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THE RELATIONSHIP OF THREE-DIMENSIONAL JOINT SPACE WIDTH ON WEIGHT BEARING CT WITH PAIN AND PHYSICAL FUNCTION

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Abstract

Limitations of plain radiographs may contribute to poor sensitivity in the detection of knee osteoarthritis and poor correlation with pain and physical function. 3D joint space width, measured from weight bearing CT images, may yield a more accurate correlation with patients' symptoms. We assessed the cross-sectional association between 3D joint space width and self-reported pain and physical function. 528 knees (57% women) were analyzed from Multicenter Osteoarthritis Study participants. An upright weight bearing CT scanner was used to acquire bilateral, weight-bearing fixed-flexion images of the knees. A 3D dataset was reconstructed from cone beam projections and joint space width was calculated across the joint surface. The percentages of the apposed medial tibiofemoral joint surface with joint space width <2.0mm and <2.5mm respectively were calculated. Pain and physical function were measured using Western Ontario and McMaster Universities Osteoarthritis Index. Participants who reported greater pain severity tended to have a greater joint area with joint space width <2.0mm ($p=.07$ for the highest vs. the lowest tertile). Participants who reported greater functional limitations had a greater joint area with joint space width <2.0mm ($p=.02$ for the highest vs. the lowest tertile). There appears to be an association between the medial tibiofemoral area with joint space width <2.0mm and pain and physical function.

Keywords

Imaging; Three-dimensional; Knee Joint; Arthralgia; Physical Function

Introduction

Osteoarthritis (OA) is the most common musculoskeletal disorder in older adults, and the knee is the most commonly affected weight-bearing joint. The diagnosis of knee OA is

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based on a combination of symptoms, clinical signs, and radiographic abnormalities. Despite the high prevalence of knee OA, plain radiographs, the most common test for diagnosis, are insensitive to diagnosing early disease.[1]

Joint space width (JSW) is used as an indicator of knee joint health and is most often measured as the distance between the projected femoral and tibial margins on weight bearing radiographs. Change in tibiofemoral JSW has been found to be associated with the change in cartilage volume.[2] Joint space narrowing (JSN) due to loss of articular cartilage and meniscal thickness can be calculated based on the change in JSW. Currently, JSN is the only structural outcome measure recommended by the U.S. Food and Drug Administration (FDA) and the European Medications Agency (EMA) for determining the change in OA disease activity in Phase III clinical trials.[1]

Since plain radiographs capture only a 2D projection of a 3D structure, the reliability and precision of 2D JSW measurements are highly dependent on the acquisition conditions, such as the position of the knee, knee flexion angle and the alignment of the X-ray beam with the tibial plateau.[1] Even with optimal acquisition conditions, conventional radiographs can remain insensitive, inaccurate and have poor concurrent validity for knee OA features,[3; 4] in comparison with 3D weight bearing computed tomography (WBCT),[5] MRI,[6] and arthroscopy.[7] These factors contribute to potential for radiographs to fail to detect evidence of OA in the knee for years after the disease process begins. A previous study found that more than two-thirds of knees with no evidence of OA on plain radiographs demonstrate cartilage damage visualized by MRI.[1] The challenges with clearly visualizing the joint on plain radiographs may also limit responsiveness to the detection of change in radiographic JSW over time.

WBCT imaging has been shown to be more sensitive and accurate for the detection of osteophytes, subchondral cysts, cartilage and meniscal morphology than conventional fixed-flexion radiography.[5] In contrast to MRI, which is excellent for visualizing cartilage and other soft tissues, WBCT requires less scanning time (less than 2 minutes), floor space (1.2 × 1.5m), purchase (approximately US$200,000) and maintenance costs (no liquid coolant or other ongoing maintenance). While WBCT scans can be acquired in a bilateral standing and fixed-flexion position, MRI is most commonly acquired in a supine, non-weight bearing position[8]. A recent study revealed that radiographic measurement of tibiofemoral 2D JSW poorly correlates with articular cartilage thickness measured with MRI.[9] This study, comparing JSW measurements obtained from weight-bearing vs. non-weight bearing imaging, provides additional evidence of the importance of obtaining weight-bearing knee imaging.

