Bone Scintigraphy Is Not a Better Predictor of Progression of Knee Osteoarthritis Than Kellgren and Lawrence Grade

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ABSTRACT. ***Objective.*** To determine the predictive value of bone scintigraphy with respect to joint space narrowing (JSN) in patients with knee osteoarthritis (OA), based on quantitative estimates of uptake of a bone-seeking radiopharmaceutical and fluoroscopically standardized knee radiography.

Methods. Our study group included 86 obese women, 45–64 years of age, with unilateral knee OA. Uptake of technetium medronate (^{99m}Tc-MDP) in late-phase bone scans was measured at baseline in 5 regions of interest (ROI: lateral femur, lateral tibia, medial femur, medial tibia, and patellofemoral joint) and was adjusted for uptake (i.e., expressed as a ratio to uptake) in a ROI in the shaft of the tibia, which served as an internal standard. Each subject underwent a fluoroscopically standardized radiograph of the knees (semiflexed anteroposterior view) at baseline, 16, and 30 months. Magnification-corrected minimum joint space width in the medial tibiofemoral compartment was measured by digital image analysis.

Results. Followup was available for 79 patients (92%) at 16 months and from 73 patients (85%) at 30 months. On average, ^{99m}Tc-MDP uptake in each ROI and in the whole knee (average of 4 tibiofemoral ROI) was 170–240% of that in the tibial shaft. Uptake in the medial tibia and in the whole knee was significantly correlated with JSN at 16 and 30 months ($r = 0.22–0.30$, $p < 0.05$). However, after controlling for age, body mass index, and radiographic severity of OA, the associations between adjusted uptake and JSN were not significant. The rate of JSN in knees of patients with OA who were in the lower tertile with respect to adjusted ^{99m}Tc-MDP uptake in the medial tibia was significantly less rapid than in patients in whom uptake was in the middle and upper tertiles (0.04 mm/yr vs 0.18 mm/yr; $p < 0.05$). However, after controlling for overall radiographic severity at baseline, the difference in 30-month JSN in knees of patients with OA in the lower versus middle/upper tertiles was not significant.

Conclusion. The predictive utility of bone scintigraphy is confirmed by these data. However, its practical value is considerably diminished, insofar as similarly predictive information may be obtained by routine radiographic examination, without the radiation exposure and cost of scintigraphy. (J Rheumatol 2004;31:329–32)

Key Indexing Terms:
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Drugs such as doxycycline and diacerhein have been shown to slow the progression of osteoarthritis (OA) in animal models[1,2]. Considerable hope exists, therefore, that such agents, disease modifying OA drugs (DMOAD), may have similarly beneficial effects in humans[3-6]. However, because the rates of incidence and progression of OA in the general population are low (i.e., 2–4%/year for knee OA, depending on risk factors[7]), randomized clinical trials of DMOAD in humans are costly and require a relatively long duration and large numbers of patients to demonstrate that a drug will retard the rate of progression of joint damage in comparison with placebo.

Bone scintigraphy has been identified as a test that could be used to disqualify potential patients for a DMOAD study whose joint disease is unlikely to progress. Specifically, Dieppe, *et al*[8] reported that OA knees in which a late-phase bone scan did not show any focal areas of retention of a bone-seeking radiopharmaceutical do not exhibit progression of OA over the ensuing 5 years. In comparison, in OA knees with abnormal patterns of uptake, the likelihood of disease progression within 5 years was roughly 50%[8].

Our study was designed to ascertain the predictive value of bone scintigraphy using controlled, quantitative estimates of uptake of a bone-seeking radiopharmaceutical and a stan-

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dardized radiographic protocol to quantify joint space narrowing (JSN), the surrogate for thinning of articular cartilage, in patients with knee OA.

MATERIALS AND METHODS

The procedures, radiation exposure, other research risks, and associated safeguards for this study were approved by the Radiation Safety Committee and the Institutional Review Board of Indiana University, Purdue University, Indianapolis.

Patients. This study involved 86 obese women, 45–64 years of age, with unilateral knee OA. All patients were also in the upper tertile of age, race, and sex-appropriate norms for body mass index (BMI) from the Second National Health and Nutrition Examination Survey[9]. Radiographic eligibility criteria required grade 2 or 3 severity of knee OA by Kellgren and Lawrence (K&L) criteria[10] for one knee and grade 0 or 1 for the contralateral knee. Grading of radiographic severity was based on the standing anteroposterior (AP) view. The intra-rater reproducibility of K&L grades, based on repeat readings of a random sample of 30 OA knees, was very high ($\kappa = 0.87$).

