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Mechanical Biomarkers in Bone Using Image-Based Finite Element Analysis

Hannah L. Dailey[1] · Mariana E. Kersh[2,3,4] · Caitlyn J. Collins[5] · Karen L. Troy[6]

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Abstract

Purpose of Review The purpose of this review is to summarize insights gained by finite element (FE) model-based mechanical biomarkers of bone for in vivo assessment of bone development and adaptation, fracture risk, and fracture healing.

Recent Findings Muscle-driven FE models have been used to establish correlations between prenatal strains and morphological development. Postnatal ontogenetic studies have identified potential origins of bone fracture risk and quantified the mechanical environment during stereotypical locomotion and in response to increased loading. FE-based virtual mechanical tests have been used to assess fracture healing with higher fidelity than the current clinical standard; here, virtual torsion test data was a better predictor of torsional rigidity than morphometric measures or radiographic scores. Virtual mechanical biomarkers of strength have also been used to deepen the insights from both preclinical and clinical studies with predictions of strength of union at different stages of healing and reliable predictions of time to healing.

Summary Image-based FE models allow for noninvasive measurement of mechanical biomarkers in bone and have emerged as powerful tools for translational research on bone. More work to develop nonirradiating imaging techniques and validate models of bone during particularly dynamic phases (e.g., during growth and the callus region during fracture healing) will allow for continued progress in our understanding of how bone responds along the lifespan.

Keywords Bone · Imaging · Finite element analysis · Quantitative

Introduction

What are mechanical biomarkers in bone? Biomarkers are indicators of biological phenomena or physiologic function that can be measured accurately and reproducibly. In modern medicine, a *biomarker* is used as a surrogate measure of the health and function of specific organs and systems and often originates from blood or tissue biopsies. Recently, the definition of a biomarker has expanded to include data from medical images [1] and biomechanical assessments [2, 3] that can provide insight into physiological phenomena. For bone, plane film radiographs (X-rays) are the oldest and most broadly accepted clinical measurement tool [4] used for diagnosing bone fractures and monitoring healing. Traditionally, X-ray images are nonquantitative and are therefore not a biomarker of bone function.

The primary function of bone is structural, so relevant biomarkers for bone should include measures related to mechanical quality. Ideally, such biomarkers would be sensitive to clinically relevant changes and useful for monitoring the effects of interventions or predicting individual

✉ Mariana E. Kersh
mkersh@illinois.edu

1 Department of Mechanical Engineering & Mechanics, P.C. Rossin College of Engineering and Applied Science, Lehigh University, Bethlehem, PA, USA

2 Department of Mechanical Science and Engineering, Grainger College of Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, USA

3 Beckman Institute for Advanced Science and Engineering, University of Illinois at Urbana-Champaign, 405 N Mathews Ave Rm 4043, Urbana, IL 61801, USA

4 Carle Illinois College of Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA

5 Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg, VA, USA

6 Department of Biomedical Engineering, Worcester Polytechnic Institute, Worcester, MA, USA

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outcomes. Here, we define mechanical biomarkers as measures of the mechanical response of bone to external loads. These measures include organ-level mechanical behavior (e.g., stiffness or rigidity) or tissue-level behavior (e.g., stress, load to failure, or strain energy density), and there are several helpful sources describing their derivation in the context of bone [5–7].

Why are bone mechanical biomarkers important? Mechanical biomarkers are useful measures of bone quality at multiple length scales and can serve as (1) explanatory variables of bone development and predictive indicators of adaptation at the organism level and (2) measures of organ and tissue quality for fracture risk assessment, evaluation of healing, and the effect of treatments for bone disease.

The contribution of mechanical loading to bone (re) modeling has been probed using a variety of animal models [8, 9] that have mimicked observations in humans. There remains the potential to harness the natural mechanoadaptive response of bone to improve bone quality via exercise. Unfortunately, recommendations for exercise tend to be qualitatively described (e.g., one should engage in impact loading exercises). There is a missed opportunity in using quantitative mechanical biomarkers of bone adaptation to develop informed, and possibly patient-specific, exercise interventions that induce beneficial adaptations in fracture prone regions.

Unfortunately, regardless of preventive measures, bone fractures from a loss in bone quality or trauma inevitably still occur. The etiology of bone pathology is complex, and currently, there are no serological biomarkers that directly reflect bone mechanical quality. Instead, treatment decisions are based on indirect measures like bone mineral density, clinical risk prediction tools [10], or visual interpretation of imaging. The prognostic limitations of most clinical assessments reinforce patterns of care that tend to be conservative and reactive—waiting for clinical pathology to present unambiguously—rather than proactive and preventive. The rationale for developing mechanical biomarkers from imaging data lies in the capacity to reorient the diagnosis of bone disease and subsequent treatment planning to target the endpoint functional measure of interest—the mechanical integrity of a patient's bone—using methods that are objective, quantitative, precise, and patient-specific.

