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EDITORIAL

Bone Reading to Predict the Future

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Human skeletal remains may provide information about health status and injuries from hundreds of thousands of years ago. However, the bones in living individuals have the potential to tell us something about future health as well. In this issue of *Arthritis & Rheumatology,* Kraus et al report their findings regarding the prediction of osteoarthritis (OA) progression using medial tibial subchondral trabecular bone texture (TBT) from plain knee radiographs (1). The ability of medial TBT to predict pain progression (an increase in Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] score), radiographic OA progression (a loss of joint space width [JSW]), and OA status (a combination of pain and radiographic OA progression), over 24–48 months was assessed. The covariates age, sex, body mass index, race, and baseline JSW, WOMAC pain score, and pain medication use were also included in the predictive models. The authors report that the predictive capabilities of the models for progression of OA that included medial TBT as a covariate were improved (area under the receiver operating characteristic curve [AUC] 0.633–0.649) compared to those that did not include TBT (AUC 0.608). They suggest that the finding supports the hypothesis that TBT could be valuable in OA clinical trials as a means of increasing study power, reducing costs, and/or enhancing trial efficiency, by enriching the trials with participants who have a predicted high risk of OA. Although the reported improvement was modest, the finding is another important step toward developing tools that can be used to predict clinically relevant OA.

Plain knee radiography is a cheap, widely available, low-radiation, and, in general, safe imaging technique that is routinely used in everyday health care. It allows for not only ruling out serious injuries or disease such as fracture or bone tumor, but also verifying structural changes in the knee joints that are indicative of OA. The loss of joint space and the formation of osteophytes detected on plain radiographs are, however, relatively late structural evidence of OA. Interestingly, routine knee radiographs contain more information than is provided in the radiologist's or treating physician's typical review or measurements. Tools that use such additional information from plain knee radiographs to predict OA or OA progression at earlier stages are therefore highly attractive. Subchondral TBT analysis is an example of a biologically relevant way of predicting OA from plain knee radiographs. Bone is not a static tissue. On the contrary, it is constantly undergoing remodeling depending on both systemic and local biomechanical signaling pathways. The trabecular network is the key structure of the part of the tibia that sits below the compact cortical surface (Figure 1). The dimension and orientation of the individual trabecula and its complete 3-dimensional networks change under biomechanical load. Biomechanics play an important role in the initiation and progression of OA (2). Secondary analysis of subchondral TBT from plain knee radiographs using fractal image analysis software has already produced promising results for predicting current and future joint health.

Fractals were introduced by Lynch et al, who applied fractal signature analysis to macroradiographs of knees with OA and knees without OA (3). They defined the fractal signature as a set of fractal dimensions calculated at different trabeculae sizes. Fractal dimension is a

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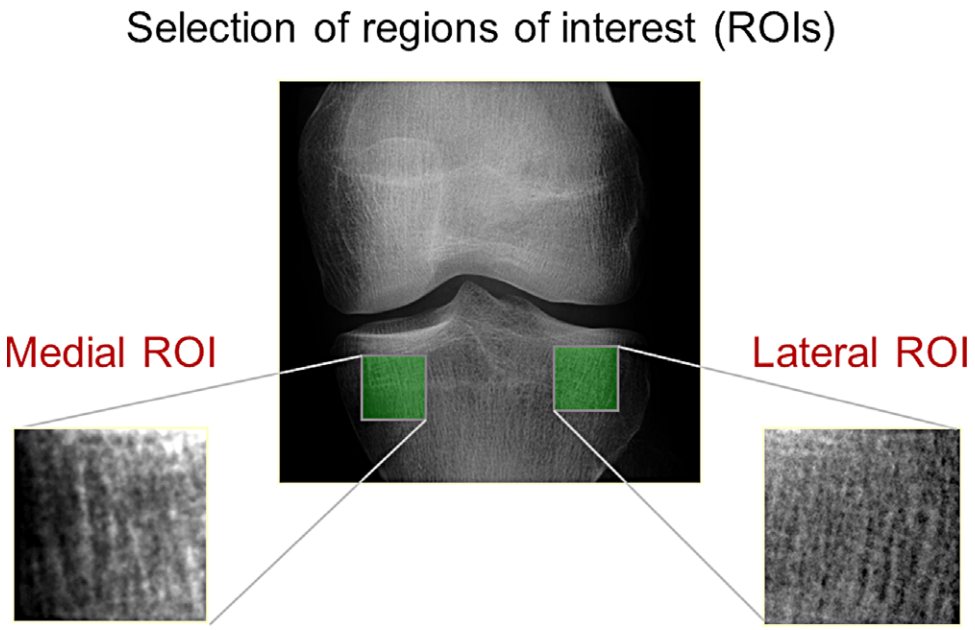

