Implementation of Z-Scores as an Age- and Sex-independent Parameter for Estimating Joint Space Widths in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To compare normative data of joint space distances (JSD) with the JSD of patients with rheumatoid arthritis (RA) as measured by computer-aided joint space analysis (CAJSA) at the metacarpophalangeal (MCP) articulations, and to differentiate age- and sex-related alterations from the disease-related joint space narrowing.

Methods. In total, 256 healthy subjects and 248 patients with verified RA (following revised ACR criteria) underwent computerized semiautomated measurements of JSD (CAJSA, version 1.3.6) at the MCP articulation (JSD-MCP) based on digital radiographs. The Z-score, a comparative parameter that differentiates joint space alterations caused by RA-related cartilage destruction from age- and sex-related changes, was calculated.

Results. Our data showed a relationship between measured joint space widths (MCP total and MCP thumb to little finger) and age for healthy subjects and also the RA group. The RA group revealed an age-related joint space narrowing that was surpassed by the RA-related narrowing of joint space widths classified by Sharp joint space narrowing score and resulting in smaller Z-scores for RA patients.

Conclusion. The CAJSA technique seems to distinguish age-related JSD changes in healthy volunteers from RA-induced alterations. In addition the Z-score was also able to differentiate RA-dependent narrowing of JSD. Calculation of the Z-scores based on sex- and age-specific reference data may facilitate earlier identification of patients with RA, allowing initiation of a more optimal, individually adapted therapeutic strategy. (J Rheumatol First Release March 15 2009; doi:10.3899/jrheum.080651)

Key Indexing Terms:
COMPUTER-AIDED DIAGNOSIS COMPUTER-AIDED JOINT SPACE ANALYSIS
JOINT SPACE WIDTH FINGER RHEUMATOID ARTHRITIS Z-SCORE

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Rheumatoid arthritis (RA) is a systemic disease characterized by the juxtaarticular inflammatory involvement of cartilage and bone tissue, frequently and predominantly affecting the small joints of the hand[1]. Conventional radiography has always played a major role in the diagnosis and followup of RA[2,3]. The major radiological characteristics in RA include periarticular osteoporosis, erosions, and joint space narrowing. The disadvantages of conventional imaging include more limited sensitivity in the detection of joint space narrowing and a higher interobserver variability in early RA[4].

For a more reliable quantification of RA-related changes, resulting in a better prognosis and improved success of treatment strategies, the use of digital techniques for acquisition and processing of radiographs has substantially increased and has gained wider acceptance in recent years. The availability of digital methods provides the opportunity for quantitative measurements of radiographic features as a part of computer-aided diagnosis (CAD) systems[5,6].

Standardized measurement of periarticular demineralization, erosions, and joint space narrowing based on CAD systems offers directly available data with high reproducibility. In particular, CAD techniques have been developed for estimating periarticular demineralization based on digital X-ray radiogrammetry[7-9]; some studies have also reported a measurement of erosion size[6,10,11] and joint space width[5,10-17].

Computer-aided joint space analysis (CAJSA) is a new CAD program enabling semiautomated measurement of joint space distances (JSD) at the metacarpophalangeal (MCP) articulation (JSD-MCP) based on digitized hand radiographs. Recently, normative data for the finger articulations were published, and a strong relationship between age and joint space narrowing was revealed[18-20]. Studies have consistently shown evidence of decreased joint space widths dependent on the severity of RA, and have demonstrated the excellent reproducibility of the MCP articulation by the CAJSA technique[15,16].

Our study provides reference values of the radiogeometrically detectable joint space widths of the MCP articulation measured by CAJSA in healthy individuals, demonstrating age-related changes, and compares these data with age-matched controls with RA. Further, a Z-score is introduced to distinguish RA-induced joint space narrowing from age-related changes.

