Structural Factors Associated with Malalignment in Knee Osteoarthritis: The Boston Osteoarthritis Knee Study

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ABSTRACT. ***Objective.*** Osteoarthritis (OA) is a multifactorial condition. The progression of knee OA is determined in part by mechanical effects on local structures. One of the mechanical influences on cartilage loss is limb alignment. We explored the structural factors associated with malalignment in subjects with symptomatic OA.

Methods. We conducted a cross-sectional assessment using The Boston Osteoarthritis of the Knee Study, a natural history study of symptomatic knee OA. Baseline assessments included knee magnetic resonance imaging (MRI) and information on weight and height. Long-limb radiographs to assess mechanical alignment were obtained at 15 months. Subarticular bone attrition, meniscal degeneration, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, marginal osteophytes, and cartilage morphology were assessed on MRI using a semiquantitative, multi-feature scoring method (Whole-Organ MRI Score) for whole-organ evaluation of the knee that is applicable to conventional MRI techniques. We also quantified the following meniscal position measures on coronal MRI images in both medial and lateral compartments: subluxation, meniscal height, and meniscal covering of the tibial plateau. Using the long-limb radiographs, mechanical alignment was measured in degrees on a continuous scale. The purpose of this cross-sectional analysis was to determine the individual and relative contribution of various structural factors to alignment of the lower extremity. We assessed the cross-sectional association between various structural factors and alignment of the lower extremity using a linear regression model.

Results. The 162 subjects with all measures acquired had a mean age of 67.0 years (SD 9.2), body mass index 31.4 (SD 5.6); 30% were female and 77% of knees had a Kellgren-Lawrence grade $\geq$ 2. The main univariate determinants of varus alignment in decreasing order of influence were medial bone attrition, medial meniscal degeneration, medial meniscal subluxation, and medial tibiofemoral cartilage loss. Multivariable analysis revealed that medial bone attrition and medial tibiofemoral cartilage loss explained more of the variance in varus malalignment than other variables. The main univariate determinants of valgus malalignment in decreasing order of influence were lateral tibiofemoral cartilage loss, lateral osteophyte score, and lateral meniscal degeneration.

Conclusion. Cartilage loss has been thought to be the major determinant of alignment. We found that other factors including meniscal degeneration and position, bone attrition, osteophytes, and ligament damage contribute to the variance of malalignment. Further longitudinal analysis is required to determine cause and effect relationships. This should assist researchers in determining strategies to ameliorate the potent effects of this mechanical disturbance. (J Rheumatol 2005;32:2192–9)

Key Indexing Terms:
MALALIGNMENT KNEE OSTEOARTHRITIS

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Knee osteoarthritis (OA) is one of the leading causes of disability in elders, and a growing public health concern[1]. OA is a multifactorial condition in which mechanical factors play an important role. The progression of knee OA is determined in part by mechanical effects on local structures. One of the mechanical influences on cartilage loss is limb alignment.

Hip-knee-ankle alignment contributes to load distribution across the articular surface, by proportionately dividing load between the medial and lateral compartments. The load-bearing axis is represented by a line drawn from mid-femoral head to mid-ankle. In neutrally aligned limbs, the medial compartment bears 60%–70% of the force across the knee during weight-bearing[2], and, in part because it is subjected to more load than the lateral compartment, OA affects the medial tibiofemoral compartment more often than the lateral[3]. In a varus knee, this line passes medial to the knee and a moment arm is created, which further increases force across the medial compartment. In a valgus knee, the load-bearing axis passes lateral to the knee, and the resulting moment arm increases force across the lateral compartment[4].

Varus and valgus malalignment have been shown to increase the risk of subsequent medial and lateral knee OA structural progression, respectively, on plain radiographs[5]. The effect of malalignment extends beyond its direct effect on cartilage, as it affects other knee tissues such as bone marrow lesions that further propagate OA disease[6]. This process perpetuates a cycle of events that determines, in large part, the rate of structural progression in knee OA. Risk factors for knee OA including obesity, quadriceps strength, laxity, and stage of disease are all mediated by malalignment[5,7-9].

