Progression of digital osteoarthritis: a sequential scintigraphic and radiographic study

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Summary

Hand radiographs and scintigraphy were obtained initially and at the 4-year follow-up in 15 patients with symptomatic osteoarthritis (OA) of distal and/or proximal interphalangeal joints. For each joint, a 0–15 score was obtained for the OA radiographic lesions read blind by the same observer. An abnormal isotope retention over a bone reference area was assessed and quantified. The predictive value of scintigraphy for the OA radiographic progression was confirmed and shown to be improved by a second investigation. During the study period, the percentage of radiographic OA joints increased from 66.3 to 76.6%, but joints showing an abnormal scan decreased from 40 to 22.5%. Progression of the OA radiographic score was closely related to scintigraphic changes. The mean difference between the final and initial OA score was −0.08 in joints with two normal scans (N=115), +0.73 in joints showing a first abnormal and a second normal scan (N=94) and +1.8 in joints with two abnormal scans (N=14) or a scan becoming abnormal (N=47). An abnormal scan appears to represent a transient event, and this event is associated with a period of progression of digital OA. Potentially, anti-OA therapies that suppress joint isotope retention might slow down OA progression. The magnitude of joint isotope retention was positively correlated with the OA radiographic score established at the same time (R=0.61 and P<0.001), but showed no predictive value for progression of the latter.

Key words: Osteoarthritis, Hand, Radiography, Scintigraphy.

Introduction

OSTEOARTHRITIS (OA) of distal and proximal interphalangeal joints (DIP, PIP) commonly presents in post-menopausal women. Radiography is a sensitive method for the assessment of digital OA progression [1–5]. However, it is not able to detect early structural or biochemical changes of OA, commonly the only lesions present with the initial symptoms [6–8]. Digital OA, is associated with occasional painful flares and progression towards indolence over a number of years [5–7] that cannot be predicted by radiography. It has been suggested that bone scintigraphy is a sensitive method for detecting OA at an early stage and retention of isotope around the hand or knee has been correlated with subsequent radiographic progression of OA [9–16]. The present work investigates the predictive value of scintigraphy in digital OA, studying both a quantitative score of isotope retention, initially and upon follow-up.

Patients and methods

Fifteen patients (14 women and one man, mean age 59 years, ranging from 42–69 years old) were included in a 4-year prospective study conducted between 1989 and 1993. Patients were selected on the presence of a clinically and radiographically established OA, according to Altman et al. [8]. Patients were excluded if they had psoriasis, rheumatoid arthritis, gout and chondrocalcinosis, abnormal erythrocyte sedimentation rate and C reactive protein, abnormal serum level of uric acid and a positive Latex test. Dorsal radiographs of the hands were carried out by the same operator. Only DIP and PIP joints were examined. Joint space narrowing, osteophytes, subchondral sclerosis, subchondral bone cysts and subluxation of each joint were each scored from 0–3. The total radiographic score of a joint thus ranged from 0–15. Joints showing a score greater than 0 were recorded as OA. Films were read blind by the same observer. The intra- and interobserver reproducibility of the scoring system was assessed using 10 randomly selected radiographs. They were read blind a second time 8 days later by the main
observer, and similarly read two times independently by another observer. Reproducibility was assessed using a regression analysis and the paired Student's t-test.

Ten mm (approximately 400 Kcounts) planar anterior hand scans were obtained 4 h after intravenous injection of 700 MBq of 99m technetium-labeled methylene diphosphonate, using a rectangular large field of view DSX Sopha Camera, a low energy-high resolution parallel-hole collimator, a 140 KeV-20% window, a 2.66 zoom acquisition factor and a 256 x 256 matrix computer collection on a F-83 Sopha computer. No attenuation correction was applied to the data. After 10% background subtraction, free-hand regions of interest (ROIs) were drawn over each joint and distal radius taken as reference. The mean radiotracer count per pixel of each joint ROI was divided by the mean radiotracer count of the distal radius ROI. This ratio was used as a quantitative scintigraphic score of isotope retention. Only joints showing a ratio greater than 1 were recorded as positive. The observer was blinded to the radiographic data.

