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Semi-Automated Quantification of Finger Joint Space Narrowing Using Tomosynthesis in Patients with Rheumatoid Arthritis

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Abstract The purpose of the study is to validate the semi-automated method using tomosynthesis images for the assessment of finger joint space narrowing (JSN) in patients with rheumatoid arthritis (RA), by using the semi-quantitative scoring method as the reference standard. Twenty patients (14 females and 6 males) with RA were included in this retrospective study. All patients underwent radiography and tomosynthesis of the bilateral hand and wrist. Two rheumatologists and a radiologist independently scored JSN with two modalities according to the Sharp/van der Heijde score. Two observers independently measured joint space width on tomosynthesis images using an in-house semi-automated method. More joints with JSN were revealed with tomosynthesis score (243 joints) and the semi-automated method (215 joints) than with radiography (120 joints), and the associations between tomosynthesis scores and radiography scores were demonstrated ($P < 0.001$). There was significant, negative correlation between measured joint space width and tomosynthesis scores with $r = -0.606$ ($P < 0.001$) in metacarpophalangeal joints and $r = -0.518$ ($P < 0.001$) in proximal interphalangeal joints. Inter-observer and intra-observer agreement of the semi-automated method using tomosynthesis images was in almost perfect agreement with intra-class correlation coefficient (ICC) values of 0.964 and 0.963, respectively. The semi-automated method using tomosynthesis images provided sensitive, quantitative, and

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reproducible measurement of finger joint space in patients with RA.

Keywords Computer-aided diagnosis · Conventional radiography · Tomosynthesis · Rheumatoid arthritis · Joint space narrowing

Introduction

Radiography of the hand and wrist is traditionally used for diagnosis, follow-up, and evaluation of treatment effectiveness in patients with rheumatoid arthritis (RA). The advantages of radiography include low cost and high availability, and it is currently accepted as the gold standard for imaging of RA [1]. However, there is a disadvantage of low sensitivity for early bone damage from RA due to the two-dimensional projection of the three-dimensional joint structure [2].

Tomosynthesis is a relatively new technique that acquires section images at arbitrary depths by collecting multiple projected images at different angles with a digital detector [3]. Several studies have revealed that tomosynthesis can identify more bone erosions than radiography in RA patients [4–6]. As for joint space narrowing (JSN), tomosynthesis has been reported to facilitate accurate evaluation of joint space width better than radiography, even with oblique incidence of the X-ray beam [7]. In addition, Martini et al. have shown that tomosynthesis depicts JSN with higher sensitivity than radiography in cadaveric hands with osteoarthritis [8].

The importance of quantification and standardization for measurement of features within images has recently been advocated in the field of radiology [9]. Quantifying bone damage on images in patients with RA could be helpful in the management of the disease. Actually, semi-quantitative radiographic damage scoring methods such as the Sharp/van der Heijde method [10] have been used in a number of clinical trials to evaluate the efficacy of treatment in RA [11, 12]. Until now, various computer-based methods for the measurement of joint space width on hand radiography have been introduced from multiple institutions to provide more sensitive, quantitative, and reproducible measurement [13–20]. To our knowledge, however, no studies have been published concerning computer-based joint space measurement using tomosynthesis images.

We developed a semi-automated method that can detect and define the joint contours to measure joint space width on tomosynthesis images. The purpose of this study was to validate the semi-automated method using tomosynthesis images for the assessment of finger JSN in patients with RA, by using the semi-quantitative scoring method as the reference standard.

Materials and Methods

Patients

We retrospectively reviewed 14 female (mean age, 58.5 years; range 32–81 years) and 6 male consecutive patients (mean age, 70.7 years; range 56–88 years) with RA from July to October 2012. All patients met the American College of Rheumatology criteria for RA [21]. Details of our patient population have been previously reported [7]. All patients underwent radiography and tomosynthesis of the bilateral hand with an average of 14-day interval.

The study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Conventional Radiography

The radiographic examinations were performed using a standard clinical radiography unit (RADspeed, Shimadzu, Kyoto) in posteroanterior view. Radiographs were obtained at a tube voltage of 50 kV, a tube current of 100 mA, and an exposure time of 0.02 s, according to the standard protocol of the institution. All radiographs were displayed as Digital Imaging and Communications in Medicine (DICOM) images with 2010 × 1670 pixels and a 0.15 × 0.15 mm pixel size at 10-bit grayscale.

