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The Role of Varus and Valgus Alignment in the Initial Development of Knee Cartilage Damage by MRI: the MOST Study

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Abstract

Objective—Varus and valgus alignment are associated with progression of knee osteoarthritis, but their role in incident disease is less certain. Radiographic measures of incident knee osteoarthritis may be capturing early progression rather than disease development. We tested the hypothesis: in knees with normal cartilage morphology by MRI, varus is associated with incident medial cartilage damage and valgus with incident lateral damage.

Methods—In MOST, a prospective study of persons at risk for or with knee osteoarthritis, baseline full-limb x-rays and baseline and 30-month MRIs were acquired. In knees with normal baseline cartilage morphology in all tibiofemoral subregions, we used logistic regression with GEE to examine the association between alignment and incident cartilage damage adjusting for age, gender, BMI, laxity, meniscal tear, and extrusion.

Results—Of 1881 knees, 293 from 256 persons met criteria. Varus vs. non-varus was associated with incident medial damage (adjusted OR 3.59, 95% CI: 1.59, 8.10), as was varus vs. neutral, with evidence of a dose effect (adjusted OR 1.38/1° varus, 95% CI: 1.19, 1.59). Findings held even excluding knees with medial meniscal damage. Valgus was not associated with incident lateral damage. Varus and valgus were associated with a reduced risk of incident lateral and medial damage, respectively.

Conclusion—In knees with normal cartilage morphology, varus was associated with incident cartilage damage in the medial compartment, and varus and valgus with a reduced risk of incident

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damage in the less loaded compartment. These results support that varus increases the risk for initial development of knee osteoarthritis.

INTRODUCTION

In persons with established knee osteoarthritis (OA), varus alignment is associated with subsequent progression of medial tibiofemoral OA and valgus with progression of lateral OA (1–6). Varus alignment has also been found to be associated with *incident* radiographic knee OA in the two cohort studies evaluating this (4, 6) but not in a case-control study (7); the association between valgus alignment and incident radiographic OA was borderline (4) or not evident (6). The role of alignment in the initial development of knee OA is less certain, in large part due to inherent limitations of radiography to define incident OA.

The established radiographic definition of incident knee OA [Kellgren/Lawrence (K/L) grade 2, presence of definite osteophytes] cannot fully capture the magnitude of the effect of a risk factor like varus alignment, that potentially stresses one compartment (medial tibiofemoral) while off-loading the other (lateral) compartment. Osteophyte development is an early but not compartment-specific event in OA; this definition cannot distinguish incident medial vs. lateral OA. Also, radiography is insensitive to early cartilage damage. Cartilage damage may already be present in knees defined as “at risk” for incident radiographic OA, i.e., knees graded K/L 0 or 1 (8), particularly in individuals at higher risk for developing knee OA, begging the question: does a radiographic measure of incident knee OA capture initial development of disease or worsening of early, established disease? In contrast to radiography, MRI allows identification of knees that are free of any cartilage damage at baseline for prospective study *and* provides a compartment-specific outcome measure.

The load-bearing axis, femoral head center to ankle joint center, passes medial to knee center in a varus knee, increasing force across the medial compartment and lateral to knee center in a valgus knee, increasing force across the lateral compartment. In a healthy knee during normal gait, load distribution is not equal between medial and lateral compartments: 70% of load passes through the medial compartment, primarily due to an external knee adduction moment (9, 10). With greater varus, the proportion of load distributed medially increases further (11, 12). With greater valgus, load distribution shifts from greater medial, to equal, to greater lateral (with more severe valgus) (13–15). It is likely that in a healthy knee, the mechanical impact of varus on the medial compartment exceeds that of valgus on the lateral compartment.

We identified knees with normal cartilage morphology by MRI in all tibial and femoral subregions at baseline to test the hypothesis: varus alignment is associated with incident medial cartilage damage and valgus alignment is associated with incident lateral damage.

METHODS

Sample

MOST is an observational cohort study of incident and progressive knee OA in community-dwelling individuals (Iowa City and Birmingham), ages 50–79 years, recruited via mailings and community outreach. Participants were required to have symptomatic knee OA or characteristics that placed them at increased risk for developing it (16). Exclusion criteria were: bilateral knee replacement or plan for this within a year; inability to walk without another person or walker; serious health condition; inflammatory arthritis; dialysis; malignancy; plan to move away. The study protocol was approved by each site’s institutional review board. All participants provided written, informed consent.