While malalignment appears to be critical in determining disease progression, little is known of factors that contribute to alignment. Certain site-specific factors in the local joint environment such as the tibiofemoral congruence, anterior cruciate ligament (ACL) integrity, and meniscal degeneration and position also govern how load is distributed across the articular cartilage of a given joint. The relative contributions these factors make to alignment is unclear (Figure 1). Cooke, *et al*[10] have suggested that loss of joint space may account for some of the malalignment, but this has not been quantified. Disentangling the factors that determine malalignment may contribute to knowledge about OA pathophysiology and provide insight into therapeutic options. If some of these factors are modifiable, malalignment itself may be addressable. We explored the structural factors associated with alignment in subjects with symptomatic OA. Understanding these correlates of alignment might help us understand the process by which a limb becomes malaligned and help us prevent this prognostically important feature of OA.

MATERIALS AND METHODS

Patients were recruited to participate in a natural history study of symptomatic knee OA, the Boston Osteoarthritis of the Knee Study (BOKS), as described[6]. Briefly, patients were recruited from 2 prospective studies, one in men and one in women, of quality of life among veterans; from clinics at Boston Medical Center in Boston, Massachusetts; and from advertisements in local newspapers. Potential participants were asked 2 questions: "Do you have pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?". For patients who answered yes to both questions, we conducted a followup interview in which we asked about other types of arthritis that could cause knee symptoms. If no other form of arthritis was identified, then the individual was eligible for recruitment. A series of knee radiographs (posteroanterior, lateral, and skyline) was obtained for each patient to determine whether radiographic OA was present. If patients had a definite osteophyte on any view in the symptomatic knee, they were eligible for the study. Because they had frequent knee symptoms and radiographic OA, all patients met American College of Rheumatology criteria for symptomatic knee OA[11].

The study included a baseline and followup examinations at 15 and 30 months. At baseline, patients who did not have contraindications to magnetic resonance imaging (MRI) had an MRI of the more symptomatic knee. This knee was used in this analysis for both MRI measures and alignment measures. Patients were also weighed, with shoes off, on a balance-beam

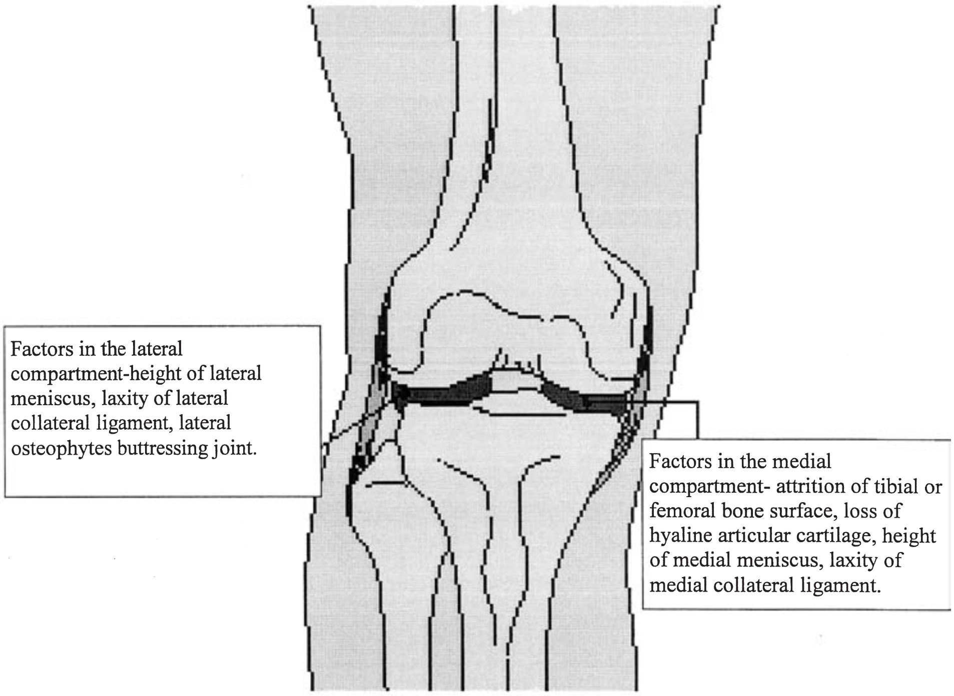

Figure 1. Structural factors that could contribute to the degree of varus malalignment in OA.

scale, and height was assessed. At the first followup visit, long-limb radiographs were obtained with a 14 × 51 cassette, as described[12]. Our study focused on MRI findings as factors that may be associated with alignment in long-limb radiographs.

