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Association of Bone Scintigraphic Abnormalities with Knee Malalignment and Pain

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Abstract

Objective—We evaluated the information content of knee bone scintigraphy, including pattern, localization and intensity of retention relative to radiographic features of knee osteoarthritis (rOA), knee alignment, and knee symptoms.

Methods—A total of 308 knees (159 subjects) with symptomatic and radiographic knee OA (rOA) of at least one knee were assessed by late phase technetium-99m-methylene disphosphonate bone scintigraph, fixed-flexion knee radiograph, full limb radiograph for knee alignment, and for self-reported knee symptom severity. Generalized linear models were used to control for within subject correlation of knee data.

Results—The compartmental localization (medial versus lateral) and intensity of knee bone scan retention were associated with the pattern (varus versus valgus) ($p < 0.001$) and severity ($p = 0.0008$) of knee malalignment, and localization and severity of rOA ($p < 0.0001$). Bone scan agent retention in the tibiofemoral, but not patellofemoral compartment, was associated with severity of knee symptoms ($p = 0.0009$), and persisted after adjusting for rOA ($p = 0.0012$).

Conclusion—To our knowledge, this is the first study describing a relationship between knee malalignment, joint symptom severity, and compartment specific abnormalities by bone scintigraphy. This work demonstrates that bone scintigraphy as a sensitive and quantitative indicator of symptomatic knee OA. Used selectively, bone scintigraphy is a dynamic imaging modality that holds great promise as a clinical trial screening tool and outcome measure.

Keywords

osteoarthritis; bone scintigraphy; malalignment; knee

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INTRODUCTION

Bone scintigraphy is a functional imaging modality that reflects alterations in the metabolic activity of bone. Bone scintigraphy is readily clinically available and used routinely for surveillance of bony metastases related to cancer. Bone scintigraphy is also useful for the evaluation of a variety of conditions including bone trauma, stress fracture, plantar fasciitis, Paget's disease and osteomyelitis [1]. Bone scintigraphy uses ^{99m}Tc labeled methylene diphosphonate (MDP). This compound accumulates rapidly in bone by adsorption to the mineral phase of bone with relatively little binding to the organic phase [1], thereby detecting areas of high skeletal bone turnover. Imaging is performed 2–3 hours after intravenous administration, allowing clearance of the radiotracer from the vasculature and soft tissue, resulting in improved visualization of bone.

Osteoarthritis (OA) is the leading cause of disability among adults in the USA [2]. OA is a whole joint organ disease characterized by cartilage degeneration and variable degrees of synovitis. OA also involves significant bone reactivity manifested as subchondral sclerosis and osteophyte formation in and around the joint. Progressive OA is associated with high bone turnover [3], which would be expected to result in exposure of bone mineral, thereby increasing the potential for ^{99m}Tc -MDP binding. This effect likely accounts for the association of bone scintigraphic agent retention with progression of established knee and hand OA [4–8]. Bone scintigraphy provides an early detection method for OA in animals [9–11] and may also be useful for detecting early OA in humans [7].

We hypothesized that the compartmental localization and severity of radiographic OA, and attendant compartmental specific alterations of knee joint bone turnover, would be reflected in the localization and intensity of retention of ^{99m}Tc -MDP by bone scintigraphy. We also hypothesized that variation in tibiofemoral load distribution due to knee malalignment would strongly impact the localization and intensity of ^{99m}Tc -MDP retention by articular bone. We were also interested in exploring possible associations of joint pain and intensity and localization of ^{99m}Tc -MDP retention in the joint, because OA joint pain is associated in part with bone abnormalities, such as intraosseous hypertension arising from impaired venous drainage, and bone marrow lesions detected on magnetic resonance imaging [12]. In a knee OA cohort, we evaluated the association of lower limb malalignment, compartmental localization of OA, and joint pain, with bone scintigraphy pattern and intensity of retention. This is the first description of an association of bone scintigraphic abnormalities and knee malalignment direction and severity, and this study represents an advance with respect to the scope of OA indicators examined.

