EXTENDED REPORT

Relationship between radiographic joint space narrowing, sonographic cartilage thickness and anatomy in rheumatoid arthritis and control joints

P Mandl, G Supp, G Baksa, H Radner, P Studenic, J Gyebnar, R Kurucz, D Niedermayer, D Aletaha, P V Balint, J S Smolen

ABSTRACT

Objective To validate ultrasound (US) for measuring metacarpal cartilage thickness (MCT), by comparing it with anatomical measurement using cadaver specimens. To correlate US MCT with radiographic joint space narrowing (JSN) or width (JSW) in patients with rheumatoid arthritis (RA).

Methods Bilateral metacarpophalangeal (MCP) joints of 35 consecutive outpatients, with recent hand X-rays, were included in the analysis. Metacarpal and phalangeal cartilage of MCP 2–5 was assessed bilaterally by US. JSW and JSN were evaluated on X-rays by the van der Heijde modified Sharp method (vdHS). In addition, cadaver specimens of MCP 2–5 joints (n=19) were evaluated by anatomical measurement and US.

Results The agreement (intraclass correlation coefficient) between sonographic and anatomical MCT on cadaveric specimens of MCP joints was 0.61. MCT of individual MCP joints correlated with individual MCP JSN (r=0.32, p<0.001) and individual MCP JSW (r=0.72, p<0.001). No correlation was found between phalangeal cartilage thickness and JSN in individual MCP joints. The US MCT summary score for MCP joints 2–5 correlated with summary scores for JSW (r=0.78, p<0.001), JSN (r=0.5, p<0.001), erosion score of the vdHS (r=0.39, p<0.001) and total vdHS (r=−0.47, p<0.001).

Conclusions Sonographic cartilage assessment in MCPs is closely related to anatomical cartilage thickness. Both JSW and JSN by radiography represent cartilage thickness in the MCP joints of patients with RA quite well. Thus, US is a valid tool for measuring MCT if radiographs are not available or in case of joint malalignment.

Joint destruction in rheumatoid arthritis (RA) involves damage of the bone and cartilage. Given that loss of cartilage may be more clearly associated with irreversible physical disability than bony damage,1–3 and therapy directed solely against the erosive process does not ensure the reduction of cartilage loss,4 particular attention should be given to early detection of and therapeutic interference with cartilage destruction.1–4

The most widely used measure of cartilage damage is the Sharp score and its modifications5–7 since they enable the separate, semiquantitative evaluation of erosions (ERO) and joint space narrowing (JSN), together providing the total radiographic damage score. However, although JSN is an accepted surrogate marker for cartilage loss, it may also be caused by joint dislocation due to damage of the soft tissues. Discrimination of the relative contributions of damage to cartilage and other soft tissue structures within the JSN score is not possible. The quantitative measurement of joint space width (JSW) is an alternative method, which may be more reproducible and sensitive to change than the semiquantitative scoring of JSN,5–9 but is more time consuming, may vary with the extent of joint effusion and may still require further refinement before widespread use.

Musculoskeletal ultrasonography (US) was shown to be a reliable and reproducible tool for the assessment of cartilage in RA in the small joints of the hand.10–13 Ultrasonography allows the quantitative measurement of cartilage thickness that was found to correlate with JSN as measured by radiography both in patients with osteoarthritis (OA) and RA.12 However, none of these studies have validated ultrasonography as an imaging tool by correlating it to a gold standard, that is, anatomical measurement of cartilage.

The objective of the present study was to evaluate the reliability, face and construct validity of ultrasound for measuring metacarpal cartilage thickness (MCT) by correlating it with conventional anatomical measurements performed on cadaver specimens of metacarpophalangeal (MCP) joints. We then investigated the relationship between cartilage thickness, as measured by US, with JSN and JSW, as measured on X-rays in both individual and summary scores of MCP joints of patients with RA.

