The Role of Knee Alignment in Disease Progression and Functional Decline in Knee Osteoarthritis

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Context Knee osteoarthritis (OA) is a leading cause of disability in older persons. Few risk factors for disease progression or functional decline have been identified. Hip-knee-ankle alignment influences load distribution at the knee; varus and valgus alignment increase medial and lateral load, respectively.

Objective To test the hypotheses that (1) varus alignment increases risk of medial knee OA progression during the subsequent 18 months, (2) valgus alignment increases risk of subsequent lateral knee OA progression, (3) greater severity of malalignment is associated with greater subsequent loss of joint space, and (4) greater burden of malalignment is associated with greater subsequent decline in physical function.

Design and Setting Prospective longitudinal cohort study conducted March 1997 to March 2000 at an academic medical center in Chicago, Ill.

Participants A total of 237 persons recruited from the community with primary knee OA, defined by presence of definite tibiofemoral osteophytes and at least some difficulty with knee-requiring activity; 230 (97%) completed the study.

Main Outcome Measures Progression of OA, defined as a 1-grade increase in severity of joint space narrowing on semiflexed, fluoroscopically confirmed knee radiographs; change in narrowest joint space width; and change in physical function between baseline and 18 months, compared by knee alignment at baseline.

Results Varus alignment at baseline was associated with a 4-fold increase in the odds of medial progression, adjusting for age, sex, and body mass index (adjusted odds ratio [OR], 4.09; 95% confidence interval [CI], 2.20-7.62). Valgus alignment at baseline was associated with a nearly 5-fold increase in the odds of lateral progression (adjusted OR, 4.89; 95% CI, 2.13-11.20). Severity of varus correlated with greater medial joint space loss during the subsequent 18 months ($R=0.52$; 95% CI, 0.40-0.62 in dominant knees), and severity of valgus correlated with greater subsequent lateral joint space loss ($R=0.35$; 95% CI, 0.21-0.47 in dominant knees). Having alignment of more than 5° (in either direction) in both knees at baseline was associated with significantly greater functional deterioration during the 18 months than having alignment of 5° or less in both knees, after adjusting for age, sex, body mass index, and pain.

Conclusion This is, to our knowledge, the first demonstration that in primary knee OA varus alignment increases risk of medial OA progression, that valgus alignment increases risk of lateral OA progression, that burden of malalignment predicts decline in physical function, and that these effects can be detected after as little as 18 months of observation.

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Twelve percent of the US population aged 25 to 75 years has symptoms and signs of osteoarthritis (OA).[1] Disability due to OA is largely a result of knee or hip involvement. The risk of disability attributable to knee OA alone is as great as that due to cardiac disease and greater than that due to any other medical condition in elderly persons.[2] Knee OA also substantially increases risk of disability due to other medical conditions.[3] Increased awareness of the impact of knee OA has provided impetus to accelerate development of disease-modifying agents (ie, treatments that delay OA progression).[4] At present, there are no disease-modifying drugs for OA.

Poor understanding of the natural history of OA contributes to the slow development of interventions that modify the course of the disease. This deficiency of knowledge hinders development of novel interventions to target factors responsible for disease progression and functional decline; it also clouds the ability to identify patients who are unlikely to benefit from investigational treatments.

In the investigation of a candidate risk factor in OA studies, 3 key questions arise. Does the factor contribute to (1) incidence (ie, new occurrence) of osteoarthritic disease? (2) disease progression in those who already have OA? and (3) disability in those with OA? The literature on knee OA is weighted toward the first question. However, the second

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and third questions are crucial to the goal of reducing the burden of knee OA. In a subset of individuals, knee OA remains in the mild state that characterizes newly developed OA; Dieppe[5] has stated that in this subset, OA should not even be considered a disease—OA that progresses beyond mild stages is responsible for the bulk of both individual and societal costs of OA. Knowledge of the factors that lead to progression and functional decline will aid development of interventions to modify disease course and patient-centered outcomes.

In the investigation of knee OA progression, the recommended primary outcome is joint space change, measured via radiographic images acquired using special protocols that maximize accuracy and reliability.[6-13] The sparse literature regarding progression is limited by its reliance on conventional, extended-knee radiography (ie, without the protocols now considered essential).