Previous studies revealed associations between 2D JSW and pain.[10–12] However, lower baseline minimum 2D JSW was not associated with physical performance measures, such as walking pace or repeat chair stand time.[12] One factor that may contribute to the lack of association with physical function is error in measurement of JSW due to bony overlap on plain radiography obscuring the edges of the joint margin. In contrast, 3D JSW measured using an imaging modality that is unencumbered by bony overlap, such as WBCT, could potentially correlate better with pain and physical function. The objective of this study was to characterize, for the first time, an association of 3D JSW (measured from WBCT) with pain and physical function.

Methods

Participants

In this cohort study (Level of Evidence: IIB), data were analyzed from the Multicenter Osteoarthritis Study (MOST) participants at the 144-month clinic visit. Community-based recruitment was used to assemble this longitudinal cohort of participants who were either 1) age 62–91 years with or at risk for symptomatic knee OA,[13] or 2) over age 45 years, with knee pain, aching or stiffness in the past 30 days, with neither knee having constant severe pain or participants without any knee aching or stiffness in the past 30 days. All participants who attended the 144-month visit of the MOST study at the Iowa site were eligible for this ancillary study. Knees were excluded if they had either severe knee OA (Kellgren-Lawrence grade 4 (KL4)) or total knee arthroplasty (TKA) as there was no joint space to measure, or if there was motion artifact on the WBCT scan that prevented accurate measurement. All participants completed a University of Iowa institutional review board-approved informed consent process, culminating in signing a consent document, in compliance with the Helsinki Declaration.

Assessment of Radiographic Knee Osteoarthritis—At the MOST clinic visit, a bilateral, standing fixed-flexion postero-anterior (PA) view of the tibiofemoral compartments was acquired,[14–16] using a protocol in which knees were flexed 20–30° and feet externally rotated 10° using a plexiglass positioning frame (SynaFlexer).[17] Radiographs were Kellgren-Lawrence (KL) graded, with disagreements adjudicated by consensus reading.[14; 18]

Anthropometric Measures—Body mass index (BMI, kg/m^2) was calculated from weight in kilograms divided by the square of the height in meters (stadiometer, Holtain, Wales, UK), as measured by trained and certified staff.[19]

Weight Bearing CT Image Acquisition and 3D JSW Measurements

A prototype of a commercial scanner (InLine, Curvebeam LLC., Warrington, PA) was used to acquire bilateral, fixed-flexion, weight bearing images of the knees. A custom radiolucent positioning system was used to maintain foot external rotation and fixed knee flexion angles. with participants' thighs and hands contacting the unit for stability. The scanner produced pulsed cone-beam X-ray on a 30 X 30 cm amorphous silicon flat-panel detector over a 360° projection angle, with a total scan time of 32 seconds (effective dose of 0.1 mSv, equivalent to the average environmental radiation experienced by a person living at sea level for one week).

A 3D dataset with an isotropic resolution of 0.37mm and a field of view of 200 X 350mm was reconstructed from initial cone-beam projections. Tibiofemoral geometries were obtained through semi-automated segmentation of the WBCT images as triangulated 3D surface meshes (Seg3D Version 2.4.0). Segmentation of tibial and femoral margins on the WBCT images utilized custom MATLAB (MathWorks, Inc. Natick, MA) coding to identify bone and non-bone portions, by applying thresholding algorithms based on the higher density of bone in comparison with the adjacent soft tissues. The segmentation masks for each sagittal slice were manually assessed to ensure the accuracy of the segmented bone models, and any spurious segmentations were corrected. The voxellated triangulated mesh surfaces of the tibia and femur from the raw segmentations were lightly smoothed using Geomagic Studio software (3D Systems, Inc., Rock Hill, SC) to repair local errors invariably introduced during surface generation from the segmentations.

These smoothed tibial and femoral subchondral surfaces were used to locate the nearest-neighboring element of the femur for each element on the tibia. The Euclidean distance between each element on the tibial subchondral bone surface and its nearest neighbor on the femoral subchondral surface, defined as the 3D JSW, was computed in MATLAB. Each distance was assigned a color, and these colors were overlaid on the tibial articular surface, producing a color-coded map of the 3D JSW at every point on the subchondral surface (Figure 1).

