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Improved Responsiveness to Change in Joint Space Width over 24-Month Follow-up: Comparison of 3D JSW on Weight-Bearing CT vs. 2D JSW on Radiographs in the MOST Study

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Abstract

Objective: Radiographic joint space width (JSW) has been a standard for measuring knee osteoarthritis structural change. Limitations in the responsiveness of this approach might be overcome by instead measuring 3D JSW on weight-bearing CT (WBCT). This study compared the responsiveness of 3D JSW measurements using WBCT with the responsiveness of radiographic 2D JSW.

Design: Standing, fixed-flexion knee radiographs (XR) and WBCT were acquired ancillary to the 144- and 168-month Multicenter Osteoarthritis Study visits. Tibiofemoral JSW was measured on both XR and WBCT. Responsiveness to change was defined by the standardized response mean (SRM) for change in JSW 1) at predetermined mediolateral locations (JSWx) on both modalities

Author Contributions
NAS, DDA, and MCN contributed to the study conception and design. NAS, JD, MH, EM, and DDA completed data collection. NAS, MH, DDA, HC, IT, and JH contributed to data analysis and interpretation. NAS, MCN and MMA drafted the manuscript. All authors provided comments and revised the manuscript. All authors provided final approval of the manuscript. NAS supervised all aspects of this study.

Competing Interest Statement
No author declares conflicts of interest related to the current study. NAS has consulted for Trice Medical and Integra BioLife for unrelated work.

Availability of Data and Materials
All data generated and analysed in this study are available upon reasonable request. Access to data generated in this report should be sent to the corresponding author at segal-research@kumc.edu.

Public and Patient Involvement (PPI) statement
PPI was not required nor involved with any aspect of the work presented.

Ethical Approval:
Ethical approval was granted by the investigators' institutions, including University of Iowa Institutional Review Board (#201403723 and #20003064).

and 2) in the following subregions measured on WBCT images: central medial and lateral femur (CMF/CLF) and tibia (CMT/CLT), and anterior and posterior tibia (AMT/ALT, PMT/MLT).

Results: Baseline and 24-month follow-up JSWx measurements were completed for 265 participants (58.1% women). Responsiveness of 3D JSWx for medial tibiofemoral compartment on coronal WBCT (SRM range: −0.18, −0.24) exceeded that for 2D JSWx (−0.10, −0.16). Responsiveness of 3D JSW subregional mean (−0.06, −0.36) and maximal (−1.14, −1.75) CMF and CMT and maximal CLF/CLT 3D JSW changes were statistically significantly greater in comparison with respective medial and lateral 2D JSWx ($p \leq 0.002$).

Conclusions: Subregional 3D JSW on WBCT is substantially more responsive to 24-month changes in tibiofemoral joint structure compared to radiographic measurements. Use of subregional 3D JSW on WBCT could enable improved detection of OA structural progression over a 24-month duration in comparison with measurements made on XR.

Keywords

Osteoarthritis; Knee; diagnostic imaging; epidemiology

Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis and one of the most common causes of disability in the US [1]. The most commonly affected weight-bearing joint is the knee.[2] With increasing prevalence due to aging and obesity and no known cure, there is a need to accelerate therapeutic development through efficient clinical trials with measures responsive to change.

Despite the high prevalence, and the associated high costs of knee OA, clinical trials have yielded insufficient progress towards developing candidate therapeutics [3]. Key barriers include the high cost of clinical trials and challenges in accurately and reliably assessing the structural progression of OA. Introducing affordable, more responsive imaging markers could accelerate therapeutic development by reducing the sample sizes and duration necessary for clinical trials [4]. Thus, imaging markers that are responsive to progression of structural damage are needed. A responsive marker of OA progression is one that measures enough change relative to the variability and error in that measurement to determine differences in rates of progression between groups [5]. The standardized response mean (SRM) is a commonly used measure of responsiveness that assesses the magnitude of mean change in a group relative to the standard deviation of the change [6].