Osteoarthritis is widely believed to be the result of local mechanical factors acting within the context of systemic susceptibility.[14-16] Certain site-specific factors in the local joint environment govern how load is distributed across the articular cartilage of a given joint. However, the effect of such factors on OA progression or patient-centered outcomes is largely unexamined.

At the knee, alignment (ie, the hip-knee-ankle angle) is a key determinant of load distribution. In theory, any shift from a neutral or collinear alignment of the hip, knee, and ankle affects load distribution at the knee.[17] The load-bearing axis is represented by a line drawn from mid femoral head to mid ankle. In a varus knee, this line passes medial to the knee and a moment arm is created, which 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.[17] Disproportionate medial transmission of load results from a stance-phase adduction moment.[18] This adduction moment reflects the magnitude of intrinsic compressive load on the medial compartment during gait.[19] Varus-valgus alignment is a key determinant of this moment.

These mechanical effects of alignment on load distribution make it biologically plausible that both varus and valgus alignment contribute to OA progression. Further support comes from animal studies[17] as well as surgical studies, which identify knee alignment as a predictor of knee procedure outcomes. The question that has not been answered is, does knee alignment influence risk of structural progression and functional decline in knee OA?

In this study, we tested whether (1) varus alignment at baseline increases risk of subsequent medial tibiofemoral compartment OA progression, (2) valgus alignment at baseline increases risk of subsequent lateral compartment OA progression, (3) severity of varus or valgus malalignment at baseline is correlated with subsequent change in medial or lateral joint space width, respectively, and (4) greater burden of malalignment at baseline is associated with greater subsequent deterioration in physical function.

METHODS

Participants

The Mechanical Factors in Arthritis of the Knee (MAK) study is a longitudinal study of the contribution of mechanical factors to disease progression and functional decline in knee OA. Participants were recruited from the community through advertising in periodicals targeting elderly persons, 67 neighborhood organizations, letters to members of the registry of the Buehler Center on Aging at Northwestern University, Chicago, Ill, and local referrals.

Inclusion and exclusion criteria were based on National Institute of Arthritis and Musculoskeletal and Skin Diseases/National Institute on Aging–sponsored multidisciplinary workshop recommendations for knee OA progression studies.[6] Inclusion criteria were definite tibiofemoral osteophyte presence (Kellgren/Lawrence [K/L] radiographic grade $\geq$2) of 1 or both knees and at least some difficulty with knee-requiring activity. Exclusion criteria were corticosteroid injection within the previous 3 months or history of avascular necrosis, rheumatoid or other inflammatory arthritis, periarticular fracture, Paget disease, villonodular synovitis, joint infection, ochronosis, neuropathic arthropathy, acromegaly, hemochromatosis, Wilson disease, osteochondromatosis, gout, pseudogout, or osteopetrosis. Approval was obtained from the Office for the Protection of Research Subjects–Institutional Review Board of Northwestern University. Written informed consent was obtained from all participants.

Alignment

To assess alignment, a single anteroposterior radiograph of the lower extremity was obtained. A 130×36-cm graduated grid cassette was used to include the full limb of tall participants.[20] By filtering the x-ray beam in a graduated fashion, this cassette accounts for the unique soft tissue characteristics of the hip and ankle. Participants stood without footwear, with tibial tubercles facing forward. The tibial tubercle, a knee-adjacent site not distorted by OA, was used as positioning landmark.[21] The patella is often used to position normal knees,[20] but the possibility of patellofemoral OA precluded this approach. The x-ray beam was centered at the knee at a distance of 2.4 m. A setting of 100 to 300 mA/s and 80-90 kV was used, depending on limb size and tissue characteristics.

Alignment was measured as the angle formed by the intersection of the mechanical axes of the femur (the line from femoral head center to femoral intercondylar notch center) and the tibia (the line from ankle talus center to the center of the tibial spine tips).[17,21,22] A knee was defined as varus when alignment was more than 0° in the varus direction, valgus when it was more than 0° in the valgus direction, and neutral when alignment was 0°.[20,22-24] The angle made by the femur and tibia on a knee x-ray was not used because it does not consider the proximal femur, femoral or tibial shafts, or ankle[25]; is highly variable as opposed to full-limb measurements[22]; and is not typically used in orthopedic clinical or biomechanical studies.