The statistical study used the chi-squared test for qualitative data, Student’s unpaired or paired t-test, variance analysis and simple regression analysis for quantitative data.

Results

REPRODUCIBILITY OF THE RADIOGRAPHIC SCORE

The total score and the score of each OA lesion were compared with the paired Student's t-test, and no significant intra- and interobserver difference was demonstrated. Table I shows the intra- and interobserver coefficients of regression for total and detailed scores. The coefficients of correlation of the main observer ranged from 0.68-0.90, the best one being obtained with joint space narrowing, and the poorest one with joint subluxation. Intraobserver reliability was similar, except for bone cyst scoring. Intraobserver reliability was better than interobserver reliability.

RADIOGRAPHIC AND SCINTIGRAPHIC DATA AT THE SAME TIME

At entry and follow-up, respectively, 66.3 and 76.6% of the 270 examined joints were radiographically classified as OA and 40 and 22.5% were demonstrated with an abnormal scan.

An abnormal scan at entry and follow-up, respectively, was seen in 53 and 28.5% of OA joints and 14.2 and 3.1% of radiologically normal joints (Fig. 1).

A significant positive correlation (R = 0.61, \( P < 0.0001 \)) between the radiographic score and the scintigraphic score of the 270 joints was found. A similar correlation was found when considering OA joints alone either at entry (R = 0.54, \( P < 0.0001 \)) or at follow-up (R = 0.53, \( P < 0.001 \)).

RADIOGRAPHIC PROGRESSION OF OA IN RELATION TO THE FIRST SCINTIGRAPHY

Over the 4-year study, the radiographic score increased from 2.58 + 3.16 to 3.33 + 3.63 (\( P < 0.0001 \)) in the 270 joints, from 3.9 + 3.15 to 4.67 + 3.74 (\( P < 0.001 \)) in initially OA joints, and from 0 to 0.69 + 1.01 in initially normal joints (mean + s.d.).

The change during the study in the radiographic score of each of the 270 joints was expressed as the difference between final and initial values. This change in the radiographic score was significantly (\( P < 0.001 \)) but weakly positively correlated (R = 0.14) with the initial scintigraphic score. However, such a correlation was not significant when considering joints with an initial abnormal scan alone.

Fig. 2 shows that the mean increase in the radiographic score of the 270 joints was much

<table>
<thead>
<tr>
<th>OA lesion</th>
<th>Main observer</th>
<th>Second observer</th>
<th>Interobserver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint space narrowing</td>
<td>0.90</td>
<td>0.89</td>
<td>0.83</td>
</tr>
<tr>
<td>Osteophyte</td>
<td>0.82</td>
<td>0.82</td>
<td>0.77</td>
</tr>
<tr>
<td>Bone sclerosis</td>
<td>0.79</td>
<td>0.76</td>
<td>0.67</td>
</tr>
<tr>
<td>Bone cysts</td>
<td>0.75</td>
<td>0.81</td>
<td>0.66</td>
</tr>
<tr>
<td>Subluxation</td>
<td>0.68</td>
<td>0.67</td>
<td>0.73</td>
</tr>
<tr>
<td>Total OA score</td>
<td>0.78</td>
<td>0.79</td>
<td>0.74</td>
</tr>
</tbody>
</table>

The reproducibility of the total score, and of each OA lesion quoted from 9-3, was assessed in 10 randomly selected films twice analysed blindly by two observers. Values are the coefficients of correlation given by a simple regression analysis.
greater (2.81 times) during the study in joints showing an initial abnormal scan than in joints with a normal one (mean ± s.d.: 1.21 ± 2.52 and 0.43 ± 1.5, respectively; \( P < 0.002 \)). The increase was even higher (3.62 times) when considering initially OA joints alone (1.16 ± 2.65 and 0.32 ± 1.99, respectively; \( P < 0.01 \)).

