How normal are the hands of normal controls? A study with dedicated magnetic resonance imaging

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Abstract

Objective

To investigate bone and soft tissue changes in the hands of normal subjects by MRI.

Methods

Twenty-three normal volunteers (16 women) agreed to be examined. MRI of the hand was performed with a dedicated-extremity 0.2 Tesla device using gradient echo, spin echo and STIR sequences. Joint space width was measured in 16 different locations of the hand. Bone lesions, including bone oedema, ankylosis, and erosions, as well as the presence of tenosynovitis were investigated.

Results

Reproducibility of measures of joint space width was relatively good with an intraclass correlation coefficient of 0.82 and 0.71 in the intra-observer and inter-observer evaluations, respectively. No age- or sex-related differences of joint space were observed. Reproducibility of the readings of bone oedema and tenosynovitis were optimal. Bone oedema and erosions were observed in 2/23 (8.7%) and in 6/23 (26.1%) subjects, respectively. Tenosynovitis of the extensor tendons was present in 1/23 subjects (4.3%), whereas tenosynovitis of the flexor tendons was seen in 4/23 (17.4%).

Conclusions

This study demonstrates that joint changes considered to be peculiar of arthritis can be found by MRI in a relevant percentage of healthy subjects. Our data suggest that a control group of healthy subjects should be included in MRI studies on the appearance of the wrist in disease.

Key words

MRI, hand, wrist, healthy controls.

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Conflicts of interest: none.

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Introduction

Magnetic resonance imaging (MRI) is increasingly used to visualize joint lesions in the hand of patients with rheumatoid arthritis (RA) (1). Several recent papers have addressed the issue of MRI sensitivity in order to: (a) evaluate synovitis of the metacarpophalangeal and proximal interphalangeal joints (2), (b) calculate pannus volume in the hands as an indicator of disease activity (3), (c) establish the predictive value of bone oedema for radiographic joint damage (4), and (d) detect early erosions (5). All these studies demonstrated that MRI is an extremely sensitive technique in comparison with traditional radiology. However, they failed to include a normal control population. Sensitive techniques can visualize even subtle changes of the joints whose significance, however, is not always clear. The possibility of false positive results due to the low specificity of MRI should be considered. MRI studies of the rheumatoid hand have rarely included normal controls (6-8) and only two systematic studies on the occurrence of synovitis and bone changes in the hands of relatively young controls have been published in the literature (9, 10). This fact is probably due to the high costs of scans, the low acceptance of the technique by healthy individuals, and the high rate of utilization of the machines for severe non-articular conditions. Recently, low-cost, low-field, dedicated extremity MRI (E-MRI) systems have been developed to overcome most of these problems (11). This work is concerned with the E-MRI features of the hand in a group of normal subjects of a wide age spectrum. We have examined the presence of bone changes and of tendon sheaths abnormalities and measured the width of the articular space, including cartilage, synovial membrane and synovial fluid, in different sex and age groups, in order to evaluate if the bone and tissue changes considered to be peculiar of arthritis can also occur in normal individuals.

Patients and methods

Twenty-three normal volunteers (16 women) agreed to be examined by E-MRI. They were all healthy relatives of patients with soft tissue diseases attending the rheumatology outpatient clinic of the University of Genova. Their informed consent was obtained according to the declaration of Helsinki. Both hands were studied. Age range was 25-86 years with median age 59 years. None of the subjects had a history of joint complaints involving the hand or of systemic muscoloskeletal conditions at the time of examination, nor of significant joint trauma or injury of the hands in the past. In no case elevated acute phase reactants or IgM rheumatoid factor were demonstrated in a recent (within two months) blood examination. Of the 23 subjects, 18 (78.3%) could be re-evaluated after a mean period of 5 years from MRI examination to ascertain the incidence of arthritis or other muscoloskeletal conditions, if any. Thirteen did not show any such conditions, one man was died because of prostatic carcinoma 46 months after MRI examination, one developed osteoarthritis of the hip, one osteoarthritis of the knee, one psoriatic dactylitis, and two developed hand osteoarthritis. Of the last three patients, who had arthritis of the hand at follow-up, the patient with psoriatic arthritis and the one with hand OA did not show any abnormal finding at baseline MRI. The other patient with hand OA had an erosion of the capitate. Of the remaining 5 subjects, who could not be reevaluated at follow-up, none showed abnormalities at baseline MRI. On clinical examination by a rheumatologist, the hands were normal except for mild pain on pressure of the first carpo-metacarpal joint in 4 elderly subjects. We therefore decided not to consider this joint for evaluation of erosions, lest bone changes due to slight subclinical osteoarthritis could be included.