PATIENTS AND METHODS

Patients

A total of 159 participants (118 female, 41 male) were enrolled in the NIH sponsored Strategies to Predict Osteoarthritis Progression (POP) study, approved and in accordance with the policies of the Duke Institutional Review Board. Participants were recruited primarily through Rheumatology and Orthopaedic clinics and met the American College of Rheumatology criteria for symptomatic OA of at least one knee. In addition, all participants met radiographic criteria for OA with a Kellgren-Lawrence (KL) [13] score of 1–3 in at least one knee. Exclusion criteria included the following: bilateral knee KL4 scores; exposure to a corticosteroid (either parenteral or oral) within 3 months prior to the study evaluation; knee arthroscopic surgery within 6 months prior to the study evaluation; known history of avascular necrosis, inflammatory arthritis, Paget's disease, joint infection, periarticular fracture, neuropathic arthropathy, reactive arthritis, or gout involving the knee, and current anticoagulation. A total of 186 participants were screened to identify the final 159

participants with radiographic and symptomatic knee OA of at least one knee who were willing to undergo arthrocentesis. Of the total 318 knees available for analysis, 10 knees were excluded from evaluation on the basis of knee replacement for a total of 308 knees included in the final analyses. The final knee sample included 8 participants that had undergone unilateral hip replacement for OA and one subject who had unilateral internal hip fixation secondary to a traumatic fracture. Knee symptoms were ascertained by the NHANES I criterion [14] of pain, aching or stiffness on most days of any one month in the last year; for subjects answering yes, symptoms were quantified as mild, moderate, or severe yielding a total score of 0–4 for each knee. Current analgesic medication use was recorded (numbers of participants using): acetaminophen (32), narcotics (9), tramadol (2), non-selective non-steroidals (67), cyclooxygenase inhibitors (45), glucosamine and chondroitin sulfate (51), and any of these analgesics (118).

Radiographic Imaging

Posteroanterior fixed-flexion knee radiographs were obtained with the SynaFlexer™ lower limb positioning frame (Synarc, San Francisco) with a ten degree caudal x-ray beam angle [15]. X-rays were scored by 2 graders (VBK and GV), blinded to the clinical and scintigraphic data, for KL grade (0–4), and individual radiographic features of OA in the medial and lateral compartments of joint space narrowing (JSN) and osteophyte (OST) scored 0–3 using the OARSI standardized atlas [16]. This resulted in total JSN scores of 0–6 and OST scores of 0–12 as all four margins on the knee joint were scored for this feature. To evaluate the patellofemoral joint, sunrise views of the knee were obtained and scored for JSN (0–3) and OST (0–3) using the OARSI atlas [16].

Knee alignment was measured to within 0.5 degrees on a weight-bearing “long-limb” (pelvis to ankle) anteroposterior radiograph as previously reported [17] using the center at the base of the tibial spines as the vertex of the angle. Although the average frontal plane knee alignment of asymptomatic non-arthritic adults is close to neutral, i.e. 1° varus from 180° (summarized [18], the definition of varus and valgus alignment has not been standardized. Therefore, in agreement with previous studies (summarized in [19]), knee alignment of 180° from the full-limb radiograph was taken as the reference value for the purposes of these analyses. Angles <180° were labeled varus/bow-legged alignment, and angles >180° were labeled valgus/knock-kneed alignment. There was one unreadable long-limb radiograph so data for this variable were available on 307 knees.

Scintigraphic Imaging

Four bone scintigraphic views were obtained of each knee (anteroposterior, mediolateral, lateromedial, and posteroanterior), 2.5 hours after injection of ^{99m}Tc-MDP. All bone scan images were scored semi-quantitatively by a consensus of two readers, an experienced nuclear medicine physician (REC) and a nuclear medicine resident who were blinded to the clinical and radiographic data. All four views were consulted to optimize the accuracy of the semiquantitative scoring of the images for location (medial-M, lateral-L and/or patellofemoral-P) and intensity of bone scintigraphic radiolabel retention (0–3: 0=normal, 1=mild, 2=moderate, 3=intense) in the knee joint. Knees were categorized according to retention patterns into mutually exclusive groups (isolated medial-M; isolated lateral-L; isolated patellar-P; medial and lateral-ML; medial and patellar-MP; lateral and patellar-LP; or medial, lateral and patellar-MLP) based upon the location(s) of any (grade >0) bone scan abnormality. The knee scintigrams were also scored for the following four patterns as described by McCrae et al [20]: generalized (widespread retention around the joint), extended (retention extending into the subchondral bone), rim or tramline (retention in the joint line), and hot patella (retention in the patella). A total of 30 of the knee scintigrams (60 knees, 20% of the total) were scored one year later by one of the same readers (REC)

blinded to the original readings, and intra-class correlation coefficients (ICCs) were calculated for the scores for each compartment of the knee for late phase scans.