MATERIALS AND METHODS

Patients. Reference group. A total of 256 healthy subjects (122 women, 134 men) with digital hand radiographs underwent measurements of JSD (in mm) using CAJSA. Mean age was 55.5 years (SD 11.6 yrs, range 30.0 to 80.0). Digital radiographs of the nondominant hand were taken for all subjects, who were admitted to the university clinic due to trauma. Each hand radiograph was read in a blind manner by 2 radiologists for evidence of osteoarthritis using the Kellgren-Lawrence grading system with a standard atlas[21], where grade 0 = normal joint; grade 1 = small osteophyte of doubtful significance; grade 2 = definite osteophyte; grade 3 = osteophyte and joint space narrowing; and grade 4 = severe joint space narrowing. In the case of ambiguity a third radiologist reviewed the radiographs.

Exclusion criteria were determined by an extensive questionnaire, and included (1) visible metallic material, (2) signs of fracture, (3) amputation, (4) rheumatic diseases, (5) genetic diseases, (6) incorrect hand positioning, and (7) Kellgren-Lawrence grade > 1.

RA group. A total of 248 Caucasian patients (186 women, 62 men) with verified RA were included. All patients were admitted to the ambulance of the Department of Rheumatology at our university clinic. These patients were 31.0–80.0 years old (mean 56.6 ± 11.6 yrs), and RA was diagnosed according to the revised criteria of the American College of Rheumatology[22]. Median disease duration was 5 years. No preselection regarding the grade of RA or steroid therapy was performed. All patients were treated with disease modifying antirheumatic drugs (methotrexate n = 211, leflunomide n = 21, sulfasalazine n = 16). A total of 168 patients had had prednisolone therapy (median 5 mg per day). Disease activity measured by C-reactive protein level was stable (median 5 mg/l).

Patients with signs of fracture, visible osteosynthetic material, or a Sharp joint space narrowing score[23] = 4 were also excluded (described below).

Quantification of joint space width. Each radiograph was scored by the same 2 radiologists in a blinded manner using the joint space narrowing method of Sharp[23], which evaluates the MCP articulations of both hands: score 0 = normal joint; score 1 = initial reduction of the joint space width; score 2 = reduction of the joint space width < 50%; score 3 = joint space narrowing > 50%; and score 4 = ankylosis. The individual sum of scoring points was then divided by the number of evaluated joints. In the case of ambiguity a third radiologist reviewed the radiographs again.

Methods. Measurement of JSD. CAJSA (version 1.3.6; Sectra Imtec AB, Linköping, Sweden) is able to estimate the JSD of the MCP joint (JSD-MCP) from the thumb to the little finger. This technique allows a joint space analysis of a finger joint by detection of the joint edges within a rectangular region of interest as defined by the user. The positioning of this region of interest to mark the chosen joint is the only operator-dependent procedure in the measurement process. The software is based on automatic edge-filtering within the region of interest identifying the joint. A 1.5 cm-long edge across each bone is further determined, and the distance between the 2 edges is estimated as a function of the horizontal position. The mean average and standard deviation of the distance over a moving interval of 0.8 cm is calculated. The distance between the bones is defined to be the edge interval for which the standard deviation is minimal. The JSD are given in millimeters. Analysis time needed for one joint averages 1 minute. The short-term precision regarding all CAJSA parameters is verified by intraradiograph reproducibility (10 measurements of the same hand radiograph) and showed the following coefficients of variation: JSD-MCP thumb 0.61%; JSD-MCP index finger 0.49%; JSD-MCP middle finger 0.50%; JSD-MCP ring finger 0.52%; JSD-MCP little finger 0.55%; and JSD-MCP total 0.53%.

All examinations were performed in accord with the rules and regulations of the local human research and ethics committee. The authors emphasize that all radiographs used for CAJSA calculations were performed as part of routine clinical care; no additional radiographs were obtained for study purposes.

Statistical analysis. Statistical analysis was performed using SPSS version 14.0 (SPSS, Chicago, IL, USA) for Windows. Results are expressed as mean and standard deviation. The study consisted of a healthy cohort and a group of patients with RA. In the first segment of the study the JSD in the reference group and in the RA group were assessed. In the second segment JSD-MCP in patients with RA was compared to the age-matched reference values of healthy subjects using the Z-score.

