Cancellous bone changes in the radius of patients with rheumatoid arthritis: a cross-sectional quantitative macroradiographic study

L. Disini, M. Foster, P. J. Milligan and J. C. Buckland-Wright

Objective. Fractal signature analysis (FSA), a computerized method of textural analysis, permits the separate measurement of changes in vertical and horizontal trabeculae based on the fractal dimension over a range of trabecular widths (fractal signature). We determined whether the FSA of high-definition macroradiographs (×5 magnification) quantified radiographic changes at sites of osteopenia and erosion formation in the rheumatoid arthritis (RA) hand.

Methods. Sixty-seven RA patients had macroradiographs of the left wrist and hand. The distal radius was scored and grouped from very mild (RA1) to moderate (RA4) disease. Macroradiographs were digitized and FSA of horizontal and vertical trabecular organization was performed in the radius at sites of periarticular osteopenia, erosion formation and at a mid-metaphyseal site. The RA groups were compared with 11 healthy non-arthritic subjects using ANOVA and Dunnett’s tests.

Results. Compared to the non-arthritic hands, FSA at the distal radius in groups RA1 to RA4 measured significantly lower (P < 0.05) fractal signatures. The fractal signatures were lowest in RA4 involving small, medium to large sized vertical trabeculae at the periarticular osteopenic (0.18 to 0.84 mm, P < 0.01) and mid-metaphyseal sites (0.12 to 0.60 and 0.84 to 1.02 mm, P ≤ 0.04), and small to medium sized vertical trabeculae at the periarticular erosion site (0.24 to 0.84 mm, P < 0.01).

Conclusion. FSA quantified radiographic bone loss in the distal radius of RA patients with increasing radiographic severity in terms of lower fractal signatures compared with the non-arthritics. Disease-related bone loss was demonstrated by FSA to involve mainly vertical trabeculae at the periarticular osteopenic, periartricular erosion and the mid-metaphyseal sites indicating directionality of bone resorption in RA.

Key words: Hand, Rheumatoid arthritis, Trabecular bone, Fractal analysis.
technique is unique in that it measures the fractal dimension of cancellous bone separately for vertical and horizontally oriented trabeculae by applying a rod-like structural element over a range of scales corresponding to a range of trabecular widths, i.e. the fractal signature. FSA calculates fractal dimension as a function of resolution which is achieved by using morphological operators of dilation and erosion whose mathematical functions have been described [36]. Studies have shown that FSA appears to be a robust method which is independent of a range of factors that are susceptible to variation during routine radiographic procedures: the effect of radiographic magnification and geometry [21, 29, 36], changes in object or patient position [21, 29], and variations in the sensitometric properties of radiographs such as film contrast and mean density [21, 29, 36, 37]. The FSA of macroradiographic cancellous bone images is, however, limited by the size of the region being studied, which rules out the use of small bones such as the carpal bones and phalangeal bones of the hand.

In this investigation the detailed trabecular structure of the radius in RA patients was quantified using FSA on cancellous bone images recorded in macroradiographs. By providing enlarged images of the original (×5), macroradiography is superior to conventional radiography by producing images of unusually good resolution detailing the structural organization of bone. We compared the differences in the organization of cancellous bone between a non-arthritis reference group and RA patients of increasing disease severity at three sites within the distal radius, namely the sites of juxta-articular osteopenia, erosion formation and a mid-metaphyseal site corresponding to a region of generalized osteopenia.

Patients and methods

Patients and reference group

Following Lewisham and North Southwark Ethical Committee approval, 67 patients [43 females, mean age and standard deviation (s.d.) 53 ± 13 yr] meeting the criteria of the American Rheumatism Association [38] for RA were recruited from the Rheumatology Department of Guy’s Hospital. They had a mean (s.d.) disease duration of 3 ± 4 yr (range 3 months to 12 yr). Drug therapy was not controlled and therapeutic agents included disease modifying anti-rheumatic drugs.

Eleven volunteers comprising the non-arthritis reference group (5 females, mean age and s.d. of 42 ± 8 yr) with no pain or abnormality at the wrist and hand were recruited from medical and laboratory staff.