Radiography is the most common imaging examination used in knee OA clinical trials, with narrowing of joint space width (JSW) a well-established indicator of disease status and structural progression. 2D JSW is typically measured as the distance between projected femoral and tibial bone margins on weight-bearing coronal knee radiographs. However, 2D JSW has been shown to have low responsiveness in detecting disease progression and poor prediction of disease and symptom progression [3, 4, 7-9]. Optimal knee positioning and x-ray beam angle for assessment of JSW on knee radiographs differ by person and can be unreliable, leading to difficulty in detecting disease progression [8, 10]. Prior work demonstrated systematic differences between 2D JSW on radiographs and JSW on 3D weight-bearing imaging [11], which may have related to 1) the effect of x-ray beam angle on varying degrees of tibial plateau rim parallel alignment on radiographs while 3D imaging does not depend on x-ray beam angle,[10] 2) greater uncertainty in tibial and femoral point selection on a silhouette (radiograph) vs. on opposing 3D curved surfaces due to inability to know the sagittal tibiofemoral alignment on coronal plane radiographs (as demonstrated previously [11]), 3) greater difficulty distinguishing between subchondral bone and bony surface on radiographs (the most radiopaque line) than on 3D imaging, and/or 4) sagittal alignment influencing perceived distances on coronal radiographs [11]. These limitations have contributed to low construct validity of coronal plane radiographic 2D JSW[12-14], and led to increases in the sample size, trial duration, and costs of studies needed to demonstrate the structural benefit of proposed therapies, resulting in decreased enthusiasm for support of necessary clinical trials [3, 7, 9].

Low-dose[15] weight-bearing CT (WBCT) addresses these limitations of radiographs by providing 3D images obtained in a standardized reproducible standing position [11, 16], the position necessary for measurement of JSW. 3D JSW can be measured from WBCT by segmenting knee images to produce digital surface models of the femur and tibia bones [11]. Imaging markers from WBCT could offer substantial advantages over 2D radiographic biomarkers and better reflect disease severity and symptoms [15, 17, 18]. WBCT more accurately images patients' loaded knees[17, 19], which could have implications for improving timeliness of interventions to mitigate the long-term effects of OA. Compared to MRI, WBCT imaging markers cost less, are delivered in a scan time of only 1-2 minutes, and do not exclude patients with implanted metal. Furthermore, due to the lack of dependence on beam angle and the clear visualization of the bony margins across the full articular surface [11, 17], WBCT imaging markers could identify changes in early disease stages when people are most likely to respond to interventions, thereby enabling evaluation of the efficacy of therapies.

Despite the low responsiveness to detecting change, until recently, JSW on weight-bearing radiographs was the most common structural outcome for FDA-approved Phase 3 clinical trials of knee OA [20-23]. A necessary next step toward qualification of WBCT imaging biomarkers is to establish the responsiveness for monitoring knee structural worsening over time [22, 24, 25]. Therefore, this study aimed to determine the responsiveness of 3D JSW measured on WBCT vs. 2D JSW on fixed-flexion radiographs (FF-XR) for assessing loss of JSW as a marker for structural worsening. Specifically, we tested the hypothesis that, in comparison with radiographic JSW over 24 months, 3D JSW on WBCT demonstrates greater responsiveness (standardized response mean) for assessing knee structural worsening.

Methods

Participants and Design

This observational clinical study was conducted ancillary to the Multicenter Osteoarthritis Study (MOST), an NIA-funded investigation of opportunities for prevention and treatment of knee OA, including among people at risk for disease or with mild disease. Data collection at the University of Iowa MOST clinic (UI-MOST) was initiated in June 2016. UI-MOST followed a cohort of 1503 participants for 12 years (Existing Cohort) who had OA or were at risk of OA and subsequently recruited an additional 750 participants with at most mild OA and at most mild knee pain (New Cohort) with selection criteria described below. These participants represent those who would most likely benefit from the development of improved imaging markers for knee OA. Participants were drawn from the general population

