BJR

Received: 17 May 2015 | Revised: 8 October 2015 | Accepted: 19 October 2015

doi: 10.1259/bjr.20150403

Cite this article as:
Ichikawa S, Kamishima T, Sutherland K, Okubo T, Katayama K. Radiographic quantifications of joint space narrowing progression by computer-based approach using temporal subtraction in rheumatoid wrist. *Br J Radiol* 2016; **89**: 20150403.

FULL PAPER

Radiographic quantifications of joint space narrowing progression by computer-based approach using temporal subtraction in rheumatoid wrist

[1]SHOTA ICHIKAWA, RT, [2]TAMOTSU KAMISHIMA, MD, PhD, [3]KENNETH SUTHERLAND, PhD, [4]TAKANOBU OKUBO, RT and [4]KOU KATAYAMA, MD

[1]Graduate School of Health Sciences, Hokkaido University, Sapporo, Japan
[2]Faculty of Health Sciences, Hokkaido University, Sapporo, Japan
[3]Graduate School of Medicine, Hokkaido University, Sapporo, Japan
[4]Katayama Orthopedic Rheumatology Clinic, Asahikawa, Japan

Address correspondence to: Dr Tamotsu Kamishima
E-mail: *ktamotamo2@yahoo.co.jp*

Objective: To investigate the validity of a computer-based method using temporal subtraction in carpal joints of patients with rheumatoid arthritis (RA), which can detect the difference in joint space between two images with the joint space difference index (JSDI).
Methods: The study consisted of 43 patients with RA (39 females and 4 males) who underwent radiography at baseline and at 1-year follow-up. The joint space narrowing (JSN) of carpal joints on bilateral hand radiographs was assessed by our computer-based method, using the Sharp/van der Heijde method as the standard of reference. We compared the JSDI of joints with JSN progression in the follow-up period with that of those without JSN progression. In addition, we examined whether there is a significant difference in JSDI in terms of laterality or topology of the joint.
Results: The JSDI of joints with JSN progression was significantly higher than that of those without JSN progression (Mann–Whitney *U* test, $p < 0.001$). There was no statistically significant difference in the JSDI between the left and right carpal joints, which was analysed for five different joints altogether and each joint separately (Mann–Whitney *U* test, $p > 0.05$). There was statistically significant difference in JSDI among different joints (Kruskal–Wallis test, $p = 0.003$).
Conclusion: These results suggest that our computer-based method may be useful to recognize the JSN progression on radiographs of rheumatoid wrists.
Advances in knowledge: The computer-based temporal subtraction method can detect the JSN progression in the wrist, which is the single most commonly involved site in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by joint swelling, joint tenderness and destruction of synovial joints, which leads to progressive joint destruction resulting in severe disability.[1] The optimal use of disease-modifying antirheumatic drugs[2,3] and the clinical application of several biological agents[4,5] were facilitated in the past decade. In this context, remission has become a realistic goal in the treatment of early RA.[6] The optimal adjustment of therapies and sensitive monitoring of the disease process are required to achieve this goal. Thus, quantifying the subtle structural changes with high sensitivity is of importance in the assessment of therapeutic efficacy.

Structural damage in RA has traditionally been assessed by conventional radiography. Although radiography is extensively used in clinical trials as the primary outcome measure, it requires a relatively long duration of follow-up to evaluate therapy effectiveness because it lacks sensitivity to change. Improvement in the ability to detect the subtle structural changes would therefore be a significant advance in clinical trials. Radiography is considered the gold standard for assessment of both disease progression and the effectiveness of treatment in RA,[7] although ultrasound and MRI are thought to be better suited to monitor disease progression. There are two main structural changes from RA visible on radiographs: bone erosion and joint space narrowing (JSN). Several visual scoring methods have been proposed to quantify the joint damage on the radiographs of patients with RA. Of these, the Sharp scoring method, especially in the modified forms suggested by van der Heijde, is the most widely used method to assess the bone erosion and JSN for joints of both hands and feet.[8] However, traditional scoring methods are subjective and are not

able to assess subtle changes with sufficient sensitivity. In addition, these methods are time consuming, require specialized training and suffer from interreader and intrareader variations.[9] For routine use, initial quantification methods could be performed by non-specialists who have not necessarily received any specialized training. In recent years, computer-based methods focusing on assessment of joint space widths have been developed to overcome the disadvantages of traditional scoring methods.[10–14] Computer-based methods provide a more sensitive, objective, quantitative and reproducible measurement compared with assessment by visual scoring methods for JSN. However, these methods can only be applied to finger joints such as metacarpophalangeal and proximal interphalangeal joints.

Recently, we have developed a computer-based method using a temporal subtraction technique for the assessment of JSN, which can detect the difference of joint space width between two radiographs with the joint space difference index (JSDI). Although a previous study[15] showed the relatively high sensitivity and specificity of the computer-based method for JSN progression in carpal joints as well as finger joints, it is unclear whether our computer-based method can quantify the JSN progression as well as the Sharp/van der Heijde (SvdH) method in carpal joints. Our aim in this study was to investigate the validity of our computer-based method in rheumatoid wrists.