The area of each element on the tibial surface was calculated and paired with the previously calculated distance to produce distance-surface area data. A proximity threshold of 10mm was selected to define the contacting regions of the joint, and the surface areas of every element with a distance < 10mm were summed to generate the total tibial subchondral area. The medial tibial subchondral area was computed. Then, the percentages of the medial tibial surface areas with JSW < 2.0mm and < 2.5mm respectively were calculated, a technique that was previously validated.[1; 20] These thresholds were chosen to indicate the amount of the tibial surface that was in abnormally close proximity to the opposing femoral surface. The reproducibility of medial tibiofemoral JSW measurements acquired using these methods was previously shown to have a test-retest reliability ICC of 0.97 (95% CI: 0.94 – 1.00), a root mean square error of 1.5% and a root mean square standard deviation of 2.7%.[21]

WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores

Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, a validated instrument recommended by the WHO for monitoring knee OA progression, was completed at baseline. This study utilized a modified version of WOMAC Likert format 3.0.[22]

A. *Knee-Specific* Pain—The knee pain subscale of WOMAC was utilized for the present study. This subscale is comprised of 5 items with responses that range from no (0) to extreme (4) pain with a possible total score of 20. Participants provided pain scores for each knee (knee-based score). Higher scores on WOMAC indicate greater knee-specific pain.

B. Physical Function—Self-reported physical function (PF) was assessed using the physical function subscale of WOMAC. This instrument comprises 17 questions related to physical function with responses that range from no (0) to extreme (4) difficulty in completing daily physical activities. The total possible score is 68, with higher scores indicating worse physical function.

Statistical Analysis

In this cohort study, all analyses were knee-based. The following characteristics were summarized: participant characteristics including age, sex, and BMI, as well as knee characteristics including 3D JSW, WOMAC-Pain, and WOMAC- PF at 144 months. To accommodate skew of WOMAC scores and 3D JSW variables towards zero, these data were split into the best approximation of tertiles (Tables 1, 2 and 3), with zero being the reference tertile, and the remaining observations were divided into 2 equal groups (sex-specific strata for 3D JSW). The predictors were the tertiles of % of area of the medial tibiofemoral compartment with 3D JSW <2.0mm and <2.5mm respectively. For each threshold, two models were analyzed using ordinal logistic regression, where the outcomes were tertiles of WOMAC pain and WOMAC-PF respectively. All analyses were adjusted for age, sex, and BMI. Although sex-specific strata of the predictor variable afforded a gross correction for sex differences, including sex as a covariate adjusted for any potential residual confounding based on sex. Alpha level was set at <0.05 for statistical significance.

Results

528 right knees (Figure 2) of participants (57% women) with a mean±SD age of 63.6±10.1 years and BMI of 28.5±5.1 kg/m^2 were analyzed. More than half of the participants had pain scores of zero. Similarly, more than 1/3 of the participants had physical function scores <2, demonstrating minimal physical functional limitations. Participants who had a greater % area with 3D JSW<2.0mm tended to report greater pain severity but did not reach statistical significance (Table 4; p=.07 for the highest vs. the lowest tertile). Participants who had a greater % area with 3D JSW<2.0mm reported greater functional limitations (Table 5; p=.02 for the highest vs. the lowest tertile). Figure 3 presents box plots illustrating the percent joint area with JSW <2.0mm for each a) WOMAC Pain tertile and b) WOMAC Physical Function tertile. For the 2.5mm threshold, although there was a greater % area with 3D JSW<2.5mm in participants with worse WOMAC and a lower % area with 3D JSW<2.5mm in participants with low WOMAC scores, this was not statistically significant for pain (Table 6; p=0.54) or physical function (Table 7; p=0.41).

Discussion

Change in standing fixed-flexion radiographic JSW is the primary outcome measure utilized in clinical trials to determine the structural progression of knee OA. In this study, we assessed the cross-sectional associations between 3D JSW and pain and physical function. 3D JSW measurements were made with WBCT imaging of the tibiofemoral joint, using the same Relative Radiation Level as knee radiography.[23] After adjusting for age, sex, and BMI, our results suggest that there is a statistically significant association between the percent of the joint with a 3D JSW <2.0mm and physical function, but there was no such association between 3D JSW and either pain or physical function at the 3D JSW <2.5mm threshold.