The institutional review boards of Boston University Medical Center and the Veterans Administration Boston Health Care System approved the examinations.

MRI measurements. All studies were performed with a Signa 1.5 T MRI system (General Electric Medical Systems, Milwaukee, WI, USA) using a phased-array knee coil. A positioning device was used to ensure uniformity among patients. Coronal, sagittal, and axial images were obtained. Fat suppressed fast spin-echo (FSE) proton density and T2 weighted images were obtained (repetition time 2200 ms; echo time 20/80 ms), with a slice thickness of 3 mm, a 1 mm interslice gap, one excitation, a field of view of 11 to 12 cm, and a matrix of 256 × 128 pixels.

Subarticular bone attrition, meniscal degeneration, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, marginal osteophytes, and cartilage morphology were assessed using a semiquantitative, multi-feature scoring method, the Whole-Organ Magnetic Resonance Imaging Score (WORMS), for whole-organ evaluation of the knee that is applicable to conventional MRI techniques[13]. Three of the features examined (cartilage morphology, subarticular bone attrition, and marginal osteophytes) are related to the articular surfaces. These features were evaluated in 14 different regions subdivided by anatomical landmarks in the fully extended knee.

Cartilage morphology. Cartilage morphology was scored in each of the 14 articular surface regions (excluding region S) using fat-suppressed fast spin-echo proton density and T2 weighted images with a 7 point scale: 0 = normal thickness and signal; 1 = normal thickness but increased signal intensity on proton density and T2 weighted images; 2.0 = partial-thickness focal defect < 1 cm in greatest width; 3.0 = multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but < 75% of the region; 4 = diffuse (≥ 75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but < 75% of the region; 6 = diffuse (≥ 75% of the region) full-thickness loss.

Flattening or depression of the articular surfaces was termed bone attrition and graded from 0 to 3 based on the subjective degree of deviation from the normal contour: 0 = normal; 1 = mild; 2 = moderate; 3 = severe.

Osteophytes along the anterior (a), central weight-bearing (c), and posterior (p) margins of the femoral condyles and tibial plateaus were graded from 0 to 7 using the following scale: 0 = none; 1 = equivocal; 2 = small; 3 = small-moderate; 4 = moderate; 5 = moderate-large; 6 = large; 7 = very large. For the purposes of this analysis we considered only the osteophytes in the central weight-bearing portion of both the femoral condyles and tibial plateaus.

The anterior cruciate ligament and posterior cruciate ligament (PCL) were independently scored as intact (0) or torn/deficient (1) using the sagittal images. The medial collateral ligament (MCL) and lateral collateral ligament (LCL) were independently scored as intact (0) or thickened/torn (1) using the coronal images.

The anterior horn, body segment, and posterior horn of the medial and lateral menisci were graded for meniscal degeneration separately from 0 to 4 based on both sagittal and coronal images: 0 = intact; 1 = minor radial tear or parrot-beak tear; 2 = nondisplaced tear or prior surgical repair; 3 = displaced tear or partial resection; and 4 = complete maceration/destruction or complete resection.

For intraobserver agreement for reading these lesions, the kappa value ranged from 0.56 to 0.97. We defined a lesion as occurring in either the medial or lateral compartment if it was present in the femur or tibia of that compartment.

Using coronal MRI and EFilm workstation software, we measured the following meniscal position measures to the nearest millimeter in both medial and lateral compartments: subluxation, meniscal height, and meniscal covering and uncovering of the tibial plateau (Figure 2). This was measured on the mid-tibial slice in the coronal plane. Proportion of coverage was defined as (meniscal covering)/(meniscal covering + meniscal uncovering). A meniscus that was completely macerated or destroyed did not generate a measure of subluxation and was considered as missing data. Interobserver reliability (intraclass correlation coefficient, ICC) for reading these measures ranged from 0.86 to 0.93.

Mechanical alignment. Mechanical alignment, assessed at the first followup examination, was measured in degrees on a continuous scale from the long-limb radiograph. For interobserver agreement for reading alignment, the ICC was 0.97 ($p < 0.001$).