METHODS AND MATERIALS

Patients

43 patients with RA (39 females and 4 males) treated with tocilizumab and/or disease-modifying antirheumatic drugs were included in the study. Some patients had been pre-treated with biological agents (seven patients with infliximab, three patients with etanercept, one patient with adalimumab, one patient with abatacept and three patients with combination therapy). We recruited patients who visited a local clinic for RA from October 2008 to October 2013 and were available for baseline and follow-up bilateral hand radiographs. No pre-selection regarding severity of RA was performed. Clinical and laboratory characteristics of the patients at baseline are shown in Table 1. All patients satisfied the American College of Rheumatology revised 1987 criteria for RA.[16] A portion of our patient population has been previously reported.[15]

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

Radiograph acquisition

Radiographs were obtained at baseline and at 1-year follow-up with a median of 12 months. All plain radiographs of the bilateral hand were acquired at anteroposterior view by an experienced X-ray technologist using digital X-ray equipment (Shimadzu UD150L-40E, Kyoto, Japan) under the following standardized conditions: X-ray aluminium filter of 1.5-mm thickness, film–focus distance 1 m, tube voltage 40 kV, tube current 200 mA and exposure 0.025 s. The X-ray beam centred on the midpoint between both hands at the level of the third metacarpophalangeal head. All radiographs were acquired by one radiological technologist under the same imaging conditions including positioning of the hand. In the computer-based analysis, all radiographs were digitized as bit-mapped images with a 1 × 1-mm pixel size at 8-bit greyscale.

Radiographic visual assessment

Each hand radiograph was scored using the SvdH score for JSN by two experts (Readers 1 and 2) who were blind to other clinical information. The readers' professional situations were somewhat different: Reader 1 was an experienced rheumatologist who was mainly working as a general practitioner; Reader 2 was an experienced radiologist who was also working as a researcher. The SvdH by Reader 1 was considered as the "standard of reference" because Reader 1 had more experience assessing radiographs using visual scoring methods than Reader 2. Interobserver reliability for the baseline, follow-up and delta SvdH (ΔSvdH) was assessed; here, "delta" is the interval difference in the values between baseline and follow-up images. In this study, JSN for carpal joints was graded as follows: Score 0 = normal; Score 1 = focal or doubtful; Score 2 = >50% of the original joint space; Score 3 = <50% of the original joint space or subluxation; and Score 4 = ankylosis or complete luxation.[17] The readers scored the radiographs in pairs, in which the baseline and follow-up bilateral hand radiographs of the same patient were presented together. The chronological order was

Table 1. Clinical and laboratory characteristics of patients with rheumatoid arthritis at baseline

Characteristic	Value
Total number of subjects included	43
Age, mean (range) (years)	58 (31–83)
Sex, number of females/males	39/4
Duration of symptoms, median (IQR) (months)	65 (24–108)
Follow-up time between the first and second radiograph, median (IQR) (months)	12 (8.8–14)
ESR, median (IQR) ($mm\,h^{-1}$)	50 (32–80)
CRP level, median (IQR) ($mg\,dl^{-1}$)	2.9 (1.6–6.8)
Swollen joint count, median (IQR)	15 (10–17)
Tender joint count, median (IQR)	13 (10–23)
VAS, median (IQR)	70 (56–77)
DMARDs, *n*	
None	2
Methotrexate	23
Mizoribine	1
Bucillamine	1
Salazosulfapyridine	1
Tacrolimus	1
Combination therapy	14

CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; IQR, inerquartile range; VAS, visual analogue scale.

known to the readers. The distribution of changes in SvdH for JSN between baseline and follow-up images by Reader 1 is shown in Table 2.

Computer-based analysis for joint space narrowing progression

The computer-based method can detect the difference in joint space width between baseline and follow-up images with the JSDI. This method visualizes JSN progression between the baseline image and the follow-up image by displaying narrowing with a red shadow (Figure 1). If there were no changes in joint space width between the baseline and the follow-up images, the joint space in the fused image was visualized as grey shadow (Figure 2). The JSDI is defined as the average absolute value of the difference of the pixel value in each pixel for baseline and follow-up images inside the region of interest (ROI). The details of the computer-based method are presented in a previous article.[15]

The computer-based method assessed the JSN progression of carpal joints (third carpometacarpal joint, fifth carpometacarpal joint, scaphoid–trapezium joint, scaphoid–capitate joint and radius–scaphoid joint), using the SvdH method as the standard of reference on bilateral hand radiographs. We excluded the fourth carpometacarpal joints because of the difficulty in discriminating from adjoining bone during ROI placement for JSDI. To increase the homogeneity of the study sample, severely damaged (subluxation, ankylosed and complete luxation) joints were also excluded based on the SvdH by each reader. Computer-based analysis was performed by a non-specialist who had not received specialized training in scoring of JSN and was blinded to other clinical information. Computer-based analysis was repeated twice, and intraobserver reliability was assessed based on each reader's score.

