 3.3	47.1 ± 3.1	38.7 ± 3.5

Table 2: Global values and knee joint region divided (M=medial, L=lateral, c=central, p=posterior, F=femur, T=tibia, Tr=trochlea, P=patella) T2 relaxation in ms among subjects with neutral, mild varus, severe varus and valgus alignment of both lower extremities (n=12 subjects, n=24 knees/group), mean ± SD. Significance provided within results section.

Figure 4: T2 values of selected knee joint regions

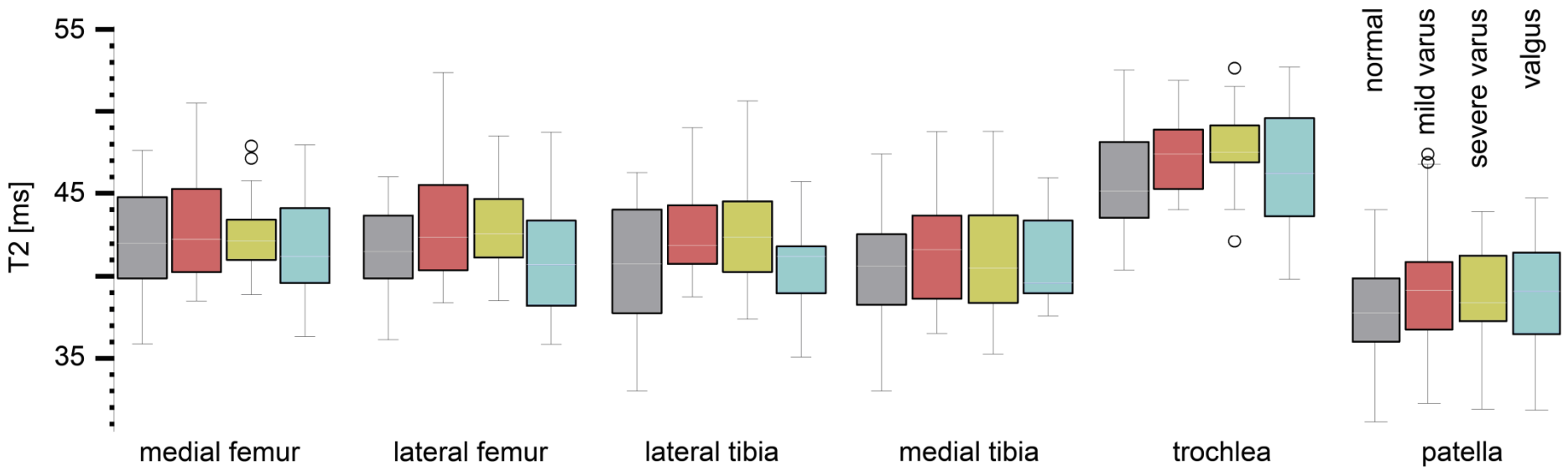

Figure 4: T2 values in ms of selected knee joint regions: weight-bearing medial (cMF), lateral femur (cLF); weight-bearing lateral (LT) and medial (MT) tibia as well as the patellofemoral joint (Tr, P) among subjects with neutral, mild varus, severe varus and valgus mechanical axis alignment of the lower extremities (n=12 subjects, n=24 knees/group). Median and interquartile range. Significance provided within results section.