Tomosynthesis

Tomosynthesis examinations were performed with a commercially available product (Sonialvision safire II, Shimadzu, Kyoto). Images were obtained with a tube voltage of 47 kV, a tube current of 160 mA, and an exposure time of 0.016 s. The data acquisition rate was 15 frames per second. The detector position was fixed, whereas the X-ray tube displaced in a continuous horizontal movement from −20°to 20° around the standard orthogonal posteroanterior position. The examination resulted in a range of 20 to 40 reconstructed coronal images with a thickness of 2 mm. All tomosynthesis images were displayed as DICOM images with 1024 × 1024 pixels and a 0.2793 × 0.2793 mm pixel size at 12-bit grayscale.

Image Evaluation by Scoring Method

Images from radiography and tomosynthesis were read independently in random order by three readers: two rheumatologists (H.K. and Y.S.) and one musculoskeletal radiologist (T.K.), with 20, 7, and 15 years of experience, respectively. The readers were blinded to other clinical information.

The Sharp/van der Heijde method [10] was applied to score JSN of the hand in both modalities. Each reader evaluated JSN of metacarpophalangeal (MCP) and proximal interphalangeal

(PIP) joints using a four-point scale (0 = normal, 1 = focal or doubtful, 2 = >50% of the original joint space, 3 = <50% of the original joint space or subluxation, and 4 = ankyloses or complete luxation). Consensus was reached, and any disagreement among three readers was resolved by using the most experienced reader's score.

Image Processing for Tomosynthesis Image

We utilized an in-house software application programmed with Microsoft Visual C# 2013. After reading a tomosynthesis image into the software, an operator selected the coronal section in which analyzed finger joint margins were delineated clearly and located the region of interest (ROI) with size fixed at 80 × 100 pixels in the center of the joints to create the cropped image. When making the cropped image, we resized the original images to three times their original size, i.e., an image of 80 × 100 pixels was resized to 240 × 300 pixels. The cropped image was then rotated until the joint space was approximately horizontal on the display. Resizing and rotating the image were performed using bicubic interpolation.

The cropped image was then divided into vertical columns, and a gradient profile was made by calculating the difference between adjacent vertical pixel values in each column. We determined the highest gradient profile values to be the upper margin of the joint, and these pixels were marked with 20 pixel diameter. To eliminate isolated pixels, the number of connected pixels was counted for the marked pixels, and any pixel that belonged to a group whose number was less than 2 pixels was excluded. To determine the final upper margin, a sixth-order polynomial was fitted to marked pixels. The operator made corrections in the process of contouring the joint margin whenever necessary. The lower margin of the joint was determined from the lowest gradient profile value, and the same procedure was performed to determine the final lower joint margin. Finally, the average distance (JSW_{tomo}) between the upper and lower margins was calculated (Fig. 1).

Semi-Automated Measurement of Joint Space Width Using Tomosynthesis Images

Semi-automated joint space width measurement of the MCP and the second through fifth PIP joints on bilateral hand tomosynthesis images were verified independently by two non-specialists (S.I. and M.F.) for RA assessment, who were blinded to other clinical information. Severely damaged (subluxation, ankylosed, and complete luxation) joints were excluded based on the tomosynthesis score. The most experienced operator (S.I.) in the use of software selected the coronal section for joint space width measurement and performed a second measurement to assess intra-observer reliability with the same coronal section used at first measurement. The time between the two measurements was greater than 1 month.

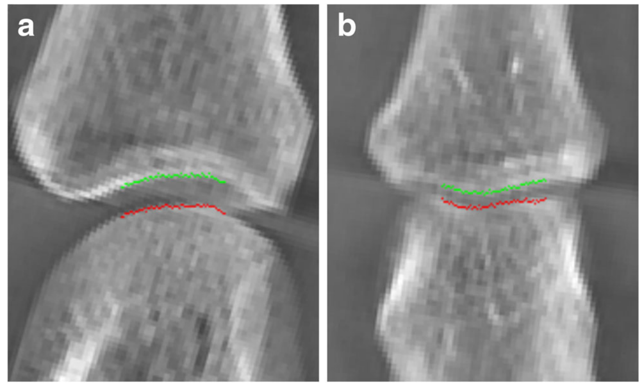

Fig. 1 Semi-automated measurement of joint space width using tomosynthesis images. Tomosynthesis images of the second metacarpophalangeal (**a**) and the second proximal interphalangeal (**b**) joints obtained in an 88-year-old man with rheumatoid arthritis are shown. The semi-automated method determined the upper margin (*green*) and the lower margin (*red*) of the joint. The joint distance was calculated as an average between the two margins over 20 pixels