The measurement procedure was performed as follows. First, the software read the two images for each case and fused them into a single colour image by assigning cyan to the baseline and red to the follow-up image. Second, a single reference bone in the two images was aligned visually. The chosen reference bone was as follows: third carpometacarpal joint, third metacarpal bone; fifth carpometacarpal joint, fifth metacarpal bone; scaphoid–trapezium joint, trapezium; scaphoid–capitate joint, capitate; and radius–scaphoid joint, radius. Third, a rectangular ROI with a size of 20×7 pixels was located manually in the centre of the joint space with attention so that the edges of bones forming the joint were placed inside the ROI. At this time, the horizontal ROI borders were approximately parallel to the joint edges (Figure 1d and Figure 2d). Finally, information on each pixel value for the baseline and follow-up images inside the ROI was output to a text file that can be read by Microsoft Excel® (Microsoft, Redmond, WA), and the JSDI was calculated.

We compared the JSDI of joints with JSN progression in the follow-up period (increase in SvdH) with that of those without JSN progression (no change in SvdH) based on each reader's score. Additionally, we examined whether there is a significant difference in JSDI in terms of laterality or topology of the joint based on each reader's score. In addition, a direct correlation of the JSDI with the ΔSvdH was evaluated. Data from the first time measurement were used for these analyses.

Statistical analyses

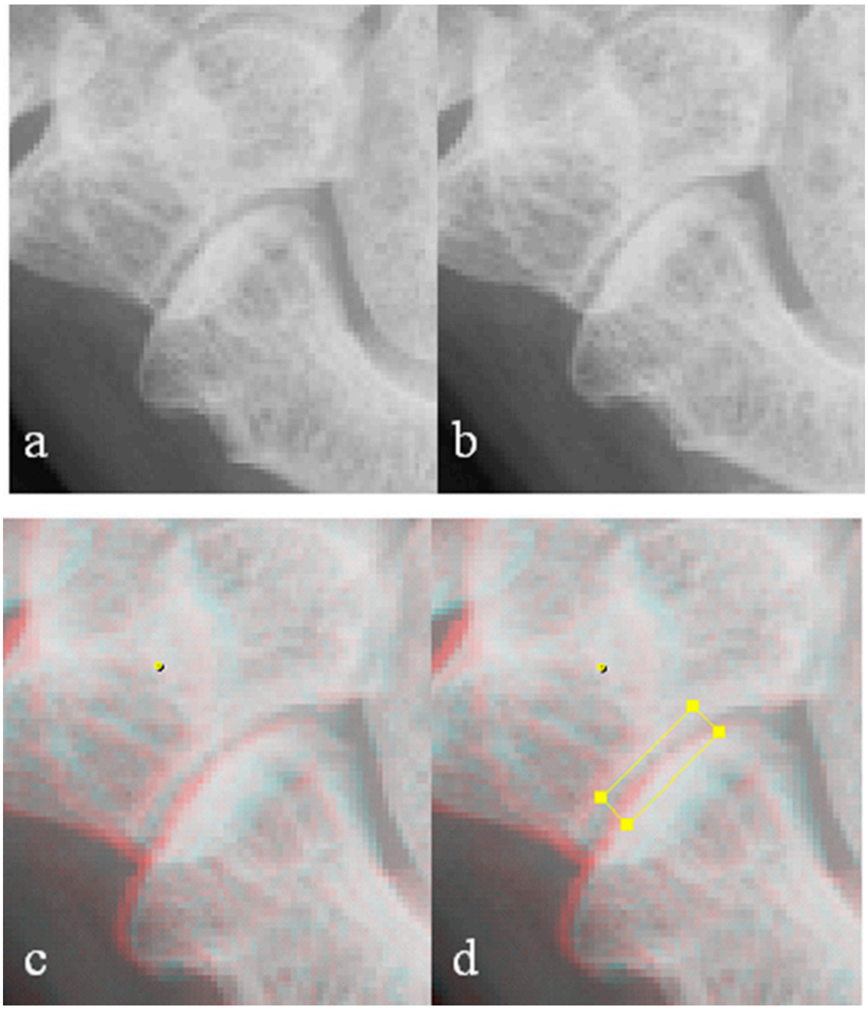
Statistical analyses were calculated with the use of SPSS® v. 22.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) for Windows® and Excel (Microsoft). Intraobserver and interobserver reliabilities were estimated using calculations of intraclass correlation coefficients (ICCs). The ICC ranged from -1 to $+1$. ICC values are interpreted as follows: <0.40, poor to fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, almost perfect agreement.[18] Differences between two independent samples were examined using the Mann–Whitney *U* test. To assess the significance of differences in terms of topology, the Kruskal–Wallis test was used. *p*-values <0.05 were considered statistically significant. Correlations between the JSDI and the ΔSvdH were examined using Spearman's rank correlation test.