Figure 5: Colour coded T2 maps of the knee joint

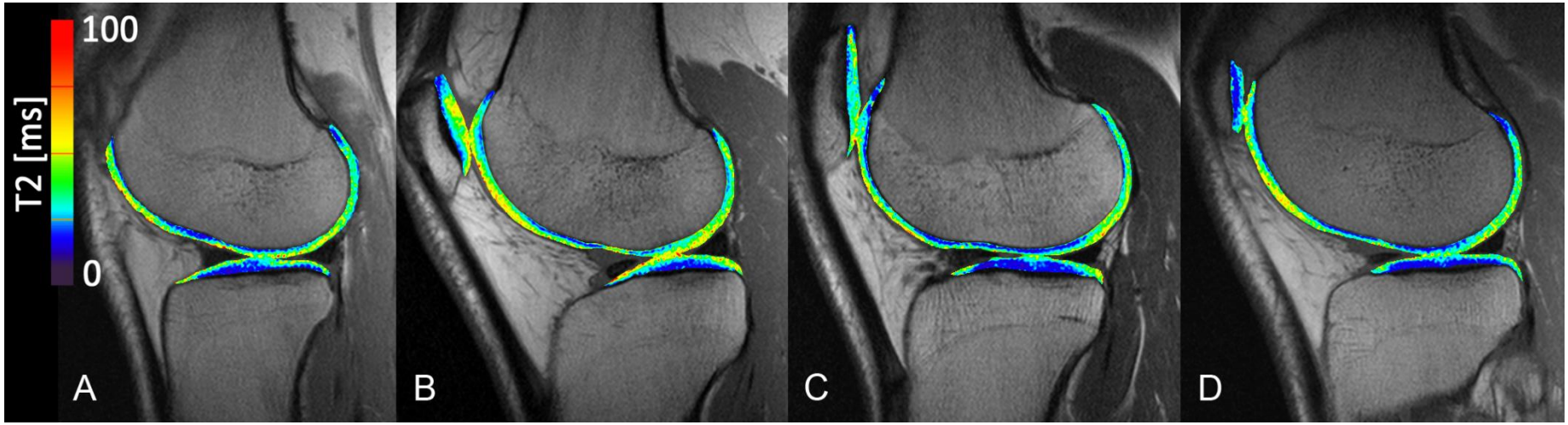

Figure 5: Colour coded T2 maps of the lateral knee joint (LT, LF) of four asymptomatic volunteers with different mechanical axis alignment of the lower extremities: valgus (A); neutral (B); varus (C); severe varus (D); corresponding to the four groups compared.

Subchondral Bone Architecture

An overview of the unadjusted values of the trabecular bone structure parameters in each compartment is given in Figure 6. A rather large variation among these parameters was observed among individual subjects in each group. However, after Bonferroniôs correction to control the family-wise error rate and adjustment for age, gender and BMI, app.TbTh in the MT compartment was significantly lower in the valgus group (mean ± standard error: 0.353 ± 0.012 mm) compared to the neutral (0.396 ± 0.011mm; p = 0.043), mild varus (0.403 ± 0.011 mm; p = 0.038) and severe varus group (0.416 ± 0.013 mm; p = 0.015).

Furthermore in the MF compartment, fractal dimension was significantly greater among mild varus (1.697 ± 0.005; p = 0.015) and severe varus (1.698 ± 0.005; p = 0.036) than in the valgus group (1.674 ± 0.005).

