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A novel quantitative metric for joint space width: data from the Osteoarthritis Initiative (OAI)

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SUMMARY

Objective: Joint space width (JSW) has been the gold standard to assess loss of cartilage in knee osteoarthritis (OA). Here we describe a novel quantitative measure of joint space width: standardized JSW (stdJSW). We assess the performance of this quantitative metric for JSW at tracking Osteoarthritis Research Society International (OARSI) joint space narrowing grade (JSN) changes and provide reference values for different JSN grades and their annual change.
Methods: We collected 18,934 individual knee images along with JSW and JSN readings from baseline up to month 48 (4 follow-ups) from the OAI study. Standardized JSW and 12-month JSN grade changes were calculated for each knee. For each JSN grade and 12-month grade change, the distribution of JSW loss was calculated for JSW and stdJSW. Area under the ROC curves was calculated on discrimination between different JSN grades for JSW and stdJSW. Standardized response mean (SRM) was used to compare the responsiveness of the two measures to changes in JSN grade.
Results: The areas under the receiver operating characteristic (ROC) curve (AUC) for stdJSW at discriminating between successive JSN grades were $AUC_{stdJSW} = 0.87$, 0.95, and 0.96, for JSN>0, JSN>1 and JSN>2, respectively, whereas these were $AUC_{fJSW} = 0.79$, 0.90, 0.98 for absolute JSW. We find that standardized JSW is significantly more responsive than absolute JSW, as measured by the SRM.
Conclusions: Our results show that stdJSW outperforms absolute JSW at discriminating and tracking changes in JSN and further that this effect is in part because stdJSW cancels JSW variations attributed to patient height variations.

Introduction

Joint space width (JSW), as measured in knee AP/PA radiographs[1], is an indirect measure of cartilage width[2] and currently the only recommended imaging biomarker by the United States Food and Drug Administration (FDA) as a structural endpoint in clinical trials of knee OA[3]. Even though MRI imaging is now recommended for cartilage morphology assessment, the low-cost and high availability of radiography makes JSW still the *de facto* gold-standard for assessing progression of osteoarthritis (OA).

Previously, it was shown that JSW measured at fixed positions (fJSW), and in particular more central positions along the tibiofemoral joint, were more responsive than minimum JSW (mJSW) to changes in Osteoarthritis Research Society International (OARSI) joint space narrowing grade (JSN)[4], especially for higher Kellgren-Lawrence (KL) grades. The rationale presented for this phenomenon is that, as the degree of narrowing increases and the bone becomes more exposed, changes in mJSW become relatively smaller, and therefore less responsive, while more central positions in the tibia-femoral joint continue to display changes[4]. Recently, reference values for the annual change in fixed position JSW (fJSW)

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have been provided[5] and it was argued that a quantitative metric for loss of JSW can provide better sensitivity to change than semi-quantitative grades, such as the KL or JSN grading schemes.

However, measuring fJSW using the method described in[4,6] was reported to incur time penalties, as the method is semi-automated and depends on a reader adjusting landmarks. Moreover, even though it is useful to have reference values for JSW, the results in Ratzlaff *et al.*[5], show that there is significant overlap between the distributions of JSW of healthy and OA individuals and between the yearly change in JSW for individuals that progressed (ΔJSN = 1) and for those that did not progress (ΔJSN = 0)[5], which may limit its usefulness to assign and track changes in JSN grade. As such, radiographic constructs that allow a better discrimination between JSN grades and are easily calculated are needed.

Here, we describe a novel JSW measurement method that provides JSWs measurements at fixed positions along the tibio-femoral joint and takes into account particular anatomical features, allowing a standardization of JSW across individuals. We compare this novel metric to fJSW in terms of the ability to discriminate between JSN grades and its responsiveness to JSN change.

Materials and methods

The Osteoarthritis Initiative (OAI) study is a large, multicenter, prospective, longitudinal study that followed 4,796 subjects diagnosed with or at risk of knee OA over 8 years (grants-funding/funded-research/osteoarthritis-initiative" title="https://www.niams.nih.gov/grants-funding/funded-research/osteoarthritis-initiative">https://www.niams.nih.gov/grants-funding/funded-research/osteoarthritis-initiative). The OAI study provides knee radiographs, as well as KL and OARSI grade readings and JSW measurements, acquired at baseline and annually up to the 48-month follow-up visit, as well as at 72, 96 and either 120 or 132 month follow-up visits.