Patient consent was not required or obtained since the data presented in this paper were derived mathematically from a portion of the image of the hand radiographs and consequently unattributable to any individual patient.

Macroradiography and digitization of macroradiographs

Macroradiographs of both hands were taken as previously described [15, 39] with a micrometre-sized X-ray source producing enlarged radiographic images of the radius and wrist approximately five times the original size by placing the object close to the X-ray source. All the macroradiographs were bar coded and digitized using the high-resolution Lumisys 200HR laser film digitizer (Lumisys, Sunnyvale, CA). Automatic magnification correction at the time of digitization gave an effective pixel resolution of 60 mm × 60 mm.

RA patient grouping

Due to the previously documented symmetry of macroradiographic features in RA patients [40], only macroradiographs of the left hand were used for this study. Radiographs of the RA patients were grouped on the basis of increasing severity measured by structural changes in the radius, excluding joint space narrowing and bone changes at the medial aspect of the radius due to its superimposition with the ulna. The authors evaluated cortical and cancellous bone changes, with attention being paid to the degree of bone loss at the sites of erosion formation in the radius opposite the scapho-lunate joint and the radial styloid process. In order to compare the extent of the changes observed in the radius of RA patients with normal, healthy joints, a six-point scale was devised ranging from 0 (normal) to 5 (marked erosion).

The grading system defined Grade 0 as those radii that had a full-thickness cortical plate and no osteopenia in the subchondral region or styloid process. Grades 1 and 2 had mild and moderate thinning of the cortical plate and osteopenia in the subcortical cancellous bone respectively. Grade 3 had marked thinning of the cortical plate with a cortical break in some cases, and marked osteopenia with the formation of an erosion. Grade 4 (Fig. 1) had a definite break in the subchondral cortical plate and a large subcortical erosion with clearly defined margin. Grade 5 had marked destructive bone changes involving erosion formation in the styloid process and collapse of the cortical plate in the mid-articular region.

Regions of interest for fractal signature analysis

FSA requires definition of a region of interest (ROI) for measurement at sites of periarticular osteopenia and erosion formation and at a mid-metaphyseal region to assess generalized osteoporosis. The ROI (6 × 6 mm; 100 × 100 pixels) for the site associated with erosion formation [13, 39] was centred directly opposite the scapho-lunate articulation and beneath the distal radial cortex (Fig. 2). The ROI (6 × 6 mm; 100 × 100 pixels) for

Fig. 1. Macroradiograph of the wrist of a patient showing an erosion in the radius adjacent to the scapho-lunate joint and the presence of periarticular osteopenia in the rest of the distal radius. Other erosions can be identified in the scaphoid and lunate bones. This film was scored Grade 4 for disease severity. The horizontal bar represents 20 mm in the film.
Fractal signature analysis measurement

The fractal signature of vertical and horizontal trabecular structures for each ROI quantified trabecular structures at scales ranging from 0.12 mm to 1.14 mm in increments of 1 pixel (0.06 mm) [21]. Using the rodlike structural element for fractal dimension measurement, the vertical trabeculae were defined as structures parallel to the long axis of the radius and horizontal trabeculae were perpendicular to this axis.

Statistical analysis and presentation of data

Intra-observer reproducibility of the radiographic grading system was assessed by scoring 30 randomly selected radiographs within a 1-week period. Inter-observer agreement was determined by the independent classification of these films by two of the authors (LD, CBW). The intra- and inter-observer agreements for classifying the RA macroradiographs was determined by weighted kappa statistics [41].

For each scale or trabecular size measured by FSA, the fractal signatures for vertical and horizontal trabecular structures of the non-arthritis and RA groups were initially compared for statistical difference with analysis of variance (ANOVA). Between-group comparisons at $P < 0.05$ level by ANOVA indicates that the fractal signatures among the non-arthritis and RA patients were not equivalent. To determine which RA group differed from the non-arthritis reference group, post hoc testing with Dunnett’s test [42] was used. Dunnett’s test allows for the statistical comparison of the fractal signature values of each RA group with the reference group and compensates for the increased number of Type I errors for multiple comparisons of this type. Significant comparisons were determined at $P < 0.05$ and carried out for each trabecular size measured. Statistically significant results were given more importance when these occurred consistently over a wide range of adjacent trabecular sizes. Furthermore, statistically significant comparisons by Dunnett’s ($P < 0.05$) but not determined by ANOVA ($P > 0.05$) were discounted but noted when it occurred consistently for a range of trabecular sizes. ANOVA and the post hoc Dunnett’s test determines which particular trabecular size had statistically significant differences between RA groups and the reference group.