Figure 6: Trabecular bone structure parameters

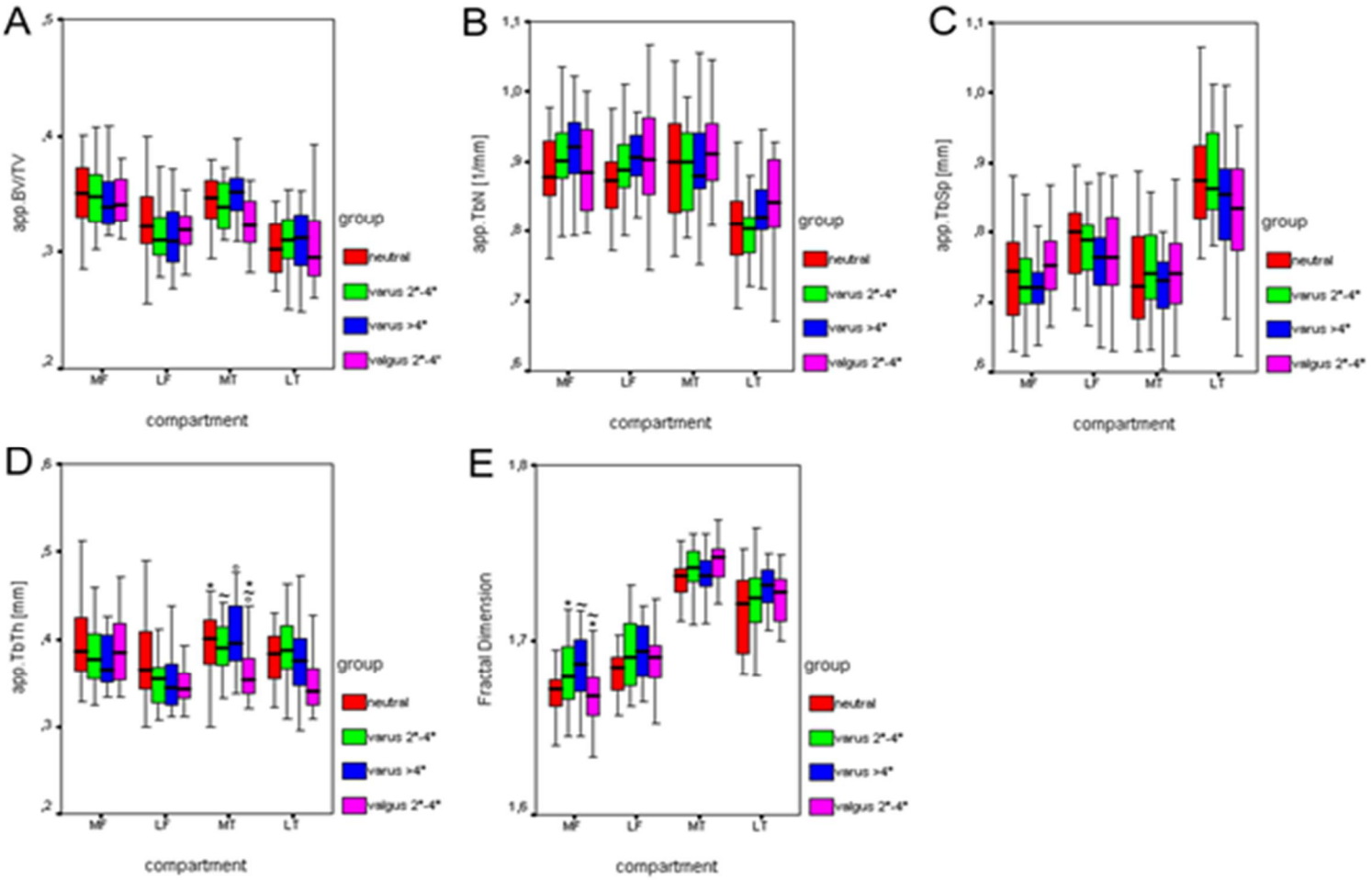

Figure 6: Trabecular bone structure parameters (app.BV/TV (A), app.TbN (B), app.TbSp (C), app.TbTh (D), and Fractal Dimension (E)) of the four groups (neutral, varus 2°-4°, varus >4°, and valgus 2°-4°) in the medial femur (MF), lateral femur (LF), medial tibia (MT), and lateral tibia (LT) compartment. Symbols *, ~, and ° indicate statistically significant differences ($p<0.05$) between the respective groups.

VII. Discussion

In light of knee OA as a rising socioeconomic burden, it is of paramount importance to examine any potential predisposition for disease incidence or progression, in particular, if early intervention might be possible (17). Frontal plane knee mechanical axis malalignment is considered as an independent risk factor for the progression of OA (52), while strong controversy persists regarding malalignment and incidence of OA. In the study presented here, malalignment did not appear to impose negative effects on T2 relaxation time as a surrogate of cartilage integrity nor on physical activity among a total of 96 knees of healthy, active young volunteers while early changes whithin subchondral bone architecture were already detectable. The latter alterations of the trabecular bone happened to be relatively subtle, since differences appeared more obvious comparing varus and valgus aligned subjects rather than varus/valgus alignment compared to neutral controls. Those changes among the subchondral bone structure may be caused by altered loading conditions due to different alignment and corresponding adaptation of the subchondral bone as a sign of bone remodelling.
Longitudinal studies will have to investigate whether such slight changes within the realms of the subchondral bone are bound to be physiological adaption associated with different levels of strain or represent already early signs of OA with the potential to progress even further.

Previous studies showed that altered loading without any pre-existing structural damage to the joint does not represent a peculiar risk factor of knee OA (26, 27, 41). Among elderly subjects burdened with osteoarthritis, controversial findings were reported: alterations of the mechanical axis appear to be associated with compartment-specific cartilage defects in patients older than 40 years (31). However, among the cited study the association with other injuries like meniscal defects was not investigated, thus the pathophysiological onset still remains unclear.