Statistical Analyses

Generalized linear models (Genmod procedure in SAS) and linear mixed models (Mixed procedure in SAS) were used to assess the within subject correlation between knees. P-values were estimated by a two-sided t-test and the significance level (type 1 error rate) was controlled at 5%. Bivariate analyses were conducted to evaluate the association of bone scintigraphy with radiographic OA (JSN, OST), knee alignment angle, and knee symptoms, in addition to age, body mass index (BMI) and gender. R^2 were generated from multivariable linear regression models to derive an approximate estimate of the proportion of variance in tibiofemoral bone scan retention predicted by the independent variables. The intraclass correlation coefficient was determined for repeat readings of the knee scintigrams.

RESULTS

A total of 308 knees of 159 participants were evaluated. The cohort consisted of 118 (74%) women, overall mean age 63 (12 SD) years, and mean body mass index 31 (3 SD) kg/m². The range of knee mechanical axes ranged from 161° to 197.5°. Overall 65% of knees were varus, 31% valgus, and 4% neutral (defined as 180° for purposes of these analyses). Increased bone scan retention was present in 91% of knees, consisting of increased retention in the tibiofemoral compartments of 72% of knees, and in the patellofemoral compartments of 62% of knees. Figure 1 demonstrates representative bone scan images of the various patterns of knee abnormality. Isolated P and MLP retention were the most common patterns of bone scan abnormalities (20% each), followed by MP (17%), isolated L (8.5%), and isolated M (7.2%) retention. A total of 20% of the knee bone scan images were reread, blinded to the original grading, and intraclass correlation coefficients (ICCs) were determined. Overall ICCs were highest for the medial compartment (0.887) followed by the lateral compartment (0.864). ICCs were lowest for the patellofemoral compartment (0.647). ICCs for the total knee (sum of tibiofemoral and patellofemoral scores) were high (0.822–0.863).

The direction of malalignment was reflected in the localization of the bone scan abnormality (Figure 2). Bone scan abnormalities of the medial compartment (M, MP) were associated with varus malalignment (mean 176.46°, SD 4.46; n=78, 25%), while bone scan abnormalities of the lateral compartment (L and LP) were associated with valgus malalignment (mean 181.08°, SD 3.98; n=42, 14%). Simultaneous abnormalities of both compartments (ML, MLP) were associated with a wide range of alignment angles (mean 178.30°, SD 5.49, n=96, 31%). Knees with isolated P retention and normal bone scans had mean knee alignments near neutral [18, 21], of 179.15°, SD 3.30 (n=62, 20%), and 178.88° (SD 3.36) (n=29, 9%) respectively. The mean knee alignment angle associated with L and LP patterns was significantly different ($p<0.001$) from that associated with M, MP, and MLP patterns of retention. The intensity of tibiofemoral bone scan retention (M or L) was associated positively with severity of malalignment ($p=0.0002$) in the varus and valgus directions respectively (Figure 3A bottom).

The intensity and localization of bone scan retention was also associated with severity and localization of radiographic features of OA (JSN and OST) (Figure 3A top). There was a significant positive association between intensity of medial compartment bone scan retention and medial JSN, and medial OST (Figure 3A top left, $p<0.0001$). There was also a significant positive association between intensity of lateral compartment bone scan retention, lateral JSN, and lateral OST (Figure 3A top right, $p<0.0001$). In bivariate analyses, the intensity of medial compartment bone scan retention was associated with BMI

but not age or gender (Table 1). The intensity of lateral compartment bone scan retention was associated with age, but not BMI or gender (Table 1).

Knee alignment was also separated into quartiles from the most varus (Q1) to the most valgus (Q4) yielding the following ranges of knee alignment angles for each quartile: Q1 161.0°–175.5°; Q2 175.5°–178.5°; Q3 178.5°–181.5°; and Q4 181.5°–197.5°. The more varus the knee, the greater the severity of knee OA radiographic features (JSN and OST) in the medial compartment (Figure 3B top left); the more valgus the knee, the greater the severity of knee OA radiographic features in the lateral compartment (Figure 3B top right). Moreover, the more varus the knee the greater the bone scan retention in the medial compartment (Figure 3B bottom left); the more valgus the knee, the greater the bone scan retention in the lateral compartment (Figure 3B bottom right). Multivariable generalized linear modeling of tibiofemoral bone scan retention revealed significant and independent compartmental specific associations with both JSN and OST scores for the medial and lateral compartments (Table 1). Bone scan retention scores in the lateral compartment were also independently associated with age. The associations of knee alignment and BMI with bone scan retention were not independent of knee radiographic features.