Statistical Analysis

All statistical analyses were performed using statistical software (SPSS; version 22.0, IBM Corp., New York, NY). Continuous data were expressed as the mean and standard deviation. $P < 0.05$ was deemed as statistically significant difference. Only the first measurement of the most experienced operator (S.I.) was taken into account except for assessment of inter-observer and intra-observer agreement.

We chose the optical cutoff level on JSW_{tomo} using a receiver operating characteristic (ROC) curve with setting tomosynthesis scores as standard of reference. The optimal cutoff level was defined as yielding the minimum value for $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$, which is the point closest to the upper left hand corner in the ROC curve diagram [22]. Pearson's chi-squared test was performed to compare the detection rate for JSN and to assess associations between tomosynthesis scores and radiography scores and between JSW_{tomo} and radiography scores.

Spearman correlation coefficients were calculated between JSW_{tomo} and tomosynthesis scores. Disease-related JSW_{tomo} was evaluated by tomosynthesis scores, and the significance difference was checked using the Mann-Whitney *U* test.

Inter-observer and intra-observer agreement was estimated using intra-class correlation coefficients (ICC) employing a two-way mixed effects model using consistency definition for inter-observer agreement and a one-way random effects model for intra-observer agreement. The strength of agreement was considered poor to fair agreement for ICC values of 0.40 or less, moderate agreement for ICC values of 0.41–0.60, substantial agreement for ICC values of 0.61–0.80, and almost perfect agreement for ICC values of 0.81 or greater [23].

Table 1 Distribution of joint space narrowing score for radiography and tomosynthesis

Radiography	Tomosynthesis				
	Score 0	Score 1	Score 2	Score 3	Total
Score 0	107	1	122	4	234
Score 1	1	0	1	1	3
Score 2	3	0	63	24	90
Score 3	0	0	7	20	27
Total	111	1	193	49	354

Results

Out of 360 joints (10 MCP and 8 PIP joints per patient) from 20 patients, a total of 354 (197 MCP and 157 PIP) joints were analyzed by the semi-automated method using tomosynthesis images after excluding 6 severely damaged joints. Table 1 shows the distribution of the Sharp/van der Heijde score for JSN on radiography and tomosynthesis images. The operator made corrections in 83 (42.1%) MCP joints and 84 (53.5%) PIP joints in the process of contouring the joint margins.

The optical cutoff point on JSW_{tomo} was estimated to be 1.257 and 0.605 mm for MCP and PIP joints, respectively (Fig. 2). The detection rate of JSN for radiography scores, tomosynthesis score, and JSW_{tomo} was 120 (33.9%) joints, 243 (68.6%) joints, and 215 (60.7%) joints, respectively (Fig. 3). There were significant associations between tomosynthesis scores and radiography scores and between JSW_{tomo} and radiography scores (Table 2).

There was significant, negative correlation between JSW_{tomo} and tomosynthesis scores with $r = -0.606$ ($P < 0.001$) in MCP joints and $r = -0.518$ ($P < 0.001$) in PIP joints. The JSW_{tomo} significantly decreased (22.5%; $P < 0.001$) from 1.371 ± 0.214 mm (score 0, $n = 93$) to 1.063 ± 0.243 mm (scores 1, 2, and 3; $n = 104$) in MCP joints. The JSW_{tomo} revealed significant reduction (26.5%, $P < 0.001$) from 0.698 ± 0.164 mm (score 0, $n = 18$) to 0.513 ± 0.146 mm (scores 1, 2, and 3; $n = 139$) in PIP joints.

