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The contribution of 3D quantitative meniscal and cartilage measures to variation in normal radiographic joint space width—Data from the Osteoarthritis Initiative healthy reference cohort

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ABSTRACT

Objective: To explore to what extent three-dimensional measures of the meniscus and femorotibial cartilage explain the variation in medial and lateral femorotibial radiographic joint space width (JSW), in healthy men and women.

Methods: The right knees of 87 Osteoarthritis Initiative healthy reference participants (no symptoms, radiographic signs or risk factors of osteoarthritis; 37 men, 50 women; age 55.0 ± 7.6; BMI 24.4 ± 3.1) were assessed. Quantitative measures of subregional femorotibial cartilage thickness and meniscal position and morphology were computed from segmented magnetic resonance images. Minimal and medial/lateral fixed-location JSW were determined from fixed-flexion radiographs. Correlation and regression analyses were used to explore the contribution of demographic, cartilage and meniscal parameters to JSW in healthy subjects.

Results: The correlation with (medial) minimal JSW was somewhat stronger for cartilage thickness ($0.54 \le r \le 0.67$) than for meniscal ($-0.31 \le r \le 0.50$) or demographic measures ($-0.15 \le r \le 0.48$), in particular in men. In women, in contrast, the strength of the correlations of cartilage thickness and meniscal measures with minimal JSW were in the same range. Fixed-location JSW measures showed stronger correlations with cartilage thickness ($r \ge 0.68$ medially; $r \ge 0.59$ laterally) than with meniscal measures ($r \le |0.32|$ medially; $r \le |0.32|$ laterally). Stepwise regression models revealed that meniscal measures added significant independent information to the total variance explained in minimal JSW (adjusted multiple $r^2 = 58\%$) but not in medial or lateral fixed-location JSW ($r^2 = 60/51\%$, respectively).

Conclusions: In healthy subjects, minimal JSW was observed to reflect a combination of cartilage and meniscal measures, particularly in women. Fixed-location JSW, in contrast, was found to be dominated by variance in cartilage thickness in both men and women, with somewhat higher correlations between cartilage and JSW in the medial than lateral femorotibial compartment. The significant contribution of the meniscus' position on minimal JSW reinforces concerns over validity of JSW as an indirect measure of hyaline cartilage.

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1. Introduction

Medial minimum radiographic femorotibial joint space width (minimal JSW) is currently recommended by the Food and Drug Administration as the relevant outcome measure for evaluating the structural effect of disease-modifying osteoarthritis drugs (DMOADs) on knee osteoarthritis (KOA) progression [1]. Reduction of minimal JSW (or joint space narrowing) has been suggested to not only reflect cartilage thickness loss in KOA, but to result from

Abbreviations: KOA, knee osteoarthritis; JSW, radiographic joint space width.

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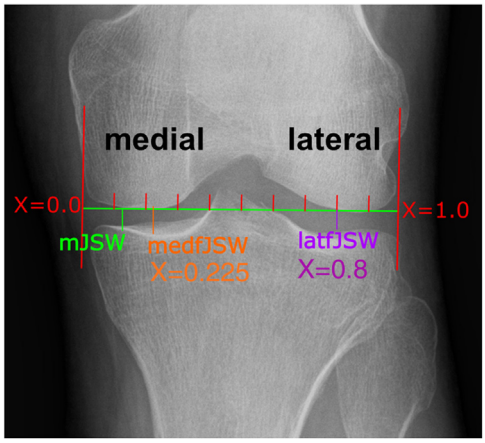

Fig. 1. Radiographic joint space width.
Fixed-flexion radiograph depicting the medial to lateral coordinate system used for fixed-location measurements (medfJSW: medial fixed joint space width at 22.5%, latfJSW: lateral fixed joint space width at 80%), as well as the minimal medial joint space width (mJSW).

a combined contribution of structural change in articular cartilage and the menisci [2–7].

To capture the relationship between radiographic JSW measures and the actual three-dimensional (3D) shape of cartilage and menisci, measurement technologies for the 3D, quantitative analysis of subregional cartilage thickness in the medial and lateral femorotibial joint [8] and for the 3D analysis of the meniscal morphology and position [9] have been developed. Further, reference data of cartilage thickness and meniscal morphology and position have been provided based on these techniques in healthy men and women [10,11].