Figure 1. Example of a knee radiograph (from ReadMyXray [http://readmyxray.curtin.edu.au]) with regions of interest selected for analysis of the subchondral trabecular bone texture.

measure of irregularity in bone texture represented by changes in pixel brightness, and its higher values correspond to more irregular bone textures. They detected changes in vertical and horizontal TBT at individual trabeculae sizes at different stages of OA. Buckland-Wright et al extended the study to knees and hands without OA and with early, moderate, and advanced OA (4). Their work was followed by the work of Podsiadlo and colleagues using directional fractal signature analysis (5–7). They have reported the ability of TBT to predict joint replacement and detect preradiographic and early OA. Other groups have reported predictive capabilities of TBT in loss of joint space (8) or differences in bone texture in knees with and without cartilage damage or bone marrow lesions (9). The studies described above consistently indicate that TBT has the potential to be a useful imaging-based marker for OA prediction.

It is against this backdrop that Kraus et al set out to predict OA progression. For well-selected subjects from the Osteoarthritis Initiative, they constructed regression models with 6 TBT parameters derived from the nadir and center of the curves with linear and quadratic components fitted into fractal signatures. There are advantages to this interesting approach. Collinearity between parameters is reduced. This improves the assessment of which parameters are the most related to outcome. Using the curves instead of fractal dimensions at individual scales has the positive result of reducing the amount of data. However, there is also loss of detail using this method; past studies suggest that fractal signatures might not follow any particular form or curve, but rather exhibit changes specific to small, medium, and large scale ranges (4–7). Therefore, the analysis based on curves could potentially miss changes in TBT such as those reported for early OA in previous studies. Further, for the TBT analysis, the authors used a semiautomated method that is initialized with 6 bone landmarks selected manually by a human expert. High interrater reliability and reproducibility of the method were reported. However, because of the human involvement, reading a large number of knee radiographs would become inevitably time-consuming using this method. Fortunately, this barrier has been overcome by the use of a validated and fully automated bone selection method (9). With this tool, large-scale studies such as the recently conducted analysis of over 6,000 knee radiographs at baseline and 3 follow-ups from the Multicenter Osteoarthritis Study have become feasible (7).

The present study is the authors' third assessment of the ability of medial TBT to predict OA progression. Unlike the 2 others (10,11), this study also includes prediction of pain progression (an increase in WOMAC score) and its combination with structural OA progression (a loss of JSW). The inclusion of pain progression is a valuable and important addition because that is ultimately what is relevant to the patient, and it is well established in the literature that progression of structural changes in OA does not necessarily come with pain. The cases displaying progression were characterized by thickening of

horizontal and thinning of vertical trabeculae of the affected medial TBT. These results are consistent with those reported in previous fractal-based prediction studies, and have support from validations of predictive ability of medial and lateral TBT that were conducted using alternative prediction systems based on dissimilarity measures (12,13).

We would like to highlight that prediction research poses distinct methodologic challenges. Specifically, its performance measures and validation techniques are different from those commonly used in association research. The two basic measures used in prediction research are discrimination and calibration. Discrimination is the ability of a prediction model to distinguish between subjects with and those without the outcome of interest. Kraus et al used AUC as a measure of discrimination. Calibration is a measure of the agreement between predicted and observed outcome. In a well-calibrated model, we can expect that in a group of persons with predicted risk between 80% and 90%, the outcome would be observed in ~85% of the group members. The study by Kraus et al did not include this important measure that could suggest TBT to be potentially useful for enriching clinical trials. Validation techniques in predictive modeling can be either internal or external. Internal validation uses resampling techniques, such as repeated cross-validation, bootstrapping, or split-set on the study sample, while external validation requires data from a new independent sample. None of these validations were provided in the present study by Kraus and colleagues. Because the prediction models were generated to provide the best fit for the study sample, they could potentially be overfitted, and hence provide an optimistic assessment of the predictive ability.

In conclusion, there is a need for a cheap, accurate, and widely available tool that would support clinicians and researchers in predicting risk or making an earlier diagnosis of knee OA, so that clinical trials, treatments, and preventive actions can be initiated earlier and justified more convincingly. Bone texture analysis of often already existing knee radiographs is a promising approach. However, further work on validation, especially external validation, and improved reporting of performance measures, including calibration, are needed to establish the capability and utility of bone texture analysis in the prediction of OA risk. OA web sites featuring online tools and analyses such as MyJointPain (https://www.myjointpain.org.au) and ReadMyXray (http://readmyxray.curtin.edu.au) could be useful in the validation process.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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