For this study, knee radiographs up to the 48-month follow-up visit were collected. Digitized film images (RG modality) were excluded from this study due to uncertainty regarding the physical pixel size. The remaining images were analyzed by the Knee Osteoarthritis Labelling Assistant (KOALA, IB Lab GmbH, Vienna, Austria http://www.imagebiopsy.com) automated computer detection system, and resulting measurements of standardized JSW (stdJSW) were collected. OAI assessments for JSN for medial and lateral compartments (JSM and JSL) were subsequently merged with this dataset. Knees with no readings from either KOALA or the OAI study were excluded resulting in a dataset of 18.934 individual knees.

For the 12-month time-period between every consecutive visit, the change in JSN grade was computed, as well as the change is standardized JSW (measured by IB Lab KOALA), and the measurements of absolute fJSW provided by project 16 of the OAI study, resulting in 7.960 annual transitions (one transition from JSN one to three was excluded since it was the only one of its type and no useful statistics could be calculated from it).

Software assessment of JSW

StdJSW is calculated as the ratio of absolute JSW to normalized tibia width. Normalized tibia width is the ratio of absolute tibia width to the average tibia width in the population. IB Lab KOALA calculated tibia width as the distance between the two landmarks placed at the medial and lateral edges of the tibia plateau.

StdJSWs were calculated using IB Lab KOALA by running it on the set of radiographs selected for this study. KOALA measures stdJSWs at four positions along the medial compartment (M0 – M4 in Fig. 1) of the tibiofemoral joint. Absolute JSWs were collected from the data provided by the OAI study and were obtained using a semi-automated method by J. Duryea[4,6]. The two methods are similar in that they make use of anatomical features to establish a coordinate system along the tibiofemoral joint and use that to standardize measurement locations. However, KOALA makes use of landmarks on the tibia while the Duryea method makes use of landmarks on the femur. Furthermore, the Duryea method is semi-automated in that it depends on manual placement of these landmarks while KOALA is fully automated.

Linear regressions between tibia width over time were performed for each individual. The mean change in tibia width per year was 0.27% of the tibia width at baseline and the 95% percentiles were −2.3% and 1.8% per year, showing that there is no significant change in tibia width over time or any definite direction for this change (no tendency to increase or decrease).

From the absolute JSW measurements provided by the OAI study, we used only the position at $x = 0.250$ (JSW250), as this position was deemed to be the most responsive to radiographic OA changes[5].

Population

The demographics of the population (3.129 individuals) present in our study are described in Table I.

Statistical methods

Standardized response mean (SRM): SRM was calculated by the ratio of the mean and standard deviation of the annual empirical ΔJSW distribution, stratified by each of the base JSN grades and annual ΔJSN. Confidence intervals for SRM were constructed by resampling 1,000 independent samples with replacement (bootstrap) from the original data and calculating the 2.5% and 97.5% percentiles. For each of the base JSN grades, SRM ratios were calculated between SRM for ΔJSN = 1 and the sum of the SRMs for ΔJSN = 1 and ΔJSN = 0. Bootstrapped distributions were calculated for this ratio for each of the measurement methods and differences between these distributions were assessed for statistical significance using 2-sample *t*-tests.

ROC curves and AUC: Receiver operating characteristic (ROC) curves for the ability to distinguish between different JSN grades were constructed by quantifying the true positive rate and false

Fig. 1 Calculation of the standardized JSW. Tibia width was calculated by the distance between landmarks automatically placed at the edge of the tibia and mJSW was calculated from the distance between tibia and femur on the medial compartment.