MRI of the wrist was performed with a dedicated-extremity 0.2 Tesla device (Artoscan, ESAOTE, Genova, Italy) equipped with a permanent magnet and using a dedicated hand and wrist coil of 13 cm in diameter. The hand was fixed in neutral position and the fingers were fixed in extended position with the thumb up by the application of several

cushions. The field of view is 120 mm and allowed the evaluation of the carpal bones, the proximal metacarpal heads, as well as the distal radius and ulna. After the first scan, the hand was repositioned to evaluate the metacarpophalangeal and proximal interphalangeal joints. The procedure for both hands and wrists lasted about one hour. Sequences included a T1-weighed gradient echo (GE) and a short tau inversion recovery (STIR) for the suppression of fat. The flip angle was 75°; repetition time was 600 msec and 1800 msec and echo time was 18 msec and 28 msec for GE and STIR, respectively. Slice thickness was 3.5 mm and interslice gap was 0.3 mm.

In a subject showing two erosions on his first examination, a second one was performed after 2 years to evaluate possible changes. On this occasion, also Spin Echo scans (repetition time/echo time 100/16 ms, 160x128 matrix, 150x150 field of view) were taken after intravenous injection of 0.2 ml/kg of G-DTPA (Omniscan; Schering, Berlin, Germany) as enhancing contrast agent into a cubital vein.

Both hands were evaluated, in coronal and axial sections. The right hand was scanned first. The articular space was measured on coronal STIR images in the 16 locations shown in Figure 1. Measurements were taken perpendicularly to the joint surface in the area where the articular space was wider. For each joint, the most central section was chosen. A further measurement of the hyperintense area between radius and ulna on the axial section was taken (location 16). Measurement was performed with an electronic linear caliper using the Artoscan software. The measure included the entire hyperintense signal, between the hypointense bony extremities, corresponding to cartilage, synovial membrane and synovial fluid. Joint space was measured by a single observer, but reproducibility studies, including intra- and inter-observer reliability by two readers, were performed on 10 hands.

Bone lesions were separately investigated on the distal radius and distal ulna, the carpal bones, the proximal metacarpal heads, and the digits. Erosion was defined as a sharply marginated focal loss of the normal low signal intensity from cortical bone and the normal high signal from trabecular bone on T1 GE images with cortical break, and focal regions of high (white) signal on STIR sequences (1). In addition, it had to be seen in both coronal and axial sections. Bone oedema was defined as irregularly diminished signal on GE sequence and high signal within the black or dark gray-appearing bone on STIR sequence, suggestive of increased water content. Ankylosis consisted of fusion of contiguous bones. Definitions of bone erosions and oedema are consistent with those suggested by OMERACT studies (12). Wrist tenosynovitis was arbitrarily diagnosed when the thickness of the enlarged synovial sheath was at least equal to the diameter of the corresponding tendon.

