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ORIGINAL ARTICLE

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A comparison of bone loss in early and late rheumatoid arthritis using quantitative phalangeal ultrasound

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Abstract This study compares amplitude-dependent speed of sound (AD-SoS) measured by phalangeal ultrasonography in a group of 60 patients with early rheumatoid arthritis (RA) with those who had had the disease for more than 4 years. The mean duration of the early disease group was 1.4 years, and the mean of the established RA group was 14.6 years. Plasma viscosity (PV), C-reactive protein (CRP) and HAQ scores were obtained. Forty-nine patients with early RA had hand radiographs assessed by the Larsen score method. The DBM Sonic system was assessed on normal volunteers and a coefficient of variation of 0.88% obtained. A significant correlation was found between the left and right hands of the patients groups studied ($r = 0.84$). The mean Z score of both hands was therefore used in comparing the two clinical groups. Results showed no correlation between CRP, PV and Z scores of AD-SoS. The HAQ scores showed a weak negative correlation, and there was no correlation between the Larsen score and Z score, or the number of swollen joints and Z score. However, the early and established groups with RA were significantly different ($P = 0.004$). Within the early RA group the Z score for AD-SoS was lower in those with disease duration of less than 2 years (−1.71) than in those with disease duration of 2–4 years (−1.01). This suggests that bone loss in the fingers is greater in the first 2 years of disease than in the following 2 years, which might reflect an effect of treatment.

Keywords Bone loss · Early RA · Finger · Phalangeal ultrasonography · Rheumatoid arthritis

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Introduction

The association between osteoporosis and rheumatoid arthritis (RA) is well documented. It occurs both in a generalised form and in sites adjacent to joints [1]. Bone loss in both forms occurs early on in the disease. Juxta-articular bone loss is one of the earliest radiological changes [2] and is thought to be part of a progressive process [3]. Bone density in the hands is significantly reduced within the first year of RA [4]. Similarly, bone loss in the spine and hips has been documented as early as the first 2 years of disease in one study using dual-energy X-ray absorptiometry (DEXA) [5].

The mechanism of bone loss in RA is likely to be multifactorial. Various factors have been proposed, including excessive osteoclastic activation [6] suppression of bone formation [7], increased vascularity, invasion by pannus, and inflammatory mediators in nearby joints [8]. In chronic RA additional influences such as immobility, disease modifying medication and corticosteroids play a part [9].

Ultrasonic bone assessment of the phalanges provides a non-invasive means to study the onset and course of demineralisation in juxta-articular sites in the hands. This is a useful area to study because it is one of the principal sites affected early on in RA. Moreover, the phalanges consist of both cortical and trabecular bone. In RA bone loss in the hand correlates well with bone loss at other sites when assessed using DEXA imaging [10, 11].

A number of techniques exist to assess bone loss in rheumatoid arthritis. The Larsen scoring system of plain radiographs is often used as a means of quantifying disease progression over time [3]. It is, however, subjective and may not detect subtle changes in early disease [12]. Other imaging methods are more commonly used, including DEXA, quantitative CT, quantitative ultrasound and, to a lesser extent, MRI.

Quantitative ultrasound for bone assessment is gaining popularity, particularly at the calcaneum [13]. Latterly attention has been given to the use of digital

ultrasound [14, 15]. The DBM Sonic (IGEA Italy) is designed to measure amplitude-dependent speed of sound (AD-SoS) at the proximal phalanx. Studies have shown that it can detect osteoporosis and may have a role in fracture prediction [16–18]. It has the advantage of being portable, avoiding ionising radiation, is inexpensive and relatively quick. The technique is easy to use after basic instruction.

It is thought that resorption of bone increases the medullary canal and the porosity of cortical bone, resulting in decreased velocity of ultrasound transmission through the finger [19, 20]. In chronic RA, bone loss at the finger, as measured by ultrasound, correlated with bone loss measured using DEXA [21, 22].

This study compares bone loss in the proximal phalanges in early and late rheumatoid arthritis using digital ultrasound AD-SoS. We also investigated the effect of disease activity on bone loss in early disease.