The Z-score is calculated as follows:

$$\text{Z-score} = (\text{JSD-MCP}_{\text{patient}} - \text{JSD-MCP}_{\text{age and sex matched control}}) / \text{SD}_{\text{age and sex matched control}}$$

The differences were calculated with the Mann-Whitney U test, and $p < 0.05$ was considered significant.

RESULTS

Sex-related differences of joint space widths

Healthy subjects. In healthy subjects, women (1.52 ± 0.29 mm) had a significantly smaller joint space width of total JSD-MCP (–18.4%; $p < 0.01$) compared to men (1.80 ± 0.32 mm). The pronounced sex-associated difference ($p < 0.01$) was observed for JSD-MCP (ring finger), with a reduction of –23.9% in women compared to men. The female JSD-MCP for thumb (–17.3%; $p < 0.01$), index finger (–14.7%; $p < 0.01$), middle finger (–21.8%; $p < 0.01$), and little finger (–17.8%; $p < 0.01$) were also significantly smaller in comparison to men.

RA patients. For the patients with RA the age-independent results showed that women (1.34 ± 0.37 mm) had a significantly lower total JSD-MCP (–14.2%; $p < 0.01$) compared

to men (1.53 ± 0.38 mm). The highest difference between women (1.30 ± 0.46 mm) and men (1.58 ± 0.46 mm) was observed for JSD-MCP thumb (–21.5%; $p < 0.01$). The female JSD-MCP index finger and JSD-MCP middle finger were significantly smaller (–10.4%; $p < 0.01$ vs –10.3%; $p < 0.01$, respectively) as were JSD-MCP ring finger and JSD-MCP little finger (–13.0%; $p < 0.01$, and –13.4%; $p < 0.01$, respectively) compared to men.

Age-related joint space narrowing

Healthy subjects (Table 1). The JSD-MCP total was significantly ($p < 0.01$) narrowed from 1.82 ± 0.28 mm (age < 39 yrs) to 1.48 ± 0.30 mm (age > 70 yrs) with a relative value of –18.9%. The greatest significant narrowing ($p < 0.01$) was observed for JSD-MCP middle finger, –22.3%, between the age < 39 years (1.88 ± 0.37 mm) and > 70 years (1.46 ± 0.34 mm). Similar results were revealed for JSD-MCP index finger, –21.7% ($p < 0.01$), and JSD-MCP ring finger, –19.4% ($p < 0.01$). A significant narrowing could also be observed for JSD-MCP little finger and JSD-MCP thumb.

RA patients (Table 2). The JSD-MCP total revealed a significant ($p < 0.01$) narrowing of –26.5% from 1.55 ± 0.33 mm (age < 39 yrs) to 1.14 ± 0.50 mm (age > 70 yrs). The greatest narrowing ($p < 0.01$) was observed for JSD-MCP thumb, –33.8%, from 1.57 ± 0.53 mm (age < 39 yrs) to 1.04 mm ± 0.52 mm (age > 70 yrs). Similar results were observed for JSD-MCP index finger, –29.9% ($p < 0.01$), and for JSD-MCP middle finger, –28.0% ($p < 0.01$). Additionally, a significant narrowing of –20.1% ($p < 0.01$) was observed for JSD-MCP ring finger. The smallest joint space narrowing was revealed for JSD-MCP little finger, –10.6% ($p < 0.05$), from 1.42 ± 0.33 mm (age < 39 yrs) to 1.27 ± 0.11 mm (age > 70 yrs).

Comparison of JSD between healthy subjects and patients with RA (Table 3)

The results showed that RA patients had a significantly smaller JSD (JSD-MCP total –16.8%; $p < 0.01$) compared to healthy subjects, although the effect of sex was not differentiated from the effect of disease. The greatest difference between the 2 groups was observed for JSD-MCP index finger, –21.6% ($p < 0.01$). JSD-MCP middle finger and JSD-MCP thumb were smaller, –17.2% versus –15.3% in the RA group ($p < 0.01$). A significant narrowing could also be confirmed in the RA group compared to normative data for JSD-MCP ring finger and JSD-MCP little finger (Table 3).