Bone scintigraphy. Patients underwent late-phase bone scintigraphy 3 h after injection of 20 mCi of technetium medronate (^{99m}Tc-MDP, Bristol-Myers Squibb, Princeton, NJ, USA). Radiopharmaceutical uptake (counts/pixel) in anterior (600,000 count) and lateral (300,000 count) images was measured in 5 regions of interest (ROI): lateral femur, lateral tibia, medial femur, medial tibia, and patellofemoral joint. The ROI for the lateral femur in the anterior image also included the patella. Uptake in each ROI was adjusted for uptake (i.e., expressed as a ratio to uptake) in a standard-sized region drawn approximately at the junction of the proximal and middle thirds of the tibia (Figure 1), which served as an internal standard. Based on 2 sets of measurements from scintigrams of 6 randomly selected patients (12 knees, 60 ROI), the inter-rater reproducibility (intraclass correlation) of adjusted ^{99m}Tc-MDP estimates was 0.93.

Knee radiography. Each patient underwent a fluoroscopically standardized radiograph at baseline, according to the procedures and quality control criteria for the fluoroscopically assisted semiflexed AP view[11,12]. Radioanatomic positioning of the knee in each radiograph was standardized so that (1) the medial tibial plateau was parallel to the central ray of the radiograph beam, as evidenced by superimposition ± 1 mm of the anterior and posterior margins of the plateau; and (2) the knee rotation was minimal (i.e., both tibial spines were centered under the femoral notch). Followup knee radiographs were obtained 16 and 30 months after baseline.

Minimum joint space width (JSW) in the medial tibiofemoral compartment was measured by digital image analysis, using xJSW software[13]. JSW measurements were corrected for radiographic magnification by the software, based on the diameter of the projected image of a magnification marker, a 6.35 mm chrome steel ball encased in methyl methacrylate that was affixed with tape to the skin over the head of the fibula. The reproducibility (intraclass correlation) of JSW measurements on semiflexed AP radiographs of acceptable quality, based on repeat examinations within 7 to 10 days, has been established at 0.92[14]; the 95% confidence interval (CI) for individual estimates of JSW is ± 0.50 mm.

Statistical analysis. Because all patients had unilateral knee OA, analyses were performed on data derived from the OA knee of each patient. Pearson correlation coefficients and partial correlation coefficients were used to evaluate the association between adjusted uptake in the various ROI and JSN. Partial correlation coefficients were adjusted for age, BMI, and the K&L grade. Student's t test was used to determine whether OA knees with a cold scan [i.e., in the lower third (tertile) of the distribution for radiopharmaceutical uptake] were different than OA knees in the middle and upper tertiles with respect to JSN. The effect of radiographic severity of OA at baseline on JSN in knees with cold versus hot scans was determined by analysis of variance (ANOVA) with K&L grade (2 or 3) as an additional independent variable.

RESULTS

Demographic, clinical, and radiographic characteristics of the patients are shown in Table 1. Eighty-one percent of the entirely female sample was white. Mean age (± SD) was 55.2 ± 5.8 years. Mean BMI (± SD) was 36.5 ± 6.6 m/kg^2. Forty-eight (56%) of the 86 patients had grade 2 OA severity by K&L criteria[7].

Followup examinations were performed on 79 patients (92%) at 16 months and on 73 (85%) at 30 months. Mean