Materials and methods

Sixty female patients with inflammatory arthritis were recruited from a dedicated early synovitis clinic (early synovitis group). Patients selected had early signs of inflammatory arthritis ranging from a few weeks up to duration of 4 years. Although most patients had early disease there were some patients with disease duration of up to 4 years, either because of late presentation to the clinic or due to subclinical disease. Patients were under regular review by the same clinician. Investigations in clinic included serial blood tests, including inflammatory markers and rheumatoid factor and X-rays. The diagnosis of rheumatoid arthritis was made as soon as apparent, according to the ACR criteria [23]. As the diagnosis was not always apparent at the time of digital ultrasound measurement, patient records were examined at the end of the study to establish final diagnosis and ongoing follow-up. Patients who subsequently had no definite diagnosis of rheumatoid arthritis were excluded. The final diagnoses in the early synovitis group were seropositive RA (24) and seronegative RA (32). Two patients had additional diagnoses of osteoarthritis and psoriasis. All except five were under regular rheumatological review (two were discharged as symptoms resolved and three were lost to follow-up).

Thirty-nine patients with RA of more than 4 years' duration were selected from general rheumatology clinics (established RA group). The diagnosis of rheumatoid arthritis was based on the ACR criteria [23]. All patients gave informed consent to participate in the study.

Disease activity

In the early synovitis group, additional information from the clinic attendance was obtained where possible. Patients completed a modified Stanford health assessment questionnaire (HAQ), which reflects functional activity (score 0–3) [24]. The presence of any swelling at the hand and wrist joints was documented by a clinician on a modified Eular mannikin. Plasma viscosity and CRP were measured by standard laboratory procedures. These inflammatory markers were only included if taken within 6 weeks of ultrasound measurement. In our laboratory the upper limit of normal for PV is 1.7 and for CRP is 5 mg/l. X-rays of both hands, if taken within 8 months of ultrasound measurement, were examined by one doctor throughout to give a Larsen score [12].

Ultrasound measurement

All measurements were performed with the DBM Sonic 1200 (IGEA Italy). The machine was calibrated at the start of each session. The measurements were made by one of two trained operators to minimise the effect of interoperator technique. To assess operator variability, 10 normal volunteers were measured four times. The coefficient of variation (CV%) in technique varied from 0.3% to 1.9%, but overall the CV was 0.88%, which is within the manufacturer's specification. The results were also within the manufacturer's quoted reference values.

The DMB Sonic device consists of two spring-loaded calipers, which are attached to probes. Before each set of finger measurements the calipers were positioned to measure soft tissue between the thumb and forefinger. The probes were then positioned mediolaterally on the proximal phalanx. An ultrasound pulse is transmitted from one probe and received by the other after passing through the phalanx. A mean amplitude-dependent speed of sound value is automatically generated on a screen that reflects the quality of the bone the ultrasound has passed through. The calipers are adjusted around the phalanx to give an optimal signal. Where the value was below the given threshold for soft tissue measurement it was excluded. Measurements could not be made in one hand of six patients in total because of inability to remove jewellery, missing digits, and difficulty in positioning the calipers because of hand deformity.

The second to fifth fingers of each hand were measured to give a mean AD-SoS value for each hand. This was compared to the manufacturer's database to derive a Z score that reflected the standard deviation from the age- and sex-matched mean value [19]. We used the Z scores for all comparisons, as this corrects for age-related effects.

The results were analysed using statistical analysis software (SPSS). Results are given as means. The differences between groups were calculated using ANOVA with Bonferroni adjustment, Student's *t*-test or the Mann–Whitney test as appropriate. Correlation coefficients were calculated using Spearman's rank correlation coefficient, and values are shown as Spearman's ρ.

Results

The characteristics of the groups are shown in Table 1. Subjects in the established RA group were significantly older (Mann–Whitney, $P = 0.028$) than those in the early synovitis group. The hormonal status of the patients was not recorded, but both groups had a wide age range with the mean being over 51 years. Mean disease duration in the early synovitis group was 1.4 years and ranged from 0.17 to 4.0. In the established group the mean disease duration was 14.6 years, with a range of 4–40.