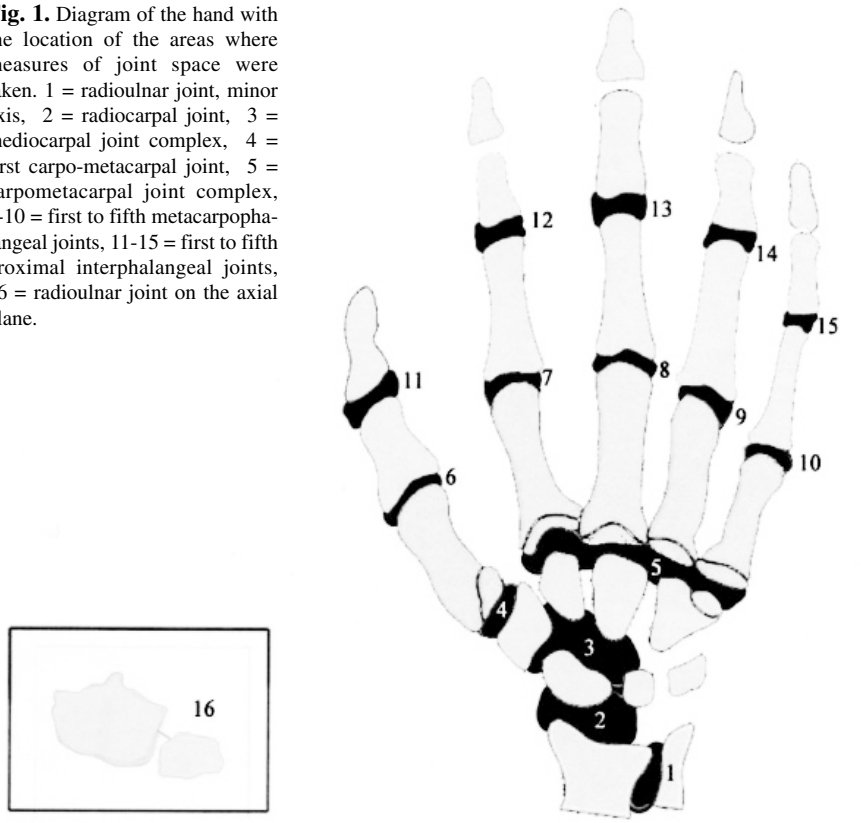

Fig. 1. Diagram of the hand with the location of the areas where measures of joint space were taken. 1 = radioulnar joint, minor axis, 2 = radiocarpal joint, 3 = mediocarpal joint complex, 4 = first carpo-metacarpal joint, 5 = carpometacarpal joint complex, 6-10 = first to fifth metacarpophalangeal joints, 11-15 = first to fifth proximal interphalangeal joints, 16 = radioulnar joint on the axial plane.

The inter- and intra-observer reproducibility for joint width measurement was assessed with the intraclass correlation coefficient and the Bland and Altman method in a series of 129 joints. The inter- and intra-observer reproducibility for bone oedema and tenosynovitis readings was evaluated on the complete set of images. The two readings of the same observer were performed one month apart. In a previous study on rheumatoid erosions, variation was determined between- and intra-observers with readings after one and 6 months from the initial one. Reproducibility was good, with standard error of the mean disagreement between observers limited to 0.1-1.1 erosions (13). Means were compared by the Student's t test or by one way analysis of variance if their distribution was normal and by the Wilcoxon test with Mann Withney correction when it was non-parametrical. Frequencies were compared by Fischer's exact test. Correlations were analyzed by the Pearson's and Spearman's rank tests.

Results

Joint space thickness

The correlation coefficients for the measurement of joint space thickness by the same observer and by different observers were 0.83 (95% CI 0.78-0.88, $p < 0.0001$) and 0.74 (95% CI 0.65-0.81, $p < 0.0001$). Reproducibility was good with intraclass correlation