One experienced reader made all measurements. Reliability was high for measurements of varus (intraclass correlation coefficient [ICC], 0.99) and valgus (ICC, 0.98) alignment.

Varus-Valgus Laxity

Because physical examination laxity tests are unreliable,[26,27] a device to measure varus-valgus laxity was designed by Thomas Buchanan, PhD.[28,29] This device and the measurement protocol address sources of variation in knee laxity tests, ie, inadequate thigh and ankle immobilization, incomplete muscle relaxation, variation of the knee flexion angle, variation of load applied, and imprecise measurement of rotation.[26,27,30]

The system consists of a bench with an arc-shaped, low-friction track running medially and laterally. The distal shank is attached to a sled, which travels within the track. A handheld dynamometer fits into the sled and is used to apply load. Participants assumed a seated position, with the thigh and ankle immobilized and the study knee at 20° flexion.[31] An auditory signal indicates when a load of 40 newtons (12 newtons/m) has been applied.[32]

Laxity was measured as the angular deviation at the sled after varus and valgus load. Total rotation, the sum of varus and valgus rotation for each knee, was examined as previously described.[32-34] All laxity measurements were performed by the same examiner and assistant. Our reliability with this device was very good (within-session ICC, 0.85-0.96; between-session ICC, 0.84-0.90).

Knee Radiographs

For knee radiographs at baseline and 18 months, the Buckland-Wright protocol[35] was followed. This protocol meets recommendations for knee OA studies provided by multidisciplinary workshops[6] and the Task Force of the Osteoarthritis Research Society International.[9] Per this protocol, knee position, criteria for beam alignment relative to knee center, radiopaque markers to account for magnification, and measurement landmarks were specified. All radiographs were obtained in the same unit by 2 trained technicians.

The standing semiflexed view of the knee in this protocol is optimal for joint space assessment because it achieves superimposition of the anterior and posterior joint margins.[12,36,37] The knee was flexed until the tibial plateau was horizontal, parallel to the beam and perpendicular to the film. To control for rotation, the heel was fixed and the foot rotated until the tibial spines were central within the femoral notch. Knee position was confirmed by fluoroscopy before films were taken. Foot maps made at baseline were used to standardize repositioning at 18 months. These protocol elements enhance accuracy and precision of joint space assessment.[12,37] Even without fluoroscopic confirmation, the semiflexed view was superior to the extended or schuss views[38]; the fluoroscopic approach, by confirming the same position in all radiographs, further reduces variability.

Radiographic Progression

Joint space assessment is the widely recommended primary outcome for knee OA progression studies[9,11,39] and provides a compartment-specific measure, which was required in this study.

Medial and lateral progression were defined as a 1-grade or greater increase in severity of joint space narrowing in the medial and lateral compartments, respectively. We used the 4-grade scale (ie, 0 = none; 1 = possible; 2 = definite; and 3 = severe) with atlas representations from Altman et al.[8]

Joint space was also measured at the narrowest point in each compartment. The femoral boundary was the distal convex margin of the condyles. The tibial boundary was the line extending from tibial spine to outer margin, across the center of the articular fossa, defined by the superior margin of the bright radiodense band of the subchondral cortex.[35,40] The narrowest interbone distance of each compartment was measured using calipers with electronic readout.[6,40,41] Joint space area and midcompartment width are less sensitive to change than narrowest joint space width.[35]

Other approaches (ie, osteophyte grade, K/L grade) had limitations. Although osteophytes can be graded per compartment, they are often more prominent in the uninvolved compartment. The K/L grade provides a global score without separate information for the medial and lateral compartments (ie, 0 = normal; 1 = possible osteophytes; 2 = definite osteophytes and possible joint space narrowing; 3 = moderate/multiple osteophytes, definite narrowing, some sclerosis, and possible attrition; and 4 = large osteophytes, marked narrowing, severe sclerosis, and definite attrition).