The results of this cross-sectional analysis differ from outcomes reported for previous studies.[10; 12; 24; 25] Muraki et al. described the association between 2D radiographic minimum JSW in the medial compartment and pain at the knee joint for participants in the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study, a large population-based Japanese cohort.[25] In that study, the investigators reported a statistically significant association between knee pain at minimum 2D JSW thresholds of <3mm and <2mm for men and women respectively. In a longitudinal study correlating 2D radiographic JSW with 4-year clinical outcomes in patients with knee OA, investigators found that, after controlling for other potential covariates (age, sex, race, BMI, and knee alignment), lower baseline minimum JSW was significantly associated with worsening of pain, symptoms, and quality of life scores (KOOS). However, the lower baseline minimum 2D JSW was not significantly associated with physical performance measures, such as walking pace or repeat chair stand time.[12] Another longitudinal study that investigated the relationship between radiographic changes and knee OA symptoms over 3 years, reported increased severity of knee symptoms such as pain with decreasing 2D JSW.[24] In contrast, Kinds et al. reported a negative correlation between minimum 2D JSW and WOMAC pain and physical function noticeable at the 5 year follow up timepoint.[10]

Our methods were similar to those of previous studies,[10; 26–29] with respect to correlating WOMAC pain data with ipsilateral knee pain. However, there are several potential explanations for the differences between our results and those of previous studies, including the intrinsic differences between 2D radiographic and 3D WBCT measurements of JSW and between cross-sectional and longitudinal studies. It is also possible that the relatively low severity of disease in our cohort may have affected the results, as the majority of participants reported no knee pain, more than one-third had WOMAC physical function scores <2 and greater than two-thirds had 0% of the 3Djoint space at or below the 2.0mm and 2.5mm thresholds.

Despite these differences in participant characteristics, this baseline dataset may prove useful for the study of associations between the longitudinal progression of structural and symptomatic knee OA in these participants. Results from prior studies have shown that there is a discordance between structural change, pain, and disability in people with knee OA.[30] It is estimated that between 40–80% of people diagnosed with radiographic knee OA have symptoms such as pain.[31]Thus, structural changes visualized on radiographs have an imperfect correlation with symptoms.[32]

Additionally, our structural predictor, 3D JSW, represents the aggregate loaded thickness of articular and meniscal cartilage, while the outcomes—pain and physical function— are certainly affected by other tissues. Knee pain generators also include pathological changes in ligaments, muscles, bursae, bone marrow, fat pads, and synovium.[30] Furthermore, pain is a subjective experience with both central and systemic contributing factors. Chronic knee pain can relate to depression, peripheral or central sensitization to sensory stimuli or widespread pain syndromes.[24] Therefore, pain may not closely correlate with the proximity of bony surfaces.

While this cross-sectional analysis detected associations between 3D JSW and physical function, it did not detect statistically significant associations with pain severity. Longitudinal analysis may reveal associations between baseline 3D JSW measured in this study and the development of worsening pain or functional limitations over planned 24-month follow-up. This study used a pre-market prototype of the WBCT that does not have the resolution of the FDA-approved model that is currently used in clinical settings. While the marketed version has greater resolution and enhanced scan parameters, the 3D JSW measurements are unlikely to have been substantially affected by this difference. The summary indicators of the 3D JSW distribution used may not be ideal for capturing the overall status of the joint space; others yet to be derived may be more (or less) sensitive indicators of joint health. Finally, the lack of adjustment for analgesic use when evaluating the association between 3D JSW and pain could have altered the magnitudes of associations.

Despite these limitations, the results of this study are generalizable because the information was gathered from participants with both symptomatic and asymptomatic knees. The strengths of this study lie in the greater visualization of the articular surface on WBCT imaging and the rigor in data collection in this well-characterized, large cohort. 3D JSW measurement from WBCT images is more accurate and sensitive when compared to the 2D JSW measured on plain radiographs. The reproducibility of WBCT measurements of medial tibiofemoral JSW measurements acquired in this study had a high test-retest reliability.[21] Taken together, these observations suggest that 3D JSW measured from WBCT images can provide new insights into relationships between radiographic measures and clinical symptoms of OA that may be indicative of the incidence and state of progression of knee OA.

Conclusions

There appears to be an association between the medial tibiofemoral area with JSW<2.0mm and physical function. Longitudinal analyses will be instrumental in elucidating associations between changes in 3D JSW and changes in symptoms and function over time.

Acknowledgments

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Conception and design of the study: NAS.

Analysis and interpretation of data: NAS, MDK, KGR, DDA, MCN, JAL.

Drafting the article: NAS, MDK, KGR.

Critical revision of the article for important intellectual content: NAS, MDK, KGR, DDA, MCN, JAL.

Final approval of the version: NAS, MDK, KGR, DDA, MCN, JAL.

Statistical expertise: NAS, MCN, JAL.

Obtaining funding: NAS, MCN.