Table 2. Distribution of changes in Sharp/van der Heijde (SvdH) score for joint space narrowing (JSN) in carpal joints ($n = 355$)

Chronological changes of SvdH for JSN	CM3	CM5	ST	SC	RS
0→0	55	53	33	30	27
0→1	2	2	2	2	4
0→2	1	0	1	4	2
0→3	0	0	2	1	0
1→1	6	7	13	14	8
1→2	2	0	0	0	2
1→3	0	1	0	1	0
2→2	6	7	13	9	13
2→3	0	1	1	0	1
3→3	2	4	7	5	11

CM3, third carpometacarpal joint; CM5, fifth carpometacarpal joint; RS, radius-scaphoid joint; SC, scaphoid-capitate joint; ST, scaphoid–trapezium joint.

Figure 1. The scaphoid–trapezium joint of a 57-year-old female with rheumatoid arthritis with interval change in joint space width. Radiograph images of the scaphoid–trapezium joint for the right hand at baseline (a) and follow-up (b) are shown. These images correspond to a Sharp/van der Heijde score of 0 and 1, respectively. In the fused image (c), the joint space difference is visible as a red shadow. The rectangular region of interest, with a size of 20 × 7 pixels, was located in the centre of the joint space (d), and the chronological changes in the joint space width were measured as the joint space difference index (JSDI). The JSDI for this case was 12.70. For colour image see online.



RESULTS

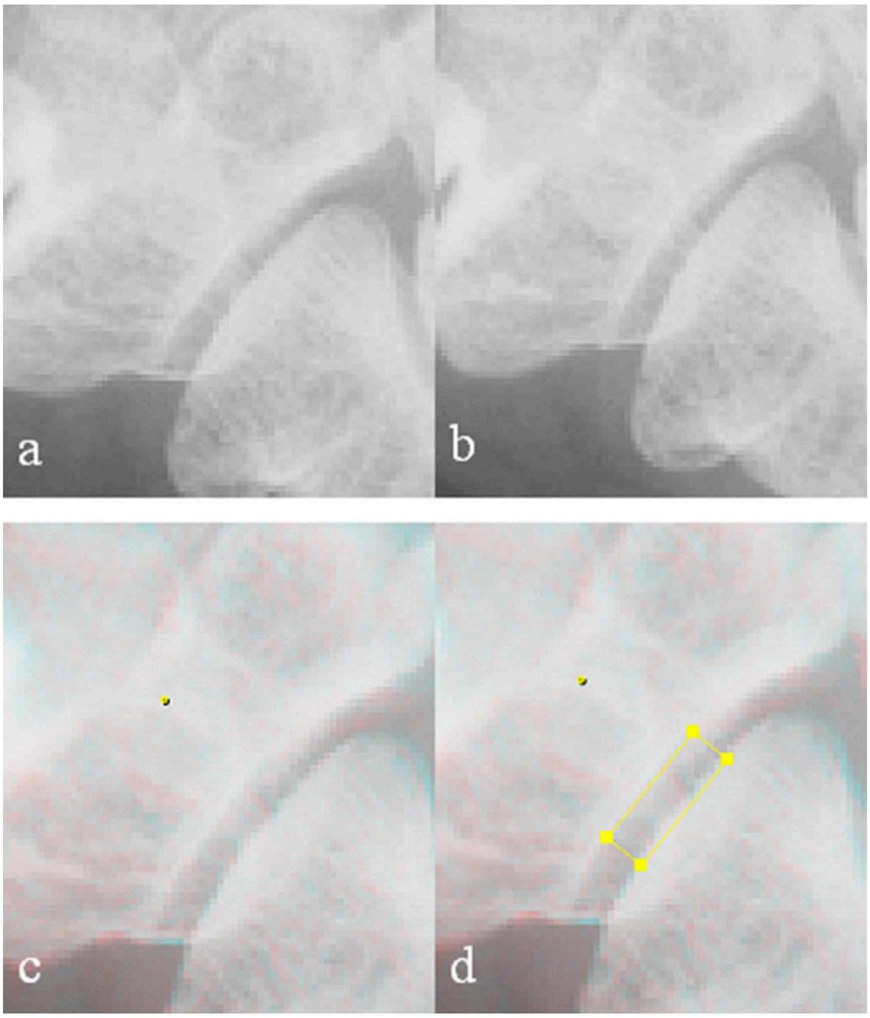
A total of 430 carpal joints on the bilateral hand radiographs in 43 patients were scored using the SvdH method by Readers 1 and 2. Interobserver reliability for baseline SvdH was in substantial agreement [ICC = 0.695; 95% confidence interval (CI), 0.643–0.741]. Interobserver reliability for follow-up SvdH was in substantial agreement (ICC = 0.678; 95% CI, 0.624–0.726). Interobserver reliability for ΔSvdH was in moderate agreement (ICC = 0.591; 95% CI, 0.526–0.649).