Table 1 Characteristics of early and established groups

	Early synovitis $n = 60$	Established RA $n = 39$
Mean age (range), years	52 (21, 74)*	58 (28, 83)*
Mean disease duration (range), years	1.4 (0.17, 4.0)	14.6 (4.0, 40.0)
Std. error of mean duration	0.13	1.28
Mean AD-SoS (range), ms^{-1}	1942 (1680, 2166)	1864 (1706, 2114)
Mean Larsen score (range)	5.1 (0, 64)	N/A

*$P = 0.028$

There was a significant correlation between Z scores of right and left hands in both the early synovitis and the established RA groups ($\rho = 0.84$; $P < 0.0001$), as shown in previous studies [22]. The mean Z score of both hands was therefore used to compare early synovitis and established groups. The distribution of Z scores with disease duration shows a marked reduction in AD-SoS in both groups (Fig.1). The early synovitis group was further subdivided for analysis into those with disease duration less than 1 year; all patients with disease duration of 1–2 years; and those with disease duration greater than 2 years (Table 2). Forty-four patients (73%) had had disease for 2 years or less. The mean Z score of every disease duration group was significantly less than zero (Student's *t*-test, $P < 0.01$). The mean Z scores of the early synovitis group (−1.52, SD 1.04) and the established RA group (−2.12, SD 0.93) were significantly different (Student's *t*-test, $P = 0.004$). In the early synovitis group those with disease duration of up to and including 2 years had a significantly different mean Z score from those with 2–4 years' disease duration: ≤2 years' duration $Z = -1.71$; 2–4 years' duration $Z = -1.01$ (Student's *t*-test, $P = 0.02$). Using ANOVA, the mean Z score for the 2–4-year group was significantly higher than that of the established RA group ($P = 0.001$); the other intergroup comparisons were not statistically significant (Table 2).

In the early synovitis group HAQ scores were available on 53 patients, plasma viscosity on 38 and CRP on 32 patients. Forty-nine patients had hand X-rays within 8 months of measurement (32 within 4 months), which were scored according to modified Larsen criteria [12]. Of these, 27 had a Larsen score of less than 2, reflecting minimal, non-erosive changes. There was no significant difference in mean Larsen score between any of the early synovitis disease duration subgroups.

Plasma viscosity correlated with CRP, as expected ($\rho = 0.73$). There was no correlation between the average Z scores and CRP (0.185) or plasma viscosity (0.006). There was a weak negative correlation between the HAQ score and average Z score (−0.284, $P = 0.04$). There was no significant correlation between the Larsen score and average Z score (−0.087, $P = 0.228$). There was no correlation between numbers of swollen joints with Z scores (−0.069, $P = 0.624$).

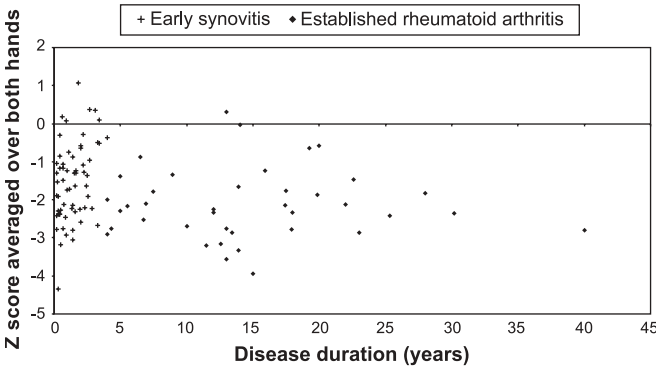

Fig. 1 The comparison of Z score results from finger ultrasound AD-SoS measurements in early and established rheumatoid arthritis patients. Marked bone loss is shown at the early stages of disease

Table 2 AD-SoS 2 scores in early and established groups

	Disease duration (years)			
	< 1	≥1, ≤2	> 2, ≤4	Established RA
n	25	19	16	39
Mean *Z* score	−1.83	−1.54	−1.01*	−2.12*
95% CI	−2.3, −1.4	−2.0, −1.1	−1.5, −0.5	−2.4, −1.8
SD	1.05	0.97	0.95	0.93