For the purposes of discussion the range of sizes of the trabeculae were grouped into trabeculae that were small (0.12 to 0.42 mm), medium (0.48 to 0.78 mm) and large (0.84 to 1.14 mm).

Results

The intra- and inter-observer agreements for classifying the degree of bone damage in macroradiographs of RA wrists gave a weighted kappa of 0.89 and 0.91 within and between observers. These kappa values were described as showing ‘very good’ agreements [43]. The grading system divided the 67 RA patients into four groups: 18 had changes characteristic of Grade 1, 22 had Grade 2, 16 had Grade 3 and 11 had Grade 4 respectively. These groups were designated RA group 1, very mild disease, to RA group 4, moderate disease.

Fractal signatures at the osteopenic site

For vertical trabeculae, the reference group had the highest fractal signatures for the entire range of trabecular sizes compared with the RA groups (Fig. 3a). Compared with the reference group, fractal signatures were significantly lower for medium-sized vertical trabeculae with RA group 1 (0.60 to 0.72 mm, $P < 0.02$) and RA group 3 (0.66 to 0.78 mm, $P < 0.02$) and for small, medium and large vertical trabeculae with RA group 4 (0.18 to 0.84 mm, $P < 0.01$) (Table 1a).

For horizontal trabeculae, the fractal signatures were similar for all RA groups and the reference group for small, medium and most of the large trabecular sizes measured (Fig. 3b). Compared with the reference group, fractal signatures were significantly lower for large horizontal trabeculae with RA groups 2 (1.08 to 1.14 mm, $P < 0.02$) and 4 (1.14 mm, $P = 0.01$) but not for RA groups 1 and 3 (Table 1b).

Fractal signatures at the erosion site

For vertical trabeculae, RA group 4 had the lowest fractal signature of the RA groups while the reference group and RA groups 1, 2 and 3 had similar fractal signatures for most of the range of trabecular sizes measured (Fig. 4a). Compared with the reference group, fractal signatures were significantly lower for small to medium vertical trabeculae for RA group 4 (0.24 to 0.60 mm, $P < 0.02$) but not for RA groups 1, 2 and 3 (Table 2a).

For horizontal trabeculae, the fractal signatures were similar for all RA groups and the reference group for the trabecular sizes measured (Fig. 4b) which was confirmed by ANOVA. However, Dunnett’s test showed that the fractal signatures were significantly lower for small-sized horizontal trabeculae for RA group 4 (0.24
Fractal signatures at the mid-metaphyseal site

For vertical trabeculae, RA group 4 had the lowest while the reference group had the highest fractal signature for the entire range of trabecular sizes while the fractal signatures for RA groups 1, 2 and 3 fell between these two lines (Fig. 5a). Compared with the reference group, fractal signatures were significantly lower for small-sized vertical trabeculae for RA group 1 (0.12, \( P = 0.04 \)) and RA group 2 (0.12 to 0.36, \( P \leq 0.02 \)) and RA group 3 (0.12 to 0.42 mm, \( P < 0.01 \)) and small, medium to large vertical trabeculae for RA group 4 (0.12 to 0.60 and 0.84 to 1.02 mm, \( P \leq 0.04 \)) (Table 3a).

For horizontal trabeculae, the fractal signatures were similar for all RA groups and the reference group for most trabecular sizes measured (Fig. 5b). Compared with the reference group, fractal signatures were significantly lower for small horizontal trabeculae for RA group 3 (0.30 mm, \( P = 0.01 \)) but not for RA groups 1, 2 and 4 (Table 3b).

