Published in final edited form as:

Arthritis Rheum. 2013 July ; 65(7): 1812–1821. doi:10.1002/art.37970.

Subchondral Bone Trabecular Integrity Predicts and Changes Concurrently with Radiographic and MRI Determined Knee Osteoarthritis Progression

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Abstract

Objective—To evaluate subchondral bone trabecular integrity (BTI) from a radiograph as a predictor of knee osteoarthritis (OA) progression.

Methods—Longitudinal (baseline, 12- and 24-month) knee radiographs were available from 60 female subjects with knee OA. OA progression was defined by 12- and 24-month change in radiographic medial compartment minimal joint space width (JSW) and medial joint space area (JSA), and medial tibial and femoral cartilage volume from magnetic resonance imaging. Bone Trabecular Integrity (BTI) of the medial tibial plateau was analyzed by fractal signature analysis

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Conflicts of Interest: Marie-Pierre Hellio Le Graverand is an employee of Pfizer and owns stock in Pfizer; Alan Brett was an employee of Optasia Medical at the time of this research and owns stock options in Optasia Medical; Felix Eckstein is an employee of Chondrometrics, GmbH, owns stock in Chondrometrics, GmbH and consults for Sanofi, Abbott and Merck Serono. No other author has any conflicts related to commercial interests in terms of stock, ownership or honoraria.

with a commercially available software. Receiver Operating Characteristic curves of BTI were used to predict 5% change in OA progression parameters.

Results—Individual terms (linear and quadratic) of baseline BTI of vertical trabeculae predicted knee OA progression based on 12- and 24-month change in JSA ($p<0.01$ for 24 months), 24-month change in tibial ($p<0.05$) but not femoral cartilage volume, and 24-month change in JSW ($p=0.05$). ROC utilizing both terms of baseline BTI predicted 5% change in the OA progression parameters over 24 months with high accuracy as reflected by the area under the curve (AUC) measures: JSW 81%, JSA 85%, tibial 75% and femoral 85% cartilage volume. Change in BTI was also significantly associated ($p<0.05$) with concurrent change in JSA over 12 and 24 months and change in tibial cartilage volume over 24 months.

Conclusions—BTI predicts structural OA progression as determined by radiographic and MRI outcomes. BTI may therefore be worthy of study as an outcome measure for OA studies and clinical trials.

Introduction

The subchondral bone is thought to play a key role in the pathogenesis of osteoarthritis (OA) (1, 2). Subchondral bone changes in OA are potentially both a result and a cause of cartilage loss (3). The intimate relationship and conjoined disease pathways of both these pathological processes are demonstrated in several ways. First, recent data support the view that cartilage and bone can communicate over the calcified tissue barrier (4-6). Second, structural changes in subchondral trabecular bone are associated with cartilage loss in animal models of OA (7-9) and in human OA (3, 10, 11). Third, attenuating the expression of Dkk-1, a Wnt inhibitor that mediates remodeling of various tissue types, promotes chondrocyte survival and protects against both cartilage degradation and loss of subchondral bone mineral density (12).

Efforts to quantify trabecular bone structural changes in patients have included computed tomography (13, 14), magnetic resonance imaging (MRI) (3, 15, 16), and radiography (17-19). One approach for assessing trabecular integrity from radiographs uses fractal signature analysis that provides an indication of the number, spacing, and cross-connectivity of bone trabeculae (20). In a cohort with symptomatic knee OA, we recently showed that the baseline bone trabecular integrity (BTI) of the medial tibial plateau predicted medial knee joint space narrowing over the ensuing three years with 75% accuracy (based on ROC curve analysis) (19); whereas, in the same cohort, baseline joint space width was no more effective than random variables for predicting structural OA progression (19). With the exception of knee alignment, meniscal pathology, bone marrow lesions (21, 22), and frequent knee pain (23), to date there have been few other parameters with any significant ability to reliably predict knee OA progression in unselected OA populations, including traditional OA risk factors (age, sex and body mass index) (24, 25).