When comparing knees with medial radiographic Osteoarthritis Research Society International [12] joint space narrowing to contralateral knees that did not exhibit joint space narrowing, it was found that 3D measures of the menisci and cartilage each provided independent information to explain side differences in JSW, and that about two thirds of these differences could be explained by a combination of quantitative cartilage and meniscal measures [5]. However, no study has previously investigated to what extent fully quantitative 3D measures of subregional cartilage thickness and the menisci contribute to explain the variance observed in normal radiographic JSW in healthy men and women without KOA. Yet, appreciating the specific contributions of each tissue in healthy reference subjects is essential for a thorough understanding of the relationship of these tissues with JSW in KOA progression, as well as for understanding the effect of DMOADs on radiographic JSW at various disease stages.

Further, fixed-location measures of JSW have recently been proposed as an alternative to measuring minimal JSW [13], with these being available for both the medial and lateral femorotibial compartment. In comparison with (medial) minimal JSW, fixed-location JSW measured in the central (x = 22.5%, Fig. 1) medial femorotibial compartment has been shown to be more sensitive to change in KOA than minimal JSW [14–16] and to better predict knee replacement than minimal JSW [17]. Yet, it is unknown to what extent the relationship between 3D subregional cartilage thickness, meniscal measures and radiographic JSW varies between minimal JSW and medial and lateral fixed-location JSWs in healthy joints.

The aim of the current study was therefore to explore comprehensively the relative contributions of 3D morphological and positional meniscal measures and cartilage thickness measures to minimal JSW, to medial and to lateral fixed-location JSW in normal, non-osteoarthritic male and female knees.

2. Material and methods

2.1. The Osteoarthritis Initiative healthy reference cohort

The Osteoarthritis Initiative (OAI) is a multicentre, prospective observational cohort study of 4796 subjects, designed to identify biomarkers and risk factors for KOA incidence and progression [18]. The OAI was approved by the institutional review board for the University of California, San Francisco and its affiliates (approval nr. H5254-20499-09), with all participants providing informed consent prior to participation. The current study used the non-exposed reference cohort of the OAI that encompassed 122 participants. These were required to have: (i) no history of pain, aching or stiffness in either knee; (ii) no radiographic femorotibial KOA in the readings performed at the four clinical sites; (iii) no rheumatoid or inflammatory arthritis; and (iv) no risk factors for KOA, specifically obesity, history of knee injury or knee surgery, family history of total knee replacement, hand OA, or repetitive knee bending at work or during other daily activities [10,18]. Of the 122 healthy reference cohort participants, 23 were later found to have a Kellgren-Lawrence Grade (KLG) > 0 in ≥1 knee based on central radiographic readings [19], and were therefore excluded from the current study. Twelve other participants could not be included due to lacking JSW measurements (n = 1), insufficient image quality for meniscal segmentation (n = 4), or lack of cartilage segmentation on the baseline magnetic resonance (MR) images (n = 7) [10]. Hence, a total of 87 participants from the OAI healthy reference cohort were studied.

2.2. Quantitative joint space width (JSW) measurements

All OAI participants underwent weight-bearing, posterioanterior fixed-flexion (10°) radiographs at each annual visit [18] (see OAI protocol: http://oai.epi-ucsf.org/). In the majority of those, semi-automated radiographic JSW measurements were performed and made publically available using validated software [14,15] (release 0.6, Fig. 1). In addition to medial compartment minimal JSW, radiographic JSW was also assessed at fixed locations in both the medial and the lateral compartment, based on a range from X = 0% to X = 100% of the mediolateral width of the distal femur [14]. For the current study, baseline minimal JSW and fixed-location measures in the centre of the medial (X = 22.5%) and lateral compartment (X = 80%) were selected as outcome measures, as these were previously shown to display a high sensitivity to change in KOA [15,16] (Fig. 1).

2.3. Quantitative cartilage thickness measurements

MR images of OAI participants were obtained using 3T MRI scanners (Siemens Magnetom Trio, Erlangen, Germany) with quadrature transmit-receive knee coils (USA Instruments, Aurora, OH) [18,20]. The OAI imaging protocol included sagittal double echo steady state sequences with water excitation (DESSwe) of both knees (0.7 mm slice thickness; 0.37 mm × 0.46 mm in-plane resolution [interpolated to 0.37 mm × 0.37 mm]) [20]. Additionally, coronal fast low angle shot images with water excitation (FLASHwe) were available for the right knees of all OAI participants (1.5 mm slice thickness; 0.31 mm x 0.31 mm in-plane resolution) [20].

Segmentation of the tibial and weight-bearing femoral cartilage and computation of the subregional mean cartilage thickness was previously performed using custom software (Chondrometrics GmbH, Ainring, Germany) using coronal FLASHwe MR images of the right knees acquired at baseline [10] as well as sagittal DESSwe MR images of the same knees (Fig. 2a). Briefly, the total subchondral bone area and the cartilage joint surface area of the medial and lat-

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