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Proximal femur shape differs between subjects with lateral and medial knee osteoarthritis and controls: the Osteoarthritis Initiative☆

B.L. Wise † *, L. Kritikos †, J.A. Lynch ‡, F. Liu ‡, N. Parimi §, K.L. Tileston ||, M.C. Nevitt ‡, N.E. Lane †

† Department of Internal Medicine, University of California, Davis School of Medicine, Sacramento, CA, USA
‡ Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA, USA
§ San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA, USA
|| Department of Orthopaedic Surgery, Stanford University School of Medicine, Palo Alto, CA, USA

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S U M M A R Y

Objective: This study examined the association of proximal femur shape with ipsilateral medial and lateral compartment knee osteoarthritis (OA).

Design: Radiographs were obtained from the NIH-funded Osteoarthritis Initiative (OAI). Cases of isolated radiographic lateral compartment knee OA were defined on baseline radiographs as Kellgren/Lawrence (K/L) Grade ≥ 2 and joint space narrowing (JSN) > 0 in the lateral compartment and JSN $= 0$ in the medial compartment; isolated medial compartment knee OA had K/L ≥ 2 and JSN > 0 medially with JSN $= 0$ in the lateral compartment. Controls had K/L < 2 and JSN $= 0$ in both compartments. Controls were frequency matched to cases by sex and 10-year age intervals. We characterized the shape of the proximal femurs on radiographs using Active Shape Modeling (ASM) and determined the association of proximal femur shape with knee OA using logistic regression.

Results: There were 168 lateral compartment knee OA cases (mean body mass index (BMI) 29.72 $\pm$ 5.26), 169 medial compartment knee OA cases (mean BMI 29.68 $\pm$ 4.83) and 168 controls (mean BMI 26.87 $\pm$ 4.2). Thirteen modes were derived for femur shape which described 95.5% of the total variance in proximal femur shape in the population. Modes 6, 8 and 12 were associated with prevalent lateral compartment knee OA. Medial compartment knee OA was associated with proximal femur modes 1, 5, 8, and 12.

Conclusions: Prevalent lateral and medial compartment knee OA are associated with different ipsilateral proximal femur shapes. Additional studies are needed to better define how the shape of the proximal femur influences compartment-specific knee OA.

Introduction

Osteoarthritis (OA) is the most common form of arthritis, and afflicts at least 27 million US adults, almost 6 million more than in 1995[1]. Although estimates for prevalence vary in different studies, the National Health and Nutrition Examination Survey III found that 12% of US adults 60 years of age or older experience symptomatic knee OA[2]. Although many risk factors for knee OA have been identified, including demographics, obesity, and malalignment of the knee, very little attention has been given to the relationship between the adjacent joint of the hip and OA of the knee.

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* Address correspondence and reprint requests to: B.L. Wise, Center for Musculoskeletal Health, University of California, Davis School of Medicine, 4625 2nd Avenue, Suite 1002, Sacramento, CA 95817, USA. Tel: 1-916-734-4534; Fax: 1-916-734-4773.

E-mail address: barton.wise@ucdmc.ucdavis.edu (B.L. Wise).

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There is a scientific rationale and some evidence supporting the hypothesis that the shape of hip or pelvis is associated with compartment-specific knee OA. Malalignment of the knee, which is a known risk factor for compartment-specific knee OA incidence[3] and progression[4], may in part represent a manifestation of hip differences being expressed at a distance, possibly by altering loading patterns in the knee. Weidow *et al.* reported that lateral OA of the knee was associated with a wider pelvis and shorter femoral neck in women[5]. Weidow found that a smaller calculated lever arm at the hip was associated with lateral compartment knee OA, which they explained as reducing abductor moment at the hip, promoting hip adduction and consequent knee alignment becoming more valgus. Although this was a small study and was restricted to women, it does provide support for the idea that biomechanical differences in the hip and pelvis may be associated with compartment-specific knee OA. There may also be less direct ways in which hip shape could be associated with knee OA. Our research group has recently reported that certain single-nucleotide polymorphisms of the FRZB gene are associated with hip shape and modify the relationship between hip shape and radiographic hip osteoarthritis (RHOA)[6], suggesting that complex relationships between genetic background, bone shape and knee osteoarthritis may exist.

Active Shape Modeling (ASM) is a statistical image analysis technique which divides differences in shape into modes of continuous variation which may be associated with prevalent or incident lateral compartment knee OA. This technique is one way to characterize a broad spectrum of variation of shape in the hip including some of the variations examined by Weidow and others but also going beyond those and allowing for previously impossible analyses of interactions between them[5,7]. Our research group used baseline hip radiographs and ASM to examine and identify the association of proximal femoral shape and incident RHOA in the Study of Osteoporotic Fractures (SOF) cohort[7]. Similarly, reports at the 2009 American College of Rheumatology conference found that hip OA was associated with hip shape modes in ASM using DXA scans[8] and that ASM modes of the hip correlate with pain and functional impairment[9].