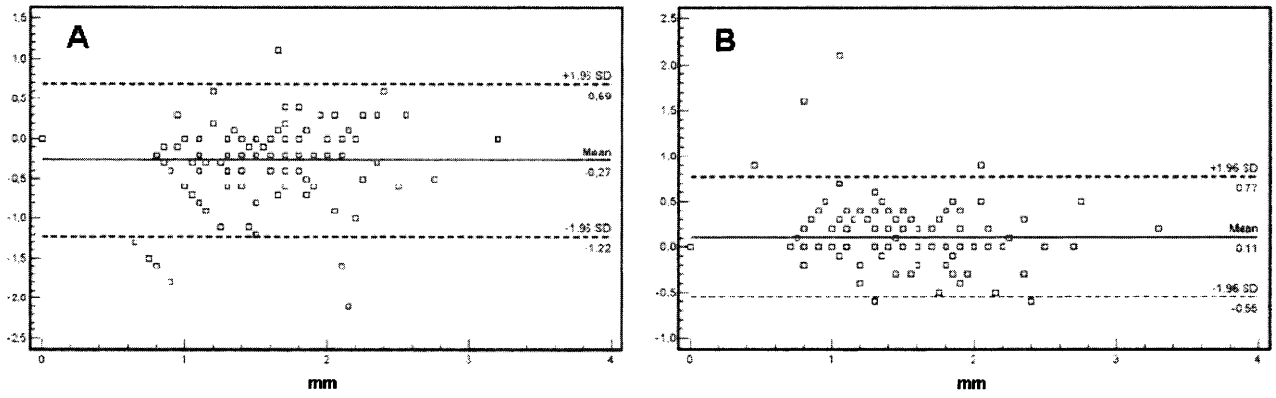

Fig. 2. Differences in joint space measurement between observers, plotted against the mean value of both observers for each subject (**A**) and between different readings by the same observer (**B**). Solid lines indicate the mean differences, dashed lines indicate the limits of agreement.

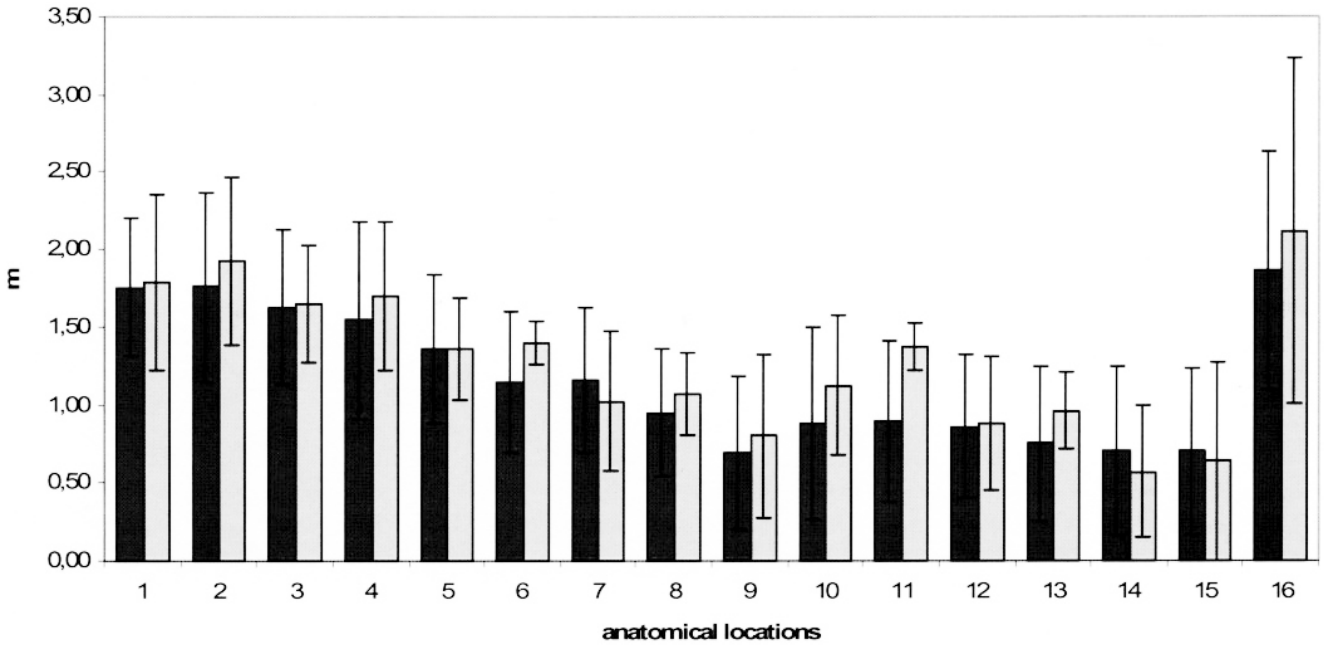

Fig. 3. Mean values of joint space, broken down by sex, in the locations shown in Figure 1 with the corresponding standard deviations (dark column = women; light column = men).

coefficients of 0.82 (95% CI 0.75-0.87) and 0.71 (95% CI 0.61-0.78) for the intra-observer and inter-observer evaluations, respectively. The Bland and Altman plots showing measurement differences against the mean are reported in Figure 2. The error of measurement was independent of the width of the joint space.

