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Serum Urate Levels Predict Joint Space Narrowing in Non-gout Patients with Medial Knee Osteoarthritis

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Abstract

Objective—OA pathogenesis includes both mechanical and inflammatory features. Studies have implicated synovial fluid urate (UA) as a potential OA biomarker, possibly reflecting chondrocyte damage. Whether serum urate (sUA) levels reflect/contribute to OA is unknown. We investigated whether sUA predicts OA progression in a non-gout knee OA population.

Methods—Eighty-eight subjects with medial knee OA (BMI <33) but without gout were included. Baseline sUA was measured in previously banked serum. At 0 and 24 months, subjects underwent standardized weight-bearing fixed-flexion posteroanterior knee radiographs to determine joint space width (JSW) and Kellgren-Lawrence (KL) grades. Joint space narrowing (JSN) was determined as JSW change from 0 to 24 months. Twenty-seven subjects underwent baseline contrast-enhanced 3T knee MRI for synovial volume (SV) assessment.

Results—sUA correlated with JSN in both univariate ($r=0.40$, $p=0.01$) and multivariate analyses ($r=0.28$, $p=0.01$). There was a significant difference in mean JSN after dichotomizing at sUA of 6.8 mg/dL, the solubility point for serum urate, even after adjustment (JSN of 0.90 mm for sUA ≥ 6.8 ; JSN of 0.31 mm for sUA <6.8, $p<0.01$). Baseline sUA distinguished progressors (JSN >0.2mm) and fast progressors (JSN >0.5mm) from nonprogressors (JSN ≤ 0.0 mm) in multivariate analyses (area under the receiver operating characteristic curve 0.63, $p=0.03$; AUC 0.62, $p=0.05$, respectively). sUA correlated with SV ($r=0.44$, $p<0.01$), a possible marker of JSN, though this correlation did not persist after controlling for age, gender and BMI ($r=0.13$, $p=0.56$).

Conclusions—In non-gout patients with knee OA, sUA predicted future JSN and may serve as a biomarker for OA progression.

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Osteoarthritis (OA), the most prevalent form of arthritis, remains poorly understood. Though historically regarded as a disease of mechanical degeneration, it is now appreciated that inflammation, on both the tissue and biochemical levels, plays an important role in OA disease pathogenesis (1–4). Various inflammatory molecules have been studied for their ability to reflect OA presence or predict OA progression. For example, 15-HETE and PGE₂ are elevated in patients with symptomatic knee OA, and IL-1 β and IL-1Ra have been reported to associate with joint space narrowing (JSN) (5–7). The potential for these molecules to serve as OA biomarkers is a matter of ongoing investigation. In addition to prognostic utility, biomarkers that predict JSN would be of considerable value when defining enrollment criteria for prospective OA clinical trials, in which limiting heterogeneity and enriching for more rapid disease progression would have significant practical benefit (8).

Uric acid (UA) is the end product of human purine catabolism, and in the form of soluble serum urate (sUA) has been recognized as a biomarker in diseases such as heart failure, hypertension and renal disease (9, 10). UA is metabolically active, and has been reported to act both intra- and extracellularly, and to denote and/or promote inflammatory states (11). In addition, UA precipitates, in the form of macro- or microscopic monosodium urate (MSU) crystals, drive inflammation by engaging and activating leukocytes and other cells (12). In its most extreme example MSU crystals are responsible for the acute, painful attacks of gout, but lower-level, chronic inflammatory states are also observed (13).

A small but accumulating body of evidence suggests that UA may participate in OA pathogenesis (14). Prior reports note an association between UA and OA (15). Gout and OA often co-localize within the same joint (16), and studies have reported that, even in the absence of gout, synovial fluid UA correlates with OA severity (17, 18). We have reported that gout patients are more likely to have OA than control subjects, with hyperuricemic non-gout patients having an intermediate level of knee OA prevalence and severity. When present, OA is also likely to be more severe in patients with compared to those without gout (19).

Whether sUA may serve as a biomarker to convey or predict OA risk is not known. To assess this possibility, we investigated whether sUA levels associate with knee OA radiographic severity and contrast MRI-measured synovial volume (SV), and whether sUA levels predict OA JSN, in a non-gout population with knee OA.