How can bone imaging be used to measure mechanical biomarkers? Direct experimental measurements of bone mechanics have yielded important insights into how bone responds to loading, but destructive mechanical tests are not translatable as clinical biomarkers [11, 12]. Measuring bone mechanics in vivo is impractical because of its invasive nature. As an alternative, image-based finite element analysis (FEA) has been used to computationally measure the mechanical function of bone. Since the first FEA of bone was performed and reported in 1972 [13], swift progress has been made using FEA in orthopedic applications and has been summarized elsewhere[14, 15]. The increasing availability and quality of medical image data, coupled with the boom in computational power at the end of the twenty-first century, has led to a rapid rise in three-dimensional image-based FEA.

Recent advances in FEA in the areas of bone response to in vivo stimuli at the whole-body level as well as assessments of bone quality at the organ and tissue level have demonstrated the value of using mechanical biomarkers (Fig. 1). Thus, the purpose of this review is to provide a brief introduction to FEA, summarize insights gained from image-based FEA mechanical biomarkers in bone at varying length scales, and offer a critical perspective on challenges remaining to be overcome.

Finite Element Analysis—a Brief Primer

Although the finite element (FE) method can be used to predict many types of physical phenomena, our focus is on the use of the FE method to predict the mechanical behavior of bone. Briefly, in an FEA, a given structure is discretized into many smaller, simple, interconnected structures (elements), each of which is assigned material properties such as elastic modulus. When a force or displacement (termed a *boundary condition*) is applied to the structure, the deflection of each element edge and corners is calculated based on equations such as Hooke's law. Once all of the equations governing element mechanical behavior, boundary conditions, and constraints have been satisfied, mechanical parameters such as stress and strain can be calculated. Note, stress and strain are computed throughout the model for each increment (i.e., load or displacement applied at the nodes) at what are called *integration points* within the element. To determine the stress distribution within a solid element, interpolation

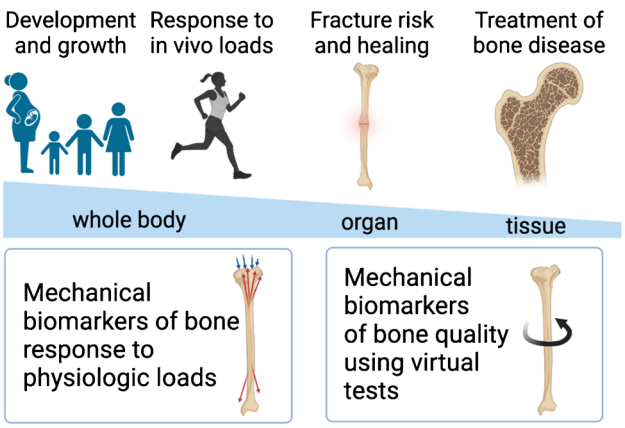

Fig. 1 Applications of mechanical biomarkers in bone at the whole body, organ, and tissue level

functions (e.g., linear vs. quadratic) are first used to determine the displacement at arbitrary points within the element, generating a displacement field. This displacement field can then be differentiated to determine the strain field. The model defined stress–strain relationships (i.e., mass density, Young's modulus, Poisson's ratio, etc.) for the element are then used to compute the stresses. A representative workflow for creating an image-based finite element model is shown in Fig. 2.

Model Geometry

Most models begin with a computed tomography (CT) image stack, which is a matrix of 3-D pixels called volume pixels, or *voxels*. Each voxel contains the local measurement of radiodensity, a measure related to X-ray attenuation, expressed in Hounsfield units. To create a model, the voxels of interest must be identified in a process termed *segmentation*. Next, the bone voxels can be directly converted into hexahedral elements (see Fig. 4 for an example) [17], a process automated by Keyak [18] to create a 3D representation of bone. Alternatively, software-aided methods can be used to define bone surfaces, which are then filled with tetrahedral or hexahedral elements. Similar procedures are used for micro-CT and high-resolution peripheral quantitative CT (HR-pQCT) image data, which produce microstructural models of bone. Thus, bone geometries can now be created at different length scales to answer a range of questions related to the mechanics of bone.

Bone Material Properties

Success with image-based FE modeling of bone requires robust methods for inferring local material properties from the voxel-level radiodensity data. Bone modulus and strength are positively related to volumetric bone mineral density (BMD) and thus with CT attenuation. BMD calibration with a calcium hydroxyapatite or hydrogen dipotassium phosphate phantom enables quantitative interpretation of radiodensity and can help mitigate differences between scanners and user settings [19–21]. Numerous CT density-to-property scaling equations have been reported in the literature and reviewed elsewhere [22, 23]. Many of these equations were derived experimentally in which samples of bone were imaged and mechanically tested to relate CT density to the mechanical properties of interest (typically modulus) using regression analysis. Notably, these relationships are site-specific owing to the broad spatial heterogeneity in bone microstructure [24]. Thus, best practice involves using an anatomically specific density-modulus relationships whenever possible.