Measurement of Varus-Valgus Alignment, Laxity, Weight, and Height

Alignment was assessed from baseline full-limb radiographs, acquired as previously described (1). One AP radiograph of both limbs was obtained, using a 51×14 inch graduated grid cassette (Iowa City) and a CR-based system of overlapping cassettes and simultaneously exposed subimages forming a stitched image (Birmingham).

Alignment (hip-knee-ankle angle) was measured as the angle at the intersection of lines: connecting femoral head and intercondylar notch centers; and connecting ankle talar surface center and tibial interspinous sulcus base. Image analysis (17) was completed by one of three trained readers using a customized program (Surveyor 3 OASYS Inc., Kingston, Ontario), blinded to all other data. In a reliability study of 200 full-limb pairs assessed by these three readers, the inter- and intra-reader ICCs were 0.95 and 0.96 (18). In analyses, varus was defined as 178° , valgus as 182° , and neutral as $179\text{--}181^\circ$.

Weight (kg) without shoes or heavy clothes or jewelry was measured on a standard balance beam scale and height without shoes at peak of inhalation using a Harpenden stadiometer (Holtain, Pembrokeshire, UK). Body mass index (BMI) was calculated as weight in kg divided by height in m^2 . Medial-lateral laxity ($^\circ$) was measured using a protocol and device previously described (19), consisting of a bench and arc-shaped track, and providing thigh and ankle immobilization, a stable knee flexion angle, and fixed medial and lateral load.

Knee X-Ray Acquisition and Assessment

Knee radiographs were acquired using the PA fixed-flexion weight-bearing protocol (20), with knees flexed to $20\text{--}30^\circ$ and feet internally rotated 10° using a plexiglass positioning frame (SynaFlexer™). Knees were imaged together on 14×17 film with a 72 inch film-to-focus distance. An experienced rheumatologist and musculoskeletal radiologist independently assessed each film for K/L grade. Disagreement was adjudicated by a panel of three readers. Weighted kappa for agreement between the readers was 0.79 for K/L grade.

MRI Acquisition and Measurements

At baseline and 30-month follow-up, bilateral knee MR images were obtained with a 1.0-T dedicated system (ONI MSK Extreme, GE Healthcare, Waukesha, WI) with a circumferential extremity coil by using fat-suppressed fast spin-echo intermediate-weighted sequences in the sagittal (repetition time msec/echo time msec, 4800/35; section thickness, 3 mm; intersection gap, 0 mm; sections, 32; matrix, 288×192 ; signals acquired, two; field of view, 140 mm^2 ; echo train length, eight) and axial (4680/13; section thickness, 3 mm; intersection gap, 0 mm; sections, 20; matrix, 288×192 ; signals acquired, two; field of view, 140 mm^2 ; echo train length, eight) planes and a short tau inversion recovery (STIR) sequence in the coronal plane (6650/15; inversion time, 100 msec; section thickness, 3 mm; intersection gap, 0 mm; sections, 28; matrix, 256×192 ; signals acquired, two; field of view, 140 mm^2 ; echo train length, eight).

Two musculoskeletal radiologists (FR and AG), blinded to all other data, evaluated the images using the Whole-Organ MRI Score (WORMS) (21). Paired baseline and follow-up images were read, with chronological order known (22). Cartilage signal intensity and morphology were scored according to WORMS from 0 to 6 (depending upon depth and extent of cartilage loss) in five subregions each in the medial and lateral tibiofemoral compartments, for a total of 10 tibiofemoral subregions. Meniscal status was graded from 0 to 4 in the anterior horn, body, and posterior horn of each meniscus, defining tear as a WORMS score >0 in 1 segment. In addition to the WORMS, extrusion of each meniscal body was scored on the coronal image as 0 to 2, defining extrusion as a score >0 (23).

Definition of Outcome—While MRI to score cartilage damage has been extensively validated, the best definition(s) of outcome in knee OA has not been established. The transition essential to our hypothesis, which deals with the initial development of cartilage damage, was from normal to the lowest score with an unequivocal cartilage lesion. All knees in the analysis sample had a cartilage score of 0 (normal cartilage signal intensity and morphology) in all tibiofemoral subregions at baseline. Incident medial cartilage damage was defined as the development of a cartilage morphology score ≥ 2 (2 = solitary partial thickness defect) in ≥ 1 medial subregion by 30 months. Incident lateral cartilage damage was defined as the development of a cartilage morphology score ≥ 2 in ≥ 1 lateral subregion by 30 months.