All UI-MOST participants who were able to stand safely were included in this ancillary study. Age, sex, race, BMI and cohort characteristics were similar for the Existing and New MOST cohort groups (Supplemental Table D1). At the baseline visit for this study (144-month visit for MOST), the Existing Cohort of UI-MOST (enrolled 2003-2005) was comprised of people over age 64 with an elevated likelihood for structural progression over 24 months. These participants had at least 1 of the 3 following characteristics at enrollment: overweight/obese, knee pain/stiffness on most of the prior 30 days, or a history of knee injury/surgery. The New Cohort (enrolled 2016-2018) was comprised of people over age 45 with early-stage OA, who were at risk for worsening disease or pain. Participants included those experiencing pain, aching, or stiffness in one or both knees in the past 30 days, with neither knee having constant pain that was of severe or greater intensity and who had radiographic findings of no greater than Kellgren-Lawrence grade (KL) 2 in either knee. Exclusion criteria included: inflammatory arthritis, inability to walk independently, serious health conditions (e.g., end-stage renal disease, cancer except non-melanoma skin cancer, severe heart failure), or inability to attend 24-month follow-up. Additional exclusion criteria for this ancillary study included: KL4, bilateral total knee replacement, inability to stand still for a WBCT scan, inability to undergo MRI (e.g., implanted metal or knee size incompatible with MRI scanner) or motion artifact on the WBCT scan that interfered with JSW measurements. This ancillary study was carried out during the parent MOST examination at the Iowa site. All participants at the Iowa site who had radiographs acquired were invited unless they could not undergo WBCT imaging (e.g., unable to stand for 2 minutes without assistance or tremor), had bilateral knee arthroplasty or if their knee had end-stage osteoarthritis at either baseline or follow-up.

Image Acquisition and Interpretation

Bilateral, standing fixed-flexion PA radiographs of the tibiofemoral compartments were acquired at baseline and 24-month follow-up per MOST protocol [26]. For WBCT, similar to FF-XR, participants' toes and the medial surface of the feet were placed against vertical portions of a custom footplate to externally rotate the feet 10° on the WBCT platform. The WBCT acquisition protocol positions the tips of the great toes, the patellae, and the anterior superior iliac spines coplanar to each other, resulting in a knee flexion angle of approximately 20° [27], consistent with the knee flexion angle used for FF-XR [28-30]. The positioning frame included a coronal bar anterior to the pelvis and parasagittal (hip positioner) bars at the participants' greater trochanters. In addition to the foot, shin, thigh, and pelvic stabilization, resting hands on the handrails further reduced motion during scanning. WBCT images (CurveBeam, Hatfield, PA) were acquired utilizing cone-beam reconstruction, with a scan spanning 20cm height x 35cm width x 35cm depth (533 slices over 360° projection angle). The effective radiation dose was approximately 0.1 mSv, equivalent to the average environmental background radiation experienced when living one week at sea level.

Radiographic Measurement of 2D JSW

The distance between the projected femoral and tibial margins is the currently accepted metric for assessment of knee OA structural progression [31]. Duryea et al. developed and documented a semi-automated software tool [32, 33], to delineate the femoral and tibial margins on digital knee radiographs and enable measurements of JSW at fixed locations (JSW_x). In brief, this method involves the establishment of a coordinate system referenced to anatomical landmarks, such that each x-location represents the position of the JSW_x measurement along the coronal projected tibiofemoral joint. These measurements were made on baseline and follow-up radiographs paired within participant but blinded to time point to minimize assessment bias. The variable 'x' is a dimensionless quantity that represents the fractional distance from the medial to the lateral extent of the femur. Prior studies established the reproducibility (root mean square standard deviation (RMSSD) reproducibility ranges of (0.08–0.15) mm and (0.12–0.25) mm for non-OA and OA knees, respectively) [33] and the responsiveness (SRM: −0.15 to −0.32) [34-36] of this technique.

WBCT Measurement of 3D JSW

A 3D dataset with an isotropic resolution of 0.37 mm was reconstructed from cone-beam projection images. The tibial and femoral bone surfaces were identified in the WBCT images using a semi-automated watershed transform-based algorithm implemented in MATLAB (The Mathworks, Natick, MA, USA) to produce digital surface models of the femur and tibia bones as triangulated 3D surface meshes (Seg3D Version 2.2.1). These segmentations were presented to a user, along with tools for correcting any spurious surface information. The user refined each segmentation until it clearly captured the boundaries of both bones. Following segmentation, the tibial and femoral surfaces were smoothed in ITK-Snap to reduce artifact, after which they were re-sampled via interpolation to yield uniformly sized triangles. The net result was a smooth triangulated surface for which normals were well defined and varied gradually over the surface (Figure 1).

Methods described by Turmezei *et al* were used to define a robust 3D JSW measure insensitive to the specific nuances of segmentation.[37] From the center of each tibia surface triangle, CT intensity values were sampled along tibia surface-normal vectors from well beneath the tibia surface extending to well beyond the opposing femur surface, with the resulting line intensity profile possessing two peaks indicating subchondral bone margins. The second derivative of the CT intensities in the original scan along this line profile were used to identify these peaks and define definitive points for JSW measurement across the surface that will be accurately placed regardless of any blurring or loss of resolution in the image. The 3D JSW was then defined as the Euclidean distance between these point pairings. Locations where the 3D JSW was >10 mm (outside bounds of knee JSW [10]) or where the newly defined points were not within 2mm of the baseline segmentation [38] were identified as erroneous points and discarded. Analysts were blinded to participant, and JSWx measurements were fully automated, minimizing assessment bias by time point.