Participants were required to have at least one symptomatic knee for entry into the study. The median total bone scan retention score for asymptomatic knees (n=18) was 1 (interquartile range 1–2), and for symptomatic knees was 3 (interquartile range 2–4). Knee symptoms were associated with bone scan retention in the tibiofemoral compartment ($p=0.0009$) but not the patellofemoral compartment ($p=0.25$) (Table 2). Knee symptoms were not associated with analgesic use, and the association of bone scan retention and pain was unchanged after adjustment for analgesic use.

The relationship between knee symptoms and tibiofemoral bone scan retention was remarkably linear (Figure 4). Knee symptoms were also associated with radiographic features of OA, including JSN ($p<0.0001$), OST ($p<0.0001$) or the sum of tibiofemoral JSN and OST scores ($p<0.0001$). Although severity of knee symptoms was associated with patellofemoral OST scores ($P<0.0001$), only tibiofemoral JSN ($p=0.04$) and tibiofemoral OST ($p=0.004$) were independently associated with knee pain severity in multivariable models (no change upon adjustment for analgesic use). In multivariable generalized linear models, controlling for within subject correlation of knee data, tibiofemoral bone scan retention was independently associated with both knee symptoms and radiographic severity of OA as well as gender (Table 2).

Four different patterns of localized radionuclide retention were recognized: generalized pattern (19%), extended pattern (35%), rim / tramline pattern (22%), and hot patella pattern (23%). The correlation of scan pattern and pain revealed an association of the extended pattern ($p=0.002$) with knee symptom severity but no association was found with the rim / tramline pattern (0.70) or hot patella pattern ($p=0.16$). The generalized pattern was also associated with knee pain ($p=0.02$) but not after controlling for the extended pattern of retention. In multivariable models, severity of pain was independently associated with the extended pattern (<0.0001), controlling for age and BMI.

DISCUSSION

The relative importance and chronology of factors which contribute to the development of knee OA remain to be fully defined; however, it is known that certain characteristics of the knee make it particularly vulnerable to OA. The inherent biomechanical properties of the knee place the majority of weight bearing force across the medial compartment. The effect of the unequal distribution of weight bearing forces in the knee is accentuated by

malalignment, a known potent risk factor for OA progression. Malalignment is also known to be associated with MRI-assessed disease features in a compartment specific manner, specifically, cartilage morphology, and subarticular bone edema and bone attrition [22]. To our knowledge, this is the first study describing a relationship between knee malalignment and knee compartment specific abnormalities by bone scintigraphy. The localization and intensity of scintigraphic abnormalities of the knee were also associated with the localization and severity of knee radiographic features of OA (JSN and OST) and knee symptoms. Unlike KL scores, which are hierarchical and depend on the presence of an osteophyte for entry, the evaluation of radiographic features provided a non-hierarchical approach to evaluate disease severity. The continuum of disease represented by sum of the radiographic features, JSN and OST, functioned as a quantitative trait with respect to variation in scintigraphic retention and pain. For each one point difference in bone scan retention, the mean radiographic score increased by 1.5 units and the pain symptom severity by 0.2 units.

It was particularly striking that tibiofemoral bone scan retention was independently associated with a bone related feature, OST, as well as a cartilage related feature, JSN. The animal OA literature provided some insight into the interpretation of these results. A two year longitudinal study of OA in rabbits identified sites of joint retention of ^{99m}Tc -MDP by autoradiogram [11]. In the rabbit, retention of ^{99m}Tc -MDP was observed in growing osteophytes early in the disease process, and in subchondral bone late in the disease process. Osteophytes were detected by bone scan prior to their detection by radiograph; osteophyte ^{99m}Tc -MDP retention was localized to sites of provisional calcification manifested during the process of endochondral ossification within the osteophyte. Retention in subchondral bone occurred in association with sites of denuded or eburnated articular surfaces. The human clinical results are remarkable for their congruence with the animal *in vivo* mechanistic data. Moreover, the mechanistic observations in the rabbit model explain how it is possible and biologically plausible for tibiofemoral bone scan retention in humans to be independently related to both osteophytes, and joint space narrowing (a proxy for cartilage loss associated with increased subchondral bone turnover). These results underscore the importance of bone in the pathogenesis of OA.