Statistical Analysis

The analysis sample included only knees with normal baseline tibiofemoral cartilage signal intensity and morphology in both the medial and lateral tibiofemoral compartments (as defined above). All statistical analyses were knee-based. Logistic regression models with generalized estimating equations (GEE) were used to account for potentially correlated observations between knees from the same person. Using these models, we examined the association between baseline alignment in each knee and subsequent development of incident cartilage damage at 30 months (as defined above).

Inferences from the analyses were based on the following three model-based comparisons for the outcome of incident medial cartilage damage by 30 months: 1) varus knees vs. all other knees (or non-varus) as reference; 2) varus knees vs. neutral knees as reference; and 3) varus alignment considered as a continuous variable in the models. A similar model-based approach was used to evaluate the association of valgus alignment and incident lateral cartilage damage.

All analyses were adjusted for age (continuous), gender, BMI (continuous), and laxity (continuous), and then further adjusted for meniscal tear and extrusion (in the compartment of interest). Results from each model are reported as adjusted odds ratios (ORs) with associated 95% confidence intervals (CIs); a 95% CI that excludes 1 represents a statistically significant association. In secondary analyses, severity of varus and valgus alignment were each analyzed as continuous variables. Because the knees with MRI data were a subset of all knees from persons enrolled in MOST, we also conducted sensitivity analyses to address the potential for selection bias due to the MOST substudy sampling mechanisms (that included several case-control and cohort samples to address specific research questions). In these sensitivity analyses, we excluded MOST substudies that selected knees for MRI reading based upon criteria that may have been linked to either alignment or to our outcome, i.e., we excluded the knees from case-control studies of incident radiographic knee OA and incident knee symptoms. Analyses were performed using SAS software version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

As shown in Figure 1, by the 30-month follow-up, of the 3026 persons enrolled, 33 had died, 24 could not be reached, and 2969 were reached by phone, of whom 2713 completed the visit. Reasons for not completing the 30-month visit were: too busy, 77 persons; health problems, 70; caregiving responsibilities, 31; deceased, 30; clinic distance, 21; had moved, 20; study dissatisfaction, 19; unable to contact, 16; refused to give reason, 8; personal problems, 7; and other reasons, 14. Those not completing the 30-month visit did not differ in age, gender, or dominant knee alignment distribution (32% neutral, 47% varus, 21% valgus) but had a higher BMI [32.0 ± 6.9 (SD) vs. 30.6 ± 5.8] than those who completed this visit.

The steps to derive the analysis sample, 293 knees (from 256 persons) without any cartilage damage in any tibiofemoral subregion at baseline, are delineated in Figure 1.

The 256 persons had a mean age of 60.0 years (± 7.5), a mean BMI of 28.6 kg/m² (± 4.5), and included 172 (67.2%) women. Eighty-two (32.0%) of the 256 had a BMI ≥ 30 kg/m². Of the 293 knees (258 K/L 0, 25 K/L 1, and 10 K/L 2), 128 (43.7%) were neutral, 110 (37.5%) were varus, and 55 (18.8%) were valgus. Knee characteristics stratified by alignment are shown in Table 1.

The distribution of 30-month outcomes by baseline alignment category is shown in Figure 2. As shown in Table 2, varus vs. non-varus was associated with incident medial cartilage damage (adjusted OR 3.59, 95% CI: 1.59, 8.10). Varus vs. *neutral* alignment was also associated with incident medial damage. Greater varus was associated with incident medial damage (adjusted OR 1.38/1° varus, 95% CI: 1.19, 1.59). Sensitivity analyses yielded similar results, i.e., adjusted effect estimates that ranged from within 1% to within 8% of the effect estimates from the fully adjusted analyses provided in the furthest right column of Table 2. As shown in Table 3, neither valgus vs. non-valgus nor valgus vs. neutral was associated with incident lateral damage. Greater valgus was associated with the outcome, but this was not significant after adjustment for meniscal tear and extrusion. Varus was associated with a reduced risk of incident damage in the off-loaded, lateral compartment (adjusted OR 0.75/1°, 95% CI: 0.59, 0.95) and valgus with a reduced risk of incident medial damage (adjusted OR 0.72/1°, 95% CI: 0.63, 0.83). Results of the fully adjusted models of Tables 2 and 3 were minimally altered by adjusting for baseline-to-30-month change in BMI.