One experienced reader assessed radiographs using an atlas.[8] Reliability for joint space grading (κ coefficient, 0.80-0.86) and measurement (ICC, 0.95-0.98) was very good. Reading of knee and full-limb radiographs occurred in separate sessions. The reader was blinded to knee data when assessing alignment and to alignment data when assessing knee radiographs.

Physical Function and Pain

Physical function was assessed using an observed measure, chair-stand performance (rate of chair stands per minute, based on the time required to complete 5 repetitions of rising from a chair and sitting down), using the protocol of Guralnik et al[42] and Seeman et al.[43] The sit-stand transfer is closely linked to knee status.[44] Of the lower-extremity joints, the knee often exhibits the greatest peak torques during this task.[45-47] Average pain during the past week was recorded on separate 0- to 100-mm visual analog scales (VASs) for each knee.

Statistical Analysis

For analyses of OA progression, knees not at risk of progressing (ie, those with the highest grade of joint space narrowing at baseline) were excluded. Descriptive data (proportions) and correlations were provided separately for dominant and nondominant knees, with dominance ascertained using the question, "In order to kick a ball, which leg would you use?" All statistical tests were conducted using a nominal α level of .05. The risk of progression was analyzed from logistic regression, using generalized estimating equations (GEEs) to include data from 1 or both knees of each participant. Odds ratios (ORs) were calculated for medial and lateral progression, first entering alignment (unadjusted OR), then adding age, sex, and body mass index (BMI) (adjusted OR). Odds ratios were recalculated after additional adjustment for laxity. The associated 95% confidence intervals (CIs) were calculated; a 95% CI of more than 1.00 indicates that alignment is significantly associated with progression. The same approach was taken to explore the relationship between alignment and progression assessed using K/L grade.

Next, the relationship between baseline varus alignment (in degrees; varus as a positive value, neutral as 0, and valgus as a negative value) and change in medial joint space width from baseline to 18 months, each as a continuous variable, was examined in dominant knees using linear regression analysis. A decrease in joint space was analyzed as a positive value. Similarly, the relationship between baseline valgus alignment (valgus as a positive value, neutral as 0, and varus as a negative value) and change in lateral joint space width from baseline to 18 months was examined.

For analyses of physical function, participants whose chair-stand performance could not further decline (ie, those who could not perform the test at baseline) were excluded. Participants were divided into 3 alignment groups based on having 0, 1, or 2 knees with baseline alignment of more than 5° from neutral (in either direction). Change from baseline to 18 months in chair-stand rate was regressed on alignment group status to evaluate unadjusted and age-, sex-, and BMI-adjusted differences between groups. To explore the mediating role of pain, further analyses additionally adjusted for pain.

Table 1. Sample Participant Characteristics

	Study Sample (n = 230)	Eligible Noncompleters (n = 7)
Age, mean (SD), y	64.0 (11.1)	64.1 (13.0)
Body mass index, mean (SD), kg/m^2	30.3 (5.8)	33.6 (9.0)
Sex, No.		
Women	173	4
Men	57	3
Osteoarthritis severity, No.*		
Kellgren/Lawrence grade		
0	1	0
1	14	0
2	108	3
3	71	3
4	36	1
Joint space narrowing grade		
0	59	0
1	63	3
2	66	2
3	42	2
Alignment, No.		
Varus	117	5
Valgus	97	1
Neutral	16	1
Laxity, mean (SD)	5.3° (2.0°)	6.3° (1.8°)

*Osteoarthritis severity is presented for dominant knees.

We also explored the relationship between baseline alignment group and functional decline, designated as at least 20% worsening in chair-stand rate. Logistic regression analysis was used to evaluate the unadjusted and adjusted odds of performance decline related to alignment group status.

RESULTS

Of 237 participants at risk for progression in at least 1 knee, 7 (3%) did not return at 18 months; 5 died and 2 could not be reached. Selected characteristics of these participants are presented in TABLE 1. No participant received therapy that might have affected the progression rate.

Radiographic Progression

In dominant knees, medial OA progression occurred in 28 (31%) of 89 varus vs 9 (9%) of 102 nonvarus knees. Of the 37 dominant knees with medial progression, 28 (76%) were varus at baseline. Mean varus alignment was 3.34° at baseline and 3.82° at 18 months. Results were similar in nondominant knees.