The computer-based method evaluated carpal joints twice on the bilateral hand radiographs in 43 patients, using the SvdH method as the standard of reference. Out of 430 carpal joints, we targeted 355 and 365 carpal joints after excluding severely damaged 75 and 65 joints based on the scores by Readers 1 and 2, respectively. Intraobserver reliability for the JSDI based on the scores by Reader 1 was in almost perfect agreement (ICC = 0.967; 95% CI, 0.959–0.973). Intraobserver reliability for the JSDI based on the scores by Reader 2 was in almost perfect agreement (ICC = 0.968; 95% CI, 0.961–0.974).

Based on the score by Reader 1, the medians of the JSDI for carpal joints were 11.26 [interquartile range (IQR) 6.86–13.37, $n = 32$] and 6.84 (IQR 5.33–9.04, $n = 323$) with and without JSN progression, respectively. Both the ΔSvdH and JSDI of joints with JSN progression were significantly higher than that of those without JSN progression, respectively ($p < 0.001$) (Table 3); while based on the score by Reader 2, the medians of the JSDI for carpal joints were 8.90 (IQR 5.78–11.92, $n = 40$) and 7.01 (IQR 5.43–9.63, $n = 325$) with and without JSN progression in carpal joints, respectively ($p = 0.02$).

We next examined whether there was a significant difference in the JSDI and ΔSvdH in terms of laterality of the joint. There was no statistically significant difference in the JSDI and ΔSvdH between the left and right carpal joints based on the score by

Figure 2. The scaphoid–trapezium joint of a 61-year-old male with rheumatoid arthritis without interval change in joint space width. Radiograph images of the scaphoid–trapezium joint for the right hand at baseline (a) and follow-up (b) are shown. Both of these images correspond to a Sharp/van der Heijde score of 0. In the fused image (c), the difference in the joint space between the baseline and the follow-up images is not recognizable. The rectangular region of interest, with a size of 20×7 pixels, was located in the centre of the joint space (d), and the chronological changes in the joint space width were measured as the joint space difference index (JSDI). The JSDI for this case was 4.10. For colour image see online.



Reader 1, which was analysed for five different joints altogether and each joint separately ($p > 0.05$) (Table 4). There was no statistically significant difference in the JSDI in terms of laterality of the joints based on the score by Reader 2 ($p > 0.05$).

In addition, we examined whether there was a significant difference in the JSDI and ΔSvdH in terms of topology of the joint. There was no statistically significant difference in the ΔSvdH among different joints based on the score by Reader 1 ($p = 0.393$). However, there was a statistically significant difference in the JSDI among different joints based on the score by Reader 1 ($p = 0.003$) (Table 5). The JSDI of the scaphoid–capitate joint was significantly lower than that of the third carpometacarpal joint and the scaphoid–trapezium joint ($p = 0.048$ and 0.003, respectively). Based on the score by Reader 2, there was a statistically significant difference in the JSDI among different joints ($p = 0.002$). The JSDI of the scaphoid–capitate joint was significantly lower than that of the fifth carpometacarpal joint and scaphoid–trapezium joint ($p = 0.038$ and 0.003, respectively).

Finally, correlations between the JSDI and the ΔSvdH were examined. The mean and standard deviation JSDI (n, the number of joints) of joints for 0, 1, 2 and 3 in Reader 1's ΔSvdH were 7.64 ± 3.16 ($n = 323$), 10.57 ± 4.28 ($n = 19$), 10.35 ± 3.95 ($n = 10$) and 11.42 ± 0.18 ($n = 3$), respectively. For this, the JSDI was not correlated with ΔSvdH ($r = 0.877$, $p = 0.123$) (Figure 3). The mean and standard deviation JSDI of joints for 0, 1, 2 and 3 in Reader 2's ΔSvdH were 7.93 ± 3.36 ($n = 325$), 9.07 ± 4.76 ($n = 14$), 9.84 ± 3.85 ($n = 23$) and 9.57 ± 5.77 ($n = 3$), respectively. For this, the JSDI was not correlated with ΔSvdH ($r = 0.870$, $p = 0.130$).

DISCUSSION

In this study, we investigated the validity of a computer-based method for detecting JSN progression in carpal joints by

Table 3. Comparison of the joint space difference index or change of the Sharp/van der Heijde score between joints with and without joint space narrowing progression

Joint	Joints with JSNP(+)			Joints with JSNP(−)			*p*-value
	n	Median	IQR	*n*	Median	IQR	
CM3	5	12.97/1.00	9.50–14.45/1.00–1.50	69	7.05/0.00	5.71–9.35/0.00–0.00	
CM5	4	10.02/1.00	5.85–11.80/1.00–1.75	71	7.23/0.00	5.70–9.51/0.00–0.00	
ST	6	12.39/1.50	11.36–16.97/1.00–3.00	66	7.38/0.00	5.57–10.76/0.00–0.00	
SC	8	6.34/2.00	5.37–11.72/1.25–2.00	58	5.84/0.00	4.87–8.13/0.00–0.00	
RS	9	8.29/1.00	6.80–13.51/1.00–1.50	59	6.53/0.00	4.84–8.47/0.00–0.00	
Carpal, overall	32	11.26/1.00	6.86–13.37/1.00–2.00	323	6.84/0.00	5.33–9.04/0.00–0.00	<0.001/<0.001