We found that tibiofemoral bone scintigraphy retention not only correlated remarkably with radiographic features of OA in the tibiofemoral joint, but there was also a striking association of tibiofemoral retention with severity of knee symptoms. Two previous studies have reported an association of knee pain and late phase knee bone scan retention [20, 23] and one with early phase knee bone scan retention [24]. Our study extends these findings, demonstrating a dose response of knee symptoms and intensity of late phase tibiofemoral bone scan agent retention. Moreover, the study by McCrae [20] demonstrated an association of knee pain and the presence of generalized knee retention on bone scan. Although we also found an association of the generalized pattern with knee pain severity, we found a much stronger association of knee pain with the extended pattern and only the extended pattern was independently associated with pain.

Although the frequency of knees with isolated patellofemoral retention was reasonably high (20% of cohort), and nearly all individuals with some patellofemoral knee bone scan retention had some degree of knee symptoms, intensity of retention in the patellofemoral compartment was not significantly associated with severity of knee symptoms. Moreover, the combination of tibiofemoral and patellofemoral retention was not more strongly associated with knee symptom severity than tibiofemoral retention alone. We noted that tibiofemoral retention was associated with knee malalignment while isolated patellofemoral retention was not. These findings suggest that bone remodeling related to altered mechanical loading in the tibiofemoral joint is a major contributor to the severity of knee symptoms of OA.

In summary, both lower extremity malalignment and bone scan abnormality of the knee are known potent predictors of risk for knee OA progression. Although the predictive utility of bone scan is accepted [4, 5], and a baseline positive knee bone scan has been incorporated into a recent disease modifying trial as an inclusion criterion [25], there is still disagreement as to whether there is a substantive advantage offered by scintigraphy as a prognostic tool compared to radiography, that would make it a practical alternative to radiography for clinical monitoring and prognostication. These results demonstrate that tibiofemoral bone scan reflects both radiographic features of OA and severity of knee symptoms. Bone scintigraphy is widely available and technical costs are approximately half to one-third those of knee magnetic resonance imaging (\$1,000 versus \$2,000–\$3,000). However, given that the major limitation of bone scintigraphy is radiation exposure, the judicious but selective use of this modality at the start and end of OA clinical trials may provide a useful screening tool and outcome measure. For purposes of comparison, the amount of radiation exposure imparted by a bone scan is 440 millirems, compared with 780 millirems for an abdominal computed tomogram, 82 millirems for a hip x-ray, 20 millirems for a chest x-ray, and 3 millirems for a knee x-ray (data from the Duke Radiation Safety Committee at www.safety.duke.edu/RadSafety/consents/default.asp). Bone scintigraphy is also a dynamic imaging modality that has the potential for change and so for this reason, may complement the current accepted static imaging method of radiography in therapeutic trials. In summary, this work validates bone scintigraphy as a sensitive and quantitative indicator of radiographic and symptomatic knee OA.

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Figure 1. Representative examples of late phase technetium-99m-disphosphonate bone scintigraphy images of the knee

Bone scintigrams of the knees were categorized according to the patterns of retention. This determination was made on the basis of four views of the knee (anteroposterior, mediolateral, lateromedial, and posteroanterior). Shown here are representative images of right knees to demonstrate the various and distinct patterns of retention (top anteroposterior views, bottom lateromedial views): (a) normal, (b) isolated medial compartment retention, (c) isolated lateral compartment retention, (d) isolated patellar retention, and (e) generalized medial, lateral and patellofemoral compartment retention.

Figure 2. Pattern of ^{99m}Tc -MDP retention by knee bone scintigraphy according to type of knee malalignment

Knees were categorized according to patterns of retention on bone scintigraphy (as described in Figure 1). The box plots depict the mean, 25th–75th percentiles, minimum and maximum values of knee alignment angle for each pattern of scintigraphic retention in the knee: M-medial, L-lateral, P-patellar, or any combination thereof. The range of normal or neutral alignment values (180° – 2°) is denoted by the horizontal gray bar in the middle of the figure.