Lateral OA progression occurred in 19 (22%) of 88 valgus vs 5 (5%) of 103 nonvalgus knees. Of 24 dominant knees with lateral progression, 19 (79%) were valgus. Mean valgus alignment was 3.21° at baseline and 3.24° at 18 months. Results were similar in nondominant knees.

The average change in the compartment that was narrower at baseline was a loss of 0.45 mm over 18 months. Definite joint space narrowing (grade ≥2) was present in either the medial or the lateral compartment but never in both. In no knee did both medial and lateral progression occur; tibiofemoral progression was a unicompartmental event.

Medial Progression

In GEE logistic regression analyses, varus vs nonvarus (referent) alignment at baseline was associated with a 5-fold increase in the odds of medial progression during the subsequent 18 months (TABLE 2). After adjustment for age, sex, and BMI, varus alignment was still associated with a 4-fold increase in the odds of medial progression.

In calculating risk in varus vs nonvarus knees, we recognized that medial OA may be associated with varus, valgus, or neutral alignment. There-

Table 2. Odds Ratios for Medial and Lateral Progression*

	Odds Ratio (95% Confidence Interval)	
	Unadjusted	Adjusted†
Varus Alignment and Medial Progression		
Nonvarus	1.00	1.00
Varus	5.00 (2.77-9.02)	4.09 (2.20-7.62)
Neutral/mild valgus	1.00	1.00
Varus	3.54 (1.85-6.77)	2.98 (1.51-5.89)
Valgus Alignment and Lateral Progression		
Nonvalgus	1.00	1.00
Valgus	3.88 (1.82-8.24)	4.89 (2.13-11.20)
Neutral/mild varus	1.00	1.00
Valgus	3.23 (1.30-8.05)	3.42 (1.31-8.96)

*Knees with grade 3 joint space narrowing at baseline were excluded. For analyses involving nonvarus and neutral/mild valgus reference groups, n = 381 and 281 knees, respectively. For analyses involving nonvalgus and neutral/mild varus reference groups, n = 381 and 278 knees, respectively. Mild varus and mild valgus were defined as ≤2° varus or valgus, respectively.
†Adjusted for age, sex, and body mass index.

fore, the risk associated with varus alignment was compared with the risk conferred by any other possible alignment for a given knee. To determine the progression risk associated with varus alignment when the comparison group was neutral or nearly neutral knees, we repeated the analysis with a referent group consisting of neutral (0°) or mildly valgus (≤2°) knees. Varus alignment was still associated with a 3-fold increase in risk of medial progression in adjusted analyses (Table 2).

Lateral Progression

In GEE logistic regression analyses, valgus vs nonvalgus (referent) alignment at baseline was associated with an almost 4-fold increase in the odds of lateral progression during the subsequent 18 months (Table 2). This relationship persisted after adjustment for age, sex, and BMI.

When the referent group was neutral or nearly neutral (≤2° varus) knees, valgus alignment was associated with a more than 3-fold increase in the odds of subsequent lateral OA progression in both unadjusted and adjusted analyses (Table 2).

These logistic regression analyses were repeated after additionally controlling for varus-valgus laxity, with little effect on results. The OR for the relationship between varus alignment and medial progression, adjusting for age, sex, BMI, and laxity, was 4.01 (95% CI, 2.19-7.62). The OR for the relationship between valgus alignment and lateral progression, adjusting for age, sex, BMI, and laxity, was 4.78 (95% CI, 2.08-11.02).

Results of analyses of medial progression were not affected by excluding lateral progressors from the nonprogressor group. Results of analyses of lateral progression also were not affected by excluding medial progressors from the nonprogressor group.

Malalignment Severity at Baseline and Change in Joint Space

The relationship between baseline severity of varus alignment and change in medial joint space width from baseline to 18 months, each as a continuous variable, was examined in dominant knees. Greater varus alignment correlated with greater subsequent loss of joint space ($R=0.52$; 95% CI, 0.40-0.62).

Similarly, the relationship between baseline severity of valgus and change in lateral joint space width from baseline to 18 months was examined in dominant knees. Severity of valgus correlated with the magnitude of loss of lateral joint space width ($R=0.35$; 95% CI, 0.21-0.47). These relationships persisted after adjustment for age, sex, BMI, and laxity.

