Seminars in Arthritis and Rheumatism ▮ (2016) ▮▮▮–▮▮▮

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

The association of distal femur and proximal tibia shape with sex: The Osteoarthritis Initiative☆

Barton L. Wise, MD, MSc[a,*], Felix Liu[b], Lisa Kritikos[a], John A. Lynch, PhD[b], Neeta Parimi, MS[c], Yuqing Zhang, DSc[d], Nancy E. Lane, MD[a]

[a] Department of Internal Medicine, University of California, Davis School of Medicine, Sacramento, CA
[b] Department of Epidemiology and Biostatistics, University of California, San Francisco, CA
[c] San Francisco Coordinating Center, California Pacific Medical Center Research Institute, San Francisco, CA
[d] Clinical Epidemiology Research and Training Unit, Boston University School of Medicine, Boston, MA

ARTICLE INFO

Keywords:
Sex
Knee
Femur
Gender
Osteoarthritis
Shape

ABSTRACT

Objectives: Risk of knee osteoarthritis (OA) is much higher in women than in men. Previous studies have shown that bone shape is a risk factor for knee OA. However, few studies have examined whether knee bone shape differs between men and women. The purpose of the present study was to determine whether there are differences between men and women in knee bone shape.
Methods: We used information from the NIH-funded Osteoarthritis Initiative (OAI), a cohort of persons aged 45–79 at baseline who either had symptomatic knee OA or were at high risk of it. Among participants aged between 45 and 60 years, we randomly sampled 340 knees without radiographic OA (i.e., Kellgren/Lawrence grade of 0 in central readings on baseline radiograph). We characterized distal femur and proximal tibia shape of these selected radiographs using statistical shape modeling (SSM). We performed linear regression analysis to examine the association between sex and each knee shape mode (proximal tibia and distal femur), adjusting for age, race, body mass index (BMI), and clinic site.
Results: The mean age was 52.7 years ($\pm$4.3 SD) for both men and women. There were 192 female and 147 male knees for the distal femur analysis. Thirteen modes were derived for femoral shape, accounting for 95.5% of the total variance. Distal femur mode 1 had the greatest difference in standardized score of knee shape between females and males (1.04, $p < 0.01$); modes 3, 5, 6, 8, and 12 were also significantly associated with sex. For tibial shape, 191 female knees and 149 male knees were used for the analysis. Overall, 10 modes explained 95.5% of shape variance. Of the significantly associated modes in the proximal tibia, mode 2 had the greatest difference in standardized score of bone shape between males and females (-0.30, $p = 0.01$); modes 3 and 4 were also significantly associated.
Conclusion: The shapes of the distal femur and proximal tibia that form the knee joint differ by sex. Additional analyses are warranted to assess whether the difference in risk of OA between the sexes arises from bone shape differences.

Introduction

Risk of either radiographic or symptomatic osteoarthritis (OA) is much higher in women than men [1]; however, the underlying causes for this sex difference in OA remain unknown. Several potential explanations have been proposed for the sex difference in OA, including differences in estrogen level, physical activity, and laxity or alignment [2–4], but each has only moderate supporting evidence, and none fully explains the observed sex differences.

Recently, several investigators have proposed that knee bone shape, assessed by anthropometric measures, cross-sectional findings, or statistical shape modeling, is associated with an increased risk of OA and with severity of OA [5–8]. We have reported that

☆This work was supported by the following funding sources: the Center for Musculoskeletal Health at University of California, Davis School of Medicine; Nancy Lane support by NIH K24 AR048841; Barton Wise and Nancy Lane support by NIH P50 AR060752; NIH P50 AR063043; and the Endowed Chair for Aging at University of California, Davis School of Medicine. The Osteoarthritis Initiative (OAI) is a public–private partnership comprised of 5 contracts (N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) funded by the NIH, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer, Novartis Pharmaceuticals, Merck Research Laboratories, and Glaxo-SmithKline. Private sector funding for the OAI is managed by the Foundation for the NIH.

*Correspondence to: Barton L. Wise, MD, MSc, Center for Musculoskeletal Health, University of California, Davis School of Medicine, 4625 2nd Ave, Suite 2002, Sacramento, CA 95817.
E-mail address: blwise@ucdavis.edu (B.L. Wise).