PATIENTS AND METHODS

Patient population

We assessed a subset of subjects enrolled in a previously reported, 24 month, prospective, natural history knee OA study with a focus on inflammatory biomarker discovery. At initial enrollment, subjects met clinical ACR criteria for knee OA and had symptomatic OA of at least one knee (index knee), with Kellgren-Lawrence (KL) score 1 in that knee. Exclusion criteria included any other form of arthritis (e.g., rheumatoid arthritis, spondyloarthritis, gout, pyrophosphate disease or other crystal arthropathy), BMI $\geq 33\text{kg/m}^2$ (chosen to minimize the impact of obesity on OA/inflammatory biomarkers, without adversely impairing recruitment potential) and other characteristics as previously described (7). For the

current study, we included only subjects whose baseline knee OA was predominantly medial (i.e., medial joint space width (JSW) < lateral JSW on radiographic assessment), consistent with Osteoarthritis Research Society International recommendations (20). Included subjects additionally had both baseline and 24-month radiographic measurements, as well as stored serum available for baseline sUA measurement. The study was approved by the Institutional review Board of New York University Medical Center, and informed consent had previously been obtained from all subjects.

Clinical and Laboratory Assessments

All subjects had completed Visual Analog Scale (VAS) and WOMAC pain assessments at baseline and every 6 months for the duration of the study. Pain questions were specific to the more painful knee (index knee). Blood samples from subjects had been collected in serum collection tubes and serum had been isolated within 60 minutes of collection. Serum samples were placed in aliquots and stored at -70°C until thawing for assessment of sUA levels. sUA measurements were performed by the NYU Hospitals Clinical Laboratory, determined by automated colorimetric assay using a VITROS analyzer (Ortho Clinical Diagnostics, Rochester, N.Y.).

Imaging – X-ray and MRI measurements

All subjects underwent weight-bearing, fixed-flexion posteroanterior knee radiography, performed in a standardized manner using a Synflexer™ X-ray positioning frame (Synarc), at baseline and a 24 months, as previously described (21). Beam position was optimized for the medial joint space compartment. The patient's index knee was evaluated radiographically with respect to both KL grade and medial JSW, the latter measured at the mid-portion of the joint space using electronic calipers. Lateral joint space width was also assessed. JSN was calculated as the change in JSW, in millimeters, from baseline to 24-month follow up. All baseline radiographs were read and measured by two experienced musculoskeletal radiologists (LR, JB) blinded to patient identification and clinical information; a high correlation was confirmed between the readers (Kappas for inter-rater agreement were 0.85 and 0.77 for KL scores of the right and left knees, respectively, and Kappas for JSW were 0.93 for medial compartments of both the right and left knees). Based on the high inter-reader correlations, a single reader (LR) was employed for the 24-month follow up results.

A subset of the subjects enrolled in the parent study (n=58) had undergone a dynamic gadolinium-enhanced 3.0 Tesla MRI of the index knee at baseline that was read for quantitative synovial volume (SV). Of these, 27 met our additional requirements for the current study and were analyzed here. The complete technical details of MRI evaluation, and the criteria for initial inclusion into MRI assessment, have been previously described (21). Briefly, the pre-contrast portion of the imaging protocol included a sagittal 3-D high-resolution T1-weighted fast low-angle shoot (FLASH) sequence with selective water excitation, as well as a sagittal T2-weighted fat-saturated spin-echo sequence. The post-contrast portion of the examination consisted of a dynamic gadolinium-enhanced 3-D T1-weighted FLASH sequence obtained in the sagittal plane. Assessment of the SV was performed using MatLab custom tools for manual segmentation of the entire knee joint,

using contrast-enhanced dynamic images of the knees in relation to the pre-contrast images obtained at baseline. Patterns of signal enhancement were evaluated in the infrapatellar and suprapatellar fat pads, in the intercondylar notch, and along the periphery of joint effusion. All MRIs were evaluated blindly by a single expert reader (RR).

Outcomes and analysis

Our primary objective was to examine whether baseline sUA associates with medial joint space narrowing (JSN) over 2 years. Secondary outcomes included the association of baseline sUA with baseline KL grade, JSW, SV on dynamic enhanced contrast MRI and VAS and WOMAC pain scores.