Discussion

This study has demonstrated that the FSA textural image analysis technique can be used to quantify the radiographic changes in the early RA hand based on comparisons of fractal signature between a reference group and RA disease groups. In the radius, fractal signatures of RA patients with increasing radiographic severity from very mild to moderate disease were lower compared with non-arthritis. This was consistent with decreasing complexity of the radiographic image secondary to the loss of bone at sites of involvement of a wider range of trabecular sizes. Thus, the smallest amount of trabecular bone loss seen in very mild disease (RA group 1) involved the smallest reduction of the fewest trabecular sizes in comparison with the reference group. With disease progression, in mild disease (RA groups 2 and 3) greater amounts of bone loss were observed with a larger magnitude of fractal signature decrease along with the involvement of a wider range of trabecular sizes. In moderate

Table 1. The comparison of fractal signatures between RA groups and reference group in the periarticular osteopenic site with one-way analysis of variance and the post hoc Dunnett’s test. \( P \) values were significant at \( P < 0.05 \) for both tests. Dunnett’s test determined which RA group differed from the reference group. The mean difference in fractal signatures between the RA groups and the reference group is shown for trabecular sizes with \( P < 0.05 \) for both tests.

<table>
<thead>
<tr>
<th>Size (mm)</th>
<th>ANOVA test</th>
<th>Dunnett’s test*</th>
<th>Mean difference = RA group – reference group (95% CI, lower and upper bound)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(a) Vertical structures</td>
</tr>
<tr>
<td>0.12</td>
<td>( P &gt; 0.05 )</td>
<td>RA4 ( P = 0.04 )</td>
<td>-0.142 (−0.221 to −0.064)</td>
</tr>
<tr>
<td>0.18</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P &lt; 0.005 )</td>
<td>-0.181 (−0.279 to −0.084)</td>
</tr>
<tr>
<td>0.24</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P &lt; 0.005 )</td>
<td>-0.176 (−0.294 to −0.058)</td>
</tr>
<tr>
<td>0.30</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P &lt; 0.005 )</td>
<td>-0.200 (−0.342 to −0.057)</td>
</tr>
<tr>
<td>0.36</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P &lt; 0.005 )</td>
<td>-0.223 (−0.386 to −0.060)</td>
</tr>
<tr>
<td>0.42</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P &lt; 0.01 )</td>
<td>-0.236 (−0.425 to −0.049)</td>
</tr>
<tr>
<td>0.48</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.276 (−0.454 to −0.098)</td>
</tr>
<tr>
<td>0.60</td>
<td>( P &lt; 0.05 )</td>
<td>RA1 ( P = 0.02 )</td>
<td>-0.200 (−0.370 to −0.031)</td>
</tr>
<tr>
<td>0.66</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P &lt; 0.005 )</td>
<td>-0.325 (−0.514 to −0.137)</td>
</tr>
<tr>
<td>0.72</td>
<td>( P &lt; 0.05 )</td>
<td>RA1 ( P &lt; 0.005 )</td>
<td>-0.315 (−0.515 to −0.114)</td>
</tr>
<tr>
<td>0.78</td>
<td>( P &lt; 0.05 )</td>
<td>RA3 ( P &lt; 0.02 )</td>
<td>-0.261 (−0.488 to −0.036)</td>
</tr>
<tr>
<td>0.84</td>
<td>( P &lt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.341 (−0.589 to −0.095)</td>
</tr>
<tr>
<td>0.90</td>
<td>( P &gt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.331 (−0.590 to −0.072)</td>
</tr>
<tr>
<td>0.96</td>
<td>( P &gt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.325 (−0.514 to −0.114)</td>
</tr>
<tr>
<td>1.02</td>
<td>( P &gt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.325 (−0.514 to −0.114)</td>
</tr>
<tr>
<td>1.08</td>
<td>( P &gt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.325 (−0.514 to −0.114)</td>
</tr>
<tr>
<td>1.14</td>
<td>( P &gt; 0.05 )</td>
<td>RA4 ( P = 0.01 )</td>
<td>-0.325 (−0.514 to −0.114)</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \) in all cases.
disease (RA group 4), the greatest amount of bone loss was noted in all three sites studied with the lowest fractal signatures over the greatest range of trabecular sizes measured.