Joint space was measured at the 16 locations described in Figure 1. The mean values of joint space are reported in Figure 3, where they are broken down by gender. There were no age-related or gender-related differences in joint space, although it tended to be wider in men.

Bone

I. Bone oedema. Concordance for bone oedema evaluation was complete both intra and inter-observer. Bone oedema was seen in 2/23 subjects (8.7%) aged 74 and 86 years. It was localized around a cystic lesion of the hamate in the first patient, and in the trapezium in the second one (Fig. 4). The scores of bone oedema, according to OMERACT (12), were 2 and 1, respectively.

II. Erosions. Seven erosions were observed in 6/23 (26.1%) of the subjects (Fig. 5). There was only one erosion in 5 subjects; it involved the metacarpal head (1 subject), ulna (1), capitate (2), and scaphoid (1). In the sixth subject, concomitant right scaphoid and capitate erosions were seen. Four erosions were seen in the right wrist and 3 in the left wrist. The scores of erosions, according to OMERACT (12), were always 1, except for the erosion of the metacarpal head which had a score of 2. Erosions occurred in 6/598 (1%) wrist bones and in 1/460 (0.2%) MCP joint bones. Erosions were seen in 4/16 (25%) women and in 2/7 (28.6%) men. The mean age of subjects with erosions was 66±16 years, in comparison with 56±18 years in those without erosions (n.s.). One out of six (16.7%) subjects with erosions had also tenosynovitis in

comparison with 3/17 (17.6%) subjects without erosions. Subjects with erosions had a smaller joint space at the radial part of the radio-carpal joint (1.5 ± 0.4 mm vs 1.9 ± 0.6 mm; p = 0.03) and at the mediocarpal joint (1.3 ± 0.3 mm vs 1.7 ± 0.5 mm; p = 0.003) in comparison with those without erosions. Conversely, a larger mean joint space was seen at the third proximal interphalangeal joint in subjects with erosions (1.0 ± 0.2 mm vs. 0.7 ± 0.5 mm; p = 0.01). In the subject who repeated the examination after two years no changes in the extension and shape of the erosions were seen. After intravenous injection of G-DTPA, contrast enhancement of the erosions was seen.

III. Ankylosis. Ankylosis was not observed in this group of subjects.

Tendons

Concordance for tenosynovitis evaluation was complete both intra and inter-observer. Tenosynovitis of the extensor tendons was present in one subject (4.3%) (Fig. 6A) and involved the *extensor ulnaris carpi*. Tenosynovitis of the flexor tendons was seen in 4 subjects (17.4%) (Fig. 6B). It involved both deep and superficial flexors in 1 patient and only deep flexors in the remaining 3. In all, the subjects with tenosynovitis were females (ns). The mean age of subjects with tenosynovitis was 65 ± 16 years in comparison with 57 ± 18 years in the others (ns). The mean age of subjects with flexor tenosynovitis alone was 72 ± 7.2 years in comparison with 57 ± 18 years in the others (ns). Subjects with tenosynovitis had a smaller joint space at the radio-carpal joint (1.4 ± 0.6 mm vs. 1.9 ± 0.5 mm; p = 0.04) in comparison with those without tenosynovitis.