	Female	Male	Total
Age			
45-49	149 (8.07%)	115 (8.96%)	264 (8.44%)
50-59	576 (31.20%)	451 (35.15%)	1027 (32.82%)
60-69	641 (34.72%)	359 (27.98%)	1000 (31.96%)
70-79	460 (24.92%)	343 (26.73%)	803 (25.66%)
80-89	20 (1.08%)	15 (1.17%)	35 (1.12%)
Total	1846 (100.00%)	1283 (100.00%)	3129 (100.00%)
Ethnicity			
Not provided	0 (0.00%)	1 (0.08%)	1 (0.03%)
Asian	21 (1.14%)	7 (0.55%)	28 (0.89%)
Black or African American	350 (18.96%)	151 (11.77%)	501 (16.01%)
Other Non-White	26 (1.41%)	18 (1.40%)	44 (1.41%)
White or Caucasian	1449 (78.49%)	1106 (86.20%)	2555 (81.66%)
Total	1846 (100.00%)	1283 (100.00%)	3129 (100.00%)
BMI			
Not provided	5 (0.27%)	3 (0.23%)	8 (0.26%)
15–18.5	5 (0.27%)	0 (0.00%)	5 (0.16%)
18.5–20	25 (1.35%)	1 (0.08%)	26 (0.83%)
20-25	428 (23.19%)	202 (15.74%)	630 (20.13%)
25-30	638 (34.56%)	599 (46.69%)	1237 (39.53%)
30-35	491 (26.60%)	363 (28.29%)	854 (27.29%)
35-40	201 (10.89%)	102 (7.95%)	303 (9.68%)
40-45	46 (2.49%)	12 (0.94%)	58 (1.85%)
45-50	6 (0.33%)	1 (0.08%)	7 (0.22%)
>50	1 (0.05%)	0 (0.00%)	1 (0.03%)
Total	1846 (100.00%)	1283 (100.00%)	3129 (100.00%)

Table I Demographic information of the individuals included in the study at baseline

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			ΔstdJSW M0 [mm]			ΔstdJSW M1 [mm]			ΔstdJSW M2 [mm]			ΔstdJSW M3 [mm]			ΔJSW250 [mm]		
		n	Q25	Q50	Q75	Q25	Q50	Q75	Q25	Q50	Q75	Q25	Q50	Q75	Q25	Q50	Q75
JSN	**ΔJSN**																
0	**0**	4152	-0.29	0.00	0.31	-0.31	0.00	0.29	-0.36	0.00	0.32	-0.47	-0.01	0.41	-0.23	0.00	0.21
	1	53	-1.26	-0.88	-0.49	-1.14	-0.77	-0.31	-1.29	-0.72	-0.42	-1.21	-0.81	-0.20	-1.27	-0.79	-0.47
	2	26	-2.58	-2.23	-1.55	-2.42	-2.04	-1.33	-2.22	-1.88	-0.92	-2.03	-1.52	-0.59	-2.40	-1.99	-1.15
1	**-1**	4	0.26	0.45	0.59	0.03	0.20	0.46	0.32	0.46	0.66	0.12	0.44	0.92	0.26	0.52	0.94
	0	1995	-0.33	-0.01	0.21	-0.35	-0.01	0.21	-0.37	-0.02	0.27	-0.47	0.00	0.42	-0.30	-0.06	0.18
	1	105	-1.63	-0.98	-0.57	-1.31	-0.95	-0.44	-1.26	-0.81	-0.31	-1.18	-0.71	0.01	-1.25	-0.88	-0.45
2	**-1**	10	0.36	0.52	1.11	0.37	0.68	1.22	0.12	0.73	0.84	0.04	0.49	0.63	0.24	0.58	0.97
	0	1222	-0.46	-0.13	0.21	-0.46	-0.12	0.20	-0.49	-0.14	0.29	-0.55	-0.04	0.43	-0.40	-0.11	0.11
	1	97	-1.51	-0.73	-0.17	-1.25	-0.64	-0.26	-1.03	-0.45	-0.16	-1.10	-0.34	0.36	-1.09	-0.69	-0.24
3	**-1**	14	0.17	0.51	0.74	0.34	0.64	0.99	0.30	0.55	1.08	0.15	0.34	0.55	0.08	0.50	0.78
	0	283	-0.67	0.00	0.14	-0.59	-0.18	0.27	-0.66	-0.17	0.31	-0.82	-0.16	0.56	-0.58	-0.20	0.13

Table II First, second (median), and third quantiles of the distribution of 12-month change in JSW for standardized JSW at four different positions and for absolute JSW measured at position $x = 0.250$ (JSW250), stratified by JSN grade and 12-month JSN change. Row shading is provided to facilitate reading the table and has no other meaning