In the 91 initial radiographically normal joints, a positive radiographic score was found at follow-up in 76.9% (10/13) of the joints with an abnormal scan and 35.8% (28/78) of the joints with a normal one (chi square = 7.71, \( P < 0.005 \)). An increased isotope retention at entry thus gave a relative risk of 5.95 for the appearance of OA in an initially normal joint. The mean increase in the radiographic score was also significantly higher in joints with an abnormal scan than in joints with a normal one (1.53 ± 1.19 and 0.55 ± 0.92, respectively; \( P < 0.001 \)). In radiographically normal/scan positive joints, the correlation of the initial scintigraphic score and radiographic changes approached significance (\( P = 0.052 \), Spearman test).
RADIOGRAPHIC PROGRESSION OF OA IN RELATION TO CHANGES IN SCINTIGRAPHY

During the study period, the mean scintigraphic score decreased by 51.7% in the 270 joints, 64.3% in joints with an initial abnormal scan, 51.2% in initially radiographically OA joints and did not vary in initially radiographically normal joints.

Changes in the radiographic and scintigraphic score, each expressed as a percentage of the initial values, were significantly ($P < 0.05$) but weakly ($R = 0.13$) correlated. The correlation was not present when considering joints with an initial abnormal scan alone.

Qualitative changes in scintigraphy were closely related with changes of the radiographic score (Fig. 3). The latter decreased from $1.51 \pm 1.65$ to $1.46 \pm 1.8$ ($P = 0.02$) in joints with two normal scans, increased from $3.91 \pm 3.69$ to $4.64 \pm 3.53$ ($P < 0.001$) in those showing a disappearance of the initial abnormal isotope uptake, from $5.26 \pm 3.52$ to $7.13 \pm 4.15$ ($P < 0.001$) in those with two abnormal scans and from $2.87 \pm 3.32$ to $4.68 \pm 3.71$ ($P < 0.001$) in joints only positive in the second scintigraphy. Similar changes were observed in initial radiographically OA joints alone. The radiographic score did not vary in joints with two normal scans, increased by $11.5\%$ in joints becoming scintigraphically normal, by $34.1\%$ in those with two abnormal scans and by $52.1\%$ in those becoming scintigraphically positive.

Discussion

The present study of DIP and PIP joints shows that an initially abnormal scan, over a 4-year period, has a relative risk of 5.95 for the radiographic appearance of OA lesions, and increases by 3.6, the mean progression of the radiographic score of initially radiographically OA joints. Thus, it confirms a positive predictive value of scintigraphy for the subsequent radiographic change in digital OA [11, 13, 14]. This study reports 15 patients followed for 4 years and previous studies included between 14 and 67 patients over 18 months to 5 years.

A positive scan at entry was a strong predictor (77%) of the presence of radiographic OA, agreeing with similar studies of symptomatic patients [11, 14], and less predictive in asymptomatic patients [13]. A negative scan at entry was reported previously as a strong negative predictor of subsequent radiographic OA progression with only 1–2% of such joints showing OA progression [11, 13, 14]. This is in contrast to the present study where there was a progression of OA in $38.5\%$ of
joints with an initial normal scan. The discrepancy might be explained by the use of different methods. In the present study, the definition and progression of OA were assessed using a radiographic quantitative score read blindly, while previous studies used a qualitative definition of OA and direct comparison of the two films for evaluation of progression. The radiographic score used herein was close to those reported by Altman et al. [1] who used a 0–3 scale for each lesion. Kallman et al. [17] used a 0–3 scale for joint space narrowing and osteophytes, and a 0–1 scale for bone sclerosis, cysts and lateral deformity. For collapse of central joint cortical bone, an additional 0–1 scale was used. The different scoring systems seemed to be similarly reliable. A decreased radiographic score, observed in 17.4% of OA joints, could be related to problems of reproducibility but also to the possibility of an actual improvement of OA radiographic lesions. The magnitude of the mean decrease—that is 37% in these joints—argues for the later possibility, at least in some joints.

