

Metabolic activity of erosions in rheumatoid arthritis

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SUMMARY The hands of 10 patients with rheumatoid arthritis were investigated with diphosphonate scanning and radiology. Increased uptake of isotope can be associated with some erosions but not all and also reflects other processes more linked to acute inflammatory areas unassociated with the development of erosions. If the latter are the hallmark of active rheumatoid arthritis then bone scans are not.

Key words: diphosphonate, radionuclide imaging, radiology.

It is not clear whether rheumatoid erosions ever heal.^{1–3} As erosions might demonstrate variable metabolic activity, we were interested to investigate this possibility by scanning the joints of patients with rheumatoid disease with the bone seeking isotope methylene diphosphonate.

This isotope has been used widely in patients with rheumatoid disease. Some authors⁴ have correlated disease activity with isotope uptake and others⁵ suggest that scans predict radiological outcome. As therapeutic decisions are often based on the appearance of erosions, scans might enable decisions about pharmacological intervention to be taken earlier in the disease process. This study attempts to test these claims and also to investigate the reproducibility of radiographic assessments.

Materials and methods

Ten patients (five male and five female) with classical or definite rheumatoid arthritis (American Rheumatism Association (ARA) criteria) were investigated. Their age range was 43 to 65 years (average 57.4 years), and the disease duration was 2–47 years (average 11.3 years). Seven patients were seropositive, three patients were receiving gold, penicillamine, or long term low dose steroids. One was in a drug trial on placebo and the others were on non-steroidal anti-inflammatory medication—benorylate, salicylate, indomethacin, naproxen, or diclofenac.

Local Ethical Committee approval was obtained for the study.

X-RAY INVESTIGATIONS

All patients had conventional posteroanterior (PA) *x*-rays of their hands within 24 hours of diphosphonate scanning. These *x*-rays were examined by two independent observers (a radiologist and a rheumatologist) on two separate occasions. The terminal interphalangeal, proximal interphalangeal, and metacarpophalangeal joints were assessed. Wrists were excluded. If an erosion was seen it was recorded. Each joint was therefore assessed visually on four separate occasions. If on three of these occasions an erosion was seen this designated an erosive joint. *X*-rays were repeated 12 months later and a similar assessment made by the same two observers again on two separate occasions.

CLINICAL ASSESSMENT

On the day of diphosphonate scanning each patient was examined clinically and a record of the Ritchie articular index, visual analogue pain scale, grip strength, and early morning stiffness was made.

SCANNING

The instrument used was a model 535 IGE gamma-camera interfaced to a system I ADAC nuclear medicine computer system. All recorded images were made in a 128 × 128 matrix size, which has a real element size of 4 × 4 mm. The patient's hands were placed on top of the gammacamera collimator shield in frames with lead separators for each finger. Immediately after the antecubital vein injection of

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550 MBq (15 mCi) of ^{99m}Tc -methylene diphosphonate data were recorded on a floppy disc in the ADAC system for four minutes, with each frame lasting 10 seconds. This constituted the early scan image. After two to four hours a single 200 second image was recorded similarly; an analogue image was recorded simultaneously for this late scan.

The last minute of the four minute scan was summated. Areas considered to show increased uptake by visual inspection were drawn around with a light pen, and the average number of counts in that area was calculated. The background average counts in the hand was also calculated counting over 10 similarly sized areas and determining the average background counts. Similarly, areas of increased uptake and background measurements were made from the 200 second late scan. To determine whether or not areas of increased uptake, as assessed visually, were quantitatively different from the background at $p < 0.05$ the equation shown below was used:⁶

$$\frac{S-B}{\sqrt{(S+B)}} > 2$$

S=average count density in that area, B=background counts per unit area.

If $S-B$ over the square root of $S+B$ was greater than 2 then the area of increased uptake was significantly different from the background at a p value of less than 0.05. Such areas were considered to show significantly increased uptake of isotope compared with the background.

Results

X-RAY ASSESSMENT

The initial radiological assessment yielded 30 erosive joints in five patients. The remaining five had no erosive joints. The reproducibility of x -ray observation for each observer between the two occasions when the initial x -ray was examined showed observer 1 correlation to be 0.6, observer 2, correlation to be 0.7. Each observer scored the x -rays on two occasions. Therefore, each had two observations on 28 joints in 10 patients, making a total of 560 observations. When the two observers were compared with each other the correlation was 0.5. When scoring repeat x -rays taken 12 months later observer 1 correlation was 0.9, observer 2 correlation was 0.8; when the two observers were compared the correlation was 0.7. There was no significant difference between observer analysis on either occasion.

SCANNING RESULTS

By determining the statistically significant areas of increased uptake, it was found that 30% of the joints

Table 1 Areas showing increased uptake of isotope

Late scan alone	53
Late and early scan	14
Early scan alone	8
Total	75

Table 2 Behaviour of joints with erosions when scanned with diphosphonate

No increased uptake of isotope	13 (43%)
Increased uptake on late scan alone	9 (30%)
Increased uptake on both late and early scans	5 (17%)
Increased uptake on early scan alone	3 (10%)
Total	30

considered positive by visual inspection were not significantly different at $p < 0.05$ to the background count. In the 10 patients studied, excluding the area of scan corresponding in the wrists, there were 75 areas of increased uptake. In all but two cases these were located over areas corresponding to the proximal interphalangeal and metacarpophalangeal joints. The other two areas were over distal interphalangeal joints. These 75 areas showed up on the isotope scans as indicated in Table 1. Thus of the 75 areas of increased uptake, 67 were seen on the late scan.