Clinical trials recruiting progressors on the basis of traditional OA risk factors have the disadvantage of including only a minority (~ 30%) of knee OA progressors (26). More robust means of identifying individuals at risk for OA progression over 1-3 years would be very valuable. Applied to a clinical trial testing the efficacy of a potential structure modifying

agent, such a method could enrich the trial with OA progressor subjects; this in turn could potentially lower trial costs due to the ability to maintain or boost study power with fewer subjects and/or the potential to shorten the trial duration.

The goal of this study was to validate, in a second independent cohort, the predictive capability of BTI (measured by fractal signature analysis) for radiographic OA progression. We also evaluated BTI as a predictor of OA progression based on quantitative measures of articular cartilage loss obtained from magnetic resonance (MR) imaging. Finally, we evaluated change in BTI with concurrent change in OA progression parameters based on radiographic and MR defined structural disease progression.

Methods

Patients

Included in these analyses were all subjects (n=60) with radiographic knee OA from 6 clinical study sites that participated in the Pfizer A9001140 observational study (27). Included subjects were aged ≥ 40 years, female, had knee radiographs for at least two of three timepoints (baseline, and 12 and/or 24 months), frequent symptoms in the signal knee, mild to moderate radiographic OA in the medial femoro-tibial compartment of the signal knee (Kellgren Lawrence grades 2 to 3) (28), a body mass index (BMI) ≥ 30 kg/m², and a medial tibiofemoral joint space width at baseline of ≤ 2 mm in a posteroanterior modified Lyon-Schuss view. For patients with bilateral qualifying knees, the more symptomatic knee was selected to be the signal knee. Participants were excluded on the basis of a history of intra-articular fracture, arthroplasty, meniscectomy, crystal-associated arthropathy, knee infection, or avascular necrosis. While anterior cruciate ligament (ACL) tears were not part of the exclusion criteria, a review of medical histories revealed no cases of ACL injury and/or reconstruction. Details regarding the medications permitted during the study were described previously (27). The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with the local Institutional Review Boards of the investigative sites, informed consent regulations, and International Conference on Harmonization of Good Clinical Practices Guidelines.

Radiographic Imaging

To evaluate radiographic OA progression it was important to rely on optimized knee radiographs to assure the validity of the joint space width (JSW) measurements. The Pfizer A9001140 study, utilized posteroanterior modified Lyon Schuss knee radiographs obtained with the SynaFlexer™ lower limb positioning frame (Synarc, San Francisco) (29) with a variable caudal X-ray beam angle chosen to minimize the tibial intermargin distance (the vertical distance between the anterior and posterior tibial margins at the center of the medial tibial plateau in the 2-D radiographic image) (30); this enabled extraction of reliable (accurate) quantitative JSW data for this study. Images were acquired digitally. The mean (SD) resolution was 138 (33) microns/pixel for radiographs from 6 of the clinical sites, but 300 (9) microns/pixel for one clinical site (only fluoroscopic images obtained, n=15 subjects). Because these latter images provided only half the data points from which to construct FSA curves they were excluded for the purposes of these analyses. When

necessary, more than one knee radiograph was performed for an individual, each with a different X-ray beam angle, to optimize (i.e. minimize) the intermargin distance. In these instances, the images with the smallest intermargin distances were chosen for BTI analysis. Overall, 176 images were available for analysis: 60 (baseline) + 58 (12 month) + 58 (24 month).