Statistical analysis. The purpose of this cross-sectional analysis was to determine the individual and relative contribution of various structural factors to alignment of the lower extremity. The dependent variable was mechanical alignment on the long-limb radiograph, with values < 0 defined as representing valgus alignment and values ≥ 0 representing varus alignment. The independent variables were the MRI scores for cartilage morphology; meniscal degeneration; central weight-bearing osteophytes from femoral condyles and tibial plateau; bone attrition; ACL, PCL, MCL and LCL integrity; and meniscal position measures. For this analysis MRI measures were conducted on one knee per person. This is the knee for which alignment measures are used for this analysis. The analysis consisted of 2 steps — the first univariate, to determine the contribution of each individual factor, and the second multivariable, to gain a sense of the relative contribution of each.

We conducted separate analyses of varus and valgus limbs. For each, we conducted a univariate regression analysis to determine the contribution of each predictor to valgus (excluding varus knees, i.e., < 0°) and to varus (excluding valgus knees) alignment. The variance of mechanical alignment on the long-limb radiograph explained by each independent variable was estimated from partial correlation coefficients for each regression model, adjusting for age, body mass index (BMI), and sex.

We also calculated the relative percentage of variance explained by each independent variable using the partial R^2 (correlation coefficient^2) divided by the variance explained by the regression model. The analyses were performed for valgus knees (excluding varus knees) and varus knees (excluding valgus knees), respectively.

We did this by stepwise backward elimination of variables with a p value > 0.1 and forced inclusion of age, sex, and BMI. To provide an estimate of the correlation of the individual variables we also examined this for the medial tibiofemoral joint.

RESULTS

The characteristics of the study population are presented in Table 1. They were predominantly male, reflecting the Veterans Affairs population from which many of them were drawn, and the majority had radiographic knee OA, with Kellgren-Lawrence grade ≥ 2. The distribution of alignment from this sample is presented in Figure 3.

The association of each individual MRI feature and degree of varus malalignment adjusted for age, sex, and BMI is presented in Table 2. The main determinants in decreasing order of influence were medial bone attrition, medial meniscal degeneration, medial meniscal subluxation, and medial tibiofemoral cartilage loss. Multivariable analysis revealed that medial bone attrition and medial tibiofemoral cartilage loss had the most important contribution to variability in varus malalignment (Table 4).

Table 4 shows the association of each individual MRI feature and degree of valgus malalignment adjusted for age, sex, and BMI. The main determinants in decreasing order of influence were lateral tibiofemoral cartilage loss, lateral

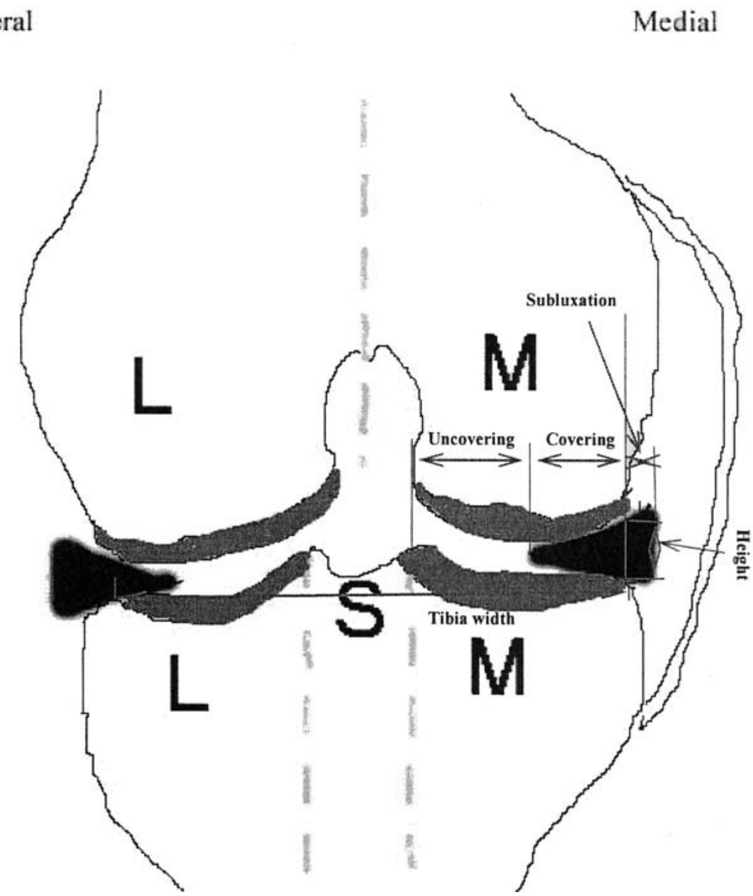

Figure 2. Meniscal position measurements taken on coronal MRI.