METHODS

Cadaveric specimens
We evaluated formalin-fixed cadaveric specimens of MCP 2–5 joints obtained from five cadavers (all women, age range at death: 65–90 years; mean age at death: 78 years) at the Department of Anatomy, Histology and Embryology at Semmelweis University, Budapest. The cadavers were part of the anonymised inventory of cadavers/parts used or stored for educational and research activities. Prior to their deaths, all persons who donated cadavers included in this study provided written and witnessed consent for anatomical examination for research and educational use. Standard posterior–anterior X-ray images were acquired of each cadaveric specimen and interpreted by an experienced...
radiologist to exclude joints with clear signs of OA or other joint diseases.

Anatomical measurement of cadaveric specimens
Cadaveric specimens were kept frozen at −12°C for at least 24 h, after which they were cut midline in the sagittal plane using a bandsaw (Keripar). Photographs were taken from the section using a 12 megapixel camera (Canon Eos 5D©). Three separate anatomical measurements, namely, on the dorsal, palmar and central surface of each metacarpal head, were made and an average calculated on static images using digitised image software (Photoshop CS5©) (figure 1A).

Ultrasound imaging of cadaveric specimens
Ultrasound scanning of cadaveric specimens and subsequent measurement on static images using an integrated calliper were performed by an examiner with longstanding expertise in ultrasoundography, using a Philips IU22 xMatrix unit with a L15-7io transducer (frequency range: 7–15 MHz; aperture length: 23 mm). Specimens were placed with the palm facing down with the MCP joints flexed to a maximum of 90° to allow the best possible view of the cartilage as suggested by a recent study. For the purpose of our study, we used a modified definition of normal articular cartilage as suggested by a recent systematic literature review. Using longitudinal scans of the dorsal aspect of MCP 2–5 joints, the largest distance between the subchondral margin and the so-called leading interface (appearing as a white band on the superficial margin of the anechoic cartilage) was measured on static images in maximal applicable magnification using an integrated calliper (figure 1B). Measurements were made under orthogonal insonation and multiplied by 1.1 in order to correct for the increased speed of sound within cartilage when compared with soft tissue (1696 vs 1540 m/s). To assess interobserver and intraobserver reliability in the cadaver cohort, ultrasound measurements were performed twice by two blinded observers on 12 randomly selected specimens 1 week apart. Intraobserver and interobserver reliability (intraclass correlation coefficient (ICC)) was 0.91 (95% CI 0.72 to 0.97) and 0.75 (95% CI 0.46 to 0.90), respectively.

In vivo assessments
Cartilage thickness measurements were collected during routine US examinations of outpatients with RA at the Division of Rheumatology, Medical University of Vienna. The study was approved by the local ethics committee and conducted according to the guidelines of the Declaration of Helsinki. All data were anonymised. Thirty-five patients with RA as well as three healthy subjects (without history or clinical evidence of joint disease) had recent conventional X-rays of both hands available and had their data included in the study. Patients were classified according to the 1987 American College of Rheumatology or the 2010 ACR/EULAR Classification Criteria for RA.

Ultrasound imaging of patient joints
Ultrasound scanning was performed by an examiner with longstanding expertise in US, who was blinded to clinical and other imaging data. Examinations were performed using a GE Logic E9 unit (ML6-15-D transducer; frequency range: 9–15 MHz, aperture length: 50 mm). Scanning and measurement was done similarly as described as above; both metacarpal cartilage thickness (MCT) and phalangeal cartilage thickness (PCT) were measured. Summary scores were calculated by the simple summation of MCT values of bilateral MCP 2–5 joints (PCT values were not included in the summary scores).

Intraobserver and interobserver reliability was assessed by measuring MCT twice by two blinded observers on 24 MCP joints of three healthy subjects 1 week apart. Intraobserver and interobserver reliability was 0.78 (95% CI 0.55 to 0.90) and 0.80 (95% CI 0.67 to 0.88), respectively.