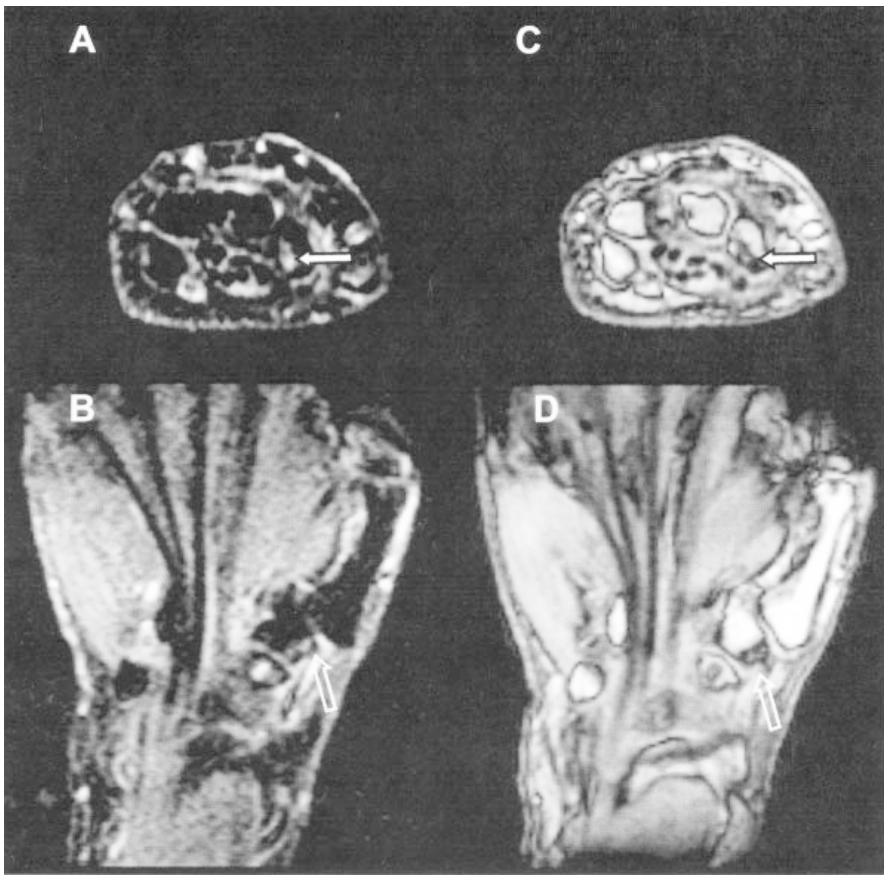

Fig. 4. Bone oedema of the trapezium (arrows) seen on the axial (**A**) and coronal (**B**) STIR and on the axial (**C**) and coronal (**D**) GE sequences. It appears irregularly hyperintense in the STIR sequences and hypointense in the GE sequences. Note also a cystic lesion of the trapezoid bone.

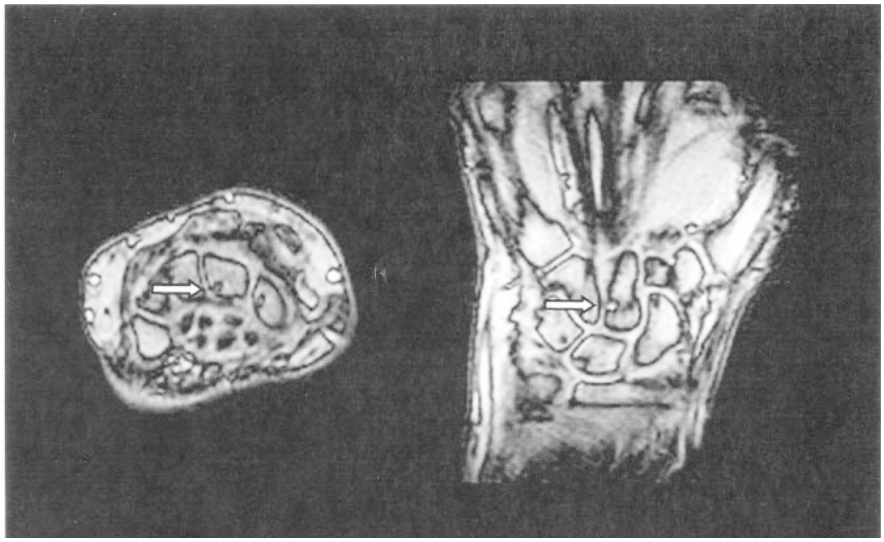

Fig. 5. An erosion of the capitate is shown in both the axial and coronal planes (arrows) in this T1-weighted GE sequence.

Discussion

The increasing diffusion of MRI for the study of synovial and bone changes in RA patients is the basis for a wide utilization of this technique in the clinical setting. However, an increase in sensitivity in the imaging of the joints is usually associated with a decrease in specificity. It is therefore useful to know the MRI appearance of the normal hand to better evaluate the significance of the changes observed in disease. Our results were obtained with a low-field extremity-dedicated MRI device. High-field MRI machines have a better signal to noise ratio and could be hypothetically more sensible in the evaluation of bone and joint lesions. However, a recent paper has suggested

that E-MRI can provide similar information on bone erosions and synovitis as high-field MRI units (14).