Severity-dependent joint space narrowing with increasing Sharp score (severity)

Computer-aided joint space analysis (Table 4). The Sharp

Table 1. Age-related joint space narrowing in healthy subjects (n = 256).

Location	Age < 39 yrs, mean ± SD mm, n = 28	40–49 yrs, mean ± SD mm, n = 67	50–59 yrs, mean ± SD mm, n = 74	60–69 yrs, mean ± SD mm, n = 52	> 70 yrs, mean ± SD mm, n = 35	Relative Difference from Age < 39 to > 70 yrs, % (p)
JSD-MCP thumb	1.71 ± 0.19	1.69 ± 0.39	1.66 ± 0.35	1.59 ± 0.35	1.52 ± 0.32	–11.1 (< 0.05)
JSD-MCP index finger	2.07 ± 0.33	1.97 ± 0.41	1.95 ± 0.44	1.82 ± 0.49	1.62 ± 0.48	–21.7 (< 0.01)
JSD-MCP middle finger	1.88 ± 1.37	1.81 ± 0.41	1.71 ± 0.38	1.55 ± 0.39	1.46 ± 0.34	–22.3 (< 0.01)
JSD-MCP ring finger	1.75 ± 0.37	1.61 ± 0.38	1.57 ± 0.36	1.49 ± 0.36	1.41 ± 0.37	–19.4 (< 0.01)
JSD-MCP little finger	1.66 ± 0.32	1.57 ± 0.36	1.54 ± 0.32	1.46 ± 0.35	1.43 ± 0.30	–13.9 (< 0.01)
JSD-MCP total	1.82 ± 0.28	1.73 ± 0.35	1.69 ± 0.32	1.62 ± 0.34	1.48 ± 0.30	–18.9 (< 0.01)

JSD-MCP: joint space distance of the metacarpophalangeal joint.

Table 2. Age-related joint space narrowing in patients with RA (n = 248).

Location	Age < 39 yrs, mean ± SD mm, n = 40	40–49 yrs, mean ± SD mm, n = 28	50–59 yrs, mean ± SD mm, n = 87	60–69 yrs, mean ± SD mm, n = 62	> 70 yrs, mean ± SD mm, n = 31	Relative Difference from Age < 39 to > 70 yrs, % (p)
JSD-MCP thumb	1.57 ± 0.53	1.50 ± 0.44	1.44 ± 0.37	1.29 ± 0.46	1.04 ± 0.52	–33.8 (< 0.01)
JSD-MCP index finger	1.67 ± 0.45	1.50 ± 0.63	1.49 ± 0.56	1.39 ± 0.47	1.17 ± 0.78	–29.9 (< 0.01)
JSD-MCP middle finger	1.61 ± 0.45	1.40 ± 0.49	1.39 ± 0.41	1.38 ± 0.42	1.16 ± 0.63	–28.0 (< 0.01)
JSD-MCP ring finger	1.49 ± 0.36	1.39 ± 0.46	1.36 ± 0.34	1.32 ± 0.38	1.19 ± 0.49	–20.1 (< 0.01)
JSD-MCP little finger	1.42 ± 0.33	1.36 ± 0.48	1.31 ± 0.33	1.28 ± 0.50	1.27 ± 0.11	–10.6 (< 0.05)
JSD-MCP total	1.55 ± 0.33	1.44 ± 0.36	1.40 ± 0.34	1.33 ± 0.36	1.14 ± 0.50	–26.5 (< 0.01)

JSD-MCP: joint space distance of the metacarpophalangeal joint.

Table 3. Difference of joint space distances (JSD-MCP) in healthy subjects (n = 256) compared to patients with RA (n = 248), although the effect of sex is not differentiated from the effect of disease.