Radiographic imaging of patient joints
Conventional posteroanterior X-rays were interpreted and scored by an experienced examiner as part of the routine analysis at our outpatient department without prior knowledge of patient inclusion in the sonoographic assessment. Both JSW, quantified as the shortest distance between the subchondral bone plates along the force-bearing axis of the joint using an integrated calliper, and JSN and ERO, calculated using the van der Heijde modified Sharp scoring method (vdHS), were evaluated for each included MCP joint (figure 1C). Summary scores were constructed for each patient by the simple addition of JSW, JSN, ERO scores, respectively, of bilateral MCP 2–5 joints. Operated, ankylosed and luxated joints were excluded from the analysis, and patients with such joints were not included in the summary score analysis.

Statistical analysis
Descriptive statistics included the median and range or the mean and SD if normally distributed. Correlations were described by Pearson’s correlation coefficient. Interobserver and intraobserver reliability as well as agreement between anatomical and US measurement of MCT was assessed by calculating intraclass correlation coefficient (ICC) employing a two-way mixed model using absolute agreement between two measurements as well as between two observers. We calculated the smallest detectable difference (SDD) by the limits of agreement method (LOA), defined as 1.96 times the SD of the differences. All statistical analyses were performed with Statistical Package for
the Social Sciences software, V15.0 and V20.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Validity and reliability of ultrasonography for measuring MCT

We first evaluated cadaveric specimens by anatomical measurement and by sonography. A single MCP joint was excluded from the analysis due to entrapped air within the tissue, which made it impossible to visualise the cartilage with US, bringing the total number of evaluated cadaveric joints to 19. The included specimens showed no radiographic, sonographic or macroscopic signs of OA. There was no significant difference between MCT measured by the anatomical or the ultrasound method (mean±SD; (range)) (0.67±0.11; (0.52–0.92 mm) vs 0.69±0.12; (0.43–0.93 mm)) (figures 1 and 2A). We found no significant difference when comparing the mean ultrasound MCT of the cadaveric specimens to the mean ultrasound MCT measured on the reliability cohort of 24 MCP joints of healthy subjects (0.69±0.1) (figure 2A). We then evaluated JSW on X-ray, which corresponds to the distance between the bony end-plates, thus including both MCT and PCT and found this to be 1.91±0.23 (1.5–2.3 mm) in the same cohort.

We found a positive linear relationship between anatomical and ultrasound MCT (figure 2B) and the ICC between the two measures on cadaveric specimens showed moderate agreement (0.61; 95% CI 0.23 to 0.83). We also cross-validated this relationship by correlating the ultrasound MCT measurement with the single, central anatomical measurement, which, due to its position, most closely corresponds to the ultrasound measurement when the joint is in the flexed position (0.73; 95% CI 0.42 to 0.88). figure 2C shows a Bland–Altman plot outlining the differences between the two measurement methods (sonographic and anatomical). The calculated SDD for MCT was 0.2 mm (95% CI 0.229 to 0.174), which corresponds to 22% of the mean maximum measured width (0.93 mm); this is only about twice the minimum discriminatory distance of the measurement method (about 0.1 mm in our and most other high-end ultrasound machines). Differences were equally distributed in relation to the mean measurements, thus higher measurements were not associated with greater measurement error.

Relationship between radiographic joint space and sonographic cartilage thickness

After validating our measurement of sonographic MCT, we then assessed its correlation with radiographic joint space using patients with RA as well as healthy subjects. Thirty-five patients with RA had conventional radiographs of both hands done <1 year before the sonographic assessment, and these data were included in the study; 82.9% were women and 54.1% were positive for rheumatoid factor. Additional characteristics are listed in table 1.

Cartilage thickness was assessed in 280 MCP joints of 35 patients. A total of 29 joints were excluded due to operation or deformity (luxation) preventing a reliable radiographic measurement of JSW, leaving a final number of 251 joints, which were analysed in the study. MCT as measured by ultrasound varied between 0 and 1.1 mm (mean±SD: 0.46±0.21 mm). JSW, quantified on X-rays, varied between 0.3 and 2.7 mm (mean±SD: 1.48±0.47 mm). JSN scores varied between 0 and 4 (mean±SD: 0.39±0.93 mm) and ERO scores between 0 and 5 (mean±SD: 0.17±0.65 mm) using the vdHS method.

