Static Knee Alignment Is Associated with the Risk of Unicompartmental Knee Cartilage Defects

Neela Janakiramanan,[1] Andrew J. Teichtahl,[1] Anita E. Wluka,[1,2] Changhai Ding,[3] Graeme Jones,[3] Susan R. Davis,[4] Flavia M. Cicuttini[1]

[1]Department of Epidemiology and Preventative Medicine, Monash University, Central and Eastern Clinical School, Alfred Hospital, Melbourne, VIC 3004, Australia

[2]Baker Heart Research Institute, Commercial Road, Melbourne, VIC 3004, Australia

[3]Menzies Research Institute, University of Tasmania, Hobart, Australia

[4]Women's Health Program, Department of Medicine, Monash University, Central and Eastern Clinical School, Alfred Hospital, Melbourne, VIC 3004 Australia, and National Health and Medical Research Council of Australia Centre of Clinical Research Excellence for the Study of Women's Health Program, Department of Medicine, Monash University Medical School, Alfred Hospital, Prahran, Victoria, Australia

ABSTRACT: Although knee malalignment is a risk factor for the progression of unicompartmental knee osteoarthritis (OA), it is unclear how this relationship is mediated. Cartilage defects are known to predate cartilage loss and the onset of knee OA, and it may be that knee malalignment increases the risk of unicompartmental knee cartilage defects. Knee radiographs and MRI were performed on a total of 202 subjects, 36.6% of whom had radiographic knee OA, to determine the relationship between static knee alignment and knee cartilage defects. Analyses were performed for the entire cohort, as well as for healthy and OA subgroups. For every 1° increase in a valgus direction, there was an associated reduced risk of the presence of cartilage defects in the medial compartment of subjects with knee OA ($p = 0.02$), healthy subjects ($p = 0.002$), and the combined ($p < 0.001$) group. Moreover, for every 1° increase in a valgus direction, there was an associated increased risk of the presence of lateral cartilage defects in the OA group ($p = 0.006$), although the relationship between change toward genu valgum and lateral compartment cartilage defects did not persist for the healthy group ($p = 0.16$). This cross-sectional study has demonstrated that knee alignment is associated with the risk for compartment specific knee cartilage defects in both healthy and arthritic people. Given that the natural history of cartilage volume reduction appears to be predated by the presence of cartilage defects, whether knee alignment affects the longitudinal progression from cartilage defects to cartilage loss requires further examination. © 2007 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res

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INTRODUCTION

Knee osteoarthritis (OA) is a major cause of disability among the elderly.[1] The disease affects articular cartilage, and although a reduction in cartilage volume is a major feature of OA, other cartilaginous variables are of growing interest. Cartilage defects, which are irregularities on the surface of the usually smooth articular cartilage, are becoming recognized as important early determinants of potential arthritic change, particularly at the knee.[2,3] These defects are graded according to the depth of loss of cartilage thickness. Clinically, knee cartilage defects have been correlated with pain and functional impairment,[4–6] and have been shown to predate localized cartilage loss and disease progression,[7] including the risk of total knee replacement.[8]

Another determinant of the progression of knee OA is lower limb alignment. We have recently shown that baseline static knee angle is associated with the rate of cartilage loss in subjects with knee OA.[9] Additionally, Sharma et al.[10] demonstrated an association between knee malalignment and progression of unicompartmental joint space narrowing. Wu et al.[11] found more severe unicompartmental

cartilage defects in rabbits that were subject to tibial osteotomy and valgus angulation, but this association has not been examined in humans. Although the natural history of cartilage reduction appears to be predated by the presence of cartilage defects,[2] no study has examined whether knee alignment is associated with these early radiological features of potential cartilage loss.

The aim of this cross-sectional study is to determine whether static knee joint alignment is associated with the risk of knee cartilage defects among subjects with and without knee OA.

