Measurement of radiographic changes occurring in rheumatoid arthritis by image analysis techniques

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SUMMARY We have applied image analysis techniques to serial measurements of bone contour in standard radiographs of single small joints of the hands in subjects with rheumatoid arthritis (RA) and controls. Adequate reproducibility was shown in 20 controls radiographed twice over a six month period. The technique showed significant changes in a proximal interphalangeal joint of 13 of 15 patients with RA studied over periods of three to 10 months. In further serial studies in selected small joints of RA hands significant changes could be shown as early as four months. These results justify further development of these techniques to allow their full scale evaluation in multiple joints in patients with RA receiving long term drug therapy.

Changes in periarticular bone are a major feature of both rheumatoid arthritis (RA) and osteoarthritis. In RA the ability of drug therapy to prevent periarticular bone destruction in severe disease is an important measure of drug efficacy. Standard methods of scoring radiological change in joints are subjective, insensitive, and difficult to measure. They are mainly based on either comparisons of radiographs with those in a standard atlas or on counting erosions in particular joints.^{1 2} Potentially measurable features of bone changes in arthritis include changes in periarticular bone density and changes in bone contour such as the bone loss or erosions in RA or osteophytosis in osteoarthritis. Techniques which have been used elsewhere to provide sensitive, in vitro measurements of bone density include photon absorptiometry and local neutron activation analysis.^{3 4} Both are limited in application to serial measurements in an individual since difficulty in accurate repositioning and neutron activation analysis requires the use of sophisticated equipment which is not universally available. A microfocal radiographic technique has been used to examine the fine details of bone changes occurring in arthritis^{5 6} but has the disadvantage that a relatively small field is examined in each film. We have developed image analysis techniques to measure the serial changes in bone contour occur-

ring in RA, and in the present study have investigated the feasibility of applying these techniques to the investigation of radiographs taken with standard radiographic apparatus available to routine hospital x ray departments. We have examined both the reproducibility of the measurements in non-RA hands and their sensitivity in detecting changes in selected small joints of the hands of patients with RA followed up for periods of up to two years.

Patients and methods

IMAGE ANALYSIS AND RADIOGRAPHIC TECHNIQUE

Radiographs were taken with the hands immersed in 5 cm of water to minimise soft tissue effects (in a parallel study we are analysing changes in periarticular bone density) and using a jig which ensured a constant hand position for repeated examinations. Agfa Mamoray RP3 film was used and exposed at 40 kVP, 100 mA at six seconds. Films were developed by a conventional automatic film processing machine.

The analysis of radiographs was performed with Magiscan 2 image processor which digitised at video frame rate a signal from a standard TV camera. A spatial resolution of 512×512 pixels and 6 bit grey level resolution (64 levels) was available. With the aid of a light pen the operator indicated the bone chosen for examination by placing control points to define the area of interest along the edge of the image appearing on the screen. The software refined

these points and used them to segment the entire bone by fitting a Catmull-Rom spline along the perimeter.^{7 8} (A Catmull-Rom spline is a particular type of contouring technique which uses low order polynomial sections or splines to interpolate the boundary contour between control points.) The orientation of the bone in relation to the camera was not critical ($\pm 60^\circ$) since registration coding automatically aligned the image with previous bone images in a given series. After identification of the bone centroid (the centre of gravity of a plane sheet of the same shape as the bone) the 'polar signature' (Fig. 1) of a 120° arc of the bone perimeter which includes the periarticular bone contour was defined. Each polar signature consists of 240 individual points (see Fig. 1). Polar signatures of the same joint in successive radiographs could then be compared by correlation coefficients(r), perimeter ratio (that is ratio of perimeter of polar signature baseline/perimeter of polar signature on follow up), similar ratio of areas of polar signatures, ratio of area/square of perimeter, and calculation of mean and standard deviation (SD) of the mean after subtraction. Examples of polar signatures from pairs of radiographs which show no change and significant changes respectively are shown in Figs 2 and 3. From consideration of serial radiographs of control hands the 95% confidence limits for serial measurements were calculated, and changes in RA films subsequently analysed were considered as significant if they fell outside these limits.

SUBJECTS

Initial reproducibility studies were performed in 20 control subjects who had baseline and repeat radiographs at intervals of six months. These subjects were chosen from a rheumatology outpatient clinic and included patients with soft tissue rheumatic disorders, cervical and lumbar spondylosis, and excluded patients with clinical evidence of inflammatory joint disease. All subjects gave informed consent to taking part in the study. Their ages ranged from 24 to 65 years. Changes occurring

in the proximal interphalangeal joints (PIP) of the middle finger in these subjects were used to calculate 95% confidence limits.