Location	Healthy Subjects, mean ± SD mm, n = 256	Patients with RA, mean ± SD mm, n = 248	Relative Difference, % (p, Mann-Whitney U-test)
JSD-MCP thumb	1.63 ± 0.35	1.38 ± 0.47	–15.3 (< 0.01)
JSD-MCP index finger	1.90 ± 0.45	1.49 ± 0.58	–21.6 (< 0.01)
JSD-MCP middle finger	1.69 ± 0.41	1.40 ± 0.48	–17.2 (< 0.01)
JSD-MCP ring finger	1.56 ± 0.38	1.36 ± 0.39	–12.8 (< 0.01)
JSD-MCP little finger	1.53 ± 0.34	1.32 ± 0.54	–13.7 (< 0.01)
JSD-MCP total	1.67 ± 0.34	1.39 ± 0.38	–16.8 (< 0.01)

JSD-MCP: joint space distance of the metacarpophalangeal joint.

Table 4. Changes of joint space widths classified by Sharp joint space narrowing score grade 0 to 3 (n = 248).

Location	Sharp Grade 0, mean ± SD mm, n = 33	1, mean ± SD mm, n = 55	2, mean ± SD mm, n = 85	3, mean ± SD mm, n = 75	Relative Difference from Grade 0 to 3, % (p, Mann-Whitney U-test)
JSD-MCP thumb	1.86 ± 0.47	1.59 ± 0.30	1.39 ± 0.26	0.99 ± 0.47	–46.8 (< 0.01)
JSD-MCP index finger	2.07 ± 0.27	1.81 ± 0.30	1.54 ± 0.33	0.93 ± 0.59	–55.1 (< 0.01)
JSD-MCP middle finger	1.91 ± 0.20	1.61 ± 0.22	1.45 ± 0.26	0.96 ± 0.52	–49.7 (< 0.01)
JSD-MCP ring finger	1.80 ± 0.25	1.55 ± 0.21	1.35 ± 0.18	1.02 ± 0.44	–43.3 (< 0.01)
JSD-MCP little finger	1.68 ± 0.21	1.49 ± 0.29	1.41 ± 0.62	0.91 ± 0.45	–45.8 (< 0.01)
JSD-MCP total	1.86 ± 0.15	1.61 ± 0.14	1.42 ± 0.08	0.98 ± 0.40	–47.3 (< 0.01)

JSD-MCP: joint space distance of the metacarpophalangeal joint.

joint space narrowing score for JSD-MCP total was significantly ($p < 0.01$) smaller with –47.3% for score 3 (0.98 ± 0.40 mm) in comparison to score 0 (1.86 ± 0.15 mm). The significant narrowing of JSD-MCP index finger was associated with –55.1% ($p < 0.01$) from 2.07 ± 0.27 mm (score 0) to 0.93 ± 0.59 mm (score 3). Also, JSD-MCP middle finger was significantly reduced (–49.7 %; $p < 0.01$) for score 3 (0.96 ± 0.52 mm) compared to score 0 (1.91 ± 0.20 mm). For the JSD-MCP thumb, JSD-MCP ring finger, and JSD-MCP little finger, a narrowing between score 0 and score 3 with –46.8% ($p < 0.01$), –43.3% ($p < 0.01$), and –45.8% ($p < 0.01$) was observed (Table 4).

Z-score (Table 5). The Z-score (JSD-MCP total) indicated a continuous narrowing ($p < 0.05$), from 0.50 ± 0.67 (score 0) to –1.83 ± 1.28 (score 3). For example, the Z-score of JSD-MCP thumb was significantly lower ($p < 0.05$) for score 3 (–2.05 ± 1.82) compared to score 0 (0.80 ± 2.15). A significantly smaller ($p < 0.05$) Z-Score for JSD-MCP index finger from –2.36 ± 1.64 mm (score 3) compared to 0.27 ± 1.00 mm (score 0) was also observed. The Z-scores of JSD-MCP middle finger, JSD-MCP little finger, and JSD-MCP ring finger also indicated significant narrowing of joint space widths (Table 5).

DISCUSSION

Reliable assessment of finger joint-space widths remains problematic, because no definitive clinical, radiological, or pathological standards exist that distinguish sex- and age-specific alterations of finger joint space widths from disease-related changes. Our aim was to compare finger joint space widths in healthy subjects to those of patients with RA using computer-aided joint space analysis (CAJSA).