Image Analysis with the Optasia Knee Analyzer

All radiographs were analyzed using the KneeAnalyzer application developed by Optasia Medical (Manchester, UK). The KneeAnalyzer utilizes computer-aided detection based on statistical contour modeling to provide highly reproducible quantitative measurements of the medial compartment of the knee. Analysis of medial compartment BTI was performed as previously described (19). In addition, the software tool provided automated measurements of the medial minimum JSW in mm and the medial joint space area (JSA) in mm². Both of these radiographic indices of knee OA progression were evaluated in this study. Joint space area represents the joint space width integrated over the majority of the medial compartment. The inner and outer JSA boundaries for this automated measurement were defined by the position of the inner and outer margins of the tibial fossa, as determined by the model-fitting process. The two landmarks defining these margins were as follows: the inner margin of the tibial fossa was the point where the lower margin of the tibial fossa (bowl) converged with the projected edge of the tibial plateau, on the side nearest to the inner edge of the knee; the outer margin of the tibial fossa was the point where the lower margin of the tibial fossa converged with the projected edge of the tibial plateau, on the side nearest to the outer edge of the knee (Figure 1). The two points are anatomical landmarks which have been marked consistently in a training set of example images and are located by the model-based segmentation using an active shape modeling algorithm for finding the whole tibial plateau. The mean landmark positioning error for the modeling algorithm is 2.1% of the tibial width (unpublished observations). Although the KneeAnalyzer tool allows the user to edit the positions of the inner and outer joint space area boundaries, except in two instances, this was assiduously avoided to optimize reproducibility of the measure; in these two instances (one involving the medial boundary and one involving the lateral boundary), the boundary was manually repositioned immediately adjacent to the original boundary to ensure correct identification of minimal joint space location.

The interrater reliability for medial JSW measurements was assessed by intra-class correlation coefficient (ICC) testing for concordance of measurements by the KneeAnalyzer software tool with measurements made independently by a semi-automated method as reported previously (31). The ICC for JSW was 0.926; the ICC for JSA was 0.992 (based on analysis of 245 radiographs from the PfizerA9001140 study by 4 analysts). The interrater reliability of BTI is very high as previously reported (19).

Magnetic resonance imaging and extraction of medial compartment cartilage volume data

MR imaging was performed on 3.0T Trio (Siemens AG, Erlangen, Germany) and Signa Excite/Genesis Signa MRI scanners (GE Healthcare Technologies, Waukesha, WI) as previously described (27, 31, 32). Transmit Receive Birdcage CP coils (Clinical MR Solutions Brookfield, WI) with a 'split top' design were used at all clinical study sites.

Double oblique spoiled gradient recalled acquisitions (33) at steady state (SPGR) with selective water excitation were acquired at a spatial resolution of 1 mm (slice thickness) $\times$ 0.3125 mm $\times$ 0.3125 mm (in plane resolution), which were previously cross-calibrated (34). Other technical details for the acquisition were reported previously (27, 31). Overall, data from 161 images were available for analysis: 56 (baseline) + 54 (12 months) + 51 (24 months).

All MR data were sent to the Duke Image Analysis Laboratory for quality control and then shipped to the image analysis center (Chondrometrics GmbH, Aining, Germany) where images were processed using custom software (27, 31, 33). The image segmentation was performed by seven operators with formal training and >3 years experience in cartilage segmentation. The images were processed as pairs (baseline and follow-up), but with blinding to the order of acquisition; i.e. when the partner data set (baseline or follow up) was segmented, the previously segmented one was uploaded and displayed on the screen. Quality control of all segmentations was performed by an expert (F.E.), who reviewed all segmented slices of each data set (33). The segmentations were used to compute the articular cartilage volume (VC) of the medial tibia (VC_MT), and the medial femur (VC_MF); these measures have been shown previously to be able to be measured with high precision (33).

Definition of OA Progression

For each structural parameter (two radiographic and two MRI), OA progression was defined as the difference between baseline and follow-up (12 or 24 months) value as follows: 1) the change in radiographic medial minimum JSW (JSW) and medial JSA (JSA); and 2) the change in cartilage volume of the medial tibia (VC_MT) and the medial femoral condyle (VC_MF). The mean (SD) 24-month change scores and standardized response means (SRMs) were calculated for each outcome.