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JSN OAI	ΔJSN	n	ΔstdJSW M0	ΔstdJSW M1	ΔstdJSW M2	ΔstdJSW M3	ΔJSW250
			Standardized Response Mean (SRM)				
0	0	4152	-0.01 (-0.04,0.02)	-0.03 (-0.06,0.00)	-0.04 (-0.07,-0.01)	-0.04 (-0.07,-0.01)	-0.07 (-0.10,-0.04)
0	1	53	-1.60 (-1.94,-1.36)	-1.27 (-1.68,-1.01)	-1.27 (-1.73,-0.99)	-0.92 (-1.32,-0.62)	-1.41 (-1.75,-1.20)
0	2	26	-2.66	-2.60	-1.91	-1.14	-2.23
1	-1	4	1.43	0.92	1.88	1.02	1.06
1	0	1995	-0.08 (-0.13,-0.03)	-0.10 (-0.14,-0.05)	-0.09 (-0.14,-0.05)	-0.03 (-0.08,0.01)	-0.13 (-0.18,0.09)
1	1	105	-1.23 (-1.50,-1.04)	-1.26 (-1.51,-1.07)	-1.00 (-1.25,-0.82)	-0.58 (-0.80,-0.41)	-1.31 (-1.60,-1.23)
2	-1	10	1.04	1.41	1.03	0.75	1.14
2	0	1222	-0.16 (-0.24,-0.10)	-0.19 (-0.24,-0.13)	-0.15 (-0.21,0.10)	-0.07 (-0.13,-0.01)	-0.29 (-0.34,-0.23)
2	1	97	-0.89 (-1.11,-0.70)	-0.97 (-1.21,-0.78)	-0.71 (-0.91,-0.56)	-0.38 (-0.55,-0.22)	-1.05 (-1.30,-0.87)
3	-1	14	0.69	0.95	0.70	0.44	0.75
3	0	283	-0.05 (-0.18,0.06)	-0.07 (-0.20,0.04)	-0.09 (-0.24,0.03)	-0.07 (-0.20,0.03)	-0.26 (-0.40,-0.14)

Table III 12-month standardized response mean (SRM: μ/σ) for the several measurement locations of standardized JSW (stdJSW M0 – M3) as well as for JSW at position $x = 0.25$ (JSW250). Shaded rows are combinations of initial JSN and ΔJSN of interest and for which more than 50 observations existed

positive rate for each of the JSWs as the threshold varied between 0 and the maximum JSW. Area under the curve (AUC) was calculated as the integral of this curve.

Linear regression and correlation: Pearson correlations between height and each of the JSW measurement methods were calculated. Correlation coefficients were tested for difference from $r = 0$ by a two-way t-test, with statistic $= r\sqrt{\frac{n-2}{1-r^2}}$. Ordinary linear regressions were performed between JSW and height as well as between tibia width and time.

Results

For each knee assessed by the OAI study, we calculated the 12-month change JSW for both stdJSW at the four measurement positions as well as absolute JSW measured at position $x = 0.250$ (as provided by the OAI study), stratified by base JSN grade and change in JSN (ΔJSN). A statistical description of these distributions is presented in Table II.

Table II shows that, in general, the median of 12-month change in stdJSW is smaller for no change in JSN than for JSW250. Furthermore, it shows that stdJSW measured at point M0 shows larger changes than JSW250 when JSN increases by 1 grade.

Annual change of standardized JSW is more responsive to JSN change than fJSW

We compared the SRM for several measurement positions along the tibiofemoral joint to the fixed position JSW (JSW250) and show the results in Table III.

Table III shows that position M0 (the most medial position along the tibiofemoral joint) has consistently a lower response when there is no change in JSN (ΔJSN = 0). However, its response when JSN does change (ΔJSN = +1), is slightly inferior to the response of the absolute JSW (JSW250).

In order to test which of the JSW constructs has better performance, we calculated the ration of SRM (rSRM) as $rSRM = \frac{SRM_1}{SRM_1+SRM_0}$, where SRM1 is SRM for ΔJSN = +1 and SRM0 is SRM for ΔJSN = 0. This ratio rSRM quantifies the relative change in JSW when JSN increases vs when it does not.

Standardized JSW allows better discrimination between JSN grades

Since stdJSW is more responsive to JSN change, we hypothesized that it would allow a better discrimination between JSN grades. To visualize this, we plotted JSW distributions stratified by JSN grade (Fig. 2). We found that stdJSW shows more concentrated distributions.