Collection and assembly of data: NAS, MDK, KGR, MCN, JAL.

Neil A. Segal, MD, MS takes responsibility for the integrity of the work as a whole, from inception to finished article.

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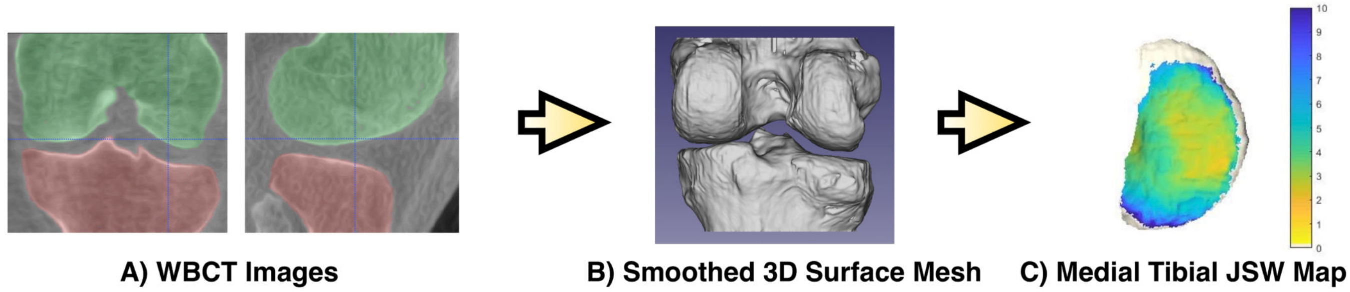

Figure 1:
3D JSW measurement methods, from A) WBCT images to B) 3D models to C) 3D JSW maps