Empirically deriving density-modulus relationships is challenging in highly heterogeneous mineralized tissues

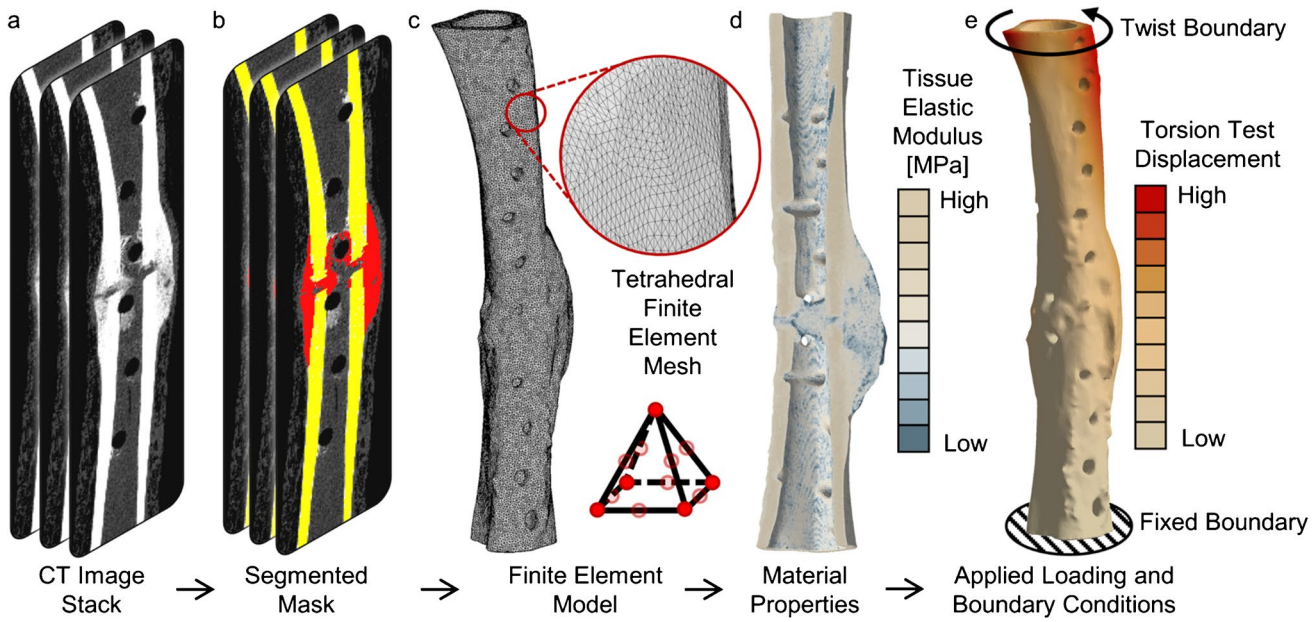

Fig. 2 General procedure for image-based finite element (FE) modeling illustrated for a healing ovine osteotomy [16]. (a, b) CT image stacks are segmented to identify the bone geometry. The volume is then meshed (c), shown here using tetrahedral finite elements. (d) Local material properties are interpolated and scaled from the radiodensity data in each voxel. (e) After material assignment, boundary conditions and loads are applied. In this example, the virtual loading conditions replicate experimental post-mortem torsion testing. Note: Direct voxel-to-FE model building can also be achieved using hexahedral finite elements (see Fig. 4)

such as the fracture callus [25]. In these situations, or when the material properties are unknown, FEA can be used to perform in situ inverse optimization of the density-modulus scaling function, where the objective is to achieve agreement between an experimental biomechanical test of bone and an equivalent virtual test performed in the model. This approach has been used to fit a density-modulus scaling function for intact ovine cortical bone [16], human metatarsals [26], and to fit a dual-zone material model that differentiates between mineralized and non-mineralized fracture callus tissue [27]. The inverse approach has also been used in voxel-based continuum FEA of trabecular bone in the ankle, without requiring trabecular binarization in the segmentation process, making it translatable to lower-resolution clinical imaging protocols [28••]. Model fidelity can be improved with the inclusion of trabecular structural anisotropy which can be measured from the attenuation gradients in clinical CT [29].

Boundary Conditions

Boundary conditions are a set of loads and constraints used to define the mechanical problem (i.e., research question) of interest as well as the nature of the model measurement being made. Broadly speaking, models can be used to predict mechanical behavior under two scenarios: (1) in response to an arbitrary load (a virtual mechanical test) or (2) in response to physiological loads.

The virtual mechanical test approach applies simple and highly controlled boundary conditions such as axial compression, torsion, or bending to estimate the stiffness or strength of a bone and produce mechanical biomarkers. The advantages of virtual mechanical tests are that the simulations can often be validated against experimental tests and the simulations rely on relatively simple assumptions (e.g., small displacements relative to the model size, no permanent deformation upon removal of the load, etc.). In contrast, the goal of modeling physiologic loads is to understand the response of bone to in vivo loading scenarios. This approach is more complex because muscles and other connective tissues that interact with bone in living organisms are included within the FE models. The advantage is the capacity to provide insights into bone development, mechanical sources of injury, and the effects of interventions.

