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3-dimensional bone shape and knee osteoarthritis: What have we learned?

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ABSTRACT

The concept that multiple joint tissues are involved in the osteoarthritis (OA) disease process is now widely accepted. There have been significant and important insights over the past two decades in the understanding of bone as a tissue undergoing pathological changes in OA. The specific bony changes of osteophyte growth and "bone attrition" associated with OA have been recognized for many years with several semi-quantitative radiographic and magnetic resonance imaging (MRI) grading systems designed to capture the magnitude of these changes. Over the past decade, there has been significant and important progress in the quantitative measurement of these changes. Manual methods for measuring bone area from 3D MR images have been improved with automation which offers both superior precision and a more responsive measurement that has been applied in several DMOAD randomized controlled trials. Measurement of true 3D bone shape, as opposed to simple geometric measures such as curvature and length, depends on automated methods of segmentation. In this field, important developments have taken place in the statistical parameterization of shape and the construction of OA vs non-OA shape metrics. Work has demonstrated that bone shape may provide an indication of OA status, may predict future OA onset, and is associated with clinical markers of OA such as pain, function and total joint replacement (TKR). Thus, bone shape may be a useful imaging biomarker for OA.

Introduction

The involvement of multiple joint tissues in the osteoarthritis (OA) disease process is now widely accepted. Subchondral bone plays a critical role in the progression of the disease [1]. The bony changes seen in knee OA radiographically have been described as "radiographic OA" (rOA) for many years and are used in diagnosis as part of the Kellgren-Lawrence (KL) grading system. KL grading describes two major bony shape changes in the knee joint: the appearance of osteophytes and deformity of the bone ends. This deformity, which is often called subchondral "bone attrition", is described as a flattening or depression of the subchondral bony surface unrelated to gross fracture. These changes are also captured in the semi-quantitative MRI Whole- Organ MRI Score (WORMS) as marginal osteophyte size and bone attrition based on the degree of flattening or depression of the articular surface. Osteophyte size scoring, but not bone attrition, is also included in the MRI Osteoarthritis Knee Score (MOAKS).

While quantitative shape change may be measured using simple geometric descriptors such as curvature, angles or lengths, the development of statistical shape modelling (SSM) to measure joint morphology has shown significant potential as an imaging biomarker for OA [2]. The SSM captures the entire shape of a class of objects (a knee, for example) as a set of independent modes of shape variation. These shape modes may then be combined to capture the shape of a particular object, with the relative weights of each of the modes producing a vector that completely describes the object shape.

The bony shape changes associated with OA have been investigated using 2D SSMs from radiographs in numerous studies of the hip but only rarely in the knee [3], possibly due to its more complex shape. Although bone shape change may be recognized in a radiograph, a radiograph is a projection of a 3D object onto a 2D plane, and the perceived change will be a mixture of both true shape change, and apparent shape changes introduced by variation in the rotation of the bone about its axes. The 2D SSM must therefore incorporate these rotational changes into the shape variation that is captured by the shape modes. In contrast, shape analysis by 3D SSM methods, while more technically challenging in terms of SSM construction [4], is more efficient and accurate as a descriptor of shape. In this narrative review, we will concentrate on the use of 3D shape measures of the knee in OA research.

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Image acquisition and segmentation for bone shape analysis

In common with quantitative cartilage morphology, 3D bone shape analysis utilizes high resolution 3D T1-weighted spoiled gradient-echo recalled (SPGR) MRI sequences at 1.5T and 3T, with fat-suppression crucial for defining the bone-cartilage interface. This type of MRI sequence is widely available and is termed fast low angle shot (FLASH) or fast field echo (FFE) by other vendors. Direct water-excitation imaging may be used rather than a fat-suppressed pre-pulse, helping to shorten acquisition time. The Osteoarthritis Initiative (OAI) has provided an invaluable source of publicly available image data for research in this area with up to 4 years of annual MRIs in almost 5000 participants. In addition to SPGR, the OAI imaging protocol [5] contained a vendor-specific near-isotropic, sagittal double echo steady stated (DESS) water excitation sequence with mixed T1/T2 contrast which has now been used in much OA bone shape research.

To compare bone shape between subjects and timepoints, the bony surfaces in the images must be segmented. Segmentation may be by manual or semi-automated means, or by fully automated methods. As an example of automated methods, the SSMs described previously may be incorporated in active shape models (ASMs) or active appearance models (AAMs) so that they use image evidence to automatically search an image and segment the bone surfaces with sub-voxel accuracy [6].