CM3, third carpometacarpal joint; CM5, fifth carpometacarpal joint; IQR, interquartile range; JSNP(−), non-joint space narrowing progression; JSNP(+), joint space narrowing progression; RS, radius–scaphoid joint; SC, scaphoid–capitate joint; ST, scaphoid–trapezium joint.

comparing the computer-based method with the SvdH method as the gold standard. The results of the computer-based method were consistent with those of the SvdH method in almost all examinations excluding assessment in terms of topology of the joints. The results indicate that our computer-based method can recognize the difference in joint space width on hand radiographs in carpal joints.

Previous computer-aided analyses were validated only in finger joints such as metacarpophalangeal, proximal interphalangeal or distal interphalangeal joints.[10,12,19] However, assessment for JSN by traditional scoring methods such as the SvdH score[17] and the Genant-modified Sharp score[20] includes carpal joints. In addition, the carpal joint is a site of predilection for rheumatoid disease. Thus, it is preferred that computer-based methods are validated not only in finger joints but also in carpal joints. The advantage of our computer-based method is that it can detect JSN progression in carpal joints as well as in finger joints. Furthermore, our method does not require highly trained personnel, as is the case of traditional scoring methods.

Other modalities (*i.e.* ultrasound and MRI) are available that directly visualize the active disease and feature a much better sensitivity in detecting the progression of RA.[21] These modalities are thought to be better suited to monitor disease progression and have increasingly been used as outcome measures in patients with RA.[18,22] While ultrasound and MRI allow direct visualization of early inflammation, conventional radiography is the standard method for diagnosing and monitoring structural joint damage such as JSN.[21,23] In addition, it is not only inexpensive but also widely available and accepted. Although radiographs are usually assessed by established scoring methods, these methods suffer from intraobserver or interobserver variations. Our data showed that interobserver reliability for SvdH were in substantial or moderate agreement, as assessed by ICC. By contrast, intraobserver reliability for the computer-based method was supported by high agreement. Consequently, the computer-based method could provide reproducible measurement of JSN progression.

In a previous study, Angwin et al[24] reported no change in Sharp scores in 47% of their 245 patients with early RA after 2 years, but a significant reduction in joint space width using a different computer-based method. This report indicates that the computer-based method is more sensitive to the change in joint space width than traditional scoring methods. In this study, we cannot determine whether our computer-based method or the SvdH method is more sensitive because of the absence of a gold standard. However, our computer-based method could detect

Table 4. Comparison of the joint space difference index or change of the Sharp/van der Heijde score between the left and right joints

Joint	Left joints			Right joints			*p*-value
	n	Median	IQR	*n*	Median	IQR	
CM3	38	6.89/0.00	5.51–9.91/0.00–0.00	36	7.81/0.00	6.65–10.10/0.00–0.00	0.261/0.673
CM5	38	6.91/0.00	5.21–10.57/0.00–0.00	37	7.67/0.00	6.27–9.18/0.00–0.00	0.641/0.957
ST	36	7.22/0.00	5.50–11.26/0.00–0.00	36	8.75/0.00	6.27–11.36/0.00–0.00	0.380/0.404
SC	33	5.42/0.00	4.92–7.12/0.00–0.00	33	6.87/0.00	4.98–8.85/0.00–0.00	0.156/0.973
RS	32	7.17/0.00	5.51–9.64/0.00–0.00	36	6.25/0.00	4.71–8.40/0.00–0.00	0.144/0.531
Carpal, overall	177	6.74/0.00	5.18–9.66/ 0.00–0.00	178	7.36/0.00	5.72–9.64/0.00–0.00	0.213/0.969

CM3, third carpometacarpal joint; CM5, fifth carpometacarpal joint; IQR, interquartile range; RS, radius–scaphoid joint; SC, scaphoid–capitate joint; ST, scaphoid–trapezium joint.