Bone Response to In Vivo Loading

Understanding how in vivo mechanical loading results in bone formation or resorption is challenging because of the complexity of muscle-bone interactions that span multiple length scales. At the whole-body level, musculoskeletal models provide predictions of muscle forces that can be integrated with FE bone models. Briefly, musculoskeletal simulations model the skeletal system as rigid body segments (bone) with kinematically prescribed joints that define the allowable movement between each segment. A system of dynamic equations of motion is used, with experimental measurements of segment (bone) motion and external loads (e.g., ground reaction force) as inputs. These equations are then iteratively solved [30, 31] for the muscle and joint reaction forces that generated the measured movement, which can then be mapped as boundary conditions onto an FE model of bone. These muscle-driven FE models have been used to understand mechanisms of both bone development and adaptation to loads.

Bone Development

Simulations of endochondral ossification in long bones have been used to model both mechanical and biological factors that contribute to bone formation [32]. Enabled by cine-MRI that can record in utero fetal kinematics, muscle-driven FEA has been used to evaluate the relationship between femur and pelvis bone strains and fetal positions [33, 34] as well as the correlation between cortical thickness and muscle forces on the iliac crest [35•]. These models can help identify associations between in utero biomechanics and congenital bone disorders such as hip dysplasia and scoliosis.

Understanding the mechanical contributions to bone growth is necessary when considering exercise interventions earlier in life as a preventive method of optimizing bone health to reduce lifetime fracture risk. Postnatal growth is a demanding period during which the skeletal system must accommodate a tenfold increase in mass. The capacity to sustain such loads is influenced by mechanical cues that mediate bone formation [36], and therefore, growth represents an ideal timeframe during which bone strength can be increased. Professional athletes in unilateral sports, such as baseball and tennis, have significant adaptations in the loading arm compared to the contralateral arm with some benefits maintained lifelong [37]. Importantly, athletes at the professional level have likely been physically active since childhood. What remains to be demonstrated is which exercises performed while young might provide the most benefit without increasing the risk of overuse injuries. Doing so requires decoupling the contribution of bone development guided by stereotypical locomotion (e.g., walking) from exercise-initiated adaptation.

Animal models are useful to characterize the evolution of mechanical strains, bone structure, and composition during ontogeny [38, 39]. Equine bone can serve as a dual benefit model because of the incidence of bone stress injuries that result in significant mortality rates in equine athletes. Similar to humans, exercise has been suggested as a preventive approach to reduce fracture risk. The ability to evaluate

exercise when young is more feasible in horses because they reach skeletal maturity within three years of age. FE models during equine development have identified reduced bone volume fraction in areas prone to fracture, thus providing a structural target for exercise in equine bone (Fig. 3a–c) [39]. Characterizing bone development provides the necessary benchmarking from which future exercise interventions can be compared to evaluate the influence of additional mechanical loading on adaptation during growth. In addition to healthy development, muscle-driven FE models have been used to evaluate the contribution of muscle forces to morphological parameters associated with developmental bone disorders in people, such as the neck-shaft angle and degree of femoral anteversion [40, 41].

Bone Adaptation to Mechanical Stimuli

While exercise when young might be the most opportune time to induce skeletal changes, exercise at any stage of life will still be beneficial for bone. Muscle-driven FEA of skeletally mature bone has been used to evaluate exercises that might induce bone adaptation. One benefit of using FEA is the capacity to evaluate spatially targeted measures wherein the mechanical biomarkers (strain, strain energy density) can be evaluated in the areas prone to fracture. Moreover, such models can provide insights into the muscle groups that induce the required strains and therefore be used to develop interventions. For example, exercises targeting the gluteal muscles, such as stair climbing, result in elevated strains in the femoral neck relative to walking and thus could be effective for inducing bone adaptation [42]. More recently, muscle-driven FEA has been used to understand tibia bone strain in basketball players during sport-relevant tasks [43••]. This data can provide a dual view of the measured biomarkers: on the one hand increased strains may be a biomarker for potential adaptation. On the other hand, elevated strains without sufficient rest may increase accumulated damage and cause fatigue-related injuries. These data are useful in the design of training regimens in athletes to ensure that overuse injuries can be avoided.

One approach to reduce the uncertainty in predicting muscle loads for muscle-driven FEA predictions of in vivo bone strain is to study simpler physiologic tasks in anatomic locations with fewer muscle attachments. For example, to investigate the link between the mechanical strain environment and bone adaptation, FEA was used to assign subject-specific strains to women who completed a simple upper extremity compressive loading task (Fig. 3d–f) [44]. Those participants who gained the most bone after 12 months had experienced significantly higher bone strains during the loading task than those who gained the least [45]. These types of studies may be able to identify osteogenic targets for future exercise interventions.