http://dx.doi.org/10.1016/j.semarthrit.2016.02.006
0049-0172/

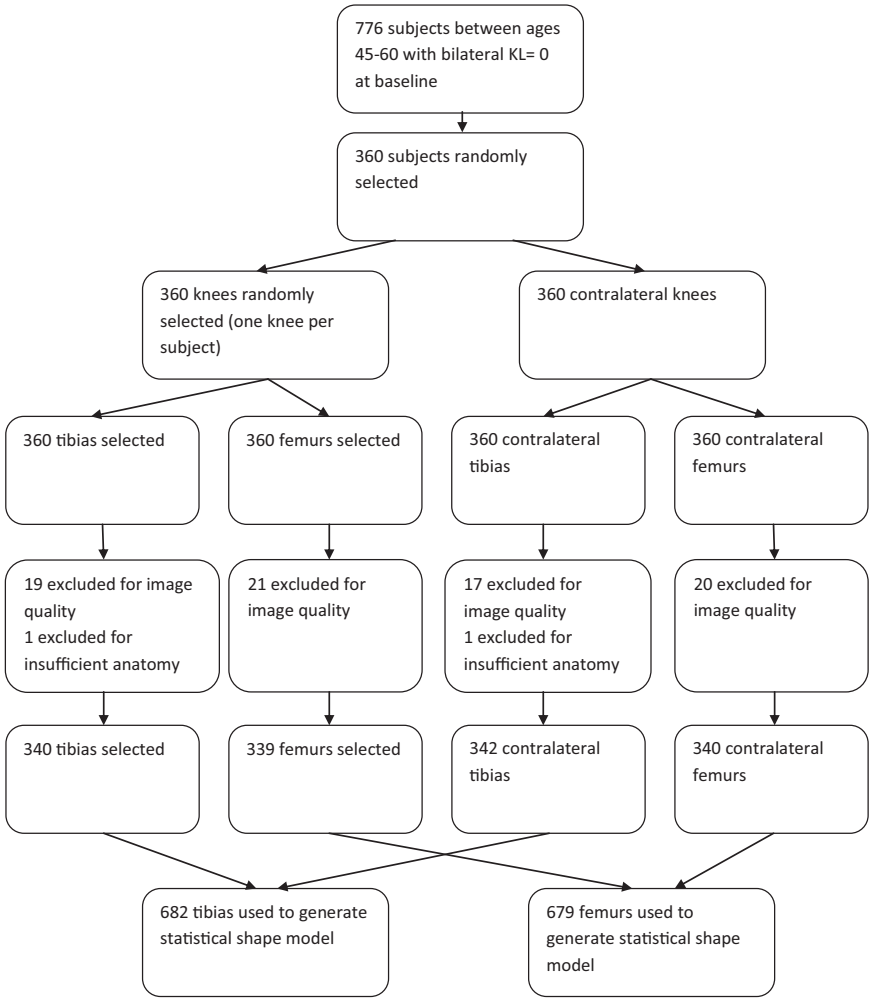

Fig. 1. Flow diagram of subject selection.

several specific proximal femoral shapes, assessed by statistical shape modeling (SSM), are associated with incident radiographic hip OA in elderly women [9] and that proximal femoral shapes are associated with compartment-specific knee OA [10]. Others have also reported that SSM-based knee shape is associated with severity of radiographic knee OA [11]. If knee bone shape is an important mediator for the differences in risk of knee OA between men and women, then one would expect knee bone shape to be different between men and women. We measured bone shape of the distal femur and proximal tibia using SSM among knees without radiographic OA and compared bone shape difference between men and women among participants in Osteoarthritis Initiative.

Methods

Study subjects and population

We selected our subjects from the Osteoarthritis Initiative (OAI) cohort, a database funded by the NIH Foundation. Four clinical centers, with a coordinating center at University of California, San Francisco, enrolled 4796 subjects with or at high risk of knee osteoarthritis at baseline. More information is 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 study subjects

Two groups were selected for this study, a female group and a male group. A sub-population of 776 subjects aged 45–60 years with a Kellgren/Lawrence (K/L) grade of 0 and with joint space narrowing (JSN) equal to 0 for both knees was selected from the OAI database. From the sub-population, 360 patients were randomly selected in the sex distribution of the total OAI. Some knees were ineligible due to poor knee film quality or if parts of the knee extended past the film window. All 679 femurs and 682 tibias remaining were used to generate the statistical shape models. Then one selected knee from each subject was used for the regression analysis. (See Fig. 1)

Radiography

In plexiglass fixed-frame positioning, bilateral fixed-flexion posterior–anterior radiographs were taken at baseline and centrally read by two experienced readers with musculoskeletal training. Any disagreements were adjudicated between the readers. From the radiographs, Kellgren/Lawrence grade (K/L grade, scale from 0 to 4) and joint space narrowing (JSN, scale of 0–3) were provided. Only knees with a K/L grade of 0 and JSN of 0 were selected. Cross-sectional K/L grade scores had a kappa of 0.7. JSN scores had a kappa of 0.75.

Statistical shape modeling

The SSM methods used in this study are similar to methods described in previous publications [10]. Radiographs where the