Alignment at Baseline and Progression of K/L Grade

Given the historical role of the K/L grading system in knee OA studies, we also examined the relationship between baseline alignment and K/L grade progression (≥1-grade increase). However, knees that progress by K/L grade include some knees with medial progression and other knees with lateral progression. Therefore, this analysis tests a different hypothesis—does varus alignment increase risk of progression in either the medial (mechanically stressed by varus alignment) or the lateral (not stressed) compartment, and does valgus alignment increase risk of progression in either the medial (not stressed) or the lateral (stressed by valgus alignment) compartment? Notably, there is no rationale to support a link between varus alignment and lateral progression or between valgus alignment and medial progression.

Even with this limitation of the K/L grading system, valgus alignment was associated with an increase in risk of K/L grade progression (OR, 2.51; 95% CI, 0.91-6.89), and varus alignment was associated with a significant increase in risk of K/L grade progression (OR, 3.61; 95% CI, 1.33-9.85), further attesting to the strength of their effects. Finally, absolute severity of malalignment as a continuous variable was significantly associated with K/L grade progression.

Burden of Knee Malalignment at Baseline and Change in Physical Function

Burden of malalignment at baseline predicted deterioration in physical function between baseline and 18 months. Participants were classified into 1 of 3 groups at baseline: those who had alignment of 5° or less in both knees (n=126), 1 knee with alignment of more than 5° (n=52), or both knees with alignment of more than 5° (n=37). Physical functional outcome was analyzed as a continuous variable, ie, change in chair-stand rate from baseline to 18 months. Change did not differ between the first 2 groups, but significantly greater deterioration in chair-stand performance was found in participants who had alignment of more than 5° in both knees vs participants who had alignment of 5° or less in both knees (**TABLE 3**). The difference between these groups persisted after adjusting for age, sex, and BMI.

We also explored the relationship between burden of malalignment and functional decline, designating decline as at least 20% worsening in chair-stand rate. Thirty-four (16%) of the 215 participants able to perform the test at baseline had functional decline by this definition, including 10% of the 126 with alignment in both knees of 5° or less, 21% of the 52 with alignment of more than 5° in 1 knee, and 27% of the 37 with alignment of more than 5° in both knees. The odds of functional decline were doubled (OR, 2.33; 95% CI, 0.97-5.62) by having 1 knee with alignment of more than 5° vs both knees with alignment of 5° or less and were tripled by having alignment of more than 5° in both knees vs alignment of 5° or less in both knees (OR, 3.22; 95% CI, 1.28-8.12). This association persisted after adjusting for age, sex, and BMI.

Table 3. Alignment Group Differences in Change in Chair-Stand Rate, Baseline to 18 Months

	Difference Between Groups (95% Confidence Interval)*		
	Unadjusted	Age-, Sex-, and BMI-Adjusted	Age-, Sex-, BMI-, and Pain-Adjusted
1 Knee >5° vs both knees ≤5°	0.48 (−1.40 to 2.36)	0.43 (−1.44 to 2.31)	0.17 (−1.66 to 2.01)
Both knees >5° vs both knees ≤5°	2.88 (0.75 to 5.01)	2.73 (0.52 to 4.94)	2.23 (0.05 to 4.41)

*BMI indicates body mass index. For each group, the change in chair-stand rate was determined, with positive values indicating a decrease in rate. The chair-stand rate is the number of stands per minute, calculated from the time required to complete 5 chair stands.

Burden of Malalignment, Functional Deterioration, and Pain

To explore whether pain is an intervening variable in the relationship between knee alignment and functional deterioration, first we examined the relationship between alignment and pain at baseline, then we examined whether the relationship between alignment and functional deterioration was lost after accounting for pain. Average pain increased as malalignment increased (alignment <4° = pain score of 25.2 mm on the VAS; alignment >4° but <8° = pain score of 37.7 mm; and alignment ≥8° = pain score of 41.2 mm). Pain severity was significantly associated with malalignment severity. Specifically, the GEE logistic regression analysis of alignment and pain showed an average VAS increase of 10 mm in knee pain with each 5° of malalignment. This relationship persisted after adjustment for age, sex, and BMI. Next, we repeated the analysis of the relationship between alignment group and change in chair-stand rate after additionally accounting for pain. As shown in Table 3, the burden of malalignment at baseline (ie, 2 vs 0 knees) continued to be significantly associated with subsequent functional deterioration.