Virtual Mechanical Tests

Fracture Risk Assessment

The occurrence of a fracture depends on an event, such as a fall, which loads the bone beyond its capacity. Because fracture events occur infrequently, clinical trials require large numbers of participants to detect a fracture reduction effect. FEA-related outcomes are attractive as a more sensitive

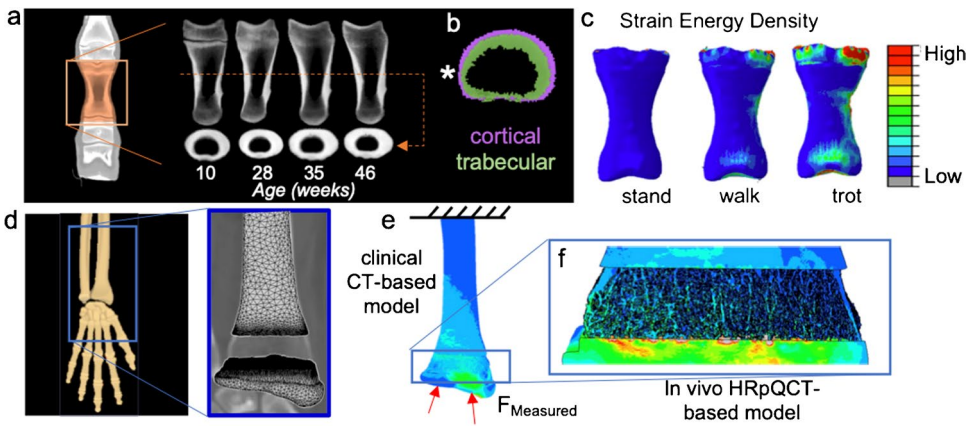

Fig. 3 (a) Longitudinal imaging of equine bone during postnatal development was used to characterize bone formation including (b) regions prone to fracture (* indicates region of low bone volume fraction). Models of equine bone under different types of exercise gaits (c) can be used as preclinical tools to determine whether strain energy density, a mechanical biomarker of remodeling, is elevated in the desired regions of bone. In humans, multi-scale modeling of the distal radius (d) using clinical CT-based models based on experimental measurement of external forces (e) have been used to understand the mechanical response in trabecular bone using higher resolution micro-finite element models (f)

and specific measure of a treatment effect than fracture incidence for osteoporosis drug studies [46••]. FEA can directly measure how an intervention affects bone mechanical behavior, which is often the target of the intervention. Virtual mechanical tests (Fig. 4) can be used to estimate bone strength parameters such as whole bone stiffness and failure load using reaction force–displacement data and appropriate failure criteria, respectively.

In vitro studies have consistently shown that CT-based FEA measures outperform areal bone mineral density (aBMD) measures, which are the current clinical standard, for fracture prediction at the hip and spine in aging and osteoporotic patient populations (e.g., higher odds ratios and sensitivity) [47–50]. However, clinical studies with prospective patient cohorts have failed to conclusively demonstrate that CT-based FEA serves as a better predictor of incident hip fracture than aBMD [15, 49]. Despite this, BMD and FE-based bone strength measures derived from opportunistic CT data have received FDA approval (VirtuOst) for identification of osteoporosis and fracture risk assessment, though clinical implementation is currently limited [15, 51].

Recent work using micro-FE models derived from HR-pQCT data found estimated failure load at the peripheral skeleton to be a strong predictor of incident fracture, independent of aBMD [52, 53]. These models are able to assess tissue-level mechanical properties, giving insight into the interplay of bone microarchitecture and strength as well as identify bone phenotypes associated with elevated fracture risk [54, 55•, 56].

Preclinical Fracture Healing

Subject-specific FE models are increasingly being used to measure bone healing and complement or replace other outcome measures. For example, predicted strains from FE models have been used to interpret histological findings in studies of load-dependent osseointegration of porous scaffolds [57] and dental implants [58–60]. Virtual compression testing using micro-FEA in rabbit models of fracture has been used to measure trabecular bone defect healing [61] and predict the strength of large-defect bone repair [62]. In rodents, micro-FE models have been used to quantify the effect of traumatic brain injury on fracture healing [63] and to characterize the strains associated with an osteotomy non-union model [64]. In ovine fracture healing studies, image-based virtual torsion testing out-performed radiographic scoring and morphometric assessments of the callus for predicting whole-bone torsional rigidity [16].

FE modeling also presents exciting opportunities to redesign experiments that reduce and refine the use of animals. Historically, the imaging data needed to build FE models has been acquired postmortem, so the analysis constitutes an endpoint of the experiment. Validated virtual mechanical tests could obviate the need for destructive postmortem sample preparation and mechanical testing. The increasing availability of live animal imaging techniques will allow for longitudinal in vivo assessments using virtual mechanical tests and reduce the number of animals needed to study the kinetics of bone repair across multiple timepoints.