Possible causes of shape change

Two key changes are seen in bone shape as OA progresses. A ridge of osteophytes grows around the periphery of the femoral articular surface; and the femoral condyles (Fig. 2) and tibial plateaus broaden and flatten, and also alter their orientation. Osteophytic bone turnover may co-locate with regions of synovitis [7] and it is therefore possible that this osteophytic ridge is an inflammatory response mediated by macrophage activity [8]. This bony deposition could affect joint alignment, and meniscal and ligamentous or tendinous insertion sites, any of which could contribute to clinical symptoms. As for the alterations of the shape of the femur and tibia, bone is known to be a dynamic tissue that adapts to loads by remodelling to meet the mechanical demands made on it (Wolff's Law). Alterations in joint geometry can lead to further changes in joint congruity, and to altered or inadequate response to biomechanical loads, which may also contribute to disease pathology. Whether these bony changes are a cause or consequence of other changes in OA is still debated.

Measurement of bone area

The first work on capturing 3D changes in bone shape used measures of bone area defined as anatomically landmarked regions over the bone surface. Bone area measures of the medial and lateral tibial plateaus from axial image slices obtained by manual contouring have been shown to have a coefficient of variation (CoV) of 2.2–2.6%. Cross-sectionally, osteophytes are associated with substantial increases in both lateral and medial tibial joint surface area [9]. Longitudinally, medial and lateral tibial areas have been found to increase in OA subjects by 2.2 ± 6.9% and 1.5 ± 4.3% per year, respectively, with male sex, higher BMI and higher baseline grade of medial joint space narrowing all associated with an increased rate of enlargement of the bone area of the medial tibial plateau [10].

Manual area segmentation has also been used to study knee alignment and adaptation of the total area of the subchondral bone surface (tAB) of the medial and lateral tibia, the central (weight bearing) medial femoral condyle and the central lateral femoral condyle regions with similar CoV. Tibiofemoral subchondral bone surface areas were shown to be associated with the medial-to-lateral load distribution, and longitudinal findings indicate that this difference may increase with age [11]. A large cross-sectional analysis of these regions in 1003 subjects has shown larger tABs at the pre-radiographic OA stage compared to healthy knees, although the differences were not larger with higher KL grades [12], possibly because these area measures exclude regions with osteophytes which are an important component of the higher KL grades. Another longitudinal study of a similar size showed 1-year differences in tAB of rOA subjects in the medial tibia, central medial femoral condyle and central lateral femoral condyle (ranging from +0.2% to +0.4%), but not in healthy controls or pre-rOA subjects [13].

An automated method of segmenting the bone surfaces and defining areal regions (Fig. 1) using AAMs has demonstrated an improved CoV of <1% compared to manual methods [14] and improved responsiveness compared to other imaging biomarkers (Table 1). Using this method on 1312 participants with radiographic knee OA, and 885 non-OA controls with MRIs at baseline, 1, 2 and 4 years from the OAI, annual changes in bone area in all knee regions segregated people with OA from controls at 12 months. There was, however, an increase of 0.8% per annum vs 0.12% in the medial femur [14], smaller than that seen from manual methods. A surprising result was the effect of age: although tAB increased over time (and hence with age) the rate of increase was slower in older participants. In another large study of 2588 OAI participants, radiographic osteophytes, joint space narrowing, and KL grade correlated significantly with OA-attributed tAB, but these variables did not explain a substantive proportion of OA-attributable tAB variance. This may reflect the lack of sensitivity of radiographic measures in detecting structural progression [15]. A further investigation used this method with data from the OAI Biomarkers consortium Foundation for the National Institute of Health (FNIH) study (600 participants in 4 groups selected for radiographic progression or pain progression, both or neither). It found that greater increases in bone area over 24 months in knees with mild-to-moderate radiographic OA were associated with increased likelihood of clinically relevant progression (a combination of radiographic and symptomatic progression) over 48 months [16]. A much smaller study of 27 women with painful medial knee OA, BMI ≥ 25 kg/m2, radiographic evidence of medial OA, and varus malalignment showed that the method was responsive enough to measures changes at 3 and 6 months: the mean change in medial femur area was 0.34% (95% CI 0.04–0.64) at 3 months and 0.61% (95% CI 0.32–0.90) at six months. Forty-one percent of the subjects had progression greater than the smallest detectable difference at 6 months [17].

Measurement of bone shape

The first use of SSMs in the analysis of 3D OA knee bone shape was a small study of twelve pairs of age and BMI matched female participants randomly selected from control and incidence (at risk) groups of the OAI database. Femur and tibia bone surfaces were segmented semi-automatically and quantitative differences in certain shape modes of the femur and tibia surfaces were demonstrated between these groups [18]. A significant advance was made when, instead of comparing individual shape modes, linear discriminant analysis was used to construct a shape vector describing a linear shape path from non-OA to OA shapes. Any knee shape could then be parameterized from an MR image using an AAM and then projected onto the shape vector to yield a metric which was constructed based on the mean non-OA shape sitting at the −1 value and the mean OA shape sitting at the +1 value on the shape vector [6]. This method demonstrated that femoral, tibial and patellar bone shapes were predictive of future OA incidence, regardless of the presence of radiographic OA features, and that a shape metric can be constructed that is associated with OA incidence.