Joint space thickness was measured with satisfactory reliability both for intra-reader an inter-reader evaluations. On the contrary, the OMERACT MR Imaging Group recommended that scoring of joint space narrowing be omitted because of the difficulty to assess it accurately in the small joints of the hand and wrist with standard equipment and sequences (15). We feel that evaluation of joint space width on STIR sequences may have a higher specificity for detection of synovitis than contrast-enhanced T-1 weighted images. Its advantage is the easy differentiation between bone, which appears black, from the contents of the articular space, which are white. By this method, we have shown that there are no age- or sex-related differences in joint space width. On the other hand, imaging of the anatomical details of the joint is much poorer with STIR sequences than with GE sequences. Reference values for the normal joint space could be calculated as mean ± 2 standard deviations so that they could be used for comparison studies with diseased joints. The clinical value of the measurement of joint space thickness on STIR sequences is not known. This measurement could be useful to differentiate normal individuals from patients with arthritis. The observation that normal subjects with erosions and tenosynovitis had a smaller joint space in several wrist areas could indicate that these findings are associated with subclinical arthropathy. Subclinical disease has been observed in clinically unaffected joints of patients with early untreated oligoarthritis (16)

Our study demonstrates that joint changes considered to be peculiar of arthritis can be found in a relatively high percentage of healthy subjects. In particular, erosions were present in one fourth of the examined subjects and tenosynovitis in one fifth. The two conditions seem not to be associated in normal subjects. Morphologically, the appearance of these findings was not different from that usually seen in RA. In addition, enhancement of erosions was seen after iv contrast injection in one subject, a feature which is considered typical of arthritis. In the same patient, the erosion did not change in shape and extension after 2 years. No significant gender-related or age-related difference could be observed, although there was a trend of increased frequency of lesions in subjects over 65 years. In our study, slices of 3.5 mm thickness with a gap of 0.3 mm were used. It is possible that, due to the limited number of relatively thick slices, several subtle changes of the wrist were overlooked. Therefore, our results are probably underestimating MRI changes of the normal hand. Gadolinium was not systematically used in the evaluation of this cohort of subjects because we felt its administration is unethical in healthy, partly aged, individuals. This is a limitation of our study because the use of gadolinium is of great relevance in the assessment of synovitis and in the evaluation of bone changes. This limitation hampered the adoption of the RAMRIS criteria to evaluate synovitis and we tried to overcome it by measuring the width of the joint space. In one subject only, in whom erosion was controlled after 2 years, gadolinium was used in the follow-up examination and showed enhancement. This occurred also in 1 out 12 erosions found by Ejbijerg *et al.* (10) in a control subject with elevated IgM rheumatoid factor and serum CRP. By contrast, none of our subjects had abnormal laboratory examinations.

Nearly one tenth of our normal population had bone oedema of the wrist; a similar prevalence (10%) has been recently observed in the metacarpophalangeal joints of healthy controls (8). Bone oedema was not observed, however, in another study of normal volunteers (10). Bone oedema has been suggested to be the earliest bone lesion in RA, before the appearance of erosion in the same location. It is likely to be related to the rheumatoid pannus and could have a prognostic value in early RA (4). Finding bone oedema in 2/23 controls without synovitis raises some questions about the pathogenesis of this type of lesion. In one of the examined subjects, bone oedema was seen in the trapezium adjacent to the 1st carpometacarpal joint. In addition (Fig. 4), a bone cyst was observed in the trapezoid in the same direction of force. This finding could reflect early osteoarthritis at this site due to overuse of the thumb, although other MRI signs of osteoarthritis or clinical symptoms were absent in this subject. Bone oedema has also been associated with trauma or heavy manual activities, two conditions, however, that were not reported by our subjects.

Tenosynovitis or enlargement of the synovial sheath was frequent in the flexor compartment. This finding is unclear because the subjects with tenosynovitis were asymptomatic. In addition, no correlation could be demonstrated with occupation because all the subjects with tenosynovitis were housewives.