Varus malalignment is a rather common observation that has been described to be more frequent in specific populations participating in sports such as soccer (55); of note, varus malalignment of the lower extremities does not noticeable limit the physiological performance of affected subjects (33). Such information is much more rare concerning valgus knee joints, which as well have been identified to increase the incidence of OA (17).

Multiple compounds have been described to claim detrimental effects on the medial joint compartment (48), which carries higher loads and has been described to be particularly susceptible to irregularities of the mechanical axis due to increased adduction moments, medial ligament laxity or superior vastus-medialis muscle function (33, 54). The same holds true concerning the lateral knee compartment which, however, has been investigated with much lesser frequency (17); while also progression of patello-femoral OA is claimed to be associated with frontal plane knee malalignment (14, 24). Preventive intervention to neutralize the mechanical load within the knee joint among asymptomatic individuals is an unexpressed matter of debate; while a decision currently would not be supported by scientific evidence.

Yet, paradigms to address malalignment are available, however, there is indeed no ratio to treat asymptomatic patients: knee and foot orthoses as initial conservative treatment modalities have shown improvement in function and pain among subjects with severe clinical symptoms (6, 42), while corrective osteotomies across the knee joint may result in improved function and pain among patients suffering from unicompartimental OA (2, 43).
However, all such corrective interventions or conservative attempts impose their positive effect only on symptomatic knee joints that are burdened with cartilage impairment or OA already while we still lack information concerning a doubtable negative influence of malalignment on healthy, asymptomatic knee joints. It still remains unclear, if malalignment results in articular cartilage impairment, vice versa or bidirectional. Based on the findings of the study presented here, it could be concluded that existing, atraumatic varus/valgus malalignment does not show any signs or symptoms of disease and does not produce cartilage ultrastructural alteration in the assumed mechanically overloaded compartments as measured via quantitative MRI while interestingly there are detectable changes in subchondral bone architecture hinged on varying alignment groups.

Bolbos et al. reported lower app.BV/TV, app.TbN, and app.TbTh, and greater app.TbSp in the medial/lateral femur/tibia in OA patients compared to normal controls (4). In consistency, Blumenkrantz et al. compared these morphometric parameters in the same compartments in severe and mild OA patients over two years and found similar results (3). The named authors explained their findings via the hypothesis that cartilage degeneration and subchondral plate sclerosis cause osteopenia and deterioration of trabecular bone architecture in the subchondral bone due to decreased load transmission.

However, Lo et al. observed in a sample size of 629 subjects from the Bone Ancillary Study of the Osteoarthritis Initiative a positive association of periarticular BMD, app.BV/TV, app.TbN, app.TbTh in the proximal medial tibia and medial JSN scores (35). Bone remodelling or small compression fractures were described by those authors as pathologic aetiologies for these findings.

Previous studies have reported that prestructural cartilage alteration is greater at the tibial plateaux than in the femoral compartments (54), which may be related to a higher chondral susceptibility. When comparing neutral with mild and severe varus-aligned groups the study presented here could only found the slight tendency of T2 relaxation differences, with generally higher values in varus-aligned knee joints, regularly at the medial tibia (MT) while valgus-aligned subjects produce higher T2 at the lateral tibia. These elevated T2 values may represent adaption to biomechanical load in the form of previously reported increased water content (37) and/or collagen assimilation (18) while the correct interpretation of elevated as well as depressed T2 values has yet to be elucidated.

Running itself has been reported to result in decreased T2 values, most likely due to reversible, physiologically depleted water content within superficial cartilage. Mosher reported on the elevation of cartilage T2 in asymptomatic subjects over 45 years of age (41), while the same group reported longer T2 among young marathoners versus young control subjects (difference not significant), potentially in light of chronic mechanical stimulation. This trend was not evident in older subjects, while it is known that articular cartilage among this cohort is of much stiffer structure.