Statistical Analysis

The analyses performed are consistent with those previously described in our development study (19). Briefly, sets of trabecular texture measurements (fractal dimensions) at a range of scales in the vertical and horizontal directions were modeled with second order (quadratic) multiple regression models using a non-centered polynomial. Hence, the multi-dimensional correlations between fractal dimension measures at these different scales were summarized by 2 polynomial terms, which describe the functional “shape” of the way that trabecular texture signals depend on scale. It is these shape terms that constitute a bone trabecular integrity or BTI measurement. Clinical study site was included in the same statistical model with an analysis of co-variances (ANCOVA) framework and repeated measures. Age was not included because age, as shown previously (19), had no effect on BTI as a predictor of progression in the current analyses. Statistical models examined the association of baseline BTI and knee OA progression at 12 and 24 months. We also assessed for concurrent change over 24 months in vertical BTI and OA progression measures.

The SRMs for change over 24 months were calculated for the knee OA progression variables by dividing the mean change by the standard deviation of the change scores. Receiver Operating Characteristic (ROC) curves were used to quantify the accuracy of the

prediction of the change in the OA progression variables by baseline BTI. The continuous 24-month change scores were recoded as binary variables where 1 equaled 5% decrease from the baseline value versus 0 (not meeting this criterion). ROC curves were constructed to predict change in medial JSA, medial JSW, VC_MT and VC_MF using 5-fold cross-validation with 300 replications (35). The prediction used the linear and quadratic BTI terms of the vertical trabeculae.

Results

Patients

A total of 60 OA knees had available knee radiographs from at least two timepoints, baseline, and 12- and/or 24-month follow-up. Of these, 35% were KLG3 at baseline. The subjects had a mean (SD) age of 58 ± 8.5 years, and a mean (SD) BMI of 35.6 ± 5.5 kg/m².

Frequency of OA progression

The SRMs were modest (Table 1), ranging from to -0.15 to -0.45. JSW correlated with JSA ($R=0.62$, $p<0.0001$), VC_MT ($R=0.39$, $p=0.008$), and VC_MF ($R=0.29$, $p=0.049$). A 5% decline in these variables was chosen as a threshold of progression as it provided a reasonable number of progressor subjects for Receiver Operator Characteristic curve analysis (see Supplementary rationale for statistical analysis plan at end). A total of 28-38% of the cohort was defined as progressors based on achieving a 5% decline in the outcome variables over two years, yielding the following numbers of OA progressors for each outcome: 17 for JSA, 21 for JSW, 18 for VC_MT, and 23 for VC_MF.

Baseline bone trabecular integrity predicted OA progression based on radiographic and MRI measures

To evaluate BTI of the medial tibial subchondral bone as a predictor of medial compartment knee OA progression, both the linear and quadratic BTI terms for the vertical and horizontal directions (vertical and horizontal trabeculae) were assessed in separate models. The BTI terms of the vertical trabeculae provided the only significant results in this cohort (Table 2). Both individual terms of baseline vertical BTI were associated with knee OA progression defined by change in JSA over 12 and 24 months, and VC_MT over 24 months. The quadratic term of baseline vertical BTI was also associated with JSW over 24 months at the $p=0.05$ level of significance but not VC_MF. These results were unchanged when controlled for baseline OA severity of each measure (Supplementary Table at end). These findings confirm our prior results demonstrating that medial tibial BTI is a predictor of radiographic OA progression of the medial compartment of the OA knee. These results further expand our prior analysis, showing prediction of an MR based OA progression parameter by BTI. In contrast, baseline severity of OA did not predict progression as neither baseline JSW ($p=0.88$), nor baseline JSA ($p=0.43$), were associated with JSW over 24 months.

Receiver Operating Characteristic Curves (ROC) for predicting OA progression

To gain an appreciation of how BTI might benefit clinical trial design, we used ROC curves to evaluate the ability of baseline BTI to predict a 5% change over 24 months in the OA