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<tbody>
<tr>
<td>Mean</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Disease duration (years)</td>
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<tr>
<td>28-swollen joint count</td>
</tr>
<tr>
<td>28-tender joint count</td>
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<tr>
<td>Clinical disease activity index (CDAI)</td>
</tr>
<tr>
<td>Health assessment questionnaire-disability index (HAQ-DI)</td>
</tr>
<tr>
<td>Total van der Heijde modified Sharp score (vdHS)</td>
</tr>
<tr>
<td>Joint space narrowing score (JSN)</td>
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<tr>
<td>Erosion score (ERO)</td>
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</tbody>
</table>

Radiographic joint space width and narrowing, erosions and sonographic cartilage thickness in individual joints

In order to evaluate the relationship between cartilage thickness as measured by US and radiographic JSN in the MCP joints of patients with RA, we first assessed correlation on the single joint level (table 2). We found significant positive correlation between radiographic JSW and ultrasound MCT (0.72; p<0.001) (figure 3). Ultrasound MCT showed a significant negative correlation (−0.32; p<0.001) with JSN as well as significant but weaker correlation with ERO (−0.22; p<0.001) as assessed within the framework of the vdHS score. We could confirm a significant positive correlation between radiographic JSW and ultrasound MCT (0.41; p<0.05) also on 24 MCP 2–5 joints of healthy subjects.

We found no correlation between PCT and any of the radiographic measures and correlation of PCT+MCT with JSN was not superior to MCT alone (data not shown), suggesting that PCT has no added value beyond the measurement of MCT.

Summary scores of radiographic joint space width and narrowing, erosions and sonographic cartilage thickness

Having found that MCT as measured by US correlates with radiographic JSW, JSN and ERO on the individual joint level, we next examined the relationship between summary scores for MCP joints 2–5 (table 3).

The summary MCT score as measured by ultrasound varied between 1.7 and 6.3 mm (mean±SD: 3.7±1.2 mm). The summary JSW score, quantified on X-ray varied, between 6.9 and 18.0 mm (mean±SD: 11.93±2.98 mm). The summary JSN and ERO score as calculated using the vdHS method varied between 0 and 54 (mean±SD: 4.49±10.0) and 0 and 27 (mean±SD: 1.37±4.63), respectively.

Similarly to the relationship observed on single joint level, summary ultrasound MCT scores of the MCP 2–5 joints correlated with corresponding measures of radiographic JSW (0.79; p<0.001). Regarding the individual components of the vdHS score, we found significant negative correlation between the summed ultrasound MCT and the corresponding JSN score (−0.50; p<0.001). There was also significant (though weaker) negative correlation between the summary ERO score and the summed ultrasound MCT (−0.39; p<0.001). Finally, the summed ultrasound MCT did not correlate with clinical variables of disease activity or physical function (28 tender joint count (TJC28), 28 swollen joint count (SJC28), simplified disease activity index (SDAI), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) health assessment questionnaire-disability index (HAQ-DI)).

**DISCUSSION**

This is the first study comparing the assessment of cartilage thickness in MCP joints by ultrasound with a ‘true’ gold standard: anatomical measurement of cartilage thickness. The data show that MCT as measured by ultrasound provides very similar results as anatomically determined cartilage thickness, that is, ultrasound indeed reflects the anatomical state at least regarding cartilage thickness. Of further importance and as further validation, sonographic cartilage thickness of healthy individuals conform to both the anatomical and sonographic assessments of cadaveric specimens. And, as a final piece of information, JSW and semi quantitative JSN assessments were also well correlated with sonographic cartilage thickness in healthy individuals, but also in patients with RA. Thus, our study cross-validates both the direct sonographic and the indirect radiographic assessment of cartilage thickness using anatomical specimens as an anchor.