The 3D JSW data were then further processed to produce JSWx values (1) for the points along the central one-third of the anteroposterior line at each mediolateral location approximating the 2D JSWx locations on radiography (Figure 2) and (2) taking advantage of the 3D surface maps, for the points included in the following 8 tibiofemoral subregions: central medial and lateral femur (CMF/CLF) and tibia (CMT/CLT), and anterior and posterior tibia (AMT/ALT, PMT/PLT) (Figure 1). For the JSWx comparisons, the average JSW value for the central one-third of the joint was measured because that is the area where most cartilage worsening occurs (Figure 2). For example, between the 144-month and 168-month MOST visits, semiquantitative cartilage readings[39] of 1854 participants revealed that the central medial tibial subregion worsened in 7.4% of knees and the central medial femoral subregion in 12.3% of knees, 5 times more frequently than anterior (1.5%) or posterior (1.3%) medial tibial subregions and more than twice as frequently as the posterior femoral subregion (5.2%). The 3D JSW measurements were found to have high test-retest reliability over a 2-week period with repetition of participant positioning, segmentations and JSW measurements (ICC 0.90–0.97) [16].

Statistical analyses—To address hypotheses for additional ancillary studies, a total of 344 knees in 265 participants were included. Some measurements at some locations could not be completed, leading to missing data for a small number of measures. For example, the JSWx=0.300 (near the tibial spine) and 0.750 (lateral compartment) locations in some knees had measurements >10mm, exceeding the predetermined threshold for inclusion. The sample size for each analysis is presented in the tables.

To address the hypothesis that, in comparison with change in radiographic 2D JSW over 24 months, 3D JSW on WBCT demonstrates greater responsiveness to change, as measured by the standardized response mean (SRM), the following methods were employed. SRMs were calculated for the JSW at each of the JSWx locations (medial: x=.150, .175, .200, .225, .250, .275, and .300; and lateral: x=.750) on radiographs (XR) and WBCT (JSWx). Taking advantage of the 3D surface maps from WBCT, subregional 3D JSW was summarized as the change in the mean JSW value (mean JSW across all points in a subregion at follow-up minus mean JSW across all points in the subregion at baseline) and the maximal change in JSW (greatest change in JSW value at any individual point matched between baseline and follow-up) for the points included in each subregion (Figure 2): central femur and tibia and anterior and posterior tibia (4 subregions in each of the medial and lateral tibiofemoral compartments). Data for all participants with 2D and 3D JSW measurements were analyzed first and then analyzed separately for those with baseline Kellgren-Lawrence (KL) grade of 2-3 indicating radiographic OA, to assess for differences in responsiveness to change based on baseline OA status. Because some participants contributed two knees, these knees were not considered as independent and identically distributed samples. Comparison of the SRMs for JSW between WBCT and radiographs were analyzed using mixed models (full details in Supplement) plus the bootstrap approach. Mixed models were used to estimate all SRMs with accommodation the correlations between two knees within subjects and bootstrap was used for its robustness in providing 95% confidence intervals. While the sample size was 344 for almost all analyses, 2D JSW at the x=.150 location for 3 knees and KL grade was missing for 1 knee, reducing the sample size for those specific analyses.

While the responsiveness of JSWx on WBCT could be compared to the responsiveness of JSWx on XR at each of the 8 comparable locations, responsiveness of CMT and CMF subregional 3D JSW was compared with the responsiveness of 2D JSWx at the x=0.225 location, as JSWx at this location has been found to be superior to minimal JSW for knees with early OA [36], similar to the cartilage morphology at the central medial tibia and most similar to 3D JSW measured on WBCT[11]. Similarly, the central lateral subregional 3D JSW (CLT/CLF) were compared with the x=0.750 2D JSWx location.

Results

A total of 266 participants completed both the baseline and 24-month follow-up imaging and had JSWx measurements in 344 knees on both XR and WBCT at both time points (bilateral knees for 79 and unilateral for 186 participants). Participants' characteristics are presented in Table 1. Of the analyzed sample of knees, 58.1% were from women and 41.9% were from men.