progression measures. This analysis used both of the BTI terms (linear and quadratic) for the vertical trabeculae as these proved to be the most highly associated with OA progression. To gain a realistic non-inflated appreciation of the predictive capabilities of BTI in this relatively small sample set, ROC curves were generated by cross-validation; curves were based on leaving out 20% of the data and regenerating the curves 300 times, i.e. 4-fold predicting 1-fold of the data iteratively). The highest area under the curve (AUC) and 95% confidence intervals (95% CIs) (corresponding to one standard deviation) were achieved for BTI prediction of 5% change in JSA over 24 months (AUC 0.85, CIs 0.82-0.95) (Table 2). These results demonstrate that BTI is a significant and relatively strong predictor of OA progression. ROCs were also performed for BTI prediction of 5% change over 24 months in the other OA progression outcomes; this analysis yielded the following AUC results: 0.81 for JSW, 0.85 for VC_MF, and 0.75 for VC_MT (see Table 2 for 95% CIs). The ROC curves for each progression outcome (and curves corresponding to $\pm$ one standard deviations) are shown in Figures 2A-D.

Concurrent change in bone trabecular integrity and measures of OA progression

Change in BTI was also associated with concurrent change in both radiographic and MR determined knee OA progression (Table 3). Specifically, the change in BTI of the vertical trabeculae was associated with JSA over 12 and 24 months and with VC_MT over 24 months. Overall the strongest association was between BTI (linear term of the vertical trabeculae) and JSA (0.016). These results were unchanged when controlled for baseline OA severity of each measure (Supplementary Table at end).

Discussion

To our knowledge, this is the first study to demonstrate that baseline BTI predicts OA progression based both on radiographic and MRI outcome measures. Although this study is smaller (60 versus 138 OA subjects) and of shorter duration (2 instead of 3 years) than our previous study (19), it confirms that baseline BTI predicted radiographic knee OA progression. Whether BTI was used to predict change in semi-quantitative joint space narrowing (AUC 0.75 from prior work (19)) or the continuous JSW variable (AUC 0.81 in this study of a different cohort), the strength of the prediction was comparable. This is a valuable advance because continuous JSW is the FDA approved outcome measure for clinical trials of disease modifying agents. This study extends our original results by demonstrating that baseline BTI also predicted JSA and cartilage volume loss by MRI. BTI was 85% predictive of JSA when 28% of the cohort was defined as progressors based on a 5% JSA for purposes of ROC analysis. We have not found baseline JSW to be a good predictor of progression in either this study (of non-stratified subjects) or in our previous study (19); however, joint space narrowing (JSN) has been predictive of MRI progression in select OA patient subsets with more severe baseline JSN (36), or cartilage thinning when using a different progressor classification based on subregional cartilage changes in comparison to those in a healthy reference cohort (37). The overall predictive capability of BTI for OA progression suggests that BTI could be used to enrich an OA clinical trial with individuals likely to progress in the intermediate future (1-3 years).

Other measures of trabecular texture from radiographs have been reported using dissimilarity measures; these have been used to classify OA status (38) and predict OA progression (39). The AUCs for predicting medial JSN in the latter study (AUC 0.77) are comparable to our own based on BTI (AUC 0.81), adding further support for bone structure as a means of predicting OA progression. Recently, the 'weighted neighbor distances using compound hierarchy of algorithms representing morphology' method (WND-CHARM) (40) has been used to classify OA progressors, but the method relies on analysis of much of the gross morphology of the knee including the joint width in addition to the texture of the trabecular structure and is sensitive to imaging conditions, such as magnification and rotation.

Goldring has stated that the differential adaptive capacity of bone, compared with cartilage, likely underlies the more rapid appearance of detectable skeletal changes in bone in OA (41). We believe that this differential adaptive capacity explains the ability of BTI to predict subsequent loss of JSW, JSA, and cartilage volume: In other words, BTI acts as the “canary in the OA mine”, changing more rapidly in response to adverse loading and events than cartilage and therefore predictive of subsequent radiographic JSW/JSA as well as MR determined OA progression. These results are consistent with a concept of BTI as an early indicator of a change in the biomechanical environment of the knee that leads to cartilage loss and disease progression.