Finally, FEA affords the ability to achieve greater standardization by adapting the experimental conditions to account for differences between animals or species. For example, real-time FEA was used in a mouse tail vertebral defect healing experiment to tune the applied mechanical loading on an individual-specific basis [65]. Applying a similar technique to a mouse femoral defect model successfully produced targeted strains in all animals, reduced variance within the experimental group, and avoided catastrophic

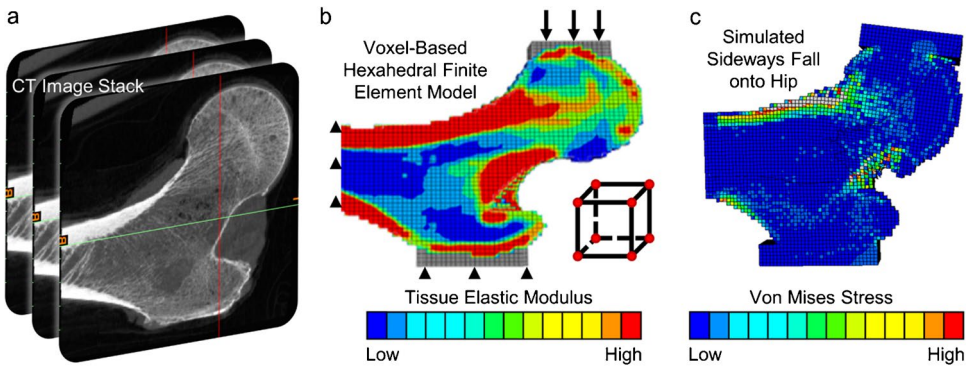

Fig. 4 Example of a proximal femur that is directly converted from a CT image to an FE model with hexahedral elements. (a) The region of interest is segmented from the CT image stack and resampled to create isotropic voxels. (b) Voxels are directly converted into linear hexahedral elements and assigned density-based material properties. Because the mesh itself is rather simple, more complex material definitions can be assigned without greatly increasing computational cost. (c) A virtual mechanical test that simulates a sideways fall onto the hip is performed. In this case, the primary outcome of interest may be stress, strain, overall stiffness, or the peak force required to generate a specific displacement (validated with mechanical testing)

overloading events [66•]. Using these techniques could also enable strategic design of translational animal models, as in one experiment that used FE analysis to justify an ovine model for testing human mandibular fixation devices [67].

Clinical Fracture Healing

When used in a clinical setting, image-based virtual mechanical testing can provide mechanical insights that are not currently available any other way (Fig. 5). For example, in tibial fractures, virtual torsion testing provides a quantitative assessment of structural callus formation that predicts time to union more reliably than patient-reported outcome measures or radiographic scores and may enable early diagnosis of compromised healing [68•]. Recently, virtual torsion testing was used to detect differences between implant groups in a tibial fracture healing study [69]. Patient-specific FEA also shows promise for tracking the longitudinal progression of bone healing following mandibular reconstruction surgery, which may support improved rehabilitation care [70].

In trabecular bone, subject-specific micro-FE modeling from HR-pQCT data has demonstrated the potential for measuring fracture healing in the scaphoid and distal radius (Fig. 6) [71–73]. Despite this potential, several challenges remain, including image registration in serial scanning, incompatibility with in situ hardware, image blur due to patient motion, and selection of an appropriate material model [74, 75]. In the applications focused on primary and metaphyseal bone healing, the inability to differentiate between bone fragments that are in close proximity versus those that are actually structurally united results in proximity-connectivity errors that likely lead to overestimation of stiffness [72].

Insight into Clinical Interventions

Because FEA can capture the mechanical effects of changes in bone structure, it can also be used to understand the effect of specific interventions. For example, FE models have documented loss of tibia strength after spinal cord injury [76] and shown that the related structural changes may not be recoverable, even with drug treatment [77]. FEA outcomes can also have better sensitivity than 2D imaging-derived measures like dual energy X-ray absorptiometry (DXA). Clinical trials using FEA outcomes have detected clinically important increases to distal femur ultimate torsional strength among people with spinal cord injury who received functional electrical stimulation assisted rowing combined with zoledronic acid, and large decreases among those with rowing only [78]. Another study in individuals with spinal cord injury showed that a combination of teriparatide and mechanical vibration significantly increased proximal tibia torsional stiffness after 12 and 24 months, compared to no change with either intervention alone [79]. These examples highlight the ability of FEA to detect clinically important changes in bone strength and stiffness, which were not always apparent from DXA data alone.

Current Challenges and Critical Needs

FEA-derived biomarkers in bone have been useful in developing fracture risk assessments, understanding fracture healing, assessing the effects of clinical interventions, and providing insights into growth and adaptation in vivo. In the near future, there are clear opportunities to expand this area of research to new indications by examining the limitations