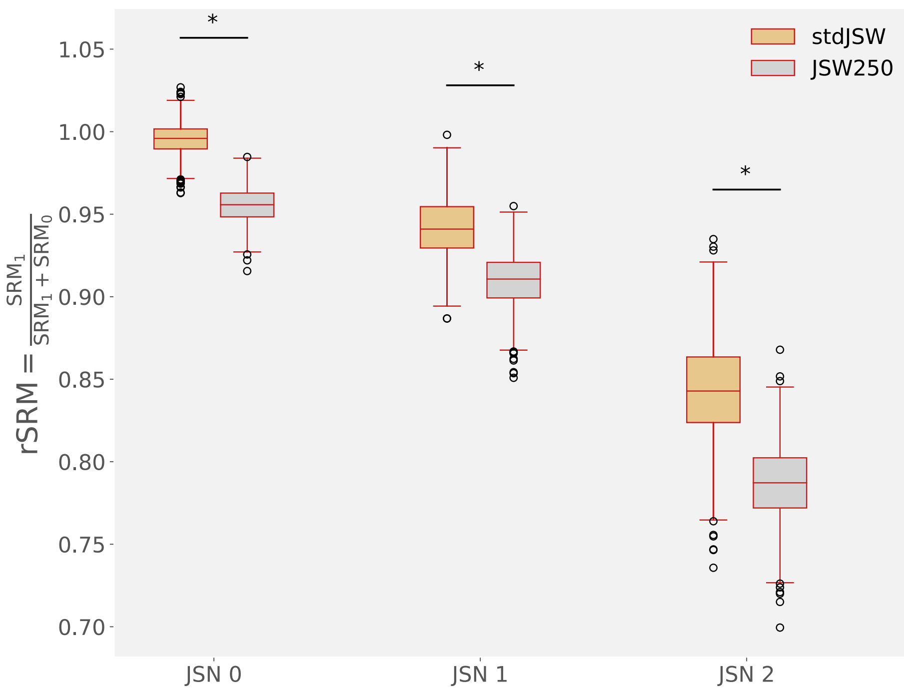

Fig. 2 SRM ratio for different base JSN for stdJSW M0 and JSW250. Asterisk indicates significant difference (all $P < 0.001$).

Fig. 3 shows that stdJSW separates better JSN grades than absolute fJSW. To quantify this, we compared the ability of stdJSW to distinguish between JSN grades by calculating the area under the ROC curve (ROC-AUC) for the successive JSN grades, using JSW as the threshold to decide if a knee belongs to a particular JSN grade (Table IV).

Standardized JSW cancels the variation in JSW due to height variation

We hypothesized that the reason why stdJSW performs better at distinguishing different JSN grades is because it takes into account anatomical features of the knee that have allometric relationships to overall size of the individual. In fact, it is intuitive that a JSW of 4 mm might be perfectly normal for a short individual but would indicate a narrowed joint for a taller individual.

In order to test this, we calculated the correlation between JSW, both standardized and absolute, and height (provided by the OAI study) (see Fig. 4). We find a significant correlation ($r = 0.27$, $t = 15.828$; $P < 0.001$) between absolute JSW and height, but no significant correlation between stdJSW and height ($r = -0.01$, $t = -0.282$; $P = 0.389$). These results suggest that normalization by the tibia width (stdJSW) cancels some of the variation inherent to variation in height. To test this, we performed the same analysis as

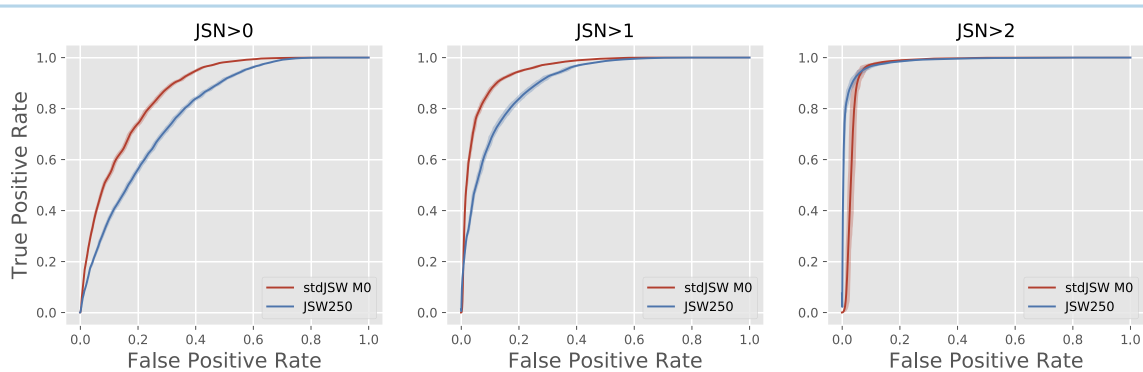

Fig. 3 ROC curve (AUC) for the detection of JSN grades higher than 0, one and two, respectively, for standardized JSW M0 and for the OAI's absolute fixed position JSW 250. Shaded areas denote the 95% confidence intervals obtained by bootstrapping. AUC scores corresponding to these curves are shown in Table IV.