Day et al demonstrated that the volume fraction of trabecular bone was increased in OA, but surprisingly, that the bone elastic tissue modulus was reduced (42, 43). They attributed the reduction in bone elastic tissue modulus to a decrease in bone mineral density secondary to an increased rate of bone remodeling and incomplete bone mineralization. Ding also noted that severe OA is characterized by a higher than normal bone volume fraction, an abnormal low bone mineralization pattern, and lower mechanical strength (44). As summarized by Martel-Pelletier, OA subchondral bone demonstrates an increased osteoid collagen matrix and an abnormal mineralization pattern resulting in hypomineralization of this tissue (1). Cox et al showed that subchondral bone volume fraction correlated strongly with a decrease in bone mineralization; furthermore they showed that these changes were related to local cartilage degeneration (45). Finally, Bailey et al have estimated that subchondral bone collagen of the OA femoral head possessed a 20-fold increase in bone turnover and a 25% decrease in mineralization (46). Taken together, these results are all consistent with a bone mineralization lag in the face of increased bone remodeling in knee OA progression. Consistent with our prior study, compared with non-progressors, structural progressors (defined as loss of joint space width or area or loss of cartilage volume) had higher fractal dimensions in vertical trabeculae; moreover they had an increase in fractal dimensions in vertical trabeculae concurrent with structural progression. This is compatible with greater fenestration and thinning of vertical trabecular structures, both at baseline and over time, in progressors. The most appropriate interpretation, in light of the recent studies described above, is that BTI reflects thinning of vertical trabeculae on radiographs due to stress shielding (from thickened horizontal trabeculae) and apparent thinning due to their hypomineralization as a result of a high bone turnover state in OA progressors.

The meniscus (position and degeneration) has been shown to account for a substantial proportion (50%) of the variability in both JSA and JSW change (47). Subchondral bone changes could also be an early consequence of meniscal extrusion and reflect the biomechanical changes resulting from meniscal extrusion (48). In this regard, it is interesting that BTI was more sensitive for predicting change in medial JSA than change in medial minimum JSW. JSA, a location specific computer-determined measure, is potentially more sensitive than minimum JSW to progressive cartilage loss because it reflects an integral width measurement around the load-bearing region of the medial compartment; therefore, JSA would be expected to reflect meniscal degeneration and extrusion as well as articular cartilage loss. It is therefore logical to expect that BTI, a measurement across the span of the medial tibial subchondral bone, would be a better predictor of the loss of JSA, as shown here, than of narrowing of an isolated site represented by change in minimum JSW. Given that the interrater reliability and standardized response mean for JSA were high, it would seem worthy of study in other cohorts to further evaluate its sensitivity to change as a radiographic outcome measure for OA and OA clinical trials.

An ideal screening test for progressive OA should be inexpensive, minimally burdensome for the patient, readily available at multiple centers, have high positive predictive value for detecting rapid progression, and a low screen failure rate (21). BTI is inexpensive, minimally burdensome as it is acquired from a plain knee radiograph, potentially readily available at multiple centers due to the commercial availability of the KneeAnalyzer software that generates the FSA data from which BTI terms can be extracted, and has high positive predictive value for detecting rapid progression; however, further work is needed in a larger prospective longitudinal trial to evaluate thresholds of BTI and their associated predictive value and screen failure rates. Moreover, BTI is minimally impacted by factors such as varying radiographic exposure, pixel size, and knee positioning (19, 49). The use of flat structuring elements instead of the usual spheres in the morphological image analysis used to extract texture, means that BTI is independent of linear changes in image intensity values. Although Lynch et al used macroradiographs rather than the standard radiographs used here, they showed very good stability of the method to a wide range of magnifications ($\times 1.0$ - $\times 2.0$) (50). Cadaveric studies of the effect of knee positioning also demonstrated good stability of the method with a reproducibility of better than 2% coefficient of variation (CoV) (49). In this regard BTI is superior to serial JSW determinations that require stringent control of knee positioning during imaging.