Responsiveness of JSWx on XR vs. on WBCT

The responsiveness to change in JSWx at each mediolateral location on XR and WBCT is presented in Table 2. For the overall group, responsiveness to change was significantly higher for JSWx on WBCT than for JSWx on XR for only the x=0.275 location (p=0.020 comparing the SRM for JSWx on XR with the SRM for JSWx on WBCT). XR JSWx had better responsiveness for the lateral (x=0.750) location. The mean±SD magnitudes of change in 2D JSW and mean 3D JSW and the 95% CI for the differences between them are presented in Supplemental Table S3.

Responsiveness of Subregional 3D JSW on WBCT

Table 3 presents the responsiveness for maximum and mean change in subregional-3D JSW over the 24-month follow-up period in each subregion. The SRMs for maximum change were generally higher for the central subregions of the medial and lateral femur and tibia, while lower for the anterior and posterior subregions of both compartments (Table 3). The SRMs for mean changes in 3D JSW subregions also tended to be higher in central than in peripheral subregions (Table 3). Compared to 2D JSWx, SRMs were significantly greater for maximal changes in the CMF, CMT, CLF and CLT subregions (p< 0.001) and for mean changes in the CMF (p< 0.001) and the CMT (p< 0.002) subregions. The SRM for knees with radiographic knee OA (KL2-3) were very similar to those for the overall cohort and are presented in Supplementary Tables S1 and S2. The mean±SD magnitudes of maximal change in 3D JSW and the 95% CI for the differences with 2D JSW are presented in Supplemental Table S3.

Discussion

Longitudinal knee OA structural disease outcomes are frequently assessed by measuring the distance between the projected femoral and tibial margins on radiographs. However, bony overlap can obscure regions of the joint since the knee is an inherently 3D structure, potentially limiting the information that can be derived from 2D representations. In contrast, WBCT provides a 3D representation of the knee joint structure, unencumbered by bony overlap, allowing greater sensitivity and accuracy for detection of OA features[17]. The present study found that extension of this legacy measurement of 2D JSWx at specific mediolateral locations on WBCT— did not significantly differ from the responsiveness of 2D JSW_x. However, taking better advantage of the 3D nature of WBCT, the responsiveness of subregional 3D JSW change over 24 months was significantly higher than the responsiveness of fixed location 2D JSW_x. The 24-month responsiveness of subregional 3D JSW remained consistent across medial and lateral tibiofemoral subregions and was significantly more responsive to change than radiographic JSW_x. Thus, subregional 3D JSW could be useful for detecting the progression of knee structural worsening.

Despite its relatively low responsiveness [3, 4, 7-9], radiographic JSW has been the primary imaging biomarker accepted by the FDA and EMA for assessment of OA structural progression in Phase 3 clinical trials. Reichmann et al. assessed the responsiveness of radiographic JSW measurements over a variety of follow-up durations and reported an overall pooled SRM for radiographic JSW of −0.33 [35]. In comparison, maximum change in 3D JSW measured by WBCT over 2 years in this study had SRM that ranged from −1.14 to −1.82 for the overall cohort. The distribution of SRM's for mean change in subregional 3D JSW ranged from −0.57 to 0.10, similar to that published for radiographs for over 2-years. This may be due to radiographs being a bony silhouette, while WBCT evaluates the volumetric continuum of the tibiofemoral joint. This is supported by prior work that found PA radiographs to have lower sensitivity and accuracy for identifying osteophytes and subchondral cysts than WBCT [17], and may account for why the differences between WBCT and radiographs are more prominent in early disease stages.

Paixao et al. assessed and compared the performance of radiographic JSW to a novel quantitative measure, standardized JSW (stdJSW). They reported that stdJSW outperforms JSW as it assesses the degree of narrowing independent of height [40]. The SRM values for WBCT measurements of maximal change in 3D JSW in the current study exceed those for radiographic stdJSW in the study by Paixao, as well as those for JSW_x. Our data indicate that subregional 3D JSW by WBCT is more responsive to longitudinal changes in the tibiofemoral joint structure than has been reported for radiographic measurements at lower levels of knee OA severity and comparable to the responsiveness of radiographic JSW_x at higher levels of OA severity. The SRMs for maximum changes in subregional 3D JSW also exceed those reported for MRI measurements of quantitative cartilage volume[41, 42]. Since the MOST study did not include measures of quantitative cartilage volume and thickness, SRM's for change in those measures could not be directly compared. Additional research is necessary to evaluate the extent to which the improved responsiveness of these novel measures of 3D JSW may better reflect disease severity and changes in patient-reported outcomes.