*$P = 0.001$

Discussion

Our study has shown that bone is lost early in disease. There was a significant reduction in the Z scores with increased disease duration in this cross-sectional study (−1.52 vs. −2.12, $P = 0.004$), but the difference was not statistically significant between the very early disease groups (< 1 year, 1–2 years) and those with established disease (> 4 years). This indicates that bone loss in the first 2 years is considerable. Recent studies using quantitative ultrasound also show bone loss in early rheumatoid arthritis [25, 26]. Similarly, measurement of BMD using DEXA has demonstrated bone loss early in the disease process. Deodhar et al. demonstrated significant loss in bone mineral content in the hands of RA patients within the first year of disease [4]. Other studies have shown similar results [10, 27].

In this study there was no correlation between disease activity (as measured by ESR or CRP) and Z score in the early synovitis group. We found a weak inverse correlation with HAQ scores (−0.28), which reflects decline in functional ability. A recent study of RA patients using the same finger ultrasound technique also failed to show correlation between Z scores and ESR or CRP [22]. A correlation was found between finger ultrasound and HAQ (−0.37) and grip strength (0.39). A study of BMD measurement at the metacarpals in RA also failed to show any relationship with disease activity [27], although there was a tendency for correlation with HAQ (−0.27) and grip strength (0.37). Deodhar et al. did note a correlation between bone loss at the hand and baseline CRP in early RA [11]. Shenstone et al. found reduced femoral neck BMD in premenopausal women with RA which correlated with HAQ but not with disease activity [28].

The possibility exists that joint swelling may influence ultrasound transmission, resulting in spuriously low Z scores and hence limiting the usefulness of this technique. A recent study by Barkmann et al. has attempted to correct for this by normalising for finger width in their calculations [21]. In our study there was no correlation between the number of swollen joints at the hand

and wrist and Z scores, suggesting that swelling did not play a major role. In addition, one of the Larsen score criteria is the presence of soft tissue swelling, and we did not find a correlation between Larsen and Z scores.

The lack of correlation between Larsen and Z scores in our study has also been corroborated by other studies using QUS [26]. Sambrook et al. [29] used quantitative ultrasound at the calcaneum and found a correlation between Larsen score and broadband ultrasound attenuation (BUA), but not AD-SoS. Moreover, their study group had higher mean Larsen scores (7.2, vs. 5.1 in our study) and significantly longer disease durations (13.6 years vs. < 4 years). Röben et al. categorised groups of early RA patients into those with non-erosive and those with erosive disease using Larsen scores [25]. They found a significant decline in Z scores in both groups compared to controls, but more decline in the group with erosions. The lack of correlation with Larsen scores in our study may have been influenced by the small sample size. In addition, the majority in our study had early disease and low Larsen scores.

We did not record details on the use of disease-modifying treatments (DMARDS) or corticosteroids. Such treatments may themselves contribute to bone loss. The recent study by Röben et al. [25] included a separate group of patients on corticosteroids without RA. They found no significant reduction in AD-SOS compared to healthy controls. Sambrook et al. found no difference in either BMD measurement by DEXA or calcaneal ultrasound in the corticosteroid-treated group [29]. Minaur et al. showed no adverse effect of low-dose methotrexate on axial BMD or bone formation in patients with RA in our centre [30].

It is possible to speculate why the bone loss is significantly greater in the first 2 years than in the 2–4 year group. This might reflect an effect of suppression of disease with treatment. We have shown that bone loss in the first 2 years is considerable. A cohort study in which newly diagnosed patients are measured at serial intervals together with markers of disease activity might show whether the early bone loss is reversible with disease suppression.

In summary, finger ultrasound has recently been introduced and used to assess bone loss in both early and late RA. It can be used to detect subtle changes of bone loss before any X-ray changes. It is well tolerated even in active disease and has a potential role in the early detection and diagnosis of RA, and also in disease progression.

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