COMMENT

Varus alignment at baseline increased risk of medial knee OA progression over the 18 months of our study, and valgus alignment increased risk of subsequent lateral knee OA progression. The severity of varus malalignment at baseline correlated with the magnitude of medial joint space loss, and the baseline severity of valgus malalignment correlated with the magnitude of lateral joint space loss. A greater burden of malalignment at baseline was linked to greater decline in an observed measure of physical function. To our knowledge, this is the first demonstration that alignment influences risk of subsequent primary OA disease progression and decline in functional status and that these effects can be detected after as little as 18 months of observation.

In theory, varus and valgus alignment may each be a cause or result of progressive knee OA; therefore, it was essential to examine alignment at the beginning of the period during which progression was evaluated. Varus or valgus alignment that predates knee OA may be due to genetic, developmental, or posttraumatic factors. Animal model data support a link between preexisting varus or valgus alignment and OA development.[17] Knee alignment that results from knee OA may be due to loss of cartilage and bone height. However, even as a consequence of osteoarthritic disease, varus or valgus alignment may contribute to subsequent progression. The results of the current study, especially given the influence of alignment on load distribution, support this concept.

The presence of a relationship between alignment and progression by 18 months underscores the importance of alignment as a risk factor. In knee OA progression studies, 18 months is a relatively early follow-up point, at which an effect may not as yet be detectable. The importance of alignment was further demonstrated by the finding of a strong relationship with progression even when the referent group included only neutral or nearly neutral knees. The alignment-associated odds of progression may be even greater at longer follow-up. The odds may be substantially greater if malalignment and knee OA are in a vicious cycle.

Varus or valgus alignment may stretch the capsule and collateral ligaments, increasing varus-valgus laxity, a potential mechanism of the alignment effect. If laxity were playing this role, then controlling for laxity should lead to a reduction in the alignment-progression relationship. In our study, this did not occur, suggesting that an increase in laxity is not a major mechanism for the alignment effect. Our study had more women than men; this sex distribution matches that of knee OA in the general population. The effects of alignment were independent of sex.

Burden of malalignment influenced patient-centered outcome, physical function assessed by chair-stand performance. In knee OA, risk factor profiles for structural disease progression and for disability overlap but are not identical.

It was necessary to specifically examine the relationship between alignment and functional status. Longitudinal studies of patient-centered outcomes in knee OA have been rare; knowledge about risk factors has been derived chiefly from cross-sectional studies. We explored whether pain was an intervening factor in the alignment effect on function. While the strength of the alignment-function relationship was reduced slightly after accounting for pain, a significant relationship persisted, suggesting that at least some portion of the alignment effect is independent of pain.

The results of this study are consistent with biomechanical studies that have revealed that varus and valgus alignment increase medial and lateral load, respectively.[17,48,49] During gait, the impact of valgus on load distribution may not be comparable with that of varus alignment. In the normally aligned ambulating knee, load is disproportionately transmitted to the medial compartment.[50] Varus alignment further increases medial load during gait.[22] Valgus alignment is associated with an increase in lateral compartment peak pressures[49]; however, more load is still borne medially until more severe valgus is present.[51,52] Therefore, we expected to find that varus alignment had a stronger effect on medial progression risk than valgus on lateral progression risk, but the effects of varus and valgus were similar in magnitude. The severity of varus was similar to that of valgus; the lack of difference in potency could not be attributed to more severe valgus malalignment. Certainly, alignment in either direction increases compartmental load, giving credence to the concept that varus and valgus alignment each may contribute to subsequent progression. Differences between the magnitude of the effects of varus and valgus alignment may emerge with further follow-up.