This study assessed responsiveness of both WBCT measurements of JSW_x as well as subregional 3D JSW. The purpose of mimicking 2D JSW_x measurements on WBCT was to assess whether adding the dimension of depth at the coronal fixed locations could more sensitively detect changes in the knee than on 2D imaging. In this study JSW_x measurements by WBCT were more responsive than by radiographs at the x=0.275 location, where structural damage of OA occurs most frequently, but not at other fixed locations. However, responsiveness of subregional 3D JSW was greater. This suggests that limiting measurements to discrete mediolateral locations, as done in the JSW_x approach, may restrict potential to detect changes in knee JSW in comparison with the greater sampling of JSW values available with subregional 3D JSW measurements. Thus, measurement of subregional 3D JSW may improve responsiveness to detecting knee joint structural change over time.

Subregional 3D JSW may enable valid stratification of patients for therapies by characterizing knee joint structural worsening more accurately than has been possible with XR. The capability to more accurately image patients' loaded knees in 3D [17] and at the same relative radiation dose as XR [43] could enable more timely interventions (e.g., bracing or surgery) to target joint areas at risk and mitigate the long-term effects of OA. Our findings support the ability of WBCT imaging markers to overcome some limitations of XR in delivering responsive measures of knee structural change.

A strength of this study is the sample size (N=344 knees). Participants were community-recruited, rather than a clinic sample, providing a range of age, disease severity, socioeconomic status, and other characteristics. While our sample was composed of >52% participants without any radiographic evidence of knee OA (KL0), the MOST cohort was recruited to follow people with knees at elevated risk of developing OA, so may demonstrate a higher rate of structural worsening over time than an unselected sample. The radiographic and WBCT measures have been validated and shown to have good test-retest reliability [16, 33]. Another strength is the rigorous XR acquisition methods used in the MOST study [26], as well as the meticulous measurements made by the developer of the JSW_x measurement. Thus, the results likely reflect comparing 3D JSW to high quality 2D JSW_x data—possibly better radiographic data than may be acquired or measured in clinical settings.

A limitation of this study is that positioning of knees at 24-month follow-up may have differed from baseline. However, given the generally lower responsiveness of radiographic JSW, this limitation may have affected radiographs to a higher degree than WBCT and this could relate to the independence of WBCT from beam angle and bony overlap which affect visualization on XR. Another limitation was the relatively few knees in the KL2 and KL3 strata. This distribution related to studying a cohort selected for being at risk for knee OA. Thus, study of people with these OA grades, who are more likely to participate in clinical trials would be useful. Finally, to make comparisons between fixed-location JSW_x measurements on XR vs. on WBCT, we had to accept limitations associated with projecting a 3D measure onto a 2D space. We chose to sample JSW_x measures on WBCT in the central one-third of the joint along the AP direction. This strategy apparently worked better in medial joint. There was only one lateral fixed point 2D JSW measurement made, at x=0.750, near the tibial spine, where the central one-third sampling strategy may be less reliable. This is a region of the joint where there is likely little weight bearing. The subregional 3D JSW measurements were not subject to this same limitation.