MATERIALS AND METHODS

Subjects

This study involved 202 subjects aged over 40 years who had radiographic and MRI assessment of the same knee within 1 month as part of studies examining knee cartilage within our department. These subjects were volunteers who had been recruited to participate using a combined strategy of advertising and referral. Some subjects were recruited via advertising to the general public in local newspapers to the Victorian branch of the Arthritis Foundation of Australia and other local media. Other subjects received information regarding the study while attending various health practitioners including the General Practitioners, Specialist Rheumatologists, Orthopaedic Surgeons, and public and private women's health consulting clinics.

After imaging, all subjects with Kellgren Lawrence equal to or greater than grade 2 were classified as having knee OA. The classification system of Kellgren and Lawrence describes grade 2 as the presence of radiographic OA, and this system has been found to correlate with arthroscopic cartilage changes by Kijowski et al.[12] The study was approved by the ethics committee of the Alfred Hospital, Melbourne, Australia, and all subjects gave written informed consent.

Subjects were excluded if any form of arthritis other than OA was present, including evidence of chondrocalcinosis on plain films, or if they had a contraindication to MRI (e.g., pacemaker, cerebral aneurysm clip, cochlear implant, presence of shrapnel in strategic locations, metal in the eye, claustrophobia), hemiparesis of either lower limb, or planned total knee replacement. Each subject had MRI and plain radiography performed on their dominant knee, defined as the lower limb from which they step off when initiating walking, if no pain was present. Where knee pain was present, the symptomatic knee was imaged. Where both knees were symptomatic, the knee with least severe radiographic OA was imaged. Weight was measured to the nearest 0.1 kg with shoes and bulky clothing removed using a single pair of electronic scales. Height was measured to the nearest 0.1 cm with shoes removed using a stadiometer. The body mass index (BMI) was calculated from this data (weight/height^2 kg/m^2).

Magnetic Resonance Imaging and Cartilage Defects

MR imaging was performed on the dominant knee (defined as the leading limb in the initiation of walking) of each subject in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Sigma Advantage HiSpeed GE Medical Systems, Milwaukee, WI) using a commercial transmit-receive extremity coil. Sequence and parameters were: a T1-weighted fat suppressed 3D gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 513×196 matrix; one acquisition time 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.83 mm (512×196 pixels). The image data were transferred to a workstation. These data were resampled by bilinear and cubic interpolation (area 312 and 312 μm and 1.5 mm thickness, continuous sections) for the final 3D rendering.[12,13] A trained observer read each MRI. Each subject's MRI scans were assessed within a 2-week period, unpaired and blinded to subject identification. The cartilage defects were defined as being present or absent. A defect was said to be present if there were irregularities on the surface or bottom and loss of cartilage thickness.[2,7] These changes were required to be present in at least two consecutive slices to be considered significant. Cartilage was considered to be normal if there was uniform thickness of the band of intermediate signal intensity.

Intraobserver reliability (expressed as intraclass correlation coefficient, ICC) was 0.90 for the medial tibiofemoral compartment, and 0.89 for the lateral tibiofemoral compartment. Interobserver reliability (expressed as ICC) in 50 random MR images was 0.90 for the medial tibiofemoral compartment 0.85 for the lateral tibiofemoral compartment.[13,14]

Radiographs and Determining Static Knee Alignment and the Presence of Knee Osteoarthritis

Knee angles were measured by a single blinded trained observer from standing AP radiographs using the software program Osiris.[15] Lines were drawn through the middle of the femoral shaft and through the middle of the tibial shaft. The angle subtended at the point at which these two lines met in the center of the tibial spines, and was recently validated by Hinman et al.[16] as an alternative to the mechanical axis on full-leg radiographs. Knee angles were considered as a continuum ranging from 0 to 360°, with 0° representing extreme varus and 360° representing extreme valgus. Although these degrees of varus and valgus are not clinically observed, this range was used to avoid defining varus and valgus from an arbitrarily chosen midline value, and allow quantification of change in alignment. Intraobserver reliability (expressed as ICC) was 0.98.[9] The presence of knee OA was determined from standing AP radiographs with a Kellgren-Lawrence score of ≥2 considered diagnostic of knee OA.