Table 5. Comparison of the joint space difference index or change of the Sharp/van der Heijde score among different carpal joints

Joint	*n*	Median	IQR	*p*-value
CM3	74	7.26/0.00	5.73–10.04/0.00–0.00	0.003/0.393
CM5	75	7.42/0.00	5.70–9.62/0.00–0.00	
ST	72	7.91/0.00	5.64–11.36/0.00–0.00	
SC	66	5.84/0.00	4.94–8.24/0.00–0.00	
RS	68	6.76/0.00	4.97–8.86/0.00–0.00	

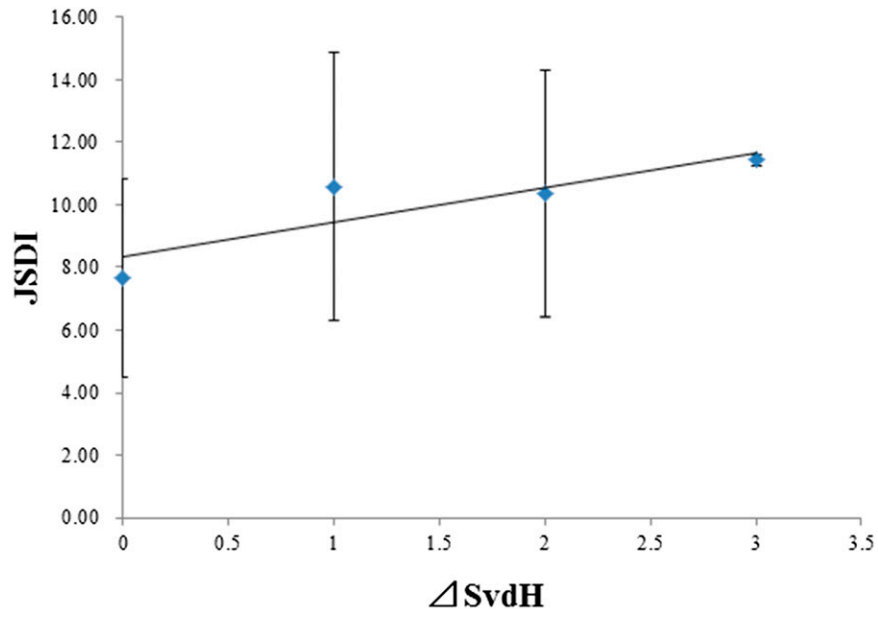
CM3, third carpometacarpal joint; CM5, fifth carpometacarpal joint; IQR, interquartile range; RS, radius–scaphoid joint; SC, scaphoid–capitate joint; ST, scaphoid–trapezium joint.

the chronological change of joint space width and is consistent with assessment by the SvdH method in almost all examinations. In addition, our methods extract the joint space difference between two images by superimposing the images, and therefore, a slight joint space difference is detected more easily than if the images were to be observed side by side. Thus, our computer-based method may be useful as a computer-aided diagnosis tool and assist the assessment of JSN by a rheumatologist.

The JSDI between progressive and stable joints revealed considerable overlap (Table 3). Although the JSDI of joints without JSN progression was expected to be 0 in theory, the median was 6.84 (IQR 5.33–9.04) (overall carpal joint) in practice. In addition, the JSDI of scaphoid–capitate joints was lower than that of other joints, showing statistically significant difference among different joints. These may be explained by the influence of different hand positions during imaging, variation in the X-ray beam angle or progression of osteopenia. This result implied that the scaphoid–capitate joints should be removed from a computer-based analysis, although further analysis is needed to confirm this. Furthermore, there was no statically significant correlation between the JSDI and ΔSvdH, although showing high correlation coefficient. This was due to a relatively small number of joints with changes in SvdH, especially in ΔSvdH "3" ($n = 3$).

Several limitations of this study should be discussed. First, only a limited number of joints with JSN progression were studied ($n = 32$ or 40). Therefore, we could validate for five different carpal joints altogether, but not for each joint separately. In addition, we could not reveal the precise relationship between the JSDI and ΔSvdH. Further study, with a larger number of joints with JSN progression, is needed to prove that the JSDI is a potential marker for the assessment of disease progression. Second, no pre-selection regarding steroid therapy was considered. Treatment of RA with steroid therapy may increase susceptibility to osteoporosis but also suppresses inflammatory activity, which is a risk factor for osteoporosis in RA. Therefore, steroid therapy may have an influence on the JSDI inside the ROI. Finally, our computer-based method tends to be time consuming. The analysis time is around 3 min per joint. We will develop an automated computer-based method that automatically aligns the

Figure 3. Relationship between the joint space difference index (JSDI) and delta Sharp/van der Heijde score (ΔSvdH). The JSDI is expressed as mean and standard deviation for each ΔSvdH score.



joint with only minimal human intervention and can evaluate JSN progression more easily and reproducibly.

In conclusion, our computer-based method, which requires no special training or experience of traditional scoring methods, can detect the difference in joint space width between two radiographs as JSDI in the rheumatoid wrist. Refinement of this method may enable us to obtain more sensitive, objective, quantitative and reproducible information about JSN progression. Further study is needed to prove that this method is useful to quantify the JSN progression on radiographs in clinical trials.