In conclusion, the present study revealed that subregional 3D JSW on WBCT is significantly more responsive to temporal changes than 2D JSWx on XR in knees with or at risk for knee OA, but that, measurement of specific mediolateral locations on WBCT (JSW_x) was not clearly more responsive than JSW_x on XR over 24-month follow-up. Responsiveness of maximum change in subregional 3D JSW greatly exceeded that for XR in this study and for responsiveness reported for MRI in prior studies. Use of subregional 3D JSW on WBCT could enable improved detection of OA structural progression over a 24-month duration in comparison with measurements made on XR.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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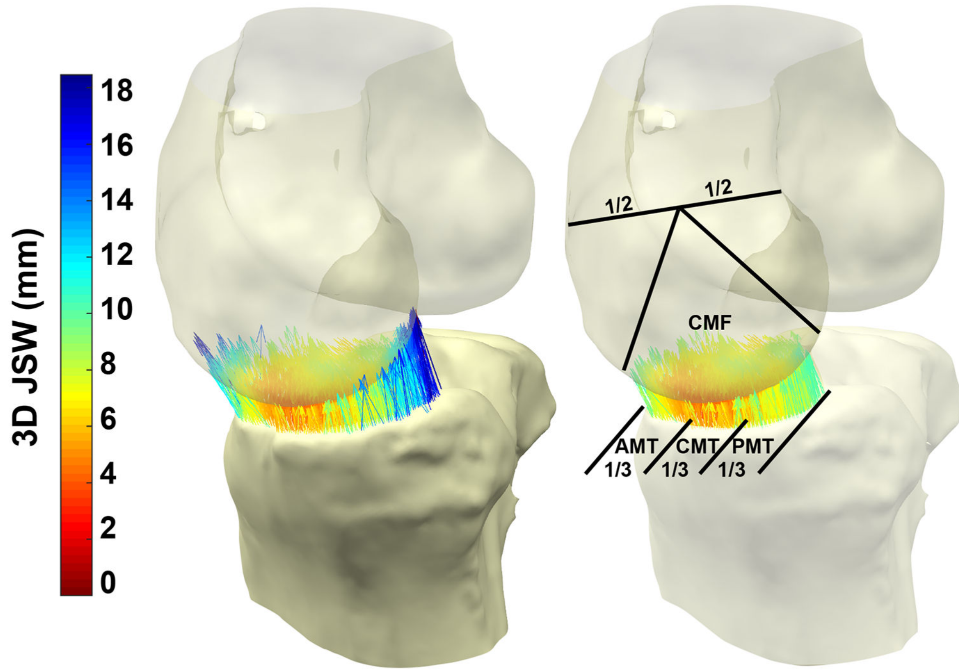
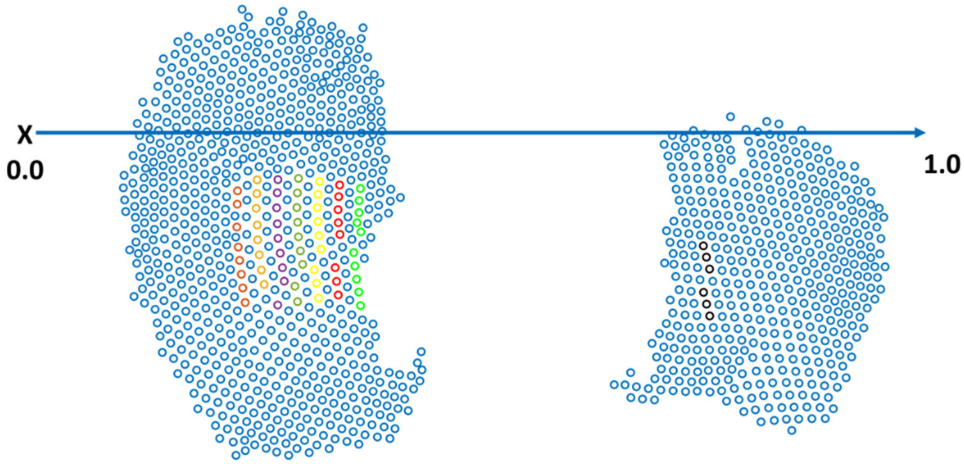


Figure 1. Subregional 3D Joint Space Width

The tibia-normal vectors and their distances on the medial condyle of a right knee are shown (left). Any vectors with length >10 mm were discarded (right) and the remaining vectors were analyzed. Medial tibiofemoral sub-regions were defined by the anterior, central, and posterior portions of the tibia, with the entire medial compartment dataset considered as the central medial femoral sub-region. Lateral compartment, subregions, ALT, CLT, PLT and CLF, were defined in the same manner. Note that the central femoral subregions articulate with all three tibial subregions in each tibiofemoral compartment.



X-Value	0.15	0.175	0.2	0.225	0.25	0.275	0.3	0.75

Figure 2. Illustration of WBCT JSWx Methods

In the medial (left) and lateral (right) tibiofemoral compartments, mediolateral x-value locations were defined using the same methodology as on radiographs and the average value along each anteroposterior line in the central 1/3 of the tibial plateau at those x-locations was output.

Table 1.