Although BTI terms of the vertical trabeculae were the stronger predictor, our previous work also demonstrated prediction of OA progression by BTI terms of the horizontal trabeculae. In contrast to the previous study, the BTI terms of the horizontal trabeculae were not predictive of OA progression in this study; this may be due to the fact that our previous study included more subjects, a longer follow-up time, and categorical measures of radiographic OA progression rather than the subtler continuous measures of progression in this study. It was to be expected that BTI was a stronger predictor of OA progression over 24 months than 12 months as this provided adequate time for measurable change in the joint parameters reflecting OA progression. BTI also changed concurrently with JSA and VC_MT. To date, three prior studies have evaluated concurrent change of subchondral medial tibial BTI and radiographic knee OA progression but results have been conflicting,

with two positive (51, 52) and one negative (53) study. The results of this study corroborate the intimate relationship and conjoined disease pathways of both bone and cartilage pathology in OA, potentially mediated by the mechanical loading environment.

A limitation of this study was the relatively small number of participants, which did not support multiple parallel testing between different cartilage metrics and implementations. Additionally only women were studied. A strength of the study was the use of high quality digital radiographs available through the Pfizer A9001140 study, providing radiographic outcomes of progression, as robust as is currently possible, and the availability of MR parameters of knee OA progression. This enabled us to evaluate the prognostic capability of BTI with the current OA clinical trial outcome, change in minimum JSW, as well as emerging outcomes, such as cartilage volume by MRI. The results with JSA in this study indicate it is worthy of additional scrutiny, study and consideration as an outcome in OA trials. It is also attractive for being extractable from the same high quality knee OA radiographs as the currently accepted JSW standard for OA trials. We *a priori* tried to minimize manual selection of points in the joint profiles and found manual selection unnecessary—therefore, similar results should be readily obtainable by others using the commercially available KneeAnalyzer software.

In summary, BTI is a somewhat complicated but nevertheless useful construct. This is the first study to show that baseline BTI can predict OA progression based on multiple measures including both radiographic and MR outcomes. Taken together with our prior study, we conclude that BTI can predict knee OA progression ensuing over a 12-36 month timespan, corresponding to the timespan of typical OA clinical trials. The fact that BTI changes concurrently with radiographic measures suggests that the pattern of BTI alterations is an integral feature of OA and OA progression. Finally, the BTI phenotype of OA progressors is compatible with thinning of vertical trabeculae secondary to stress shielding from thickened horizontal trabeculae and apparent thinning as a result of hypomineralization due to high subchondral bone turnover. BTI could be a valuable adjunct in enriching for progressor subjects in OA clinical trials, thereby providing a means of increasing power and/or reducing study costs due to the need to enroll fewer trial participants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Optasia Medical was not involved in the study design or statistical analysis; however, they generously provided the KneeAnalyzer tool for research use for this study and for this we wish to sincerely thank them.

ROLE OF THE STUDY SPONSOR

Pfizer had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Pfizer.

Supported by a generous gift from David H. Murdock; NIH/NIAMS grant P01AR050245, and by the National Center for Research Resources NIH MO1-RR-30, supporting the Duke General Clinical Research Unit where this

study was conducted in part. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH, and NIH/NIAMS. Also supported by a grant from Pfizer, Inc.

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Figure 1. Landmarks used to quantify joint space area

The inner and outer joint space area boundaries were defined by the position of the inner and outer margins of the tibial fossa landmark respectively, as determined by the model-fitting process of the KneeAnalyzer tool. These two points (indicated by black asterisks) were defined as follows: the inner margin of the tibial fossa was the point where the lower margin of the tibial fossa (bowl) converges with the projected edge of the tibial plateau, on the side nearest to the inner edge of the knee (point 35 in the annotated image); the outer margin of the tibial fossa: the point where the lower margin of the tibial fossa converges with the projected edge of the tibial plateau, on the side nearest to the outer edge of the knee (point 36 in the annotated image). These two points are located implicitly by the model-based segmentation algorithm for finding the whole tibial plateau.

Figure 2. Receiver Operating Characteristic (ROC) curve of bone trabecular integrity (BTI) for predicting osteoarthritis progression over 24 months

ROC curve analysis was performed to evaluate the capability of medial compartment subchondral tibial BTI to predict a 5% change over 24 months in: A) medial joint space area (JSA); B) medial minimum joint space width (JSW); C) medial tibial cartilage volume (VC_MT); and D) medial femoral cartilage volume (VC_MF). Curves depict the AUC (red line), plus (blue line) and minus (green line) one standard deviation (SD) derived after conservative iterative cross-validation.