Sex-related differences of joint space widths. In both groups, women had significantly smaller joint space widths of the MCP articulations (healthy subjects: –18.4%; $p < 0.01$; RA patients: –14.2%; $p < 0.01$) compared to men. Additionally, a previous study compared the joint space widths between women and men in 869 healthy subjects. The results showed that women had a significantly smaller total JSD-MCP (–11.1%) compared to men[18].

Age-related changes of joint space width. Our study demonstrated a significant narrowing of JSD-MCP total, –18.9%

Table 5. Changes of Z-score evaluated by Sharp joint space narrowing score grade 0 to 3 (n = 248).

Location	Sharp Grade 0, mean ± SD mm, n = 33	1, mean ± SD mm, n = 55	2, mean ± SD mm, n = 85	3, mean ± SD mm, n = 75	p, Mann-Whitney U-test
JSD-MCP thumb	0.80 ± 2.15	–0.17 ± 1.13	–0.53 ± 0.97	–2.05 ± 1.82	< 0.05
JSD-MCP index finger	0.27 ± 1.00	–0.24 ± 1.05	–0.73 ± 1.16	–2.36 ± 1.64	< 0.05
JSD-MCP middle finger	0.47 ± 0.88	–0.09 ± 0.93	–0.30 ± 1.06	–2.01 ± 1.72	< 0.05
JSD-MCP ring finger	0.79 ± 1.26	0.35 ± 1.29	–0.18 ± 1.00	–1.51 ± 1.77	< 0.05
JSD-MCP little finger	0.48 ± 0.80	0.01 ± 1.11	–0.14 ± 2.20	–2.21 ± 1.96	< 0.05
JSD-MCP total	0.50 ± 0.67	0.02 ± 0.70	–0.39 ± 0.57	–1.83 ± 1.28	< 0.05

JSD-MCP: joint space distance of the metacarpophalangeal joint.

($p < 0.01$), between the group age < 39 years and those over age 70 years for healthy subjects. Recent studies have evaluated finger joint space widths in healthy Caucasians measured by CAJSA; in detail continuous reductions of JSD-MCP total (–20.1%), JSD-proximal interphalangeal (PIP) total (–21.4%), and JSD-distal interphalangeal (DIP) total (–24.8%) were observed in healthy subjects between the ages of 30 years compared to 79 years[18-20].

Additionally, our study described age-related joint space narrowing in patients with RA. The JSD-MCP total revealed a significant narrowing of –26.5% ($p < 0.01$) between the group under age 39 years and those over 70 years. Goligher, *et al* assessed JSD at the MCP joints of 38 patients after onset of RA, using a computerized, semiautomated JSD analysis. Similarly to our study, the authors observed a narrowing of JSD-MCP (–7.2%; p = nonsignificant) between the group under age 50 years and those over 60 years[24]. Compared to our data, the lower age-related reduction of joint space width can be explained by the limited age interval (age < 50 yrs to age > 60 yrs)[24].

Quantification of joint space narrowing using the Z-score. The results showed that RA patients had a significantly smaller JSD (JSD-MCP total –16.8%; $p < 0.01$). Further, for all fingers JSD-MCP revealed an age-dependent narrowing of JSD in both groups (healthy subjects, –18.9%; $p < 0.01$; RA patients, –26.5%; $p < 0.01$). However, a reliable differentiation between RA-related and sex-specific as well as age-dependent joint space narrowing is complicated, emphasizing the need to implement normative data. An established solution is the use of an age-independent indicator for the quantification of joint space distances. The Z-score of the MCP joint space widths offers a reliable age- and sex-independent quantification of joint space narrowing in RA. The Z-score (MCP total) showed a continuous significant narrowing from 0.50 ± 0.67 (Sharp joint space narrowing score 0) to –1.83 ± 1.28 (Sharp joint space narrowing score 3). Therefore a calculation of Z-scores for all MCP joints based on an extended reference cohort was performed to promote a more reliable identification of initial cartilage destruction in RA.