osteophyte score, and lateral meniscal degeneration. However, given the small number of subjects in this analysis, we did not perform the multivariate regression analysis because of concern for unstable estimates.

Findings in structures in the medial tibiofemoral joint were highly correlated (Table 5). These need to be considered when interpreting the results of both the univariate and multivariate analyses.

DISCUSSION

This study quantifies structural factors associated with both varus and valgus malalignment. Previously, cartilage loss was thought to be the major determinant of alignment[10]. In this cross-sectional study we found that other factors in addition to cartilage loss including meniscal degeneration and position, bone attrition, osteophytes, and ligament damage are associated with the variance of malalignment.

Malalignment has been shown to be one of the most potent determinants of OA progression on plain radiographs[5]. To date, however, the structural factors that contribute to malalignment had not been quantified, and as a result, our understanding of the etiopathogenesis of this important risk factor has remained unclear. This study assists in clarifying that not only cartilage contributes to the extent of malalignment, but that other structural features, in particular the meniscus, ligaments, and subchondral bone, play important roles. Our study indicates that increasing structural damage within the articular structure of the knee perpetuates a cycle of events by being associated with more malalignment. Many of the factors that contributed to malalignment in this study will likely progress more rapidly as a result of increasing malalignment. Cooke, *et al*[10] have suggested that loss of joint space may account for some of the malalignment, but this was not quantified. We have not considered other data included in Cooke's analysis from standardized radiography of hips and knees, including condylar-hip angle, tibial plateau-ankle angle, and joint surface (condylar-plateau) angle.

As shown in Table 5, many of the factors we investigated are highly correlated. OA affects multiple tissues in the knee organ, and the MRI features we investigated reflect this. As one morphologic feature becomes more severely affected, other features become similarly more affected. The influence of these high correlations needs to be considered

Table 1. Characteristics of participants in the study (n = 132).

Age, mean ± SD (range), yrs	66.5 (9.7)
Sex (male %)	55.8
BMI, mean ± SD	30.2 (4.4)
K-L grade ≥ 2, %	73.5
Meniscal subluxation variables, mean (SD)	
Medial meniscus	
Subluxation, mm	4.5 (2.4)
Proportion of coverage, %	0.19 (0.18)
Height, mm	2.7 (1.9)
Lateral meniscus	
Subluxation, mm	1.7 (2.1)
Proportion of coverage, %	0.29 (0.15)
Height, mm	5.1 (2.7)
WORMS variables, mean (SD)	
Cartilage score	
Medial tibiofemoral joint (possible range 0–6)	3.1 (2.0)
Lateral tibiofemoral joint (possible range 0–6)	1.7 (1.9)
Bone attrition	
Medial tibiofemoral joint (possible range 0–3)	0.3 (0.5)
Lateral tibiofemoral joint (possible range 0–3)	0.1 (0.4)
Central weight bearing osteophytes	
Medial tibiofemoral joint (possible range 0–7)	1.6 (1.5)
Lateral tibiofemoral joint (possible range 0–7)	1.8 (1.5)
Meniscal degeneration	
Medial tibiofemoral joint (possible range 0–3)	1.3 (1.6)
Lateral tibiofemoral joint (possible range 0–3)	0.6 (1.3)
ACL deficient, %	20.5
PCL deficient, %	2.3
MCL thickened/deficient, %	16.6
Mechanical alignment: mean (SD) [range]	2.5 (5.2) [–11 to 19]

BMI: body mass index, K-L: Kellgren-Lawrence grade, WORMS: Whole-Organ Magnetic Resonance Imaging Score, ACL: anterior cruciate ligament, PCL: posterior cruciate ligament, MCL: medial collateral ligament.