Statistical Methods

The relationships between baseline sUA and clinical and demographic variables including WOMAC pain, VAS pain, JSW, MRI-determined baseline SV, age and BMI were determined by Pearson's correlation. Associations between sUA and MRI-determined SV were assessed by partial correlations controlling for age, gender and BMI. Given the limited number of subjects in our analyses of MRI-determined SV, this subject sample was assessed for normality in multiple ways. We confirmed a normal distribution on quantile-quantile plot, Lillefor's test ($p=0.14$), and on square root transforms of the data applying Lillefor's ($p=0.50$) and Shapiro-Wilk's tests ($p=0.29$). However, a Shapiro-Wilk's test on untransformed data did not support normality ($p=0.01$). Given that most but not all tests supported normality, MRI-determined SV was interpreted as generally but not strongly normal in distribution.

The relationship between sUA and binary baseline clinical and demographic variables including diuretic intake and gender were determined by Student's t-tests. To analyze the relationship between sUA and JSN, correlation was computed with and without controlling for age, gender and BMI. Additionally, thresholds were chosen to examine the potential difference in JSN at different sUA cutpoints (sUA population median for the sample (5.85 mg/dl); American College of Rheumatology (ACR) treatment target (6.0 mg/dL); and the solubility threshold for urate (6.8 mg/dL)), assessed by Student's t-tests. One-way ANOVA were used to examine the potential differences in sUA levels among patients defined as having non-(JSN 0), slow ($0 < \text{JSN} < 0.5$) and fast ($\text{JSN} \geq 0.5$) progression of JSN. Post-hoc Tukey-Kramer tests were used to assess pairwise comparisons when the omnibus was significant. To determine the predictive value of sUA for progression, receiver operating characteristic (ROC) curves were constructed and area under the curve (AUC) computed (AUC ranges from 0 to 1, with 1 indicating perfect predictivity and 0.5 indicating random guess). For these analyses, we defined non-progression vs. progression in the following three different ways: (1) JSN 0 vs. JSN>0; (2) JSN 0 vs. JSN>0.2; (3) JSN 0 vs. JSN>0.5. AUC values were compared against random models for significance using Delong's test. In addition, the relationship between the change of WOMAC and VAS measured at 24 months were correlated with sUA to examine potential relationship between sUA and progression in pain.

RESULTS

Subject demographic characteristics

From among 146 completers of the original OA natural history study, 111 had medial disease at baseline. Of those, 88 had frozen serum sufficient to be enrolled in the current study. Demographics of the enrolled subjects are summarized (Table 1). Twenty-seven of the 88 subjects had additionally undergone baseline dynamic contrast-enhanced knee MRI, with synovial volume measurements available for analysis. Subjects who enrolled in the original OA natural history study, but who were lost to follow-up after baseline assessment, had demographics and baseline synovial volume measurements similar to those in our current study cohort (data not shown).

Relationship of sUA to baseline OA severity and other characteristics

In an initial cross-sectional analysis, sUA did not correlate with baseline WOMAC pain scores ($r=0.12$, $p=0.28$) or VAS pain ($r=0.08$, $p=0.48$). Consistent with a prior report (17), sUA also did not correlate with baseline OA severity, measured as JSW ($r=-0.15$, $p=0.15$) and KL grade ($F [3,84]=1.82$, $p=0.15$). Subject age, which ranged from 43 to 85, did not correlate with sUA ($r=0.14$, $p=0.19$) in our cohort, despite reported associations in the literature. Consistent with previously published studies, sUA significantly correlated with BMI at study entry ($r=0.23$, $p=0.03$) and mean sUA for male patients was significantly higher than for female patients (7.56 vs. 5.67 mg/dL, $p<0.01$). There was no significant difference between baseline sUA of the eight subjects taking a diuretic (all hydrochlorothiazide) and the subjects not taking diuretics (6.10 vs 6.32 mg/dL, $p=0.63$). Finally, sUA correlated significantly ($r=0.44$, $p<0.01$) with MRI-determined baseline SV in univariate analysis (Figure 1). However, SV did not correlate with sUA after multivariate adjustment for age, gender and BMI, with loss of association driven by gender ($r=0.13$, $p=0.56$). Because SV has been suggested as a potential marker of OA progression (22), we next examined the relationship between sUA and medial JSN.