The sequential scintigraphic evaluation of OA gives original and interesting information. Radiographic score progression was markedly higher in joints with an abnormal scan at follow-up than in joints with a positive scan at entry (Table II). A positive scan could thus be a better indicator of what has happened than of what will occur. Progression of radiographic score was similar when comparing joints with a normal scan at entry or follow-up but more information was given by the study of changes with time in scintigraphic images. The mean radiographic score increased markedly in joints with two positive scans or becoming positive, increased modestly in joints becoming normal and did not change in joints with two normal scans. It is thus clear that an abnormal scan reflects OA progression at a given time and that qualitative scintigraphic changes parallel the variable OA progression with time.

Table II
Mean change of the OA radiographic score over a 4-year period in relation to initial scan alone, second scan alone and both scans

<table>
<thead>
<tr>
<th>Positive scan</th>
<th>1989 Yes</th>
<th>1989 No</th>
<th>1993 Yes</th>
<th>1993 No</th>
</tr>
</thead>
<tbody>
<tr>
<td>–</td>
<td>1.21</td>
<td>0.43</td>
<td>1.80</td>
<td>0.41</td>
</tr>
<tr>
<td>1993 Yes</td>
<td>1.87</td>
<td>1.81</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>1993 No</td>
<td>0.73</td>
<td>0.08</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Values are the mean of the differences between the final and initial OA score calculated for each joint.

Quantification of abnormal isotope retention seems to be less predictive. A correlation between scintigraphic and radiographic scores was observed throughout the study. But it was clear that radiographic OA progression was unrelated to the magnitude of the initial scintigraphic score when abnormal, and to the quantitative changes in the scintigraphic score during the study period. These results thus suggest that a high isotope retention only reflects an advanced stage of OA, probably related to an important subchondral bone remodeling.

Increased retention of a labelled bisphosphonate around an OA joint is certainly not due to a single OA lesion. A correlation between scintigraphy and the subsequent growth of osteophytes over an 18-month period in human digital OA has been reported [14]. Osteophytes have also been reported to be the earliest radiographic lesions of digital OA [11]. It is thus tempting to correlate the abnormal isotope retention of a radiographically normal DIP or PIP joint with the growth of osteophytes. However, in the present work the coefficients of correlation between the scintigraphic score and the individual scores for joint space narrowing, osteophytes, subchondral bone sclerosis or cysts were similar (data not shown). Lateral deformity alone was not correlated with scintigraphy. Isotope retention was similarly correlated with changes in bone and joint space, which may be explained by the close association of the lesions. But isotope retention is most likely to be related to increased bone remodeling in both osteophytes and subchondral bone, as demonstrated in an experimental model of OA [18].

From this and other studies it is clear that some digital OA joints show an abnormal scan while others do not. We also demonstrated that isotope retention changes with time both qualitatively and quantitatively, some joints becoming abnormal and others reverting to a normal scan, with an overall tendency to decrease over a 4-year period. We have been unable to explain such changes on the basis of age, sex, weight, PIP or DIP localization, probable duration and radiographic state of OA. Digital OA is known to become asymptomatic after several years, during which occasional painful flares occurred [6, 7], and scintigraphy has been correlated with spontaneous and induced pain in digital joints [15]. It is therefore tempting to suggest that for unknown reasons in any joint, there can occur scan-positive, probably painful transient periods of OA radiographic progression, alternating with normal scan, probably asymptomatic, non-progressive periods. The scintigraphically positive progressive periods can clearly occur at any time of the course of the disease, but probably more rarely in a late stage.

Finally, the present work suggests that iterative scintigraphy could be of interest for the evaluation
of disease-modifying OA drugs. The positive and negative close link between radiographic and scintigraphic progression of OA may indeed suggest that a drug able to suppress isotope retention should be similarly able to slow down or even stop the radiographic progression of the disease. This interesting hypothesis remains to be confirmed by therapeutic studies.

References