3D SSMs have also been used to determine that there are significant shape differences at baseline between control knees and knees at risk of ACL-injury, suggesting that a common shape feature may predispose these knees to injury [19]. In an important study using the shape vector approach, a nested case-control study of 310 control and 310 subjects with confirmed TKR from the OAI, demonstrated that more advanced 3D OA bone shape changes were associated with the risk of TKR, with femoral shape being the most associated [20]. The OAI Biomarkers

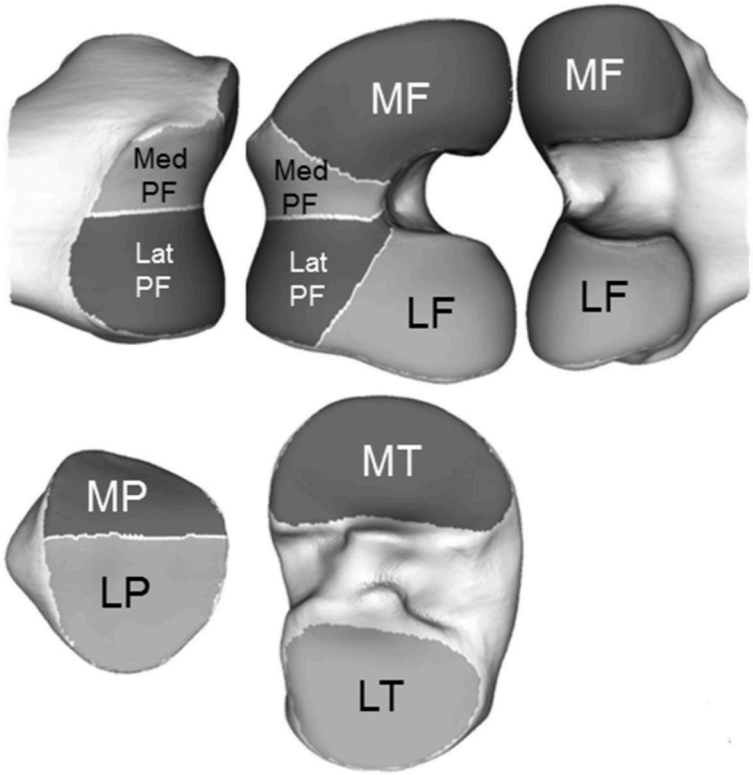

Fig. 1. Anatomical bone areas: LF (lateral femur), MF (medial femur), MT (medial tibia), LT (lateral tibia), MP (medial patella), LP (lateral patella), LatPF (lateral trochlear), MedPF (medial trochlear). Reproduced with permission from [15].

Table 1
Responsiveness of various image-based structural measures. Standardized response mean (SRM) of fixed medial ($x = 0.225$ position) radiographic joint space width (JSW), cartilage thickness measured at the central medial femorotibial compartment (cMFTC) and bone area measured at the medial femur (MF) [14].

	Medial JSW (225 position)	Cartilage thickness (cMFTC)	Bone Area (MF)
SRM at 12M	−0.22	−0.28	0.66
SRM at 24M	−0.35	−0.38	0.83

consortium FNIH study described in the section above also showed that as well as bone area, there were more changes in bone shape in OA knees than controls, and that changes in bone shape are predictive of clinically relevant OA progression (a combination of radiographic and symptomatic progression) over 48 months [16]. 3D SSMs have also been used to explore the association between bone shape and bone marrow lesions, showing that increased lesion size is associated with increasing changes in OA bone shape [21].

A somewhat different approach to shape modelling has been developed to overcome the potential problem of SSMs enforcing linear modelling on shape modes. Bone shape features were learned from spherical bone maps of knee MR images using deep learning convolutional neural networks to diagnose and predict OA [22]. The model demonstrated an AUC of 0.905 on a test set for OA diagnosis. This work was later extended with a longitudinal study that modelled shape changes over time to predict future femur bone shape changes at 48 months [23].

More recently, the SSM OA shape vector method has been developed as a statistical z-score by setting an origin at the mean of the non-OA group, and fixing a unit scale as the standard deviation of the non-OA group in the direction of the OA vector [24]. This new metric was termed the B-score and has a range of around −3 (non-OA knees) to +7 (extreme OA knees), shown in Fig. 2.