sUA and 24 Month Radiographic Disease Progression

sUA significantly correlated with the progression of OA measured as 24 month medial JSN ($r=0.40$, $p<0.01$, Figure 2A). This correlation was retained ($r=0.28$, $p=0.01$) after controlling for BMI, gender and age. Analysis of the data according to quartiles revealed an apparent step-off in 24-month JSN between second and third quartiles (Figure 2B). One-way ANOVA revealed an overall difference in mean JSN between the four quartiles ($F [3,84]=3.54$, $p=0.02$), with significant differences in mean JSN between quartiles 1 and 4 (0.24 vs. 0.94 mm, $p=0.04$), and 2 and 4 (0.23 vs 0.94 mm, $p=0.04$). We therefore assessed the difference in JSN by dichotomizing the data across three possibly relevant cut points: the median sUA for the study population (5.85 mg/dL), the American College of Rheumatology sUA treatment target for urate-lowering therapy among gout patients (6.0 mg/dL), and the solubility threshold for urate (6.8 mg/dL). We observed significant differences in mean JSN across all three cut points. After adjustment for BMI, gender and age, significance was retained only around the cut point of 6.8 mg/dL (Table 2).

We next stratified subjects by radiographic progression and analyzed for sUA differences between groups. We defined “non-progressors” as individuals who had JSN 0mm over 24 months, “slow progressors” as $0 < \text{JSN} < 0.5\text{mm}$ over 24 months, and “fast progressors” as JSN $\geq 0.5\text{mm}$ over 24 months. We observed a significant difference in sUA among the three progression groups ($F [2,87]=5.51$, $p<0.01$). Post-hoc testing confirmed a significant difference between the mean sUA of non-progressors vs. fast progressors (5.8 vs. 7.1 mg/dL, $p=0.02$) and slow vs. fast progressors (5.6 vs. 7.1 mg/dL, $p<0.01$). In contrast, the difference between mean sUA of non-progressors vs. slow progressors was not significant ($p=0.69$). After controlling for BMI, gender and age, one-way ANOVA continued to confirm an overall significant difference in sUA among the three progression groups ($F [2, 87]=3.64$, $p<0.05$), with borderline significance for the difference between mean sUA of non-progressors vs. fast progressors and slow vs. fast progressors ($p=0.07$ and $p=0.07$, respectively). The discrepancy between the omnibus and post-hoc test results was likely due to the greater statistical power of the omnibus test. As was the case for pain at baseline, sUA did not correlate with change in WOMAC pain ($r=0.05$; $p=0.68$) or VAS pain ($r= -0.04$, $p=0.72$) over 24 months.

Additionally, we defined a range of JSN thresholds (according to the degree of 24-month JSN) as outcomes, and used these to generate area under the receiver-operating characteristic (ROC-AUC) curves, and to determine the capacity of sUA to predict 24-month radiographic knee OA progression. For this analysis, non-progressors were defined as JSN 0.0mm; progressor thresholds were JSN of $>0.0\text{mm}$, $>0.2\text{mm}$ and $>0.5\text{mm}$ after 24 months. Baseline sUA distinguished non-progressors in all 3 categories of progression (AUC 0.62, $p=0.03$; AUC 0.64, $p=0.01$; AUC 0.68, $p<0.01$ for JSN $>0.0\text{mm}$, $>0.2\text{mm}$ and $>0.5\text{mm}$, respectively). After inclusion of age, gender and BMI into the model, sUA continued to significantly distinguish non-progressors from progressors with JSN $>0.2\text{mm}$ (AUC 0.63, $p=0.03$) and $>0.5\text{mm}$ (AUC 0.62, $p=0.05$) over 24 months (Table 3).

Exclusion of joint-widening artifacts

A minority of our patients experienced apparent widening of the medial compartment during the two-year observation period. Although many investigators have ascribed such phenomena to a normal distribution within the measuring process (23, 24), there are several reasons such widening might occur. Positioning errors or changes in weight bearing during imaging could hinder accurate joint space measurement. In our study, these sources of errors were mitigated through use of standardized, fixed-flexion, weight bearing imaging using a Synflexer device, used in numerous other studies including those of the Osteoarthritis Initiative (5, 7, 21, 25). Additionally, in some cases, medial compartment widening can reflect mechanical shifts resulting from lateral compartment narrowing. This phenomenon, referred to as pseudo-widening, could therefore reflect OA progression in the lateral compartment (26, 27) rather than any actual medial change. To assess for possible pseudo-widening, we first determined the degree of lateral compartment change in patients who experienced medial compartment widening vs medial compartment narrowing. We observed no significant difference in the lateral compartment change between these two groups (lateral joint space narrowing for medial compartment narrowing vs medial compartment widening subjects, 0.16 vs 0.16 mm, $p=1.00$). To further examine the possibility that lateral