	JSN >0	JSN >1	JSN >2
Std JSW M0 [mm]	0.868 ± 0.003*	0.951 ± 0.002*	0.964 ± 0.006
Std JSW M1 [mm]	0.859 ± 0.003*	0.944 ± 0.002*	0.976 ± 0.004
Std JSW M2 [mm]	0.818 ± 0.003*	0.900 ± 0.003	0.963 ± 0.004
Std JSW M3 [mm]	0.738 ± 0.004	0.790 ± 0.004	0.880 ± 0.007
JSW 250 [mm]	0.790 ± 0.003	0.902 ± 0.003	0.985 ± 0.002

Table IV Area under the ROC curve (AUC) for the detection of JSN grades higher than 0, one and two, respectively, for standardized JSW (4 different positions along the tibiofemoral joint) and for the OAI's absolute fixed position JSW 250. Error denotes the standard error for the AUC estimated by the mean of 1000 bootstrapped samples. * denotes significant difference against the null hypothesis that $AUC_{std} > AUC_{JSW250}$ (one sided paired *t*-test, all *p*-values <0.001 Bonferroni corrected)

in Table IV, but using JSW (measured at position M0) normalized by individual's height, instead of tibia width. We obtained roughly the same performance as with stdJSW M0 (AUCs of 0.850 ± 0.004, 0.942 ± 0.003 and 0.956 ± 0.008 for JSN>0, JSN>1, and JSN>2, respectively).

Discussion

The results presented here show that stdJSW allows better discrimination between consecutive JSN grades than absolute fJSW, except for the distinction between grades three and two where the performance is comparable. This is in line with the results of Neumann *et al.*[4], where it was found that more central measurement positions allowed better discrimination between healthy and diseased patients according to the KL grade criterion. However, it should be noted that the performance is high for both methods and its difference is relatively small (AUCs 0.985 and 0.965 for JSW250 and stdJSW, respectively). JSW is a construct that is meant as an indirect measure of cartilage thickness. Absolute JSW is well correlated with cartilage thickness[7], but less than half of its variance in healthy individuals can be explained by variation in cartilage thickness[8]. Aside from JSW measurement error, subject height may also explain the remaining variance. In fact, we have shown that there is a significant correlation between absolute JSW and individual height. StdJSW mitigates this variation and enables more accurate discrimination between JSN grades. By extension, stdJSW and the associated JSN grades are expected to be less sensitive to factors such as gender or ethnicity, at least to the extent that height variation is associated with these factors. Furthermore, due to the normalization included in the calculation of stdJSW, errors associated with image magnification artefacts may also be mitigated.