Subject Characteristics (N=266 ppts/344 knees)

Person level	**N=266 participants**
1 knee included	188 (70.7%)
2 knees included	78 (29.3%)
Age (years)	63.2±9.0 (range 45–87)
Sex	151 women / 115 men
Race (%)	97.7% white non-hisp(260); 2.3% (6) Other
BMI (at baseline)	28.2 ±4.9 (range 19.2–42.9) kg/m^2
Knee level	**N=344 knees**
Narrower compartment at	XR: Lateral: 2.0% Medial: 98.0%
baseline (%)	WBCT: Lateral: 6.7% Medial: 93.3%
KL Grade % (N)	0: 54.3% (187) 1: 23.0% (79) 2: 18.3% (63) 3: 4.4% (15)

Table 2.

Responsiveness to Change in JSWx on XR and WBCT over 24 months (SRM, 95% CI; N=344)

JSWx Location	Sample Size	2D JSWx (XR) SRM (95% CI)	3D JSWx (WBCT) SRM (95% CI)	(2D-3D) Mean Difference* (95% CI)	p-value for differences in SRMs*
0.150	341 knees/263 ppts	−0.10 (−0.18, −0.02)	−0.19 (−0.27, −0.10)	0.091 (−0.009, 0.191)	0.074
0.175	343 knees/265 ppts	−0.12 (−0.19, −0.04)	−0.21 (−0.30, −0.12)	0.091 (−0.011, 0.194)	0.080
0.200	344 knees/266 ppts	−0.14 (−0.22, −0.06)	−0.21 (−0.30, −0.13)	0.073 (−0.032, 0.177)	0.174
0.225	344 knees/266 ppts	−0.13 (−0.21, −0.04)	−0.19 (−0.28, −0.10)	0.058 (−0.053, 0.170)	0.306
0.250	342 knees/265 ppts	−0.14 (−0.23, −0.06)	−0.20 (−0.29, −0.10)	0.067 (−0.052, 0.185)	0.271
0.275	340 knees/264 ppts	−0.14 (−0.23, −0.06)	−0.24 (−0.33, −0.16)	0.132 (0.021, 0.244)	0.020
0.300	307 knees/243 ppts	−0.16 (−0.25, −0.08)	−0.18 (−0.27, −0.09)	0.023 (−0.088, 0.135)	0.708
0.750	329 knees/258 ppts	−0.15 (−0.25, −0.06)	0.01 (−0.07, 0.10)	−0.166 (−0.289, −0.043)	0.008

*A positive mean difference means a greater reduction in 3D than in 2D joint space width, meaning 3D measure is more responsive.

Table 3.

Responsiveness (SRM, 95% CI) of Maximum and Mean Change in 3D JSW in Tibiofemoral Subregions over 24 months and Comparison with SRM for 2D JSWx

Sub-Region	SRM for Maximum Change in 3D JSW (N=341 knees/263 ppts)		p-values for differences with 2D JSWx SRM	SRM for Mean Change in 3D JSW (N=341 knees/263 ppts)		p-values for differences with 2D JSWx SRM
CMF	−1.75	(−1.91, −1.60)	< 0.001 *	−0.31	(−0.39, −0.22)	< 0.001 *
CMT	−1.73	(−1.92, −1.55)	< 0.001 *	−0.27	(−0.35, −0.18)	0.006 *
AMT	−1.14	(−1.24, −1.04)	NA	−0.06	(−0.15, 0.03)	NA
PMT	−1.60	(−1.72, −1.47)	NA	−0.36	(−0.44, −0.29)	NA
	(N=339 knees/261 ppts)			**(N=339 knees/261 ppts)**		
CLF	−1.83	(−1.99, −1.67)	<0.001 **	−0.23	(−0.31, −0.15)	0.623 **
CLT	−1.73	(−1.97, −1.49)	<0.001 **	−0.20	(−0.29, −0.12)	0.761 **
ALT	−1.15	(−1.23, −1.06)	NA	−0.11	(−0.19, −0.02)	NA
PLT	−1.26	(−1.39, −1.12)	NA	−0.13	(−0.22, −0.02)	NA

*Medial compared with JSWx 0.225 location with SRM [−0.13 (−0.21, −0.04)] on XR

**Lateral compared with JSWx 0.750 location with SRM [−0.15 (−0.25, −0.06)] on XR; N/A indicates no 2D location specific to the anterior or posterior tibia. Central medial and lateral femur (CMF/CLF); tibia (CMT/CLT); anterior and posterior tibia (AMT/ALT, PMT/MLT); SRM (mean change/SD of change).