To explore whether an alignment effect requires existing meniscal damage, we repeated these analyses in knees without meniscal tear or extrusion. Excluding knees with baseline medial meniscal tear or extrusion left 205 knees (78 varus, 40 valgus, 87 neutral), of which 16 (7.8%) had incident medial cartilage damage by 30 months. In these 205 knees, greater varus was associated with incident medial cartilage damage, adjusting for age, gender, BMI, and lateral laxity (adjusted OR 1.37/1° varus, 95% CI: 1.11, 1.68). Excluding knees with baseline lateral meniscal tear or extrusion left 274 knees (107 varus, 49 valgus, 118 neutral), 10 (3.6%) with incident lateral damage. In these 274 knees, greater valgus was not associated with incident lateral damage (adjusted OR 1.14/1° valgus, 95% CI: 0.89, 1.46).

DISCUSSION

In knees without MRI evidence of cartilage damage in any tibiofemoral subregion, varus alignment at baseline was associated with an increased risk of incident medial tibiofemoral cartilage damage over the subsequent 30 months, whether compared to knees without varus alignment as a whole or specifically to neutral knees. Greater varus angle was associated with a greater risk of incident medial damage and a reduced risk of incident lateral damage. Valgus was not associated with an increased risk of lateral tibiofemoral cartilage damage, compared either to knees without valgus as a whole or to neutral knees. Greater valgus angle was not associated with a greater risk of incident lateral damage but was associated with a reduced risk of incident medial damage.

Previous studies of osteoarthritic knees support a relationship between varus and subsequent medial progression and between valgus and lateral progression, using radiographic and MRI outcome measures (1–6). However, a key question has not as yet been addressed: does varus or valgus alignment *preceding* OA influence the risk of OA development? Radiographic studies employing the established definition of incident OA (i.e., new development of K/L 2 in knees K/L 0 or 1 at baseline) cannot answer this question, as K/L 0–1 knees may

already have OA, given the insensitivity of x-ray to early disease (8). The possibility that a K/L 0 or 1 knee has cartilage damage may be greater in persons at higher risk for OA (such as in MOST or the Osteoarthritis Initiative) than in the general population. MRI affords an excellent means of identifying knees with normal cartilage morphology at baseline. Only knees with normal cartilage morphology in every tibiofemoral subregion at baseline, both medial and lateral, were eligible for this study. This approach provided an outcome measure to capture the initial development of cartilage damage, the transition at the core of the difficult question about the impact of alignment preceding OA. With only two time points, it was not possible for us to evaluate whether any alignment effect on subsequent cartilage damage is via changes to other tissues such as subchondral bone or synovium, an interesting question for future longer follow-up studies.

These results, an association of varus with increased risk of incident medial cartilage damage and a reduced risk of lateral damage, support that the mechanism of action of varus relates to load distribution. The low frequency of valgus and of incident lateral damage in the current study reduced our power to detect their relationship. On the other hand, a stronger finding for varus than for valgus is not surprising. Due to a stance phase knee adduction moment, greater load passes medially than laterally even in neutral, healthy knees (9, 10). The adduction moment magnitude increases as varus increases (11). Adduction moment magnitude predicted knee OA progression (24); it may lie in the causal pathway between varus and knee OA progression. Varus further increases total load passing medially (11, 12). Although valgus alignment is associated with an increase in lateral compartment peak pressures (13), more load is still borne medially until more severe valgus is present (14, 15). In keeping with a less potent effect of valgus, cohort studies have found that varus but not valgus (vs. neutral) increased risk of incident radiographic OA (4, 6).

Our study has limitations. Individuals in the MOST cohort without knee OA were at higher risk to develop it. However, the population at higher risk to develop knee OA is of public health importance and the deliberate focus of the MOST study design (16). The size of this group, already large, will grow as the aging segment expands, and it is essential to understand the impact of alignment in them. The MOST substudy sampling design to select knees for MRI reading may limit generalizability to the entire MOST cohort; however, our sensitivity analyses did not reveal evidence of bias in our findings. As noted above, the numbers of valgus knees and knees with incident lateral cartilage damage were low. Of note, image data from nearly 2000 knees were required to derive the eligible knees. To address the questions posed, it was essential to adhere to strict criteria regarding baseline cartilage morphology.

These results are not solely of academic importance. The source of malalignment predating knee OA may be genetic, developmental, or traumatic. In an individual with a varus knee, it is possible that an intervention which improves medial to lateral load distribution could help to delay the onset of OA; at this early point, such a strategy may be more powerful than when OA has established its presence in a knee. These results point to the importance of continuing to develop, refine, and test non-invasive, simple, and inexpensive interventions (e.g., orthoses, gait modifications) for varus knees.