REFERENCES

1. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; **62**: 2569–81. doi: 10.1002/art.27584
2. Bijlsma JW, Weinblatt ME. Optimal use of methotrexate: the advantages of tight control. *Ann Rheum Dis* 2007; **66**: 1409–10. doi: 10.1136/ard.2007.076463
3. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. *Ann Rheum Dis* 2009; **68**: 1094–9. doi: 10.1136/ard.2008.092668
4. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. *Lancet* 2007; **370**: 1861–74. doi: 10.1016/S0140-6736(07)60784-3
5. Doan T, Massarotti E. Rheumatoid arthritis: an overview of new and emerging therapies. *J Clin Pharmacol* 2005; **45**: 751–62. doi: 10.1177/0091270005277938
6. Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? *Clin Exp Rheumatol* 2006; **24**: 7–13.
7. van der Heijde DM. Radiographic imaging: the “gold standard” for assessment of disease progression in rheumatoid arthritis. *Rheumatology (Oxford)* 2000; **39** (**Suppl. 1**): 9–16.
8. van der Heijde DM. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. *Baillieres Clin Rheumatol* 1996; **10**: 435–53. doi: 10.1016/S0950-3579(96)80043-4
9. van der Heijde D, Boonen A, Boers M, Kostense P, van der Linden S. Reading radiographs in chronological order, in pairs or as single films has important implications for the discriminative power of rheumatoid arthritis clinical trials. *Rheumatology (Oxford)* 1999; **38**: 1213–20. doi: 10.1093/rheumatology/38.12.1213
10. Finckh A, de Pablo P, Katz JN, Neumann G, Lu Y, Wolfe F, et al. Performance of an automated computer-based scoring method to assess joint space narrowing in rheumatoid arthritis: a longitudinal study. *Arthritis Rheum* 2006; **54**: 1444–50. doi: 10.1002/art.21802
11. Pfeil A, Oelzner P, Bornholdt K, Hansch A, Lehmann G, Renz DM, et al. Joint damage in rheumatoid arthritis: assessment of a new scoring method. *Arthritis Res Ther* 2013; **15**: R27. doi: 10.1186/ar4163
12. Duryea J, Jiang Y, Zakharevich M, Genant HK. Neural network based algorithm to quantify joint space width in joints of the hand for arthritis assessment. *Med Phys* 2000; **27**: 1185–94. doi: 10.1118/1.598983
13. Böttcher J, Pfeil A, Rosholm A, Petrovitch A, Seidl BE, Malich A, et al. Digital X-ray radiogrammetry combined with semiautomated analysis of joint space widths as a new diagnostic approach in rheumatoid arthritis: a cross-sectional and longitudinal study. *Arthritis Rheum* 2005; **52**: 3850–9. doi: 10.1002/art.21606
14. Peloschek P, Langs G, Weber M, Sailer J, Reisegger M, Imhof H, et al. An automatic model-based system for joint space measurements on hand radiographs: initial experience. *Radiology* 2007; **245**: 855–62. doi: 10.1148/radiol.2452061281
15. Ichikawa S, Kamishima T, Sutherland K, Okubo T, Katayama K. Performance of computer-based analysis using temporal subtraction to assess joint space narrowing progression in rheumatoid patients. *Rheumatol Int* Aug 2015. Epub ahead of print.
16. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; **31**: 315–24. doi: 10.1002/art.1780310302
17. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000; **27**: 261–3.
18. Kamishima T, Tanimura K, Shimizu M, Matsuhashi M, Fukae J, Kon Y, et al. Monitoring anti-interleukin 6 receptor antibody treatment for rheumatoid arthritis by quantitative magnetic resonance imaging of the hand and power Doppler ultrasonography of the finger. *Skeletal Radiol* 2011; **40**: 745–55. doi: 10.1007/s00256-010-1064-4
19. Pfeil A, Renz DM, Hansch A, Kainberger F, Lehmann G, Malich A, et al. The usefulness of computer-aided joint space analysis in the assessment of rheumatoid arthritis. *Joint Bone Spine* 2013; **80**: 380–5. doi: 10.1016/j.jbspin.2012.10.022
20. Genant HK. Methods of assessing radiographic change in rheumatoid arthritis. *Am J Med.* 1983; **75**: 35–47. doi: 10.1016/0002-9343(83)90473-4
21. Østergaard M, Pedersen SJ, Døhn UM. Imaging in rheumatoid arthritis—status and recent advances for magnetic resonance imaging, ultrasonography, computed tomography and conventional radiography. *Best Pract Res Clin Rheumatol* 2008; **22**: 1019–44. doi: 10.1016/j.berh.2008.09.014
22. Iagnocco A, Finucci A, Ceccarelli F, Perricone C, Iorgoveanu V, Valesini G. Power Doppler ultrasound monitoring of response to anti-tumour necrosis factor alpha treatment in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2015; **54**: 1890–6. doi: 10.1093/rheumatology/kev211
23. Ostergaard M, Szkudlarek M. Imaging in rheumatoid arthritis–why MRI and ultrasonography can no longer be ignored. *Scand J Rheumatol.* 2003; **32**: 63–73.
24. Angwin J, Lloyd A, Heald G, Nepom G, Binks M, James MF. Radiographic hand joint space width assessed by computer is a sensitive measure of change in early rheumatoid arthritis. *J Rheumatol* 2004; **31**: 1050–61.