Significantly increased T2 values, compared to healthy controls, strained with excessive load have also been described in active early OA subjects with focal cartilage abnormalities (50). Remarkably, there was no significant difference in T2 relaxation time among the cohort of participants within the study presented here, even when comparing knees with neutral alignment to those occupied with 5° of varus malalignment. This may indicate malalignment to facilitate cartilage impairment if already established while healthy cartilage demonstrates the capacity of compensating for variant biomechanical loading.

The patellofemoral joint has been described to be affected by alignment alterations as well (14). In controversy to that, patellar as well as trochlear values were similar among all groups in the study presented here. These findings are underlined by the fact that the patellar undersurface is covered by a rather thick hyaline matrix related to overall highest biomechanical forces during locomotion, which has been described to result in different extracellular matrix (13), deformation, compensation capabilities (20) as well as chondrocyte function (21). Patellofemoral compounds offer the potential of compensation of mechanical overloading in particular among young subjects. However, other studies have reported that patellar undersurface T2 values are obviously affected by activity, OA or BMI (51).

Paralleling the interpretation of elevated/depressed T2 times, there is generally no consensus about normal T2 times, which are reported significantly different between studies (40), which usually is related to varying acquisition and/or post-processing techniques. Control subjects have to be included into every study to be able to draw intra-study comparisons, while isolated literary information is sparse as well (23, 49).

Hannila et al. (23) were the first who reported a topographical variation of T2 times among young, healthy subjects. Friedrich and colleagues have previously reported on medially elevated T2 values in varus-aligned OA patients with a mean age of 62.5 years (19). In comparison, the data presented here found no significant differences among healthy, young subjects, indicating that the T2 elevation reported by Friedrich et al. may be due to compartment specific changes in OA, not present in young and healthy volunteers.

The menisci within the knee joint play a major role in particular to protect and serve its surrounding cartilage (15, 27). Combining these with the results of the study presented here, it appears that as long as meniscal integrity is assured, malalignment and varying biomechanical strain may be well compensated by the succeeding collaboration of menisci and hyaline cartilage and malalignment alone is not capable to impose cartilage deterioration while it may be a confounding factor for the worse if combined with some compartment specific traumatic event. Yet, further quantitative investigation has to be conducted for evaluation of potential meniscal alteration among malaligned subjects.

In the light of these conflicting reports, the study presented here farther investigated the trabecular structure within the realms of the subchondral bone among the stated cohort of young, asymptomatic subjects occupied with malalignment of the lower limb. As outlined already, knee jointôs malalignment has been identified as a specific risk factor for the progression of OA (52) while controversial findings have been reported concerning the association between knee malalignment and incident knee OA (5, 29).

Malalignment causes greater biomechanical force and liability within the medial/lateral compartment while -vice versa- unloading the contralateral joint area. This intensified strain affecting one compartment at a time may trigger subchondral bone formation or even deterioration, while decreased forces among the contralateral compartment may lead to competing cascades of bone resorption (52). In the study presented here, these transformations of the subchondral bone could be demonstrated with greater app.TbTh within the realms of the medial tibia compartment and with greater fractal dimension in the medial femur compartment among varus aligned subjects compared to those occupied with valgus malalignment.

The medial compartments of the knee joint have been reported to bear 60ï80% of the compressive loads in a neutrally aligned knee already (52). The latter may be one explanation for the fact that statistically significant results in the data presented here could only be produced from medial compartments.

It remains to be investigated whether the changes of subchondral bone architecture among young, asymptomatic subjects occupied by malalignment of the lower limb not only represent signs of adaptation processes due to altered load distribution across the knee joint but rather constitute a vast initial manifestations of some osteoarthritic changes. In case of the latter, the findings presented here may claim important implications for the efforts of OA disease prevention. Therefore follow-up studies may be required in order to monitor further changes of the subchondral trabecular bone architecture or even within the articular cartilage over time among young, active, asymptomatic subjects occupied with knee malalignment only. This may further our knowledge and understanding about knee malalignment as a presumed but potentially crucial risk factor for the development and incident of knee jointôs OA.

The study presented here offers some limitations. First of all, it was designed cross-sectionally. A longitudinal approach could be stated as somehow more suitable. However, it was beyond the aims and scope of this study to evaluate alterations of the jointôs clinical performance, cartilage ultrastructure or subchondral bone architecture over a certain period of time. It was of prime interest to elucidate questionable deterioration among jointôs function, cartilage integrity and/or subchondral bone caused by asymptomatic malalignment of the lower limb.