Radiographs of 28 patients with RA were analysed. Fifteen sets of films from seven patients were used to compare image analysis and standard Larsen

Fig. 1 Principle of the polar signature measurement. For purposes of clarity the polar signature is shown with 5° increments. In practice it is 10 times this, i.e., 0.5° increments, comprising 240 readings.

Table 1 Reproducibility measurements derived from 20×2 control films, using the proximal phalanx of the middle finger (six month interval)

Parameter	Perimeter (P) ratio	Area (A) ratio	A/P ² ratio	Polar signature subtraction (mean)	Polar signature subtraction (SD)	r
Mean	0.9996	0.9967	0.9976	0.2091	2.0076	0.9984
SD	0.0097	0.0154	0.0166	0.7016	0.5059	0.0007
Reproducibility (%)	0.9704	1.5451	1.6640	—	—	0.0694
95% Confidence limits	0.9806 to 1.0186	0.9665 to 1.0269	0.9965 to 1.0301	-1.174 to 1.5842	≥ 2.992	≤ 0.9970

Fig. 2 Image subtraction of control radiographs (proximal interphalangeal (PIP) joint) showing no significant serial change of polar signatures defining periarticular surface of head of proximal phalanx. ($P*P$ =square of perimeter).

Fig. 3 Image subtraction of R radiographs (PIP joints) showing significant serial change of polar signatures.

visual scoring of radiological changes occurring in the middle finger PIP joint.

The visual grading was decided by consensus between two observers (DMG, HM), and the

change in grading subsequently calculated. In the 21 further RA patients (Tables 3 and 4) we have investigated the time taken for radiographic changes to develop in PIP and metacarpophalangeal (MCP)

Table 2 Comparison of image analysis and Larsen index measures of radiological changes in head of proximal phalanx of middle finger (RA hands)

Sex	Age (years)	Time from baseline (months)	SD	Significance	Change in Larsen score
F	37	3	3.0655	0.05	0
F	37	10	4.1872	0.001	1
F	41	6	3.4577	0.01	2
F	41	6	3.0780	0.05	2
M	53	5	5.8083	0.001	1
M	53	6	4.4162	0.001	1
M	59	4	2.4581	NS	0
M	59	8	5.2230	0.001	2
M	59	4	3.7874	0.001	0
M	59	8	4.1609	0.001	0
M	60	5	5.9135	0.001	0
M	60	10	8.0915	0.001	1
M	68	7	5.8631	0.001	1
M	68	10	5.7937	0.001	1
F	72	3	2.3221	NS	0

SD=standard deviation of polar signature subtraction values.
Significance=statistical significance of change in polar signature.

Table 3 Erosive changes in periarticular bone outlines, estimated by the standard deviation and correlation coefficient of subtracted polar signatures (female patients)

Patient No	Age (years)	Time from baseline (months)	Subtraction SD	r	Significance (of SD)
1	15	5	1.7573	0.9979	NS
		11	1.8104	0.9979	NS
		17	2.0171	0.9973	NS
2	24	1	1.4602	0.9996	NS
		9	2.4593	0.9991	NS
3	37	4	2.0471	0.9991	NS
		15	4.8055	0.9946	<0.001
4	38	4	2.9588	0.9981	<0.1
		7	3.0060	0.9981	<0.05
5	41	9	3.2276	0.9981	<0.02
		18	3.8493	0.9978	<0.001
6	45	23	4.4196	0.9970	<0.001
		4	3.1228	0.9968	<0.05
		6	3.2287	0.9966	>0.02
7	47	12	2.9938	0.9971	NS
		2	1.9623	0.9976	NS
		4	2.0238	0.9974	NS
		7	2.3698	0.9965	NS
8	51	15	2.2611	0.9968	NS
		25	2.2749	0.9968	NS
		6	2.2332	0.9975	NS
		11	2.1320	0.9977	NS
9	62	18	2.0118	0.9980	NS
		8	1.9948	0.9985	NS
		11	2.5901	0.9974	NS
10	66	18	2.8632	0.9968	NS
		2	3.6272	0.9943	<0.002
		14	4.4708	0.9907	<0.001
11	72	4	3.6271	0.9932	<0.002
		6	6.0080	0.9814	<0.001