**Table 2** Radiographic joint space width and narrowing, erosions and sonographic cartilage thickness in individual joints of rheumatoid arthritis patients

<table>
<thead>
<tr>
<th>Sonographic MCT</th>
<th>Joint space width</th>
<th>Joint space narrowing</th>
<th>Erosion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonographic MCT</td>
<td>1</td>
<td>0.719***</td>
<td>−0.324***</td>
</tr>
<tr>
<td>Joint space width</td>
<td>1</td>
<td>−0.338***</td>
<td>0.634***</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td>1</td>
<td>0.634***</td>
<td></td>
</tr>
<tr>
<td>Erosion</td>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

*Depicted are Pearson’s correlation coefficients (r); ***p<0.001; MCT: metacarpal cartilage thickness for metacarpophalangeal (MCP) joints 2–5; joint space width: radiographic joint space width for MCP 2–5 joints; joint space narrowing: radiographic joint space narrowing component of the van der Heijde/Sharp (vdHS) score for MCP 2–5 joints; erosion: radiographic erosion component of the vdHS score for MCP 2–5 joints.

**Figure 3** Correlation (Pearson’s) between sonographic MCT and radiographic joint space width. MCT, metacarpal cartilage thickness; JSW, joint space width.

**Table 3** Summary scores of radiographic joint space width and narrowing, erosions and sonographic cartilage thickness in patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Summed sonographic MCT</th>
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<tbody>
<tr>
<td>Summed joint space width</td>
</tr>
<tr>
<td>Summed joint space narrowing score</td>
</tr>
<tr>
<td>Summed erosion score</td>
</tr>
<tr>
<td>Total vdHS score</td>
</tr>
</tbody>
</table>

*Depicted are Pearson’s correlation coefficients (r); ***p<0.001; MCT: metacarpal cartilage thickness for metacarpophalangeal (MCP) joints 2–5; joint space width: summed radiographic joint space width for MCP 2–5 joints; joint space narrowing: summed radiographic joint space narrowing component of the van der Heijde/Sharp (vdHS) score for MCP 2–5 joints; erosion: summed erosion score; total sonographic cartilage thickness score, total sonographic cartilage thickness score for MCP 2–5 joints; total vdHS score: total vdHS score for MCP 2–5 joints.

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Ultrasound is thus a highly valid tool for metacarpal cartilage assessment. Our data also show that measuring phalangeal cartilage thickness conveys no added value beyond the measurement of MCT in patients with RA. Finally, our findings suggest that both radiographic JSW, which includes both metacarpal and phalangeal cartilage, and JSN may indeed represent cartilage thickness at least in the MCP joints of patients with RA.

An interesting recent study on patients with RA and OA showing that the measurement of MCT by ultrasound correlates with radiographic data in the MCP andPIP joints\(^1\) is in line with our findings. However, our study went a critical step further and evaluated whether ultrasound truly measures what it claims to measure, that is, the actual anatomical thickness of cartilage, and whether that thickness, as determined in postmortem specimens, also has a respective quantitative correlate in healthy individuals. Earlier studies on the knee have correlated anatomical and sonographic measurement;\(^1^9\)\(^2^0\) our study, however, is the first to correlate anatomical measurements with ultrasound measures in MCP joints.

A recent review highlighted the potential difficulties in assessing cartilage by using ultrasound and has shown that many of the earlier studies may have introduced non-systematic measurement errors.\(^1\)\(^4\) In order to ensure the exactness of our measurements, we avoided oblique insonation, included the entire white band and corrected the measurements by a multiplier of 1.1 to adjust for the higher speed of sound within cartilage.\(^1\)\(^2\)\(^3\)\(^4\) The excellent relationship between the anatomical and the sonographic cartilage measurements suggests that these methodological precautions were effective. Due to the lack of an appropriately sized acoustic window, we measured MCT using the largest diameter of the anechoic band visible on static ultrasound image. For the purpose of validation, we used the average of three anatomical measurements roughly encompassing the entire metacarpal cartilage on the anatomical section since this was feasible and allowed for a more valid estimation of cartilage width.