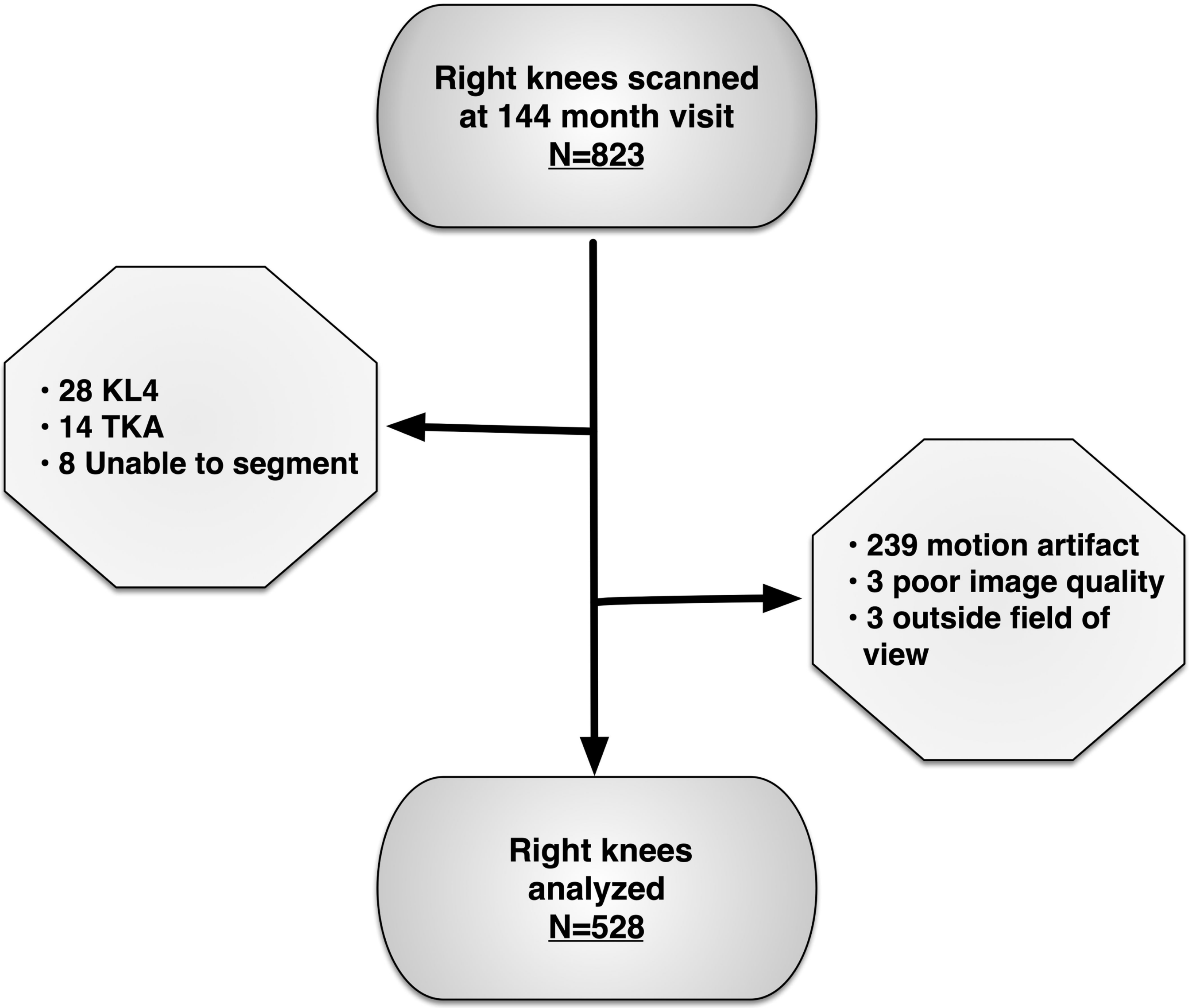

Figure 2:
Diagram of inclusion and exclusion of potential participants

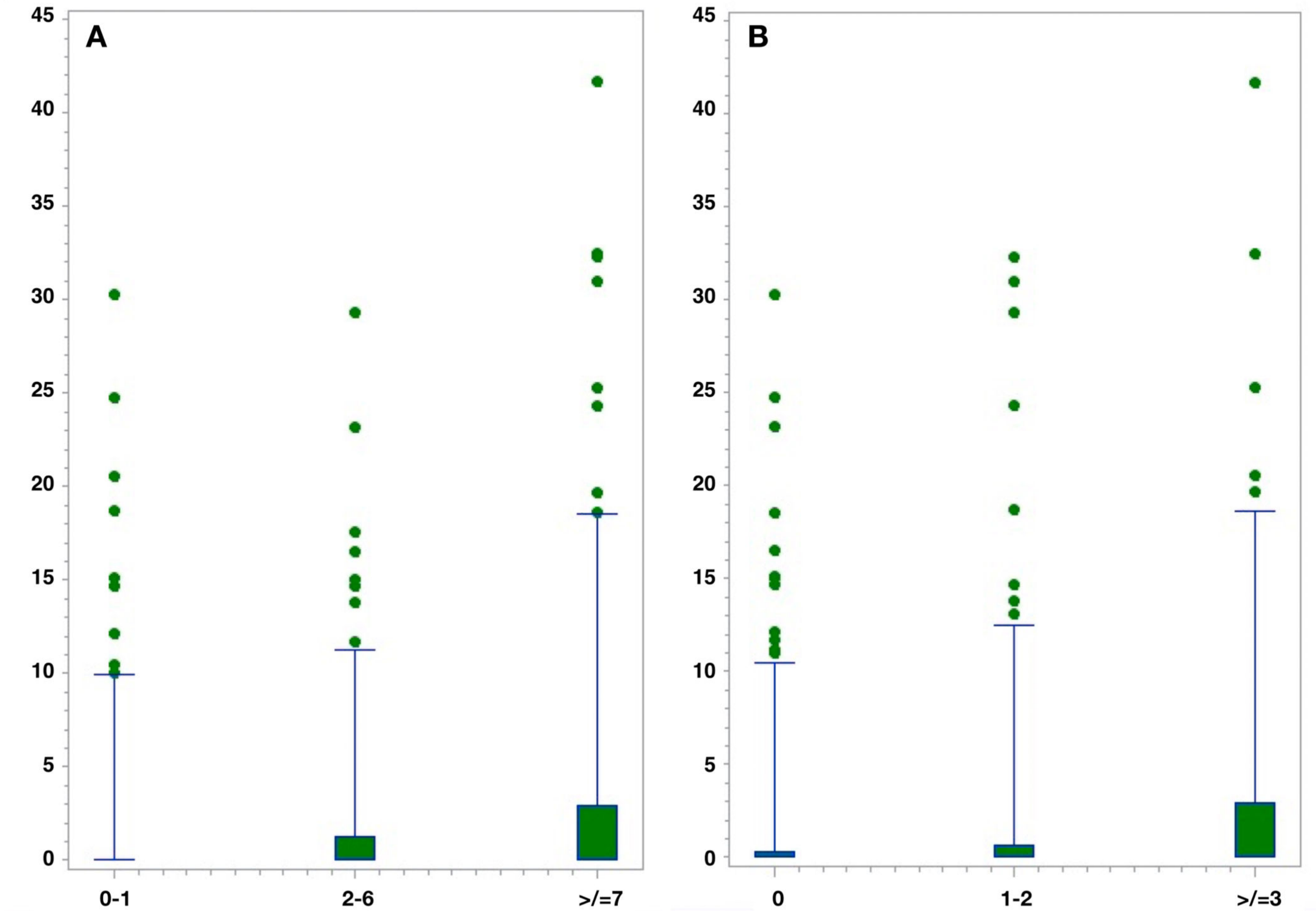

Figure 3:

Boxplot illustrating the percent joint area with JSW <2.0mm (y-axis) for each A) WOMAC Pain tertile (x-axis) and B) WOMAC Physical Function tertile (x-axis)

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Table-1:

WOMAC – Pain and Physical Function Strata

WOMAC - Pain Score (Right knee)	Strata	N
0	**Low**	258
1 or 2	**Middle**	167
3 or more	**High**	103
TOTAL		**528**

WOMAC – Physical Function Score	Strata	N
0 to 1.9	**Low**	193
2 to 6.9	**Middle**	163
7 or more	**High**	172
TOTAL		**528**

Table-2:

Tertiles of % Medial Tibiofemoral Area with 3D JSW <2.5mm for Women and Men

Sex	Tertile of % area with 3D JSW <2.5mm	N	Minimum	Maximum
Women	Low	106	0.0%	0.0%
	Middle	98	.01%	8.0%
	High	96	8.2%	53.3%
Men	Low	134	0.0%	0.0%
	Middle	47	0.009%	2.0%
	High	45	2.9%	39.2%

Table-3:

Tertiles of % Medial Tibiofemoral Area with 3D JSW <2.0 mm for Women and Men

Sex	Tertile of % area with 3D JSW <2.0mm	N	Minimum	Maximum
Women	Low	171	0.0%	0.0%
	Middle	65	.01%	3.6%
	High	65	3.7%	41.7%
Men	Low	180	0.0%	0.0%
	Middle	24	0.01%	3.8%
	High	23	4.9%	30.3%

Table 4:

Distribution of tertiles of 3D JSW <2.0mm with tertiles of Knee Pain (N, row %)

	Tertiles of WOMAC Knee Pain			