A relationship between varus or valgus alignment and the natural progression of primary knee OA has not previously been demonstrated. Beliefs regarding this relationship have rested on biomechanical models and studies that are cross-sectional or of short duration and surgical outcome studies. Testing the immediate or short-term mechanical impact of a factor is not equivalent to testing its impact on a long-term structural outcome in a patient. The stage of investigation represented by the current study was necessary, both to demonstrate and to quantify the long-term effects of knee alignment on patient outcomes. Several orthopedic studies have demonstrated that knee alignment is associated with surgical outcome (eg, arthroplasty,[53] osteotomy,[54] meniscectomy,[55-57] and meniscal debridement[58]). While extremely important, these data do not address the role played by knee alignment in the nonsurgical, natural evolution of knee OA. In the operated knee, the development or progression of OA is linked to several factors not at play in natural progression (eg, nature of surgery and stage of OA at time of surgery).

Investigation of the influence of alignment on natural structural or patient-centered outcomes in unselected populations has been rare. Schouten et al[59] found that patient recollection of "bow-legs or knock-knees in childhood" was associated with a 5-fold increase in risk of OA progression. Others found that presence of "varus/valgus deformity," not further defined, did not differ between those who progressed and those who did not.[60] In another study involving patients who were selected from a hospital practice on the basis of not having undergone surgery, and in whom alignment was considered only at the end of follow-up, 50% of 35 varus knees had progressive joint space narrowing.[61]

The proportion of participants whose OA progressed in the current study is comparable with studies using similar recruitment methods.[11,62] Also, an average joint space loss of 0.45 mm was detected over 18 months, or 0.30 mm over 12 months. This rate falls within the range of annual joint space loss in the literature (0.12 to 0.62 mm/y). Comparison with population-based studies, which have tended to use conventional, extended-knee radiography, is not possible. In previous progression studies, medial and lateral knee OA have been treated as a single condition, despite a belief that they differ in rate of progression and risk factor profile. Our results provide evidence that tibiofemoral OA progresses asymmetrically and illustrate that local risk factors are not only specific to joint but also to compartment.

The goal of this study was to examine the influence of alignment on structural and functional outcomes in patients with established OA. There is growing awareness that risk factors for incident OA differ from risk factors for OA progression. It is likely that knee alignment has a different effect on risk of incident OA from that shown here on risk of progression. The former effect may be smaller, given the less vulnerable state of the healthy knee. However, the effect on risk of incident OA cannot be inferred from these results and should be specifically examined.

These results suggest the need to develop and test, in patients with knee OA, the effect of interventions that reduce the stresses imposed by a given alignment. Interventions that reduce load in the stressed compartment on an ongoing basis may have a disease-modifying effect. Interventions that may hold promise (eg, "unloading" orthoses) have been examined in short-term studies; their long-term tolerability and effect on symptoms have been minimally evaluated, and their effect on progression and long-term functional outcomes is unknown.

In summary, varus alignment at baseline increased risk of subsequent medial OA progression and valgus alignment at baseline increased risk of subsequent lateral OA progression. Baseline severity of malalignment was correlated with the magnitude of subsequent joint space loss. Burden of malalignment at baseline was linked to greater decline in physical function.

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Analysis and interpretation of data: Sharma, Song, Felson, Shamiyeh, Dunlop.
Drafting of the manuscript: Sharma.

Critical revision of the manuscript for important intellectual content: Sharma, Song, Felson, Cahue, Shamiyeh, Dunlop.
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Obtained funding: Sharma.
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Study supervision: Sharma.

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Despite a pharmacological effect of statins on bone metabolism, our observations strongly indicate the need for prospective randomized controlled trials, or perhaps for pooling the results of prior trials, to assess the effect of statins on bone mass even before undertaking long-term prospective studies on fracture incidence.

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CORRECTION

Incorrect Unit of Measure: In the Original Contribution entitled "The Role of Knee Alignment in Disease Progression and Functional Decline in Knee Osteoarthritis" published in the July 11, 2001, issue of THE JOURNAL (2001;286:188-195), an incorrect unit of measure was given. On page 190, the last sentence in the second paragraph under "Varus-Valgus Laxity" should have read "An auditory signal indicates when a load of 40 newtons (12 newton-meters) has been applied.[32]"

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—Walter Benjamin (1892-1940)

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