Statistical Analyses

With 202 subjects in the study we had 80% power to demonstrate a correlation as low as 0.2 (alpha error 0.05, two-sided significance) between the knee angle and the cartilage defects score. Knee alignment was initially assessed for normality before being regressed against the presence of knee cartilage defects. The relationship between knee alignment and cartilage defects was assessed by univariate and multivariate binary logistic regression, with adjustment for the potential confounders of age, gender, BMI, and respective cartilage volumes. Odds ratios were then calculated for lesions in both the medial and lateral tibial, femoral, and tibiofemoral compartments. Analyses were performed separately for subjects with and without knee OA, as well as the entire cohort combined. p-Values of <0.05 were considered to be statistically significant. All analyses were performed using the SPSS statistical package (standard version 12.0.1, SPSS, Chicago, IL).

RESULTS

Two hundred two subjects met the inclusion criteria, of which 36.6% were found to have definitive osteophytes on joint radiographic OA (KL ≥ 2). Subject characteristics are shown in Table 1. Our data demonstrated significant discrepancies between people with and without OA for age ($p = 0.002$), gender ($p = 0.025$), and BMI ($p = 0.001$), all of which were subsequently adjusted for in multivariate analyses. Moreover, the prevalence of cartilage defects in the OA group were significantly greater than the prevalence of defects in the healthy group for all articular surfaces at both the medial and lateral tibiofemoral compartments (Table 1).

Relationship between the Presence of Compartment Knee Cartilage Defects and Static Knee Alignment

For every $1°$ change toward genu valgum in people with OA, there was a reduced risk for the presence of medial tibial cartilage defects (OR 0.86; 95% CI 0.75–0.93; $p = 0.001$), but an increased risk for lateral tibial cartilage defects (OR 1.06; 95% CI 1.04–1.28; $p = 0.006$) in people with knee OA. Among healthy subjects, although every $1°$ change toward genu valgum reduced the risk for medial tibial cartilage defects (OR 0.81; 95% CI 0.72–0.91; $p = 0.001$), there was not an associated statistically significant increased risk for lateral tibial cartilage defects (OR 0.93; 95% CI 0.83–1.03; $p = 0.16$) in the absence of knee OA. For the combined groups, the risk for medial tibial cartilage defects was also reduced for every $1°$ change toward genu valgum (OR 0.84; 95% CI 0.77–0.90; $p < 0.001$), but without a statistically significant increase in risk for lateral tibial cartilage defects (OR 1.05; 95% CI 0.99–1.12; $p = 0.12$). These results were similar for the femoral and tibiofemoral articular surfaces. Table 2 demonstrates medial compartment data, while Table 3 demonstrates lateral compartment data.

Table 1. Subject Characteristics[a]

	Total ($n = 202$)	OA ($n = 74$)	Healthy ($n = 128$)	p
Age (years)	61 (9)	59.4 (8.5)	63.8 (10)	0.002
Gender (% female)	73%	64%	78%	0.025
Height (m)	1.68 (0.09)	1.66 (0.08)	1.66 (0.08)	0.932
Weight (kg)	80.8 (15)	81.3 (16.1)	73.8 (14.3)	0.001
BMI (kg m^{-2})	28.7 (5)	29.4 (5.3)	26.8 (4.8)	0.001
Average angle (degrees)	180.9 (4.9)	181.2 (6.6)	180.7 (3.7)	0.578
Presence of cartilage defects				
Medial compartment				
Tibial	97 (48%)	48 (64.9%)	49 (38.3%)	0.001
Femoral	49 (24.3%)	32 (43.2%)	17 (13.3%)	<0.001
Tibiofemoral	106 (52.5%)	51 (68.9%)	55 (43%)	<0.001
Lateral compartment				
Tibial	118 (58.4%)	52 (70.3%)	66 (51.6%)	0.037
Femoral	21 (10.5%)	17 (23%)	4 (3.1%)	<0.001
Tibiofemoral	118 (58.4%)	52 (70.3%)	66 (51.6%)	0.009

[a]Values are reported as mean (SD).
p-Values displayed for differences between healthy and OA groups.