Tertile of % area with 3D JSW <2.0mm	**0 points**	**1–2 points**	**≥ 3 points**	**Total**
Low	181 51.6%	110 31.3%	60 17.1%	351
Middle	40 45.0%	29 32.6%	20 22.5%	89
High	37 42.1%	28 31.8%	23 26.1%	88
Total (N)	258	167	103	528

Table 5:

Distribution of tertiles of 3D JSW <2.0mm with tertiles of Physical Function (N, row %)

	Tertiles of WOMAC Physical Function			
Tertile of % area with 3D JSW <2.0mm	**0 points**	**2–6 points**	**≥ 7 points**	**Total**
Low	144 41.0%	106 30.2%	101 28.8%	351
Middle	30 33.7%	27 30.3%	32 36.0%	89
High	19 21.5%	30 34.1%	39 44.3%	88
Total(N)	193	163	172	528

Table 6:

Distribution of tertiles of 3D JSW <2.5mm with tertiles of Knee Pain (N, row %)

	Tertiles of WOMAC Knee Pain			
Tertile of % area with 3D JSW <2.5mm	**0 points**	**1–2 points**	**≥ 3 points**	**Total**
Low	116 47.93%	84 34.71%	42 17.36%	242
Middle	76 53.15%	39 27.27%	28 19.58%	143
High	66 46.15%	44 30.77%	33 23.08%	143
Total (N)	258	167	103	528

Table 7:

Distribution of tertiles of 3D JSW <2.5mm with tertiles of Physical Function (N, row %)

	Tertiles of WOMAC Physical Function			
Tertile of % area with 3D JSW <2.5mm	**0 points**	**2–6 points**	**≥ 7 points**	**Total**
Low	97 40.08%	74 30.58%	71 29.34%	242
Middle	54 37.76%	42 29.37%	47 32.87%	143
High	42 29.37%	47 32.87%	54 37.76%	143
Total (N)	193	163	172	528