In conclusion, in knees without MRI evidence of cartilage damage in any tibiofemoral subregion, varus alignment at baseline was associated with an increased risk of new cartilage damage in medial subregions over the subsequent 30 months, whether compared to knees without varus or specifically to neutral knees. A dose effect was present, whereby greater varus angulation was associated with a greater risk of incident medial damage and a reduced risk of incident lateral damage. These results suggest that varus alignment is a risk

factor for incident cartilage damage and provide further evidence that varus alignment increases the risk of the initial development of knee OA.

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Figure 1. Derivation of the Analysis Sample of 293 Knees

Figure 2. Distribution of 30-month Outcomes by Baseline Alignment Category (n = 293 knees)

The percent above each bar represents the percentage of knees within a given alignment category. Among the 293 knees, 34 (11.6%) knees from 33 persons had incident medial cartilage damage (in one subregion only in 21 knees, 2 subregions in 6 knees, and 3 subregions in 7 knees), and 15 (5.1%) knees from 15 persons had incident lateral damage (in one subregion in 11 knees, in 2 subregions in 3 knees, and in 3 subregions in 1 knee). Among the 128 neutral knees, 10.9% and 6.3% had incident medial and lateral damage, respectively. Among the 110 varus knees, 18.2% and 2.7% had incident medial and lateral damage. Among the 55 valgus knees, 0% and 7.3% had incident medial and lateral damage.

Table 1
Characteristics of Knees without Cartilage Damage (n = 293 knees from 256 persons)

The table includes characteristics of knees comprising the analysis sample without any cartilage defect in any tibial or femoral subregion at baseline.

	Neutral alignment 128/293 knees (43.7%)	Varus alignment 110/293 knees (37.5%)	Valgus alignment 55/293 knees (18.8%)
Medial laxity, mean (S.D.), °	1.9 (1.3)	1.6 (1.3)	1.2 (1.3)
Lateral laxity, mean (S.D.), °	2.2 (1.5)	1.8 (1.4)	1.5 (1.4)
Medial meniscal tear, % *	12.5%	13.6%	3.6%
Lateral meniscal tear, % *	4.7%	1.8%	5.5%
Medial meniscal extrusion, % *	24.2%	22.7%	25.5%
Lateral meniscal extrusion, % *	3.9%	2.7%	10.9%

* Value represents % of knees in the alignment category of each column with the given lesion

Table 2
Varus Alignment (Baseline) and Incident Medial Cartilage Defect (Outcome Variable)
between Baseline and 30-Month Follow-up (n = 293 knees with normal cartilage
morphology at baseline)

Alignment	# knees without any cartilage damage at baseline (293 knees)	# (row %) knees with incident medial cartilage damage at 30 months (34 knees, 11.6%)	OR (95%CI) adjusted for age, gender, BMI, lateral laxity	OR (95%CI) adjusted for age, gender, BMI, lateral laxity, medial meniscal tear, medial meniscal extrusion
Non-varus (reference)	183	14 (7.7%)	reference	reference
Varus	110	20 (18.2%)	3.53 (1.61, 7.76)	3.59 (1.59, 8.10)
Neutral (reference)	128	14 (10.9%)	reference	reference
Varus	110	20 (18.2%)	2.32 (1.07, 5.05)	2.42 (1.08, 5.44)
Varus (continuous), OR per 1° of greater varus	293	--	1.40 (1.21, 1.61)	1.38 (1.19, 1.59)

Table 3
Valgus Alignment (Baseline) and Incident Lateral Cartilage Defect (Outcome Variable)
between Baseline and 30-Month Follow-up (n = 293 knees with normal cartilage
morphology at baseline)

Alignment	# knees without any cartilage damage at baseline (293 knees)	# (row %) knees with incident lateral cartilage damage at 30 months (15 knees, 5.1%)	OR (95%CI) adjusted for age, gender, BMI, medial laxity	OR (95%CI) adjusted for age, gender, BMI, medial laxity, lateral meniscal tear, lateral meniscal extrusion
Non-valgus (reference)	238	11 (4.6%)	reference	reference
Valgus	55	4 (7.3%)	1.49 (0.40, 5.50)	0.97 (0.26, 3.70)
Neutral (reference)	128	8 (6.3%)	reference	reference
Valgus	55	4 (7.3%)	0.97 (0.25, 3.83)	0.62 (0.14, 2.77)
Valgus (continuous), OR per 1° of greater valgus	293	--	1.31 (1.04, 1.66)	1.18 (0.94, 1.48)