Table 4 *Erosive changes in periarticular bone outlines, estimated by the standard deviation and correlation coefficient of subtracted polar signatures (male patients)*

Patient No	Age (years)	Time from baseline (months)	Subtraction SD	r	Significance (of SD)
1	37	5	2.5541	0.9987	NS
		9	2.8950	0.9984	<0.1
		17	3.0144	0.9981	<0.05
2	49	2	1.9759	0.9987	NS
		6	1.6849	0.9990	NS
		15	1.6196	0.9992	NS
3	53	10	6.3332	0.9782	<0.001
		17	6.5075	0.9793	<0.001
4	59	6	2.8983	0.9982	<0.1
		24	3.2608	0.9978	<0.02
5	59	9	2.8601	0.9978	<0.1
		15	6.5432	0.9940	<0.001
		18	12.8876	0.9790	<0.001
6	60	5	4.7202	0.9994	<0.001
		11	4.0741	0.9961	<0.001
		17	5.5827	0.9926	<0.001
7	63	5	3.7093	0.9967	<0.001
		9	5.9026	0.9938	<0.001
8	68	2	1.9980	0.9985	NS
		7	2.5982	0.9978	NS
		11	3.9777	0.9995	<0.001
9	68	18	6.2882	0.9930	<0.001
		5	2.1697	0.9987	NS
		12	4.2282	0.9952	<0.001
10	68	5	3.0625	0.9974	<0.05
		12	3.5322	0.9963	<0.01
		18	4.0109	0.9953	<0.001

joints of the hands and in this case we have shown the worst affected joint. The patients with RA chosen all had classical or definite disease by the criteria of the American Rheumatism Association.⁹ All patients with RA had active synovitis in the small joints of the hands when entered in the study and all but two received second or third line drug therapy during at least part of the period of study.

Results

The reproducibility and 95% confidence limits of serial image analysis measurements in the head of the proximal phalanx of the middle finger in pairs of control radiographs are shown in Table 1. Using the normal ranges for mean and standard deviation of changes of polar signature subtraction thus defined, changes in serial RA films defined by image analysis were compared with changes in the Larsen index. Significant changes were found in 13 of 15 RA films by image analysis but in only nine sets of films by Larsen scoring (Table 2).

In the last part of the study we examined the rapidity with which radiological changes could be shown to develop in 21 further patients with RA, in

whom the worse affected PIP or MCP joint was chosen. Significant changes occurred in 15 of the joints (Tables 3 and 4). Changes occurred as early as four months, and in 11 of these joints change occurred in less than 12 months. In one case (patient No 6, female) radiological improvement suggestive of healing was seen.

Discussion

In this study we have investigated the potential usefulness of image analyse software in the serial measurement of radiographic changes occurring in periarticular bone in patients with RA and using hand radiographs which could be produced in any routine x ray department. We have shown firstly that these measurements appear reproducible in pairs of non-RA hand radiographs taken over a period of six months. A six month time period was chosen arbitrarily as being long enough to include any errors that might conceivably be due to repositioning, radiography, film processing, and image analysis but short enough to avoid major biological changes in normal bone in most subjects. Secondly, using 95% confidence limits calculated in these

control subjects, we then studied serial films in patients with RA and have shown changes in a single PIP joint over periods of three to 10 months. The image analysis technique appeared more sensitive than a standard visual grading. Lastly, in a study of the worst affected MCP or PIP joints in 21 further sets of RA films we found that changes appeared as early as four months from the baseline measurements. Although all but two of these patients were receiving second or 'third line' drug therapy during part of the period of study, clinical features of disease activity had been at least partially controlled in 15 and they are likely to be reasonably representative of RA patients with active synovitis in small joints of the hands seen in most hospital outpatient clinics. Thus in this study we have shown that in principle image analysis techniques may be used as an objective, reproducible and relatively sensitive measure of the changes occurring in periarticular bone of standard hand radiographs in RA. We suggest that it would now be worth applying this technique to future large scale studies of putative disease modifying drugs in RA. The present image analysis software is relatively slow (hence the restriction in this study of serial measurements to individual joints) and requires further development to allow rapid measurement in multiple joints. Although the present study was directed at measurements of the bone loss occurring in RA,

there seems no reason why similar techniques could not be applied to measurements of the new bone formation (osteophytosis) occurring in osteoarthritis.

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