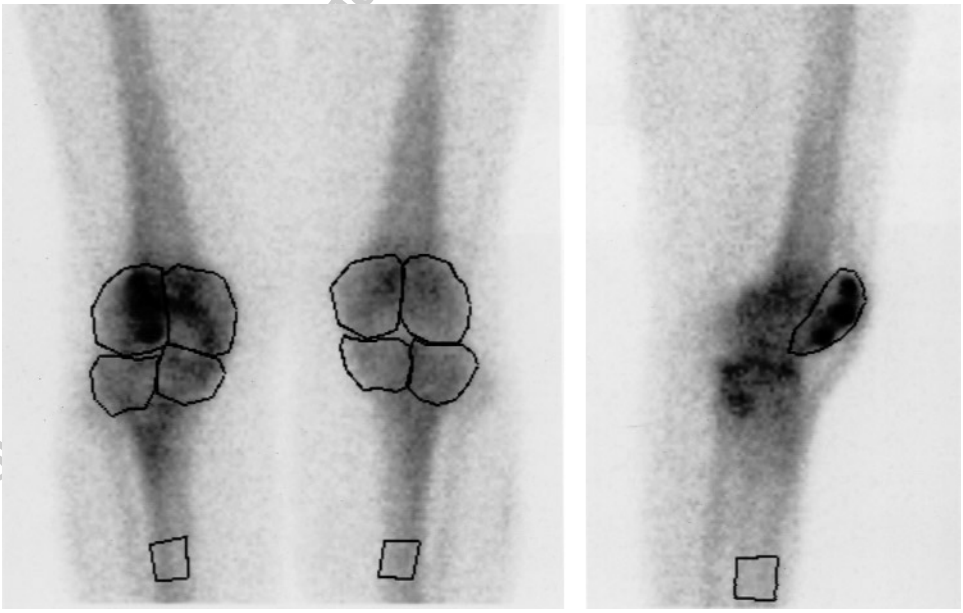

Figure 1. Regions of interest (ROI) drawn on anterior and lateral scintigrams. Uptake of ^{99m}Tc-MDP in each ROI was adjusted to that in a region drawn over the shaft of the tibia, which served as an internal standard.

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JSN (± SD) in the OA knee of these patients with unilateral disease was 0.21 ± 0.61 mm over 16 months and 0.34 ± 0.71 mm over 30 months.

Adjusted ^{99m}Tc-MDP uptake in each ROI is shown in Table 2. Zero-order (Pearson) correlations between adjusted uptake in the various ROI and JSN ranged from 0.12 to 0.28 at 16 months and from 0.18 to 0.30 at 30 months. Correlations involving uptake in the medial tibia were statistically significant (0.28 at 16 mo, 0.30 at 30 mo; $p < 0.05$). The partial correlation coefficients for the associations between adjusted uptake in each ROI and JSN (Table 2) control for age, BMI, and K&L grade (2 or 3). Notably, after controlling for these variables, none of the associations between adjusted uptake and JSN was statistically significant.

The predictive value of late-phase bone scintigraphy of the medial tibia is illustrated in Table 3. The ratio of uptake in medial tibia to that in the tibial shaft was ≤ 1.33:1 in one-third of the OA knees. Mean JSN (± SE) over 30 months in the lower tertile was 0.10 ± 0.11 mm (annual rate of JSN = 0.04 mm/yr). In contrast, among the 48 knees in the middle and upper tertiles for uptake in medial tibia, the mean of JSN (0.46 mm over 30 mo or 0.18 mm/yr) was significantly more rapid than in the lower tertile ($p = 0.045$). A similar analysis of the whole knee, based on uptake in all ROI, showed similar results: mean JSN (± SE) was 0.09 ± 0.14 mm in 12 knees whose uptake was in the lower tertiles for all 5 ROI, compared to 0.38 ± 0.10 in 61 knees with uptake in the middle/upper tertile in any ROI. However, the difference was not statistically significant ($p = 0.20$).

As in the previous correlational analyses, controlling for baseline radiographic severity of knee OA attenuated the association between ^{99m}Tc-MDP uptake and JSN. Table 3 shows that after controlling for K&L grade, the difference between the lower versus middle/upper tertiles for adjusted ^{99m}Tc-MDP uptake in the medial tibia with respect to 30-month JSN was not significant.

Loss of radiographic joint space is the dominant factor in differentiating K&L grade 3 OA from K&L grade 2[10]. The value of this alternative predictor of JSN, irrespective of bone scintigraphy results in the medial tibia, is illustrated in Table 4. Twenty-one of 25 knees in the lower tertile for adjusted ^{99m}Tc-MDP uptake exhibited grade 2 OA (i.e., a definite osteophyte, but no apparent loss of joint space) at baseline. Among these, mean JSW did not change over 30 months. In contrast, the 4 OA knees in the lower tertile that had exhibited loss of joint space at baseline (i.e., were K&L grade 3) continued to undergo thinning of articular cartilage at a rapid rate (0.27 mm/yr). This was the same rate seen in 28 K&L grade 3 knees in the middle and upper tertiles for radiopharmaceutical uptake. JSN in these patients was 4-fold more rapid than that among patients with K&L grade 2 OA who were in the middle and upper tertiles of uptake in the medial tibia.

Table 1. Characteristics of study patients.