Only a few studies have addressed

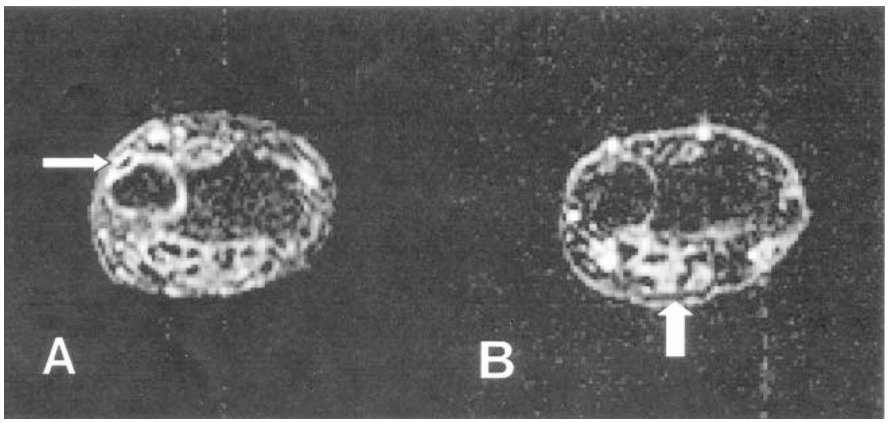

Fig. 6. Synovial sheath enlargement around the extensor ulnaris carpi (**A**) and in the flexor tendons compartments (**B**). Both images are axial STIR sequences of the wrist.

MRI findings in normal individuals. No erosions were seen in most normal controls (17,18). On the contrary, Tonolli-Serabian *et al*. (19) found 48 erosions in 10 healthy subjects. In this study, however, definition of erosion was unclear, for it included also geodes. In fact, only 16% of these erosions were enhanced after Gd-DTPA infusion as compared to 72% of the erosions in patients with RA. In contrast, we used a very conservative definition of erosion which included its presence on two planes (20) and the occurrence of a cortical break. We feel that this approach could have avoided overestimation of erosions. Timins *et al*. examined the MRI appearance of the wrist in 20 young volunteers for the presence of lesions in tendons and ligaments (21). They could not identify tenosynovitis according to our definitions but only small quantities of fluid in the extensor sheaths. In another study, 15 healthy young volunteers were studied with a dedicated high field (2.35T) MRI device (22). No mention was made of possible abnormal findings. The same observation was made by Baker *et al*. (23). The patterns of gadopentate-enhanced MR imaging of radiocarpal joints of 18 healthy subjects with mean age 30.8 years was studied by Partik *et al*. (9). Signal enhancement was seen in 44.4% of subjects in the prestyloid recess. The most complete study on the MRI appearance of the normal hand has been published recently by Ejbjerg and co-workers (10). These authors demonstrated that changes resembling bone erosions were present in 7/420 (1.7%) wrist bones and in 5/224 (2.2%) MCP joint bones. Both values were slightly higher than those observed in the present study.

Strong points of our study, in comparison with the previous one (10), are that it (a) examined both hands, (b) considered the presence of tenosynovitis, which is not included in the OMERACT MRI evaluation of joints, and (c) evaluated a wider range of patients' ages. On the contrary, most of the MRI studies performed on normal subjects considered only young volunteers.

In conclusion, joint lesions are relatively frequent also in normal individuals, mainly in the elderly. This observation suggests that caution should be used in the interpretation of joint lesions especially in early arthritis (24). One of the main advantages of the superior sensibility of MRI is the possibility of anticipating the diagnosis of chronic arthritis (25). This is of particular interest because recently developed highly effective treatments may induce clinical remission in the early stages of the disease, before severe bone damage and functional impairment appear. However, the possibility of MRI joint lesions also in normal individuals emphasizes the need for a careful integration of clinical, laboratory and imaging results, since only the combination of these features can allow treatment decisions. There is a need for validation studies of MRI findings in the early prediction of RA outcome. Our data suggest that a control group of healthy subjects should always be included in MRI studies on the appearance of the wrist in disease. This control group should not be matched necessarily for age and sex, with the possible exception of tendon studies. Because of the difficulty of enrolling normal individuals, multicenter studies, possibly using the same type of MRI machine, should be encouraged to extend our knowledge on the normal hand by MRI imaging.

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