MRI was performed at a 1.5T scanner and not at 3T as conducted in previous studies (3,4, 35). This technical fact resulted in a slightly lower in-plane resolution and signal to noise ratio compared to the studies cited. However, a recent study reported reproducibility errors within trabecular bone structure analysis to be similar at 1.5T and 3T MRI, at least concerning the distal radius (1).

There remains lack of analysis concerning T2 variation along the cartilage depth, such as superficial and deep zones of the cartilage; however, different loading affects the whole cartilage thickness and thus should result in T2 changes of the whole compartment.

Gender differences were evident in particular when comparing the severe varus and valgus groups; however, results remained similar with and without considering these differences in the statistical model.

Furthermore, the trabecular bone structure analysis required a relatively time consuming, manual segmentation procedure. Therefore the described analysis may so far only be feasible in a research setting and not to be conducted along with the clinical routine.

Conclusion

The results presented here demonstrate that subjects occupied by varus or valgus knee joint malalignment did not show any clinical signs or symptoms of joint disease when compared to neutrally aligned controls. Underlining those clinical findings, quantitative MR imaging detected no significant difference among cartilage T2 as a surrogate of cartilage ultrastructure. Contrariwise, early alterations within the realms of the subchondral bone could be already revealed among the same cohort of young, asymptomatic subjects burdened with knee jointôs malalignment.

These findings may deliver important implications for the prevention of knee OA. Longitudinal studies may be eligible in order to further improve our limited knowledge of malalignment as a risk factor for the development and/or progression of knee OA.

At the time of investigation, only slight alterations of the subchondral bone architecture constrained this cohort of otherwise healthy volunteers.

VIII. Summary

Objective. To investigate whether static knee alignment affects physiological performance, articular cartilage ultrastructures measured using T2-relaxation or subchondral bone architecture among asymptomatic, healthy subjects.

Methods. Both knee joints (n=96) of 48 asymptomatic volunteers (26 females, 22 males; 25.4±1.7 years; no history of major knee trauma or surgery) were evaluated clinically (Lysholm, Tegner) and by MRI (hip-knee-ankle angle, standard knee protocol, T2 mapping and analysis of subchondral bone architecture). Group (n=4) division was: neutral (<1° varus/valgus), mild varus (2-4° varus), severe varus (>4° varus) and valgus (2-4° valgus) deformity with n=12 subjects/group; n=24 knees/group. Regions of interest (ROI) for T2 assessment were placed within full-thickness cartilage across the whole joint surface and were divided respecting compartmental as well as functional joint anatomy. Furthermore, histomorphometric and texture parameters of subchondral trabecular bone architecture in the medial/lateral femur/tibia were assessed using a T1-weighted 3D FLASH sequence.

Results. Leg alignment was 0.7°±0.5 varus among neutral, 3.0°±0.6 varus among mild varus, 5.0°±1.1 varus among severe varus and 2.5°±0.7 valgus among valgus group subjects and thus significantly different. No differences between the groups emerged from clinical measures. No morphological pathology was detected in any knee joint. Global T2-values (42.3±2.3; 37.7-47.9ms) of ROIs placed within every knee joint per subject were not different between alignment groups or between genders, respectively. Apparent trabecular thickness in the medial tibia (MT) compartment was lower in the valgus group (0.353±0.012mm) compared to neutral (0.396±0.011mm; p=0.043), mild varus (0.403±0.011mm; p=0.038) and severe varus group (0.416±0.013mm; p=0.015). In the medial femur (MF) compartment, fractal dimension was significantly greater in the mild (1.697±0.005; p=0.015) and severe varus (1.698±0.005; p=0.036) than in the valgus group (1.674±0.005).

Conclusion. Subjects occupied by varus or valgus knee joint malalignment did not show any clinical signs or symptoms of joint disease compared to neutral aligned controls. Underlining those clinical findings, quantitative MR imaging detected no significant differences among cartilage T2 as a surrogate of cartilage ultrastructure while contrariwise alterations of subchondral trabecular bone architecture were detectable and may represent signs of adaption to increased biomechanical load.