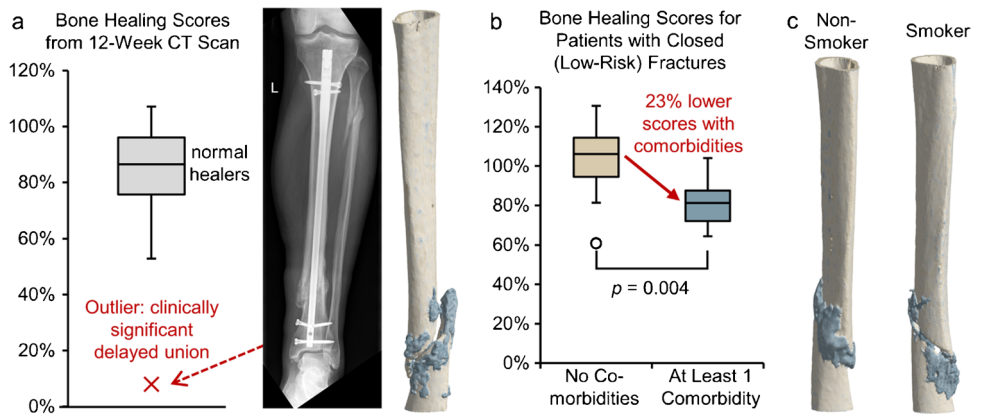

Fig. 5 Examples of clinical applications of virtual mechanical testing to measure tibial fracture healing using a bone healing score: (a) virtual mechanical testing objectively detected delayed healing in a mixed cohort of open and closed fractures; data from [68•]. (b) In a cohort of closed tibial fractures, patients with comorbidities had significantly lower bone healing scores from their virtual mechanical tests, a difference that was not captured in any other outcome measure. (c) Image-based FE models for two patients from (b) with nearly identical tibial fracture patterns; the non-smoker had a bone healing score of 116% while the smoker had a bone healing score of 78%

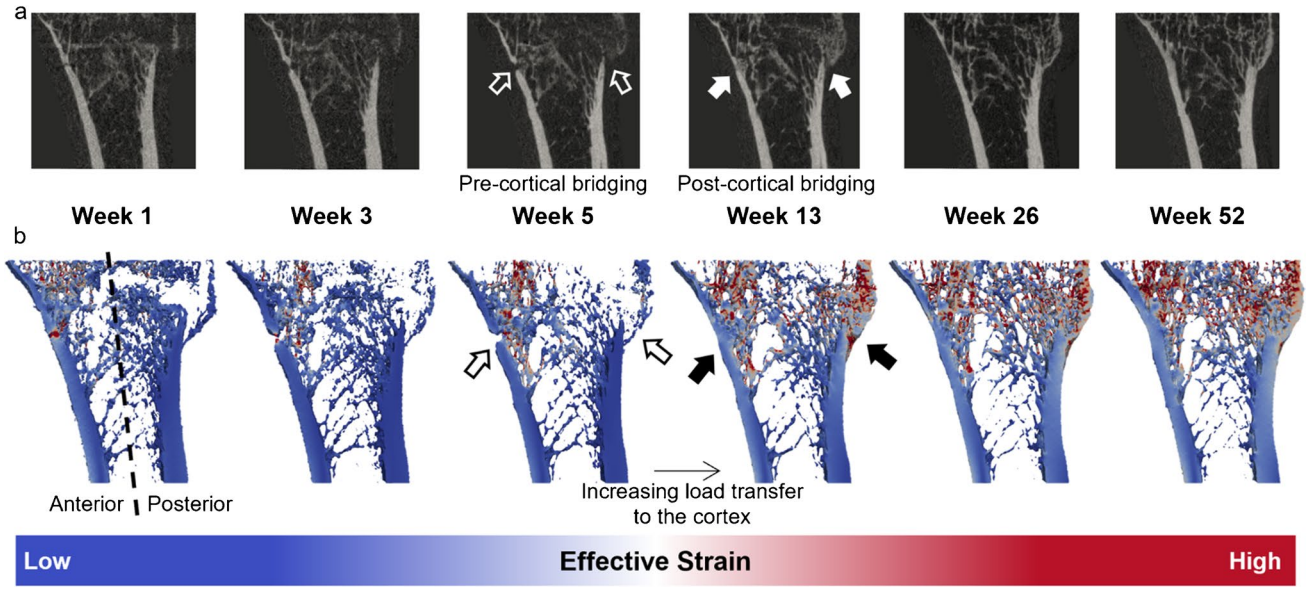

Fig. 6 (a) High-resolution peripheral quantitative computed tomography (HR-pQCT) images and (b) associated contour plots of effective strain from a 33-year-old female with a dominant arm distal radius fracture. Recovery of the load transfer from the trabecular to the cortical bone compartments occurs between 5 and 13 weeks post-fracture, concurrent with cortical bridging observed in the mid-sagittal plane of the HR-pQCT slice (arrows)

associated with the assumptions involved in creating image-based FE models.

Image-Based Material Properties

The assignment of bone material properties in FE models remains a source of debate, with various approaches used by different research groups. For the purposes of comparative studies, for example when comparing the effect of different loads on the same bone within a given study, the systematic errors introduced by material property assignment are mitigated. Critically, studies using FE models must report the imaging parameters, scanner settings, reconstruction kernels, precision, repeatability, and reproducibility of equipment and methods. Readers are referred to a summary of best practices in obtaining computed tomography data for quantitative analysis found in [80].