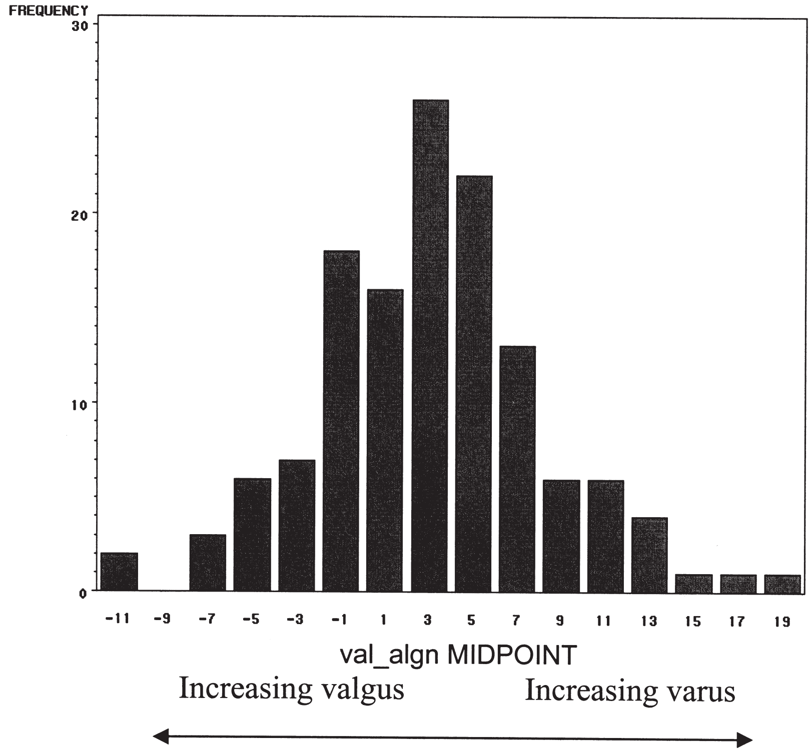

Figure 3. Distribution of alignment (n = 132).

Table 2. Factors associated with varus malalignment: univariate analyses (n = 96).

	Adjusted* R^2	F Test	p	Partial R^2
Medial meniscus				
Subluxation	0.38	22.78	< 0.0001	0.35
Proportion of coverage	0.21	10.76	< 0.0001	0.18
Height	0.23	11.57	< 0.0001	0.21
Lateral meniscus				
Subluxation	0.06	3.33	0.01	0.02
Proportion of coverage	0.06	3.45	0.01	0.03
Height	0.04	2.62	0.04	0.00
Cartilage score				
Medial tibiofemoral joint	0.37	22.88	< 0.0001	0.34
Lateral tibiofemoral joint	0.05	3.16	0.02	0.02
Bone attrition				
Medial tibiofemoral joint	0.53	45.11	< 0.0001	0.51
Lateral tibiofemoral joint	0.05	3.25	0.01	0.01
Central weight-bearing osteophytes				
Medial tibiofemoral joint	0.34	21.35	< 0.0001	0.31
Lateral tibiofemoral joint	0.26	14.53	< 0.0001	0.22
Meniscal degeneration				
Medial tibiofemoral joint	0.39	25.79	< 0.0001	0.36
Lateral tibiofemoral joint	0.05	3.02	0.02	0.00
ACL	0.22	11.68	< 0.0001	0.18
PCL	0.12	6.21	0.0001	0.08
MCL	0.17	8.93	< 0.0001	0.13
LCL	0.07	3.72	0.01	0.02

* Adjusted for age, sex, and BMI. ACL: anterior cruciate ligament, PCL: posterior cruciate ligament, MCL: medial collateral ligament, LCL: lateral collateral ligament.

Table 3. Factors associated with varus malalignment: multivariable analysis (n = 96).

Model	Adjusted*		
	F Test	p	Adjusted R^2
Model	20.0	< 0.0001	0.50
	% of variance (from partial R^2) in model explained by		
Cartilage score			
Medial tibiofemoral joint	27.0		
Bone attrition			
Medial tibiofemoral joint	50.4		
Age	2.9		
Sex	6.6		
BMI	1.4		

* Adjusted for age, sex, BMI.

when contemplating the results of the multivariate analysis. In the univariate analyses, menisci, osteophytes, and ligaments were all important contributors. However, in the multivariate analyses (likely because they are highly correlated with cartilage morphology and bone attrition), menisci, osteophytes, and ligaments are not, and the remaining factors in the model are cartilage morphology and bone attrition.