The Sharp joint space narrowing score of zero is defined as a normal joint space width in RA patients with an absence of joint space narrowing. The positive Z-scores of Sharp joint space narrowing score 0 indicate that patients with RA have a larger joint space than healthy subjects. This phenomenon is caused by joint effusion based on disease-related synovitis in the early stage of RA, before any joint space narrowing or cartilage dissolution occur[25]. A possible limitation is the unknown influence of ethnic, socioeconomic, and anthropometric factors on the Z-score.

Further, the Z-score revealed an advanced narrowing of JSD from a Sharp joint space narrowing score of 2 (–0.39 ± 0.57) to a score of 3 (–1.83 ± 1.28). This result can be explained by the advanced joint destruction in RA patients with Sharp joint space narrowing score of 3 compared to those with a score of 2.

Radiographic scoring. It is widely accepted that the established radiographic scoring methods allow the clinician to reliably assess the course of RA and, more specifically, to evaluate the effects of drug therapy on prevention of joint damage. However, a number of studies have demonstrated the limited precision of the scoring tools and have shown that scoring is both highly observer-dependent and very sensitive to variations in the radiographic procedure[26]. Sharp, *et al*[27] confirmed that variability between readers is pronounced, revealing that a reader's expertise in the scoring of radiographs, irrespective of the scoring method used, might be more important than the method of scoring itself. Limitations in similarity and correlation statistics could also produce changed results, when comparing duplicate scores from the same or different readers[27]. The use of computer-aided diagnosis tools in the assessment of RA-related alterations visualized by hand radiographs could overcome these limitations.

A previous study compared the diagnostic performance of a computer-based method (for measuring joint space widths) with the Sharp joint space narrowing score in patients with RA[28]. The results showed that the computer-based method could discriminate the dissolution of cartilage more sensitively than the semiquantitative Sharp

joint space narrowing score. Twenty-four percent of the patients demonstrated no change in the Sharp joint space narrowing score, but significant narrowing of joint space widths was shown using computer-assisted technology[28].

Our results revealed a significant joint space narrowing based on the Sharp score for JSD-MCP total up to –47.3%. In a recent study, Böttcher, *et al*[29] demonstrated a narrowing of JSD-MCP dependent on the severity of RA, with a narrowing of JSD-MCP total up to –36.2% for the Sharp joint space narrowing score and –31.9% for the Sharp erosion score[29]. Angwin, *et al*[30] used special software (developed by James, *et al*[5]) in patients with early RA to measure joint space widths for MCP and PIP joints at the 3 middle fingers of each hand and to compare these changes with alterations evaluated by the modified Sharp score method. The computer-assisted estimation of joint space widths, averaged over a maximum of 6 MCP and PIP joints, showed a valid and more sensitive measurement of disease-related changes compared to the modified Sharp score[30].

One limitation of our study is the verification of MCP joint space widths based on a local Caucasian cohort of healthy subjects. Further, the effects of different ethnic and socioeconomic factors and anthropometric data (e.g., weight, height, body mass index, and hand dominance) on joint space widths remain unclear. Based on larger cohorts and the comparison of different computer-assisted methods for quantifying joint space widths[5,10-17], it may be possible to define a threshold focusing on the differentiation of normal versus pathological changes of joint space widths. Additionally, a comparison between the threshold and the individual joint space width of RA patients could be performed to more effectively identify patients with early RA. A second limitation of our study is the absence of longitudinal data for the Z-score to verify RA-related joint space narrowing. Further prospective therapy studies are necessary to ascertain the manifestations of joint space narrowing in RA.

However, there is a potential role for the semiautomated measurement of joint space narrowing that evaluates cartilage dissolution by offering a more precise, observer-independent approach[27]. Reference values and the Z-scores of the finger joint space distances will provide objective quantitative data and complement the established scoring methods.

The development of digital imaging technology (i.e., computer-assisted diagnosis techniques) has enabled more precise measurement of a variety of different radiogeometric features. Clinical use of the CAJSA technique allowed a reliable calculation of JSD in healthy volunteers and patients with RA. Our study was able to verify a significant age-related reduction of JSD in a healthy reference cohort. Disease-related narrowing of JSD could be differentiated from age-related changes in hand radiographs of patients with RA, and the study provided quantitative information in cases of verified RA using the Z-score method.

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