Table 1

Joint structure characteristics at baseline and change over 24 months (including Standardized Response Means--SRMs) in imaging parameters of knee OA patients.

	JSA	JSA	JSW	JSW	VC_MT	VC_MT	VC_MF	VC_MF
Mean	104.25	-3.04	3.67	-0.20	12096.57	-62.8	6694.14	-14.9
SD	19.57	10.02	0.95	0.74	3087.18	138.4	2003.35	100.4
SRM	NA	-0.30	NA	-0.27	NA	-0.45	NA	-0.15

SD=standard deviation; SRM=standardized response mean; =change over 24 months; JSA=joint space area (in mm²); JSW=joint space width (in mm); VC_MT=cartilage volume of the medial tibia (in mm³); VC_MF=cartilage volume of the medial femoral condyle (in mm³); NA=not applicable;

Cartilage volume parameter estimates are in mm³ (where the 3D coronal volume had voxel dimensions of 1.0 mm × 0.3125 mm × 0.3125 mm therefore 1 voxel = 0.09765625 mm³).

Table 2

PREDICTION of osteoarthritis progression over 24 months by baseline medial tibial bone trabecular integrity (BTI).

Trabecular Structure Direction	OA Progression Outcome	Baseline Linear BTI term	Baseline Quadratic BTI term	AUC (CIs for one standard deviation) for predicting 5% change over 24 months in OA progression outcome
p values (parameter estimates)				
Vertical	JSA *	0.003 (−59.6)	0.005 (−191.9)	0.85 (0.82, 0.95)
	JSW	0.11 (−2.4)	0.05 (−9.9)	0.81 (0.79, 0.85)
	VC_MT	0.015 (−659.8)	0.036 (−1930.0)	0.75 (0.71, 0.81)
	VC_MF	0.24 (−261.1)	0.19 (−994.5)	0.85 (0.76, 0.86)

Abbreviations listed in footer of Table 1.

All models were adjusted for investigational site. Note that the baseline BTI terms for vertical trabeculae are inversely proportional (negative parameter estimates) to loss of joint space width and area and cartilage volume; this means that baseline linear and quadratic BTI terms (representing the fractal dimension of bone across a range of trabecular sizes) are higher in OA progressors consistent with a more complex image with fewer, thinner, fenestrated vertical trabeculae and/or hypomineralized trabeculae due to high subchondral bone turnover resulting in apparent thinning and fenestration on the radiograph.

* Baseline BTI of vertical trabeculae was also significantly associated with JSA at 12 months: for linear BTI term $p=0.007$ ($\beta=-50.62$), for quadratic BTI term $p=0.011$ ($\beta=-159.72$)

Table 3

Association of CONCURRENT change in subchondral medial bone trabecular integrity (BTI) and osteoarthritis progression over 24 months.

Trabecular Structure Direction	OA Progression Outcome	Linear BTI term	Quadratic BTI term
p values (parameter estimates)			
Vertical	JSA *	0.016 (−42.7)	0.035 (−116.3)
	JSW	0.12 (−2.0)	0.17 (−5.7)
	VC_MT	0.027 (−506.5)	0.044 (−1446.4)
	VC_MF	0.07 (−339.1)	0.05 (−116.9)

Abbreviations listed in footer of Table 1.

The models were adjusted for investigational site.

Note that concurrent changes in BTI terms of vertical trabeculae are inversely proportional (negative parameter estimates) to loss of joint space width and area and cartilage volume; see Table 2 footer for an interpretation of this finding.

* The concurrent change in FSA of vertical trabeculae was also significantly associated with JSA over 12 months: for the linear BTI term $p=0.007$ ($\beta=-43.55$), for the quadratic BTI term $p=0.021$ ($\beta=-116.94$).