Our study has a number of limitations that may impair interpretation of the findings. The main concern is that this is a cross-sectional analysis attempting to interpret a dynamic longitudinal process. However, until longitudinal assessments of malalignment and the factors that contribute to it have been conducted, a longitudinal analysis will be impossible. The structural factors that are associated with malalignment are highly correlated and their respective individual contributions are therefore difficult to identify. In addition, we did not have enough numbers of valgus aligned limbs to evaluate this comprehensively. The long-limb radiographs were obtained 15 months after the MRI. It is unknown what changes in alignment or MRI might have occurred during that interval. This requires further longitudinal assessment. It would have been helpful to be able to assess similar parameters in a population of persons not affected by knee OA, to better understand the effects of aging, BMI, sex, etc., in the normal joint. The study design did not permit this. In addition, meniscal position measures being classified as missing when the meniscus degeneration variable is macerated may underestimate the influence of this variable.

We observed that the variability in alignment is associated with a number of structural features including cartilage, meniscus, ligaments, and subchondral bone. Further longitudinal analysis is required to determine cause and effect relationships. This should assist researchers in determining strategies to ameliorate the potent effects of this mechanical disturbance.

Table 4. Factors associated with valgus malalignment: univariate analyses (n = 36).

	Adjusted* R^2	F Test	p	Partial R^2
Medial meniscus				
Subluxation	0.06	1.69	0.17	0.01
Proportion of coverage	0.07	1.91	0.13	0.04
Height	0.11	2.35	0.07	0.06
Lateral meniscus				
Subluxation	0.20	3.75	0.01	0.18
Proportion of coverage	0.09	2.09	0.09	0.06
Height	0.07	1.82	0.14	0.03
Cartilage score				
Medial tibiofemoral joint	0.13	2.65	0.05	0.09
Lateral tibiofemoral joint	0.26	5.04	0.002	0.23
Bone attrition				
Medial tibiofemoral joint	0.06	1.70	0.17	0.00
Lateral tibiofemoral joint	0.16	3.28	0.02	0.11
Central weight-bearing osteophytes				
Medial tibiofemoral joint	0.07	1.91	0.13	0.02
Lateral tibiofemoral joint	0.24	4.69	0.003	0.19
Meniscal degeneration				
Medial tibiofemoral joint	0.05	1.66	0.17	0.00
Lateral tibiofemoral joint	0.23	4.63	0.003	0.19
ACL	0.05	1.68	0.17	0.00
PCL	0.07	2.26	0.09	0.00
MCL	0.20	4.01	0.007	0.16
LCL	0.07	1.83	0.14	0.01

* Adjusted for age, sex, and BMI. ACL: anterior cruciate ligament, PCL: posterior cruciate ligament, MCL: medial collateral ligament, LCL: lateral collateral ligament.

Table 5. Pearson correlation coefficient of structural features from medial tibiofemoral joint. Data are Pearson correlation coefficient followed by p value.

	Meniscal Subluxation	Proportion of Coverage	Meniscal Height	Cartilage Score	Bone Attrition	Central Weight-bearing Osteophytes	Meniscal Degeneration	ACL
Meniscal		–0.54	–0.67	0.55	0.54	0.57	0.58	0.51
subluxation		< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Proportion			0.74	–0.64	–0.46	–0.54	–0.62	–0.34
of coverage			< 0.0001	< 0.0001	0.0002	< 0.0001	< 0.0001	0.008
Meniscal				–0.58	–0.55	–0.63	–0.72	–0.39
height				< 0.0001	< 0.0001	< 0.0001	< 0.0001	0.002
Cartilage					0.62	0.63	0.74	0.45
score					< 0.0001	< 0.0001	< 0.0001	0.0004
Bone attrition						0.76	0.71	0.47
						< 0.0001	< 0.0001	0.0001
Central weight-							0.68	0.39
bearing osteophytes							< 0.0001	0.002
Meniscal								0.61
degeneration								< 0.0001
ACL								

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