There were only 17 scan areas of increased isotope uptake that corresponded to joints with erosions and in all but three of these the scan showed increased uptake during the late scanning periods.

Examination of the behaviour of the 30 erosive joints with diphosphonate scanning showed four different patterns (Table 2).

43% of the joints with erosions did not show increased uptake of diphosphonate isotope on either the early or late scan. These results are illustrated in Fig. 1, which shows the heterogeneous behaviour of the joints with erosions when scanned with methylene diphosphonate.

When the clinical assessments of these patients with scanning were correlated there was a significant correlation $p < 0.01$ ($r = 0.84$) between the Ritchie articular index and the number of areas with increased uptake in the late scan. There was a less significant correlation ($p < 0.05$) between the late scans and the visual analogue scale ($r = 0.74$) and grip strength ($r = 0.73$). None of these parameters correlated significantly when the early scans were considered.

The repeat x -rays done 12 months later showed 28 new erosions. Thirteen of these occurred in one

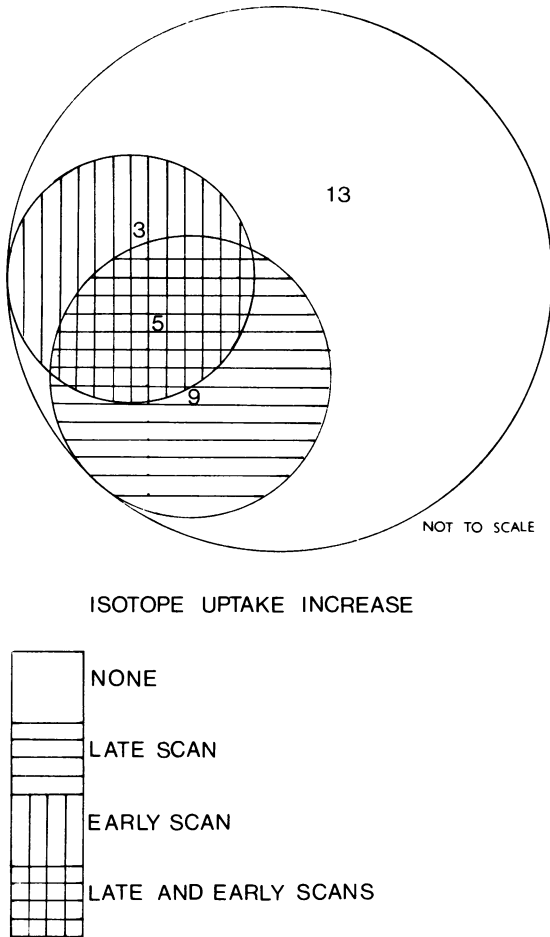


Fig. 1 Behaviour of erosive joints with scanning.

patient. The findings in these joints when scanned 12 months previously is shown in Table 3. From this it will be seen that over 50% of the joints with new erosions had not shown increased uptake on either the late or the early scan performed 12 months previously.

Table 3 Behaviour of joints showing new erosions when scanned 12 months previously with diphosphonate

No increased uptake with either scan	15 (54%)
Increased uptake on both early and late scans	5 (18%)
Increased uptake on late scan only	4 (14%)
Increased uptake on early scan only	4 (14%)
Total	28

Discussion

Extra bone seeking isotope collection, over and above other areas, is dependent on either increased blood flow or vessel permeability, so that the bone is exposed to a higher concentration of isotope in a given time. It is also dependent on the extra surfaces exposed to the isotope, particularly during acute bone repair⁷ and possibly acute bone destruction. It seems that increased late scanning collection correlated well with an index of inflammation but did not correlate well with the radiological presence of an erosion.

The natural history of erosions, on the other hand, may be due to local inflammatory mediators such as collagenase^{8,9} and elastase¹⁰ in association with pannus invasion, humorally mediated bone resorption,¹¹ or simple pressure atrophy from the invasion of joint fluid unassociated with an inflammatory or metabolic response.

It is not surprising that joints showing erosions on x-ray behave heterogeneously when scanned with a bone seeking isotope, considering the variety of pathological mechanisms that may be involved. We were certainly unable to confirm the suggestion¹² that erosions always show increased uptake of isotope and found that erosions could appear within 12 months without any preceding bone isotope changes. In many cases the presence of a positive scan was associated with healing of an erosion rather than radiological deterioration as previously suggested.¹³

Although erosions are a hallmark of rheumatoid arthritis, the bone scan only detects some metabolically active erosions and may also reflect more transient vascular and inflammatory changes in bone.

Another feature emerging from this study was the well known difficulty in clearly defining criteria for erosions which would satisfy a number of observers. Internal consistency was high, but cross observer differences were much higher.

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