Use of bone area and shape as imaging endpoints in DMOAD trials

Bone area has been used as an imaging endpoint in several prospective clinical DMOAD trials. In a phase 2 randomized control trial it was demonstrated that a cathepsin-K inhibitor (MIV-711) significantly reduced the increase in bone area in the longitudinal medial femur, but not in the tibia, [25], possibly indicating a slowing of the bony changes usually associated with OA progression. In the phase 2 trial of an anti-catabolic ADAMTS-5 inhibitor, no significant differences in bone area change between placebo and treatment were demonstrated, as was the case for both clinical and other structural endpoints including cartilage morphometry [26]. A post-hoc analysis of a large randomized control trial of knee OA showed that zoledronic acid plus methylprednisolone may retard expansion of bone area over 24 months, but zoledronic acid alone did not [27].

The development of bone shape as an imaging endpoint is more recent, although, in a retrospective analysis of the TPX-100 Phase II randomized control trial, B-score documented a statistically significant decrease in pathologic bone shape change with TPX-100 treatment vs. placebo [28].

Conclusions

The automated analysis of 3D images has demonstrated that bone area and shape may provide an indication of OA status, predict progression of OA and is associated with clinical markers of OA such as pain, function and TKR. The relationship between pathologic bone shape and other structural changes in the knee is not well understood and could usefully be explored further. The work summarized here already suggests that bone shape may prove to be a useful imaging

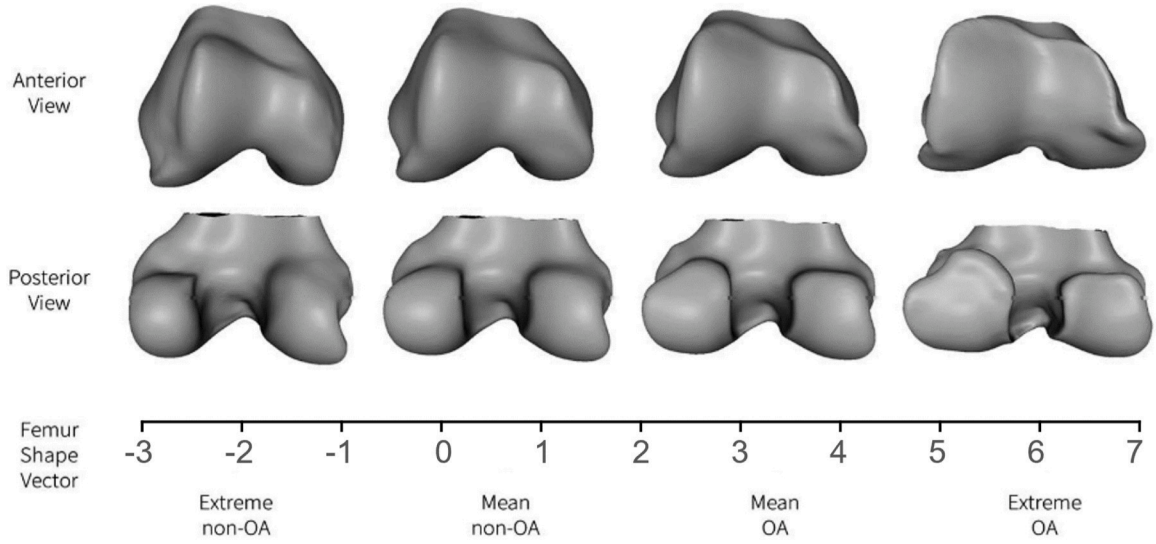

Fig. 2. Changes in 3D bone shape associated with progression of OA for the anterior (top row) and posterior femur (bottom row). Representative B-scores along the shape vector are indicated below on a scale of −3 to +7, where a unit represents one SD of shape variation in a non-OA knee, and the origin (B-score = 0) is at the mean shape of the non-OA population. Change tends to be greatest around the edge of the cartilage plate (osteophyte region) but is also apparent in central subchondral regions where the bone flattens and broadens. Reproduced with permission from [29].

biomarker for OA.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Alan Brett reports financial support was provided by Stryker Corporation. Alan Brett reports a relationship with Stryker Corporation that includes: equity or stocks. Philip G Conaghan reports a relationship with AbbVie Inc that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Eli Lilly and Company that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Galapagos NV that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Genascense that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with GSK that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Grünenthal GMBH that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Levicept that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with Stryker Corporation that includes: consulting or advisory. Philip G Conaghan reports a relationship with Takeda Pharmaceutical Company Limited that includes: consulting or advisory and speaking and lecture fees. Philip G Conaghan reports a relationship with TrialSpark Inc that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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