Out of 354 analyzed joints, 10 joints were judged as not applicable for either modality by one of the three readers in the scoring process and were excluded from the assessment of inter-observer agreement of radiography scores and tomosynthesis scores. As for inter-observer agreement, JSW_{tomo} showed almost perfect agreement (ICC = 0.964; 95% confidence interval [95% CI], 0.956–0.971), whereas radiography scores and tomosynthesis scores showed poor to fair agreement (ICC = 0.384, 95% CI, 0.317–0.450 for radiography and ICC = 0.344, 95% CI, 0.277–0.412 for tomosynthesis). Intra-observer agreement of JSW_{tomo} was also in almost perfect agreement (ICC = 0.963, 95% CI, 0.954–0.969).

Discussion

Joint inflammation and damage including bone erosion and cartilage loss are hallmarks of RA, which eventually leads to irreversible loss of physical function. Cartilage loss, which can be visualized as JSN on radiography, is more significantly associated with physical disability than bone erosion [24]. Furthermore, protection from the onset or worsening of JSN is an important factor when choosing between therapeutic modalities, especially in early stages of RA [25]. In clinical trials, radiographic changes are frequently used as surrogate endpoints [26]. Therefore, quantitative assessment of JSN is essential for the effective management of patients with RA.

Radiography remains the reference modality for the diagnosis and follow-up of patients with RA, which is recommended by American College of Rheumatism and the European League Against Rheumatism [1, 27]. However, conventional radiographic scoring methods are subjective

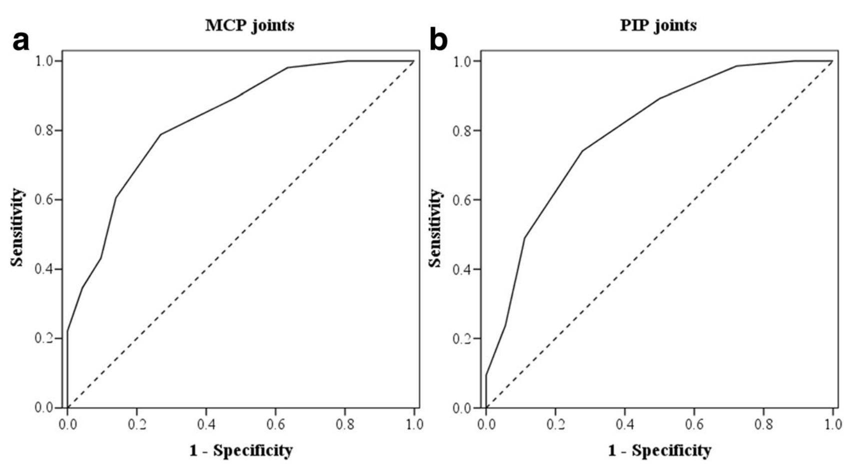

Fig. 2 Receiver operating characteristic (ROC) curve for semi-automated joint space width measurement in metacarpophalangeal (MCP) (**a**) and proximal interphalangeal (PIP) (**b**) joints. The area under the curve (AUC) of JSW_{tomo} in MCP was 0.831 (95% confidence interval [95% CI], 0.776–0.887), and the AUC of JSW_{tomo} in PIP joints was 0.799 (95% CI, 0.684–0.913)

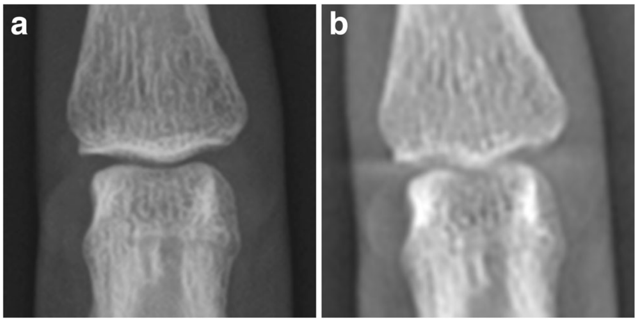

Fig. 3 Images obtained in a 66-year-old woman with rheumatoid arthritis. Radiograph (**a**) and tomosynthesis (**b**) images of the third proximal interphalangeal joints were scored as 0 and 2, respectively, according to the Sharp/van der Heijde method for joint space narrowing. The joint space narrowing is better depicted with tomosynthesis than with radiography