Table 2. Relationship between the Presence of Medial Compartment Knee Cartilage Defects and Static Knee Alignment

	Univariate Analysis Odds Ratio (95% CI)[a,b]	p	Multivariate Analysis Odd Ratio (95% CI)[a,c]	p
Combined groups				
Tibial	0.79 (0.74, 0.85)	<0.001	0.84 (0.77, 0.90)	<0.001
Femoral	0.88 (0.83, 0.93)	<0.001	0.85 (0.78, 0.92)	<0.001
Tibiofemoral	0.85 (0.81, 0.90)	<0.001	0.85 (0.78, 0.92)	<0.001
OA subgroup				
Tibial	0.82 (0.74, 0.91)	<0.001	0.86 (0.75, 0.93)	0.001
Femoral	0.84 (0.76, 0.93)	0.001	0.85 (0.76, 0.94)	0.001
Tibiofemoral	0.88 (0.81, 0.96)	0.003	0.90 (0.82, 0.98)	0.02
Healthy subgroup				
Tibial	0.80 (0.72, 0.90)	<0.001	0.81 (0.72, 0.91)	0.001
Femoral	0.86 (0.76, 0.98)	0.03	0.87 (0.75, 1.01)	0.07
Tibiofemoral	0.84 (0.75, 0.93)	<0.001	0.84 (0.75, 0.94)	0.002

[a]95% CI = 95% confidence interval.
[b]Odds ratio of medial compartment cartilage defects per degree valgus increase in knee angle.
[c]Odds ratio of medial compartment cartilage defects per degree valgus increase in knee angle after adjusting for age, sex, and body mass index in the regression equation.

DISCUSSION

This cross-sectional study is the first to have demonstrated that static knee alignment is associated with the risk of unicompartmental knee cartilage defects in both healthy and arthritic subjects. Whereas increase toward valgus alignment was associated with a reduced risk for the presence of medial tibiofemoral compartment cartilage defects, there was an associated increased risk for the presence of lateral compartment cartilage defects. Given that the natural history of cartilage reduction appears to be predated by the presence of cartilage defects, whether knee alignment affects the longitudinal progression from cartilage defects to cartilage loss requires further examination.

Previously, static knee alignment has been associated with individual unicompartmental features of knee OA, including joint space narrowing,[10] cartilage volume reduction,[10] and osteophytes.[17] Multiple factors have been implicated in the progression to OA of malaligned knees, particularly in the medial compartment. The mechanical axis

Table 3. Relationship between the Presence of Lateral Compartment Knee Cartilage Defects and Static Knee Alignment

	Univariate Analysis Odds Ratio (95% CI)[a,b]	p	Multivariate Analysis Odd Ratio (95% CI)[a,c]	p
Combined groups				
Tibial	1.12 (1.06, 1.19)	<0.001	1.05 (0.99, 1.12)	0.12
Femoral	1.10 (1.04, 1.17)	0.001	1.30 (1.15, 1.47)	<0.001
Tibiofemoral	1.07 (1.02, 1.13)	0.009	1.05 (0.99, 1.12)	0.12
OA subgroup				
Tibial	1.12 (1.02, 1.23)	0.014	1.16 (1.04, 1.28)	0.006
Femoral	1.28 (1.13, 1.45)	<0.001	1.27 (1.11, 1.46)	0.001
Tibiofemoral	1.12 (1.02, 1.23)	0.014	1.16 (1.04, 1.28)	0.006
Healthy subgroup				
Tibial	0.97 (0.89, 1.07)	0.591	0.93 (0.83, 1.03)	0.16
Femoral	0.96 (0.74, 1.24)	0.765	1.02 (0.75, 1.38)	0.91
Tibiofemoral	0.97 (0.89, 1.07)	0.591	0.93 (0.83, 1.03)	0.16