One open challenge in modeling the mechanical properties of mineralized tissues is the difficulty of characterizing tissues that cannot be readily obtained from human cadavers, such as fracture callus and physes in developing children. These tissues are unlike cortical and trabecular bone, where direct validation of FE model material properties can be performed. Similarly, collagen cross-linking, advanced glycation end products, and the water content in bone also contribute to bone properties but are currently not accounted for in CT-based FEA. The degree of error in FE models of bone from individuals with diseases that affect the non-mineral components is not known and requires further research. Modeling these specific cases requires inferences from other species and may be enhanced in the future with the development of radiation-free imaging methods such as magnetic resonance (MR) imaging.

In a clinical setting, a major challenge with current image-based FE methods for measuring and modeling bone is that CT scanning exposes the patient to ionizing radiation. Dose reduction protocols and improved reconstruction kernels now allow ultra-low-dose CT-to-FE analysis in the distal extremities [68•]. As such, in contrast to standard clinical CT, HR-pQCT offers a low effective radiation dose procedure for imaging limb extremities [74]. One limitation of this modality is that HR-pQCT scanners are not widely available and their field of view is limited to a small volume of interest in the distal extremities. Regardless of imaging modality, radiation exposure remains a significant concern for serial imaging of radiosensitive anatomic sites including the head, chest, and groin, and higher-risk patient groups such as children. An opportunity for innovation is in the development of surrogate markers for bone mechanical properties that can be obtained through MR imaging protocols. Ultrashort echo time (UTE) MR sequences have been used to generate FE models of distal tibia trabecular bone with strong correlations between experimental and virtual compressive stiffness measures [81]. Moreover, efforts are being made to develop empirical relationships between UTE-MRI measures of collagen-bound water and pore water concentrations and tissue material properties (i.e., elastic modulus and strength) at the organ scale [81]. MR-based FEA also shows promise for clinical assessment of hip fracture risk [82, 83].

Despite these successes, reliable methods for assigning material property behavior based on signal attenuation in MR-based FEA are not yet well defined or accepted, prohibiting widespread direct adaptation of CT-based FEA pipelines for MRI data. MR-to-FE methods are clearly in their infancy compared to CT-based methods, and further work is needed to validate MR-based markers of bone mineral density.

Boundary Conditions

In the case of virtual mechanical tests, FEA simulations provide noninvasive information about physiologically relevant, but simplified loading scenarios that often replicate the conditions of a benchtop mechanical test and can be validated. Thus, the majority of these models are only valid for the specific loading scenarios from which they are validated, and further work is needed to assess the potential insights to be gained from virtual loading modes that are not direct surrogates of in vitro experiments. Regardless of the loading scenario to be simulated, FE model precision must be assessed and reported [84], so that the limits of detectable change can be determined.

The potential for understanding true physiologic loading lies in muscle-driven FEA, but as these approaches become more sophisticated and includes more assumptions, it becomes more challenging to assess model accuracy and validity because experimental measures of bone mechanical biomarkers are limited. A better understanding of how model parameters affect predicted outcomes is needed and additional insight may be gained from foundational parametric studies [85]. Above all, readers should be cautious when comparing results between studies, especially when the models have high-complexity, due to potential differences in how the models are constructed. Furthermore, the labor-intensive nature of muscle-driven FEA tends to result in studies with smaller sample sizes.

Validation

The lack of a publicly available, heterogeneous, and comprehensive dataset for methods validation prohibits sufficient assessment of the robustness of mechanical bone biomarkers derived from image-based FE modeling. In the future, open access software and data repositories will help drive the selection of the appropriate analysis methods for specific applications. This will make it possible to immediately access and cross-check updates to methods and their effects on parameters. With proper validation of new technologies, we can ensure that FE-based analyses add value in patient diagnosis and care.

Clinical Translation

As mentioned, the clinical implementation of FEA-based biomarkers is in the early stages of growth [49] and more work is needed to understand how the data from FEA can be practically integrated into a clinical setting. For example, while numerous mechanical biomarkers of bone can be measured from FEA, an easily interpretable and population-normed summary score, similar to FRAX or DXA, is needed to define risk of fracture. Strategic investments are critically needed to develop image-based mechanical biomarkers for use as decision-support tools in a clinical setting.

Concluding Remarks

With continued evolution of technology and best practices, the utility of bone mechanical biomarkers using image-based FEA will undoubtedly increase. Here, we have summarized some of the methods by which computational biomarkers can be used to provide insights into the response of bone to a range of conditions spanning both healthy and pathological states at all stages of life. Effort is still needed to ensure that the context for the use of FEA is justified for the question at hand and that underlying assumptions are understood and transparent. With such effort, and continued collaborations between engineers and medical practitioners, translatable outcome measures for evaluating bone response to loads will be possible.

Data Availability Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Declarations

Conflict of Interest HD discloses stock or stock options in OrthoXel, DAC (Cork, Ireland) and is an inventor of patents licensed to or held by OrthoXel. There are no other relevant competing interests for any of the authors.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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