and suffer from reader variation [28, 29]. Specialized training is also required, which limits the number of qualified readers. Recently, several authors have reported that tomosynthesis represents more joints with JSN than radiography in RA or osteoarthritis patients [7, 8], with a small increase from 0.13 to 0.25 mGy in mean total radiation dose [5]. These results may be explained by less overlapping anatomy on tomosynthesis images in contrast to the projection radiographs [4, 30]. As higher detectability of tomosynthesis compared with radiography was confirmed by these studies, we developed in this study a semi-automated method to measure joint space width using tomosynthesis images and validated its performance by a non-expert using semi-quantitative scoring method as the reference standard. In our study, semi-automated method using tomosynthesis images as well as tomosynthesis scores showed higher detection rate of JSN than radiography. Furthermore, we found good relationship between the semi-automated method using tomosynthesis images and the semi-quantitative scoring method in MCP and PIP joints.

Intra-observer agreement of the semi-quantitative scoring method for radiography was moderate to almost perfect with ICC values of 0.589–0.839 in our previous article [28], while intra-observer agreement was almost perfect with the semi-automated method by non-experts in this study. Similarly, inter-observer agreement was poor to fair with the semi-quantitative scoring method for radiography and tomosynthesis by experts, while inter-observer agreement was almost perfect with the semi-automated method by non-experts in this study. These results suggest that the semi-automated method using tomosynthesis images would be a useful tool for quantifying JSN and as an alternative for conventional scoring methods.

The semi-automated method using tomosynthesis images detected more joints with JSN than radiography scores, but not all the joints with JSN detected by tomosynthesis scores. These false-negative findings may be explained by the fact that the conventional scoring method depends on the smallest point in joint space, whereas the semi-automated method measured average distance in a predefined interval. Furthermore, the cutoff value was determined for MCP and the second through fifth PIP joints, and therefore, the difference of sex, age, and joint configuration was not considered. In previous studies, James et al. and Goligher et al. reported that joint space width was greater in men than in women and varied among finger joints [31, 32]. Goligher et al. and Pfeil et al. revealed a significant association between JSN and age [32, 33]. Setting the cutoff point for each joint separately and normalization to differentiate RA-induced JSN from age-related and gender-related changes as shown by Pfeil et al. [34] would notably improve the performance of the semi-automated method using tomosynthesis images.

To date, various software applications have been developed for finger joint space width measurement in radiography [13–17]. On hand radiographs, Peloschek et al. proposed a fully automated computer-based joint space measurement [14]. Radiography tends to show ambiguous joint margins, and therefore, the definition of the bony margin for joint space width measurement depends on the designer of the software. On the other hand, tomosynthesis provides more obvious joint margins due to less overlapping without increasing radiation exposure to an unacceptable extent [4]. Thus, variation in contouring the joint margin would be decreased by using

Table 2 Associations for the number of joints with and without joint space narrowing

		Radiography scores			χ^2	P value
		JSN(+)	JSN(−)	Total		
Tomosynthesis scores	JSN(+)	116	127	243	66.2	<0.001
	JSN(−)	4	107	111		
	Total	120	234	354		
Semi-automated method	JSN(+)	112	103	215	80.9	<0.001
	JSN(−)	8	131	139		
	Total	120	234	354		

JSN(+) the number of joints with joint space narrowing, *JSN(−)* the number of joints without joint space narrowing tomosynthesis images for computer-based analysis, although radiography provides superior spatial resolution than tomosynthesis. However, the use of tomosynthesis images for computer-based analysis would increase the analysis process including selection of the coronal section, and this remains an issue for developing a fully automatic measurement method without human intervention.

We acknowledge that our study has several limitations. First, only a small number of patients were included. Second, we did not assess the performance of the semi-automated method using tomosynthesis images for JSN of the feet, which is a commonly involved site in RA. Third, radiography and tomosynthesis were not performed on the same day. Although the time elapsing between radiography and tomosynthesis was an average of 14 days, we consider that this interval is not long enough to progress the disease. Finally, our results cannot be compared with software applications for joint space width measurement on hand radiography. Further study may be necessary to confirm that tomosynthesis images are more suitable for computer-based analysis than radiographs.

In conclusion, the semi-automated method using tomosynthesis images provided sensitive, quantitative, and reproducible measurement of joint space width and could be a useful tool in follow-up assessment and therapeutic evaluation in patients with RA.

Compliance with Ethical Standards

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Conflict of Interest The authors declare that they have no conflict of interest.

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