While we provide novel insights, our study is not without limitations. Due to difficulties in obtaining cadaveric specimens, the number of samples used to compare anatomic and sonocheckographic cartilage thickness was limited. The general nature and/or employed fixation method of cadaveric specimens might have influenced their anatomical composition; however, the observation of similar sonographic cartilage thickness in healthy individuals when compared with the anatomic specimens suggests that this aspect may have constituted only a minor, if any limitation. Due to the limitations in measurement described above, a single sonographic measurement was correlated with an averaged anatomical measurement. While there may have been discrepancies between the measurement sites of the two methods, we could show that both the average and the single anatomic measurement most closely corresponding to the site of the ultrasound measurement correlated with the latter. Despite the fact that cartilage constitutes a very small structure, the SDD of the sonographic measurement was only about twice the minimum discriminatory capacity of the measurement method.\(^1\)\(^8\) The people from whom the cadaveric specimens were obtained had no history of and showed no evidence of OA or other joint diseases. Indeed, the similarity of results in these specimens with those observed in healthy persons without clinical or sonographic evidence of OA or other joint diseases is reassuring in this regard. Finally, the finding that PCT did not add any additional insights may be partly due to the difficulty in consistent assessment of the concave phalangeal cartilage surface compared with the convex metacarpal surface; other joints are likewise of interest and a full cartilage assessment may have to focus also on knee, shoulder and other cartilage areas.

While radiographic scoring of JSN in the hands of RA patients is a reliable, widely used and valid method,\(^2\)\(^1\)\(^2\)\(^2\) JSW was suggested to be a more reliable measure.\(^2\)\(^3\)\(^2\)\(^4\) However, although JSW is indeed more closely associated with sonocheckographic cartilage thickness than JSN scores, the latter still showed good correlation with sonometric results despite its semi-quantitative nature; given the much greater feasibility of JSN determination, the data further bolster the utility of JSN assessment. Although cartilage thickness summary scores might be misleading due to the variability of cartilage thickness among individuals, they still allow a more general view and independece from the result of just an individual joint. The value and importance of summary scores is also revealed by summarised radiographic scores, such as the vdHS score, which are widely used as surrogate endpoints in clinical trials. Given the fact that we have provided an anatomy, and thus ‘truth’-based means to assess cartilage thickness, it may now be feasible (and necessary) to assess the normal range of cartilage thickness in larger cohorts of healthy individuals as well as its range in different stages of joint diseases. In light of the evidence that cartilage damage, as depicted by JSN, is primarily responsible for the impairment of physical function,\(^1\) determination of the critical cartilage thickness that allows for normal functionality may be an important research agenda.

In conclusion, sonography depicts cartilage thickness reliably when compared with anatomic specimens. The good correlation of radiographic JSW with sonometric cartilage thickness further confirms the validity of the radiographic assessment. Taken together, measuring cartilage thickness by sonography can allow for true quantification of cartilage-related events in RA (and possibly also OA); it may be particularly valuable when radiographs are not available or in case of joint malalignment due to soft tissue changes and when radiographic joint space cannot be reliably determined. All these aspects may have a bearing in following patients throughout their treatment courses. These longitudinal analyses will have to be the next step of such assessment.

Contributors PM, PVB and JSS: study design, data analysis, drafting of manuscript. GS, JG and DN: data acquisition. GB and RK: data acquisition. HR and PS: data analysis. DA: study design.

Competing interests None.

Patient consent Obtained.

Ethics approval The study was approved by the local ethics committee of the Medical University of Vienna and conducted according to the guidelines of the Declaration of Helsinki.

Patient consent Obtained.

Ethics approval Ethical Committee of Medical University of Vienna.

Provenance and peer review Not commissioned; externally peer reviewed.

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Clinical and epidemiological research


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