Figure 3. The localization and intensity of retention by knee bone scintigraphy is associated with the localization and severity of specific radiographic features of osteoarthritis and severity of malalignment

The knee scintigram was graded for intensity of retention (0–3) in the medial and lateral compartments. Radiographic joint space narrowing (JSN) and osteophytes (OST) were graded (0–3) by knee compartment. **A-top:** mean severity of radiographic features of osteoarthritis (JSN, OST, and sum of JSN+OST) associated with the intensity of bone scan retention in the medial (top left, $p<0.0001$) and lateral (top right, $p<0.0001$) compartments of the knee. **A-bottom:** mean severity of lower limb malalignment in the varus and valgus directions associated with the intensity of bone scan retention in the medial (bottom left, $p<0.0001$) and lateral (bottom right, $p=0.0008$) compartments of the knee respectively. Knee malalignment was separated by quartiles from the most varus (Q1) to the most valgus (Q4). **B-top:** greater mean severity of radiographic features of osteoarthritis (JSN, OST, and sum of JSN+OST) in the medial (top left) and lateral (top right) knee compartments associated with varus and valgus quartiles of malalignment respectively. **B-bottom:** greater mean severity of bone scan retention in the medial (bottom left) and lateral (bottom right) knee compartments associated with the varus and valgus quartiles of malalignment respectively. The error bars represent standard errors.

Figure 4. Association of tibiofemoral bone scan retention and knee symptoms

The mean severity of knee symptoms are shown for each level of intensity of bone scan retention in the tibiofemoral compartment revealing a dose response relationship ($p=0.0009$). The maximum tibiofemoral bone scan retention score for any non-replaced knee was 5 although the possible range of scores was 0–6.

Table 1

Relationships of bone scan retention scores with radiographic features of OA.

Medial Bone Scan Retention				Lateral Bone Scan Retention			
	R ²	β estimate	P (with GLM)		R ²	β estimate	P (with GLM)
<u>Bivariate Analyses</u>							
<i>m-JSN</i>	0.264	0.484	<0.0001	<i>I-JSN</i>	0.237	0.471	<0.0001
<i>m-OST</i>	0.286	0.312	<0.0001	<i>I-OST</i>	0.198	0.270	<0.0001
<i>KneeAA</i>	0.096	-0.061	<0.0001	<i>KneeAA</i>	0.078	0.052	0.0008
<i>Age</i>	0.006	-0.006	0.300	<i>Age</i>	0.026	0.011	0.050
<i>Gender</i>	0.010		0.110	<i>Gender</i>	0.004		0.398
<i>BMI</i>	0.051	0.032	0.026	<i>BMI</i>	0.0001	0.001	0.638
<u>Multivariable Analyses</u>							
<i>m-JSN</i>		0.264	0.0005	<i>I-JSN</i>		0.294	0.001
<i>m-OST</i>		0.205	0.0002	<i>I-OST</i>		0.194	0.0002
<i>KneeAA</i>	0.371 (whole model) *		0.945	<i>KneeAA</i>	0.346 (whole model) *		0.279
<i>Age</i>			0.285	<i>Age</i>		0.005	0.035
<i>Gender</i>			0.305	<i>Gender</i>			0.200
<i>BMI</i>			0.712	<i>BMI</i>			0.951

BMI=body mass index; KneeAA=knee alignment angle

m-JSN=medial joint space narrowing; I-JSN=lateral joint space narrowing

m-OST=medial osteophyte; I-OST=lateral osteophyte

GLM=generalized linear modelling to control for within subject correlation of knee data

* R² values are not possible in GLM because of the nonlinear transformations necessary to perform the analysis. Therefore these R² values are from a multivariable model without GLM to provide an approximate measure of how much variation the model explains.

Table 2

Total tibiofemoral knee bone scan retention is associated with knee pain severity.

Intensity of Tibiofemoral Bone Scan Retention			
	R ²	β parameter estimate	P value (with GLM)
<u>Bivariate Analyses</u>			
<i>Severity of Knee Symptoms</i>	0.126	0.663	0.0009
<i>Total JSN</i>	0.201	0.481	<0.0001
<i>Total OST</i>	0.295	0.274	<0.0001
<i>Gender</i> [^]	0.013		0.077
<u>Multivariable Analyses</u>			
<i>Severity of Knee Symptoms</i>	0.375 (whole model) [*]	0.332	0.0012
<i>Total JSN</i>		0.214	0.0002
<i>Total OST</i>		0.191	<0.0001
<i>Gender</i> [*]		0.205	0.006

GLM=generalized linear modelling to control for within subject correlation of knee data

[^] Bone scan retention higher in women than men

^{*} see Table 1 for explanation