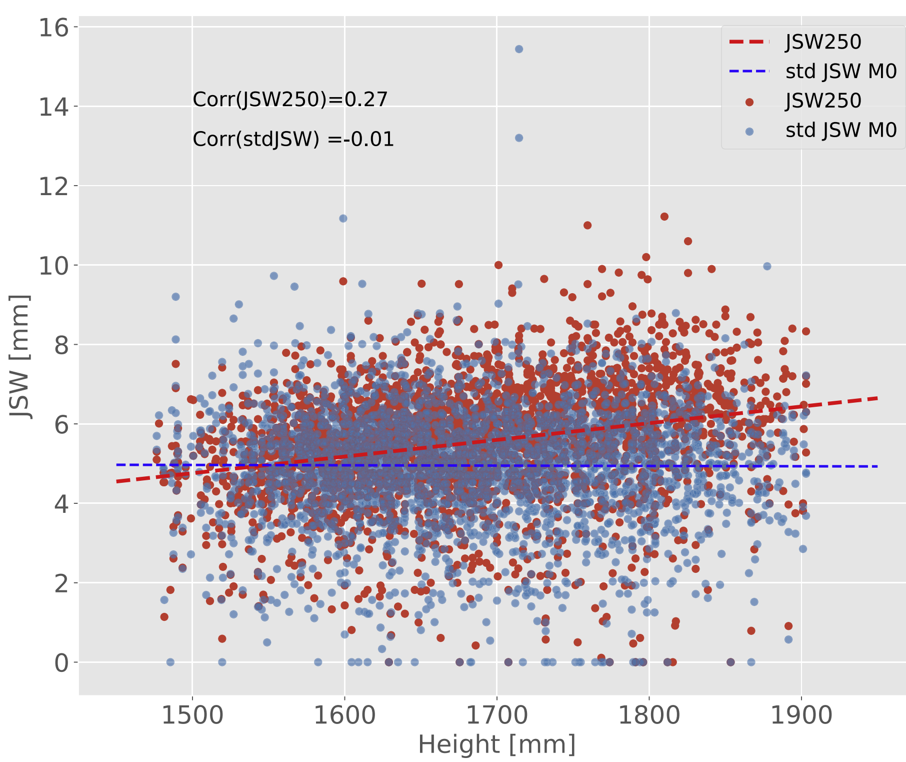

Fig. 4 Standardized JSW (blue) and fixed position absolute JSW (red as provided by the OAI study) as a function of height. Lines represent linear regressions. Inset text indicates Pearson correlation coefficient for both sets of measurements.

One possible reason for why stdJSW performs better at distinguishing between JSN grades than absolute JSW is that readers intuitively take into account the height of the individual when assessing the JSN grade. We have shown that normalizing JSW with subject height leads to performance on par with stdJSW, demonstrating that stdJSW provides a means to objectively factor subject height into JSN assessment. Although height normalization of JSW may seem more straightforward, tibia width can be obtained directly from the radiograph, which can be useful in circumstances where patient height is unavailable or erroneous.

Our results show that stdJSW, as measured by IB Lab KOALA software package, is more sensitive to change in JSN by responding less to no change and responding more to 12 month grade changes in JSN. Interestingly, we found that the most medial position (M0) measured by the software is the most responsive. This finding contrasts with previous conclusions where more central measurement positions were more responsive than positions closer to the medial edge[4]. We suggest two possible reasons for this disparity. Firstly, the original finding was for changes after 36 months, which naturally involves greater changes in JSW. Second, the two methods differ in a number of ways, including measurement locations and mode of operation. Nevertheless, we find that stdJSW measurement at position M0 is the most responsive to change in JSN, as measured by rSRM, and is more suitable to track JSN grade changes than absolute JSW.

We measured stdJSW only for the medial compartment of the tibiofemoral compartment, as this is typically the compartment that is most affected by the loss of cartilage. However, the same measurements could be performed for the lateral compartment. Due to the rarity of joint space narrowing on the lateral side, this analysis could not be performed here.

We studied the relationship between JSW and JSN grades and not with KL grade, as with other studies. The KL grading scheme takes more factors into account than narrowing, such as osteophytosis and sclerosis, which are independent of JSW. Because the JSW construct is meant as a surrogate for cartilage thickness, it is not expected to capture these other aspects of OA etiology. Nevertheless, because stdJSW normalizes the JSW with the tibia width, measurements could be affected by the presence of marginal osteophytes. Measurements of tibia width in IB Lab KOALA are based on landmarks intended to exclude marginal osteophytes, so related width changes may not be accounted for in stdJSW. IB Lab KOALA is, however, capable of assessing OARSI osteophyte scores, which could be included in future refinements to stdJSW assessment.

Conclusions

StdJSW, as assessed by software such as IB Lab KOALA, is a quick, fully-automated way of assessing the degree of narrowing, independently of height, which is associated with factors such as sex and ethnicity. StdJSW allows a more standardized and objective classification of JSN across both physicians and cohorts and a more sensitive outcome measure for relevant changes in cartilage thickness.

Contributions

Conception and design (all authors except MD); Analysis and interpretation of the data (TP, ZB); Drafting of the article (TP and MD); Critical revision of the article for important intellectual content (all authors); Final approval of the article (all authors); Statistical expertise (TP and MD); Collection and assembly of data (TP, ZB).

Conflict of interest

RL & DL are co-founders of IB Lab GmbH and own equity in the company. Further, DL is a shareholder of Braincon Technologies which is an independent company with no financial interest in IB Lab GmbH. RL is receiving a monthly honorarium from IB Lab GmbH while DL is not receiving any financial compensation from either company.

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