[a]95% CI = 95% confidence interval.
[b]Odds ratio of lateral compartment cartilage defects per degree valgus increase in knee angle.
[c]Odds ratio of lateral compartment cartilage defects per degree valgus increase in knee angle after adjusting for age, sex, and body mass index in the regression equation.

passes through the medial compartment of the knee, even when alignment is neutral, causing increased compression and pressure.[18,19] This is exacerbated in varus malalignment, which has been associated with increased joint compression[20] and cartilage pressure,[21] as well as decreased cartilage thickness[22] and volume[9] and increased stiffness of the subchondral bone.[23] Biomechanical factors in varus malalignment include greater adduction moment[19] and medial ligament laxity[25] with a consequent increase in compensatory muscle contraction,[26] particularly by quadriceps motor units.[27]

There is, however, a paucity of studies that have considered the association between knee malalignment and cartilage defects. Although Wu et al.[11] demonstrated that knee alignment is an important determinant of cartilage fibrillation in rabbits, this study is the first to confirm an association between static knee alignment and compartment specific cartilage defects in human subjects in vivo. More recently, von Eisenhart-Rothe et al.[28] found that the association between cartilage loss and malalignment was greater in the tibial compartments than the femoral compartments. Similarly, we have demonstrated a more consistent pattern between knee alignment and compartment specific knee cartilage defects at tibial rather than femoral articular surfaces. Why the tibial surface is more susceptible than the femoral surface to changes associated with knee alignment is unclear.

The same factors implicated in the development of OA in malaligned knees may also be important in the natural history of cartilage defects. Although we cannot suggest causation in this cross-sectional study, these data suggest that the medial compartment is vulnerable to the development of cartilage defects in the presence of malalignment, whether OA is established or not.

In contrast, the lateral compartment cartilage at the knee appears only vulnerable to the effects of alignment in people with established knee OA. This may be because lateral compartment cartilage is more robust than the medial compartment and not subject to the same static and dynamic forces as the medial compartment, as described above. The defects that do occur in the lateral compartment in the diseased state may be due in part to changes in supporting structures, such as collateral ligamentous laxity, which may promote further joint instability and altered load throughout the knee.

This study was potentially limited by our method for assessing knee alignment given that we did not obtain full-limb films, that is, films that included imaging from pelvis to talus inclusive. Although the anatomical axis of the tibia is supposed to be straight, it is possible that bowing curvature of the tibia or femur could lead to differences between anatomical alignment (measured by knee angle) and mechanical alignment using the entire limb. However, our method for measuring anatomical axis has been shown by Hinman et al.[16] to be a valid alternative to full-limb films to predict mechanical axis. Nevertheless, due to the absence of full-limb radiographs, we were unable to determine neutral alignment, and as such, could not determine whether a limb was either genu varum or valgum. We did, however, observe complementary findings in the medial and lateral knee joint compartments as the knee angle changed toward genu valgum, without exposing subjects to unnecessary ionizing radiation. It should also be noted that in this study, the mean weight of the OA group was 7.5 kg higher than in the control group. It is well established that increased BMI is a risk factor for the incidence of radiographic knee OA.[29,30] All multivariate analyses have been adjusted for the BMI to limit the influence of this. Finally, this study only examined the association between *static* knee alignment and knee cartilage defects, and it is possible that *dynamic* measures, such as the knee adductor moment, are associated with compartment specific knee cartilage defects.

This has been the first study to examine the relationship between static knee alignment and the presence of unicompartmental cartilage defects in vivo using human subjects. Given that the natural history of cartilage reduction appears to be predated by the presence of cartilage defects, whether knee alignment affects the longitudinal progression from cartilage defects to cartilage loss requires further examination.

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