The FSA technique also differentiated the extent and pattern of bone loss at the periarticular osteopenic and erosion sites. The extent of trabecular loss at the osteopenic site was found to be greater than that at the erosion site since the former had significantly lower fractal signatures involving very mild to moderate RA compared with the latter which only affected moderate RA disease. There were no fractal signature-related cancellous bone changes observed in very mild to mild RA in the erosion site. Examination of the macroradiographs showed that the periarticular osteopenic site in the distal radius for non-arthritics and patients with very mild RA disease had well-formed cancellous bone with good mineralization, with a comparative decrease in content and density from mild to moderate RA disease. This site contained load-bearing trabeculae which were associated with force transmission across the radio-scaphoid articulation. In contrast, at the erosion site the non-arthritic group and RA groups with very mild disease already had a localized area of reduced bone content compared with the osteopenic site which was also observed in mild to moderate RA disease. This site was adjacent to the scapho-lunate joint which contained fewer load-bearing trabeculae compared to the periarticular region of the distal radius. Consequently, the comparatively greater amount of load-bearing trabeculae in the periarticular osteopenic site may have contributed to the loss of bone in milder forms of early RA but not concurrently in the adjacent erosion site. In very mild to mild RA, this bone loss involved mainly the medium-sized vertical trabeculae (0.60 to 0.78 mm), with no bone changes noted at the adjacent site of erosion formation.

In moderate RA disease, the pattern of trabecular loss at the periarticular osteopenic site also differed from that at the erosion site. In the former, there was a loss of mainly vertical trabeculae with small, medium to large sizes (0.18 to 0.84 mm) while small to medium trabeculae (0.24 to 0.60 mm) were affected in the erosion site. There was also a loss of only a few large horizontal trabeculae (1.14 mm) in the osteopenic site. This indicates that periarticular osteopenic changes in the distal radius secondary to RA appear to involve mainly vertical trabecular loss. In the periarticular erosion site, however, fractal signature reduction was also detected for small horizontal trabeculae (0.24 to 0.42 mm) based on post hoc analysis with Dunnett’s test. These changes, which involve a wide range of horizontal trabeculae, indicate additional bone loss in erosion formation apart from the loss of vertical trabeculae. Due to the lack of statistical significance of these horizontal trabecular changes using ANOVA for between-group comparisons, further work needs to be done to investigate and confirm these trabecular changes with a larger number of cases.

The radial mid-metaphyseal site also revealed a pattern of bone loss which showed lower fractal signatures primarily for vertical
trabeculae. Here the loss of mainly small vertical trabeculae occurred in very mild to mild disease (0.12 to 0.42 mm) and only a few small vertical trabeculae (0.30 mm). In moderate disease, small, medium and large vertical trabeculae (0.12 to 1.08 mm) were lost. These cancellous bone changes appeared to extend proximally into the shaft of the radius in the form of a para-articular osteoporosis in RA disease [44]. These early RA changes were quantified away from the periarticular osteopenic and erosion sites associated with bone loss secondary to synovial and tendon sheath inflammation at the wrist. This early detection of bone loss at the mid-metaphyseal site in moderate RA can be attributed to the greater sensitivity of the techniques used in this study [23] compared with standard methods of imaging which detect generalized osteoporosis at this site only in severe RA disease.

Since bone resorption in RA is known to be mediated by osteoclastic activity [45, 46], the preferential loss of primarily vertical trabeculae in the distal radius as measured by FSA suggests that the activity of these cells was restricted mainly to the vertical trabeculae. This indicates a directionality in osteoclastic activity in RA probably due to the larger surface area associated with the greater number of vertical relative to horizontal trabeculae in the radius [47]. Further work needs to be done to explore this apparent anisotropy in osteoclastic bone resorption.

In conclusion, FSA of macroradiographic images can be used for the quantification of radiographic bone changes within the distal radius secondary to inflammatory changes in RA. At the site of periarticular erosion formation, trabecular loss affected vertical and possibly horizontal structures, whereas at the periarticular and mid-metaphyseal sites of osteoporosis it was confined to mainly vertical trabeculae. Quantification of the differential pattern of cancellous bone loss at these sites has provided an insight into the directionality of bone resorption in RA disease. Future studies with FSA may involve the analysis of trabecular morphology between regions of interest in the radius and other sites in the RA hand in addition to longitudinal comparisons from baseline macroradiographs.

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References