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X. Appendix

Lysholm Knee Score

Bitte das entsprechende ankreuzen

Hinken

- ☐ niemals
- ☐ leicht oder periodisch
- ☐ stark oder permanent

Treppen steigen

- ☐ ohne Probleme
- ☐ mit leichter Beeinträchtigung
- ☐ nur Schritt für Schritt
- ☐ überhaupt nicht, ist unmöglich

Gefühl der Instabilität

- ☐ nie
- ☐ mäßig beim Sport oder anderer starker Belastung
- ☐ häufig beim Sport oder anderer starker Belastung
- ☐ gelegentlich bei täglichen Aktivitäten
- ☐ häufig bei täglichen Aktivitäten
- ☐ bei jedem Schritt

Schwellung

- ☐ nie
- ☐ gelegentlich
- ☐ bei starker Beanspruchung
- ☐ bei leichter Beanspruchung
- ☐ permanent

Belastung

- ☐ uneingeschränkt möglich
- ☐ ist nur mit Stock oder Gehhilfe möglich
- ☐ ist überhaupt nicht möglich

In die Hocke gehen

- ☐ ohne Probleme
- ☐ mit leichter Beeinträchtigung
- ☐ nicht über 90° im Kniegelenk
- ☐ überhaupt nicht, ist unmöglich

Schmerzen

- ☐ nie
- ☐ unkonstant und leicht bei starker Belastung
- ☐ beim Wegknicken des Beines
- ☐ bei starker Beanspruchung
- ☐ bei Spaziergängen von 2km und mehr
- ☐ bereits bei Spaziergängen von weniger als 2km
- ☐ permanent und stark

Muskelschwäche des Beines

- ☐ keine
- ☐ gering (Oberschenkelumfang 1-2cm verringert)
- ☐ ausgeprägt (Oberschenkelumfang >2cm verringert)

Tegner Activity Scale

Bitte kreuzen Sie in der untenstehenden Liste die *höchste* Stufe an, in die Sie sich **derzeit** einordnen können.

10. Wettkampfsport ☐
Fussball, nationale und internationale Elite

9. Wettkampfsport ☐
Fussball, niedrige Ligen
Eishockey
Ringen oder Kampfsport
Gymnastik

8. Wettkampfsport ☐
Squash oder Badminton
Leichtathletik (Sprungdisziplinen)
Alpin Ski

7. Wettkampfsport ☐
Tennis
Leichtathletik (Laufdisziplinen)
Motorcross
Handball
Basketball

Freizeitsport ☐
Fussball
Eishockey
Squash
Leichtathletik (Sprungdisziplinen)

6. Freizeitsport ☐
Tennis
Badminton
Leichtathletik (Laufdisziplinen)
Motorcross
Handball
Basketball
Alpin Ski
Jogging (mindestens 5 Mal pro Woche)

5. Arbeit/Beruf ☐
Schwere körperliche Arbeit (z. B. Bauarbeiten, Waldarbeiten, usw.)

Wettkampfsport ☐
Velo oder Mountainbike
Langlauf

Freizeitsport ☐
Jogging auf unebenem Untergrund (mindestens 2 Mal pro Woche)

4. Arbeit/Beruf

Mässig schwere körperliche Arbeit (z. B. Chauffeur, schwere Hausarbeiten, Lagerarbeit, usw.) ☐

Freizeitsport

Rad oder Mountainbike ☐

Langlauf

Jogging auf ebenem Untergrund (mindestens 2 Mal pro Woche)

3. Arbeit/Beruf ☐

Leichte körperliche Arbeit (z. B. Gastronomie, Pflegeberufe, usw.)

Wettkampf- oder Freizeitsport ☐

Schwimmen

Waldspaziergänge (auf unebenem Untergrund) möglich ☐

2. Arbeit/Beruf ☐

Leichte Arbeit (wechselnd Sitzen, Stehen, Laufen und Treppensteigen)

Gehen auf unebenem Untergrund möglich, aber keine Waldspaziergänge ☐

1. Arbeit/Beruf ☐

Sitzende Tätigkeit (z. B. Büro, Callcenter, usw.)

Gehen auf ebenem Untergrund möglich ☐

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