N	86
Age, yrs (mean ± SD)	55.2 ± 5.8
Race, % white	81
BMI, kg/m^2 (mean ± SD)	36.5 ± 6.6
Overall severity of tibiofemoral OA, index knee*	
% K & L grade II	56
% K & L grade III	44
Overall severity of tibiofemoral OA, contralateral knee*	
% K & L grade 0	50
% K & L grade I	50
Minimum medial joint space width, mm (mean ± SD)**	3.7 ± 1.4

* Graded in the standing AP view. ** Measured in the semiflexed AP view. BMI: body mass index; K & L: Kellgren & Lawrence.

DISCUSSION

Our data support the finding of Dieppe, *et al*[8] that patients with knee OA in whom late-phase bone scintigraphy showed no focal areas of retention of ^{99m}Tc-MDP do not exhibit progression of their OA over a 5-year interval. In our study, the predictive accuracy of bone scintigraphy is most apparent in analysis of uptake in the medial tibia. However, while quantitative estimates of uptake correlated significantly with JSN in our study and differentiated between OA knees that would and would not exhibit significant JSN in as short an interval as 16 months, after controlling for the radiographic severity of knee OA, retention of ^{99m}Tc-MDP no longer predicted progression of JSN.

This latter finding varies from the results of Dieppe, *et al*[8], who indicated that radiographic severity of OA did not

Table 2. ^{99m}Tc-MDP uptake at baseline and correlation with JSN.

ROI	Adjusted Uptake, ROI:Tibia* (mean ± SD)	Zero-Order Correlation with JSN 16 mo	Zero-Order Correlation with JSN 30 mo	Partial Correlation** with JSN 16 mo	Partial Correlation** with JSN 30 mo
Medial femur	1.72 ± 0.52	0.12	0.21	–0.06	–0.01
Medial tibia	1.80 ± 0.73	0.28†	0.30†	0.13	0.08
Lateral femur	2.07 ± 0.71	0.18	0.20	0.04	0.04
Lateral tibia	1.71 ± 0.54	0.19	0.21	0.04	0.00
Patellofemoral joint	2.36 ± 0.82	0.14	0.18	–0.02	0.00

* A region of standard size drawn at approximately the junction of the proximal and middle thirds of the tibia.
** Adjusted for age, BMI, and overall radiographic severity. † $p < 0.05$.

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Table 3. Joint space narrowing (JSN) in lower versus upper/middle tertiles for ^{99m} Tc-MDP uptake in the medial tibia, before and after control for radiographic severity of knee OA.

Tertile for Adjusted ^{99m}Tc-MDP Uptake in the Medial Tibia	n	30-Month JSN, mm (mean ± SD) Before Controlling for K & L Grade	After Controlling for K & L Grade
Lower (≤ 1.33:1)	25	0.10 ± 0.57	0.33 ± 0.85
Middle/upper (> 1.33:1)	48	0.46 ± 0.76	0.48 ± 0.76
p		0.045	0.475

Table 4. Joint space narrowing (JSN) in OA knees with Kellgren and Lawrence (K & L) grade 2 and 3 radiographic severity in the lower versus upper/middle tertiles of uptake of ^{99m}Tc-MDP in late-phase bone scintigraphy.

K & L Grade	Lower Tertile n	Mean JSN (± SD), mm	Rate of JSN, mm/yr	Middle/Upper Tertile n	Mean JSN (± SD), mm	Rate of JSN, mm/yr
2	21	0.00 ± 0.53	0.00	20	0.16 ± 0.74	0.06
3	4	0.67 ± 0.48	0.27	28	0.67 ± 0.70	0.27

confound retention of the radiopharmaceutical as a predictor of disease progression. It is interesting, therefore, that ≤ 7% of patients in the earlier study had notable JSN at baseline. In contrast, 44% of patients in our study had K&L grade 3 OA severity (i.e., marginal osteophyte(s) and definite diminution of joint space)[10]. Moreover, only 27% of patients studied by Dieppe, *et al*[8] were obese (i.e., BMI > 30 kg/m^2), compared to 100% in this study. We suspect, therefore, that this discrepancy between the results may be attributable to a difference in the respective clinical populations on which the 2 studies were based.

Elevated radiopharmaceutical uptake in the knee, relative to an internal standard, may reflect increased turnover of subchondral bone that could be of pathogenetic importance in OA[15]. However, based on our results, the utility of bone scintigraphy as a means by which to exclude otherwise qualified patients, particularly obese patients, from DMOAD trials because of a low risk of OA progression is considerably diminished, insofar as similarly predictive information may be obtained by routine radiography, without the radiation exposure and cost of scintigraphy.

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