compartment narrowing could have affected our medial compartment observations, we reanalyzed our data after first excluding all patients with both medial joint space widening (any degree) and substantial lateral compartment narrowing (> 0.5 mm over two years). In this analysis, 9 subjects were excluded, leaving 79 subjects for medial compartment assessment (Supplemental Table 1). We continued to observe a direct correlation between serum urate and medial JSN ($r=0.43$; $p=0.01$), and an apparent sUA step-off for medial JSN progression in the range of 6.0–6.8 mg/dL (Supplemental Figure 1A,B). Specified sUA cut points (Supplemental Table 2) and AUC analyses also remained significant (Supplemental Table 3), even after adjustment for other potential confounders. Moreover, exclusion of the above-specified subjects from the MRI synovial volume assessments resulted in improved correlation of sUA with synovial volume (Supplemental Figure 2) ($r=0.54$, $p<0.01$).

DISCUSSION

To our knowledge, these results are the first to suggest that current baseline sUA predicts future progression of knee OA. Increased sUA was associated with increased JSN, a widely-used, FDA-endorsed marker of OA progression (28, 29), in both univariate and multivariate analyses. Subjects with sUA ≥ 6.8 mg/dL had significantly higher 24 month JSN than subjects with sUA < 6.8 mg/dL (30). Synovial tissue proliferation, measured using gadolinium-enhanced MRI, also correlated with sUA, though this correlation did not persist after multivariate analysis. This latter observation is consistent with reports that SV correlates with radiographic OA (21), and that MRI-detected synovitis may be a risk factor for OA incidence and progression (31–33). In contrast to several prior studies (34, 35), in our study SV did not correlate with OA pain (not shown), possibly because our MR protocol involved global synovial examination, whereas pain has been most closely correlated with peripatellar synovitis (36, 37). Finally, baseline sUA distinguished both mild progressors with JSN > 0.2 mm, and fast progressors with JSN > 0.5 mm over 24 months, from non-progressors through AUC analyses.

The observed association between sUA and JSN could reflect a causal relationship, with secondarily-elevated synovial fluid urate levels promoting cartilage damage, as synovial fluid is largely an ultrafiltrate of serum (17). Chondrocytes express plasma membrane urate transporters, indicating they can take up soluble urate with a potential for an intracellular pro-oxidant effect (38). Alternatively, synovial fluid urate could act in its crystallized rather than soluble form. Indeed, our observation that increased risk for JSN was best dichotomized around a sUA of 6.8 mg/dL (the saturation point for urate crystallization) supports a model in which monosodium urate (MSU) crystals promote synovitis (19, 39, 40) and cartilage disruption. Consistent with this possibility, UA has been shown to deposit on cartilage in hyperuricemic patients without gout (41), and Martinon and others have demonstrated the ability of MSU crystals to activate the NLRP3 inflammasome and drive the generation of IL-1 β , a major candidate cytokine in OA progression (38, 42). Alternatively, OA progression could be accelerated intrinsically by chondrocyte death, in a forward-feedback, UA-dependent cycle (17, 43–45). As reported by Shi et al, dying cells locally generate UA that, at concentrations sufficient to permit MSU crystallization, act as a danger signal to activate neighbor cell inflammatory responses. Although it is unlikely that chondrocyte death locally in an OA joint could be sufficient to increase systemic sUA, it is

possible that elevated serum and resultant synovial fluid UA concentrations create an environment in which chondrocyte death raises pericellular local UA concentrations sufficient to support MSU precipitation.

Finally, it is possible that the relationship between sUA and OA progression is not causal, but instead due to a common predisposing factor(s). Given concerns for confounding, we controlled for age, gender and BMI, and the correlation between JSN and sUA persisted, revealing no significant effect of these factors. However, sUA levels could predict progression of OA in a non-causative manner reflecting processes that are not at present fully appreciated, and therefore were not adjusted for in our model. It is worth noting that while our AUC analyses support that sUA is associated with OA progression, and is therefore a candidate biomarker for progression, exploration of the efficacy of sUA as a biomarker in the clinical setting would additionally require evaluation of its sensitivity and specificity trade-off. Nevertheless, the AUC values we observed are in keeping with those of other recently reported serum biomarkers for knee OA progression (5)(46).