To date, there are no studies which have examined compartment-specific knee OA and its relation to femoral hip shape in a large dataset using modern statistical image analysis techniques. We hypothesized that specific shapes of the proximal femur would be independently associated with lateral and medial compartment knee OA. Given that there are differences by sex in the compartmental distribution, we also tested for differences by sex in any associations between proximal femur shape and knee OA.

Methods

Study subjects and population

To test this question we used the NIH-Foundation funded Osteoarthritis Initiative (OAI) cohort. The OAI enrolled 4796 participants with or at high risk of knee OA at baseline in four clinical centers with a coordinating center at University of California, San Francisco (information available online at http://www.oai.ucsf.edu). Approval for the OAI project was given by the institutional review boards at each OAI center, and for this project at the IRB at University of California, Davis.

Selection of cases and non-cases for ASM

Three groups of hip and knee pairs were selected for this study, one group with lateral knee OA, one with medial knee OA and one non-case group with no knee OA. Eligible participants had no rheumatoid arthritis, osteonecrosis or amputation, and the knee had not been replaced. Similarly, eligible hips had no surgical replacement or fracture. Case knees were selected weighted back to the OAI population based on sex and age in 10 year intervals (45–54 years/female, 45–54 years/male, 55–64 years/female, 55–64 years/male, 65–79 years/female, 65–79 years/male). Control knees were frequency matched by sex and by age in the same 10 year intervals. Participants were eliminated if either the pelvic film or the knee film were of poor quality or if there were uninterpretable anatomy due to the proximal femur or knee projecting out of the film's field. The final analytic sample included 506 knees with ipsilateral hip shape modes and knee OA status data available. There were 168 knees without medial or lateral knee OA, 169 knees with lateral knee OA and 169 knees with medial knee OA.

Radiography

Bilateral fixed-flexion posterior-anterior radiographs taken in Plexiglass fixed-frame positioning were obtained at baseline and were read centrally by two experienced readers with musculoskeletal training with disagreements adjudicated. These radiographs provided Kellgren/Lawrence grade (K/L grade, scale from 0 to 4[10]) and joint space narrowing (JSN; scale 0–4) by compartment for all knees within OAI. K/L grade is registered as a knee-level variable. JSN is recorded and treated separately for each compartment (medial and lateral). The cross-sectional K/L grade scores had a kappa of 0.7. Medial JSN scores had a kappa of 0.75 and lateral JSN scores had a kappa of 0.75. Antero-posterior pelvic films were acquired standing, using a special frame to keep both limbs in 10° of internal rotation, and these pelvic films provided the radiographs from which proximal femoral shape was determined.

Definition of compartment-specific osteoarthritis

Lateral compartment knee OA was defined as a knee having a K/L grade ≥ 2 along with JSN > 0 in the lateral compartment with JSN $= 0$ in the medial compartment. Medial compartment knee OA was defined as K/L ≥ 2 with JSN > 0 in the medial compartment and JSN $= 0$ in the lateral compartment. Non-cases were defined as having K/L < 2 and JSN $= 0$ in all compartments.

ASM

We utilized ASM methods similar those described in previous publications[7,11]. Two readers outlined the shape of the proximal femoral head and neck on digitized X-rays from the OAI by guiding the placement of 60 points along the hip from the lesser trochanter to the opposite side of the femoral shaft using a standardized algorithm[7,12]. Two landmark points were defined at the inferior margin of the lesser trochanter and the point on the lateral contour of the femoral shaft that is perpendicular to the femoral shaft axis. Two more landmark points were defined on the femoral neck, perpendicular to the femoral neck axis, where the femoral neck width is the narrowest. Hip shapes were 10 evenly spaced points between the lesser trochanter and inferior neck landmarks, 30 evenly spaced points between the inferior and superior neck landmark, and 20 evenly spaced points between the superior neck and lateral femoral shaft landmarks. A total of 1096 hips derived from both ipsilateral and contralateral hips (right hips mirrored to match left hips) from all analyzed participants of both case groups and control group together were used to generate a composite proximal femur shape to be used as the reference shape for measuring modes of variation from this reference. We obtained measurements of the hip shape for the cases and controls using principal components analysis, obtaining sufficient modes of variation in hip shape to account for more than 95% of the total variance