Strengths of our study include the use of a clinical laboratory to measure sUA in a standardized fashion; the standardized acquisition of radiographs using the SynaFlexer positioning frame; blinding of radiologists reading JSW and MRI-based synovial volume; and follow-up time of two years. Additionally, our cohort was mostly community-based, and likely representative of knee OA patients in the general population. Limitations of our study include that our population was limited to subjects with knee OA, BMI<33, and no gout, and may not be generalizable to patients with knee OA without these features. In contrast to JSN over 24 months, we observed no correlation between sUA and JSW at study entry; however, our study did not set strict entry criteria on the duration of disease prior to the study, and the limitations of our data do not permit us to extrapolate in order to ascertain rate of OA progression before study entry. We note, moreover, that analysis around the sUA cutpoint of 6.8 mg/dL did indicate that patients with supersaturated sUA levels may have had significantly reduced JSW at entry (Table 2). We did not measure all factors associated with OA progression, such as meniscal pathology or malalignment. We clinically determined the absence of gout and did not perform knee aspirations to confirm the absence of crystals. We included subjects with symptoms and baseline KL 1, instead of the more conventionally defined OA of KL 2, because KL=1 has been recently described as early OA(47). Finally, our study, especially the subset of subjects receiving MRI, would have benefitted from a larger sample size. Indeed, our data set for MRI analysis was normally distributed according to most, but not all of the tests we applied. Prospective studies, and greater sample sizes, will be needed to assess the possibility of causality.

In conclusion, this is the first longitudinal study to report that sUA levels may serve as a biomarker for OA progression. As sUA measurements are inexpensive and readily obtainable, such results have the potential to impact the study of OA treatment by permitting the identification of patients more likely to progress for inclusion in investigational studies. Measurement of sUA could also potentially provide a mechanism for determining risk of progression and facilitate monitoring the treatment of patients living with OA. Whether UA-lowering therapy could potentially help limit OA progression also deserves investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Baseline sUA correlates significantly with contrast MRI-determined quantitative synovial volume.

Figure 2. Baseline sUA associates with 24-month joint space narrowing (JSN). Data are shown as scatter plot (A) and quartile groups (B)

Table 1Subject baseline demographics and osteoarthritis features¹.

Age (years)	61.26±1.01
Gender (%)	
Male:	32.95
Female	67.05
BMI ² (kg/m ²)	26.86±0.38
sUA ³ (mg/dL)	6.30±0.22
Synovial volume (mm ³)	15.49±1.49
Joint space width (mm)	3.51±0.15
KL ⁴ grade (% affected)	
1	22.72
2	20.45
3	47.73
4	9.09

Data shown are the mean±SEM, total number or percent affected, as indicated.

¹N=88 for all parameters, except synovial volume for which N=27.²BMI=body mass index.³sUA=serum urate level.⁴KL=Kellgren-Lawrence grade.

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Table 2

Mean JSN¹ differences after dichotomizing the patient population around three different sUA² cut-points.

Cut-point (mg/dL)	Mean JSW ³ below cut-point (mm)	Mean JSW above cut-point (mm)	P	Mean JSN below cut-point (mm)	Mean JSN above cut-point (mm)	P	P, adjusted ⁴
5.85	3.67	3.41	0.39	0.24	0.79	<0.01	0.06
6.0	3.74	3.33	0.16	0.26	0.78	<0.01	0.09
6.8	3.74	3.15	0.04	0.31	0.90	<0.01	<0.01

¹ JSN=joint space narrowing over 24 months
² sUA=serum urate (mg/dL);
³ JSW=Joint space width at study entry;
⁴ Adjusted for age, gender and BMI

Table 3

Area under the receiver operating characteristic curves (ROC-AUC) to determine the capacity of sUA to predict 24-month radiographic knee OA progression: comparisons between JSN non-progressors and progressors by sUA $\pm$ age, gender and BMI¹.

Comparison group ²	Model	Number of progressors	AUC (CI)	P
Any progressor (JSN>0.0 mm)	sUA	56	0.62 (0.50–0.75)	0.03
	sUA+Age/Gender/BMI	56	0.56 (0.43–0.69)	0.17
Moderate-fast progressors (JSN>0.02 mm)	sUA	50	0.64 (0.52–0.77)	0.01
	sUA+Age/Gender/BMI	50	0.63 (0.50–0.75)	0.03
Fast progressors (JSN>0.5 mm)	sUA	33	0.68 (0.54–0.81)	0.01
	sUA+Age/Gender/BMI	33	0.62 (0.48–0.76)	0.04

¹JSN=joint space narrowing; sUA=serum urate; BMI=body mass index.

²All comparisons are versus non-progressors (JSN $\leq$ 0 mm).