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Editorial

Trabecular Bone: Light as a Feather, Stiff as a Board

Trabecular bone is a crucial and unique load-bearing tissue in the skeleton found near the ends of long bones and in the vertebral bodies. Trabecular bone has the ability to rapidly adapt to the mechanical loading environment by optimizing its mass and structure in order to bear high loads with as little bone tissue as possible, allowing bones to remain strong while minimizing their weight. Measuring the load-bearing capacity of trabecular bone is crucial for assessing fracture risk, since osteoporotic fractures most often occur at skeletal sites primarily consisting of trabecular bone. However, the unique porous, heterogeneous, and anisotropic structure of trabecular bone makes quantification of its material properties technically difficult. Advances in the ability to determine trabecular bone strength therefore have the potential to drastically improve the diagnosis of fracture risk. Additionally, studying the adaptation of trabecular bone to the mechanical loading environment may provide insight into mechanisms contributing to bone fragility and fracture risk. This review focuses on state-of-the-art research being performed in these two intricately related areas: assessment of trabecular bone biomechanics and trabecular bone mechanobiology.

The optimization of bone begins when resident bone cells sense mechanical strains or other cues initiated by mechanical loads. Directional forces on bone transfer microstresses to local cells, leading to signal transduction and the initiation of bone adaptation. The end result (reactive bone growth or loss) in the renormalization of tissue strains to "desirable" magnitudes. The pathway from cell detection of physical forces (strain) to increased bone volume, trabecular mineralization, and changes in mechanical properties, however, is not well understood. Much recent work has focused on revealing singular factors to describe gross level changes. For example, the ability of the osteocyte to detect applied forces is debatably the result of three theories whose individual contributions are difficult to study in vivo [1]. Additionally, the resultant deformation is multicomponential with bone marrow, trabecular (cancellous) bone, and cortical bone all factoring in. Researchers are now attempting to bridge the gap between the mechanobiology and biomechanics while searching for new contributors and more refined parameters for predictive equations. Through the advancement of finite element (FE) analysis, multiscale modeling is improving accuracy and reliability.

The current review features several studies that investigate factors contributing to the mechano-adaptation of trabecular bone. To assess the role of tissue deformation on the mechanosensitive constituents of bone marrow, Metzger et al. [2] applied FE meshes and fluid structure interaction analysis to determine forces applied to bone marrow capable of stimulating mechanotransduction. Notably, Metzger et al. took individually assessed bone and marrow parameters and studied them in tandem. They report that bone deformation rates, bone porosity, and the mechanical properties of the bone marrow itself have the potential to impart significant stimulation leading to bone marrow morphologic changes that could be associated with aging and disease. Vaughan et al. [3] applied a similar model to explore the effects of decreased bone volume, as seen in osteoporosis, on the forces distributed throughout mesenchymal stem cells (MSC) in bone marrow. They showed that osteoporotic changes alter forces to maintain normal MSC stimulation levels. Specifically, increased trabecular stiffness and axial alignment increased the mechanical forces despite a slight shielding effect from increased adipocyte content. Banijamali et al. [4] investigated bone density changes of a human femur model as a result of different loading patterns. A program was developed that iteratively changed the structure of trabecular bone in the model by keeping the local stress in the structure within a defined stress range. Trabecular bone structure was obtained for three load cases: walking, stair climbing, and stumbling without falling. They found that the adapted trabecular bone architecture is consistent with the natural bone morphology of the femur.

Other studies featured in this review used in vivo models to study the adaptation of trabecular bone to therapeutic treatments, mechanical loading, or injury. Altman et al. [5] studied the effect of combination parathyroid hormone (PTH) and bisphosphonate therapy on trabecular connectivity and total bone volume fraction. They applied their in vivo microcomputed tomography (μCT) detection of rod connection and plate perforation filling in rats to an FE model to predict stiffness, showing that combination therapy significantly improved bone stiffness when compared to monotherapy. Similarly, Cardoso and Schaffler [6] compared the effect of disuse bone loss and risedronate therapy, while testing ultrasound wave propagation to differentiate elastic constants and anisotropy between treatment and control.

There are many examples in the literature of adaptation of bone to prolonged loading in animal models, but never in human models as is prospectively documented in an in vivo study by Bhatia et al. [7]. In this study, changes in local bone mineral properties were quantified using serial CT scans of women's nondominant wrists after a 14-week course of axial loading. FE models were used to calculate strain and relate them to bone mineral density and composition. In contrast, Christiansen et al. [8] investigated catabolic adaptation of trabecular bone following a musculoskeletal injury in mice. An array of inflammatory cytokines is released systemically following traumatic injuries, which can initiate tissue destruction away from the initial source. Christiansen and his colleagues documented trabecular bone changes in the L5 vertebral bodies of mice following noninvasive anterior cruciate ligament (ACL) injury using μCT and FE modeling. They report that trabecular bone volume and trabecular number both decrease at this distant skeletal site, which may have implications for fracture risk systemically.

While the previous papers utilized FE modeling and imaging techniques to analyze mechanotransduction and adaption of bone, other studies featured in this review focus on refining computational models for accurate in vivo assessment of trabecular bone mechanical properties and mechanisms contributing to the strength of trabecular bone. Lloyd et al. [9] aim to better understand the interplay between the microscale, mesoscale, and millimeter scale mechanical heterogeneity through their review of bone compositional and mechanical properties across these hierarchical levels, concluding that straying from homogenous models

has led to better predictive models. Furthermore, Kaynia et al. [10] add their support to heterogeneous models by investigating 12 different human trabecular specimens from a tissue mineral density (TMD) spatial variation standpoint, comparing μCT to the gold standard synchrotron radiation μCT-based model. They found that the influence of heterogeneity on apparent stiffness varies significantly from homogenous TMD models.

Others aimed to advance FE modeling by fine-tuning their equation input. By using an inverse FE algorithm, Zwahlen et al. [11] were able to create a feedback for experimental tissue strains to the FE model, such that the predictive model matched experimental results. They argue that the dimension of trabecular heterogeneity confounds current homogenous computed predictions and working backward can help overcome these obstacles, but not without limitations. Panyasantisuk et al. [12], on the other hand, investigated FE accuracy by altering the applied boundary conditions for trabecular bone. In this study, a comparison is made between theoretical conditions set by energy equivalence principles. A subset of boundary conditions, described in the author's previous work, shows promise for future applications. Finally, Fyhrie and Zauel [13] introduced a new parameter, "directional tortuosity," to the assessment of trabecular bone mechanical properties. By applying three-dimensional "shortest path" algorithms, Fyhrie and his colleague are beginning to understand trabecular bone stiffness as a function of tissue damage.

In conclusion, this special issue offers novel work to advance discoveries in the field of trabecular biomechanics. Through exploration of additional components involved in mechanobiology, reworking module constants, and expanding our understanding of the heterogeneous nature of trabecular bone, new insights into the dynamic and reactive properties of bone will aid in developing accurate models to correlate to healthy tissue, pathological tissue, and tissue under treatment. We would like to thank the editors of *Journal of Biomechanical Engineering* for providing the opportunity to share this special issue with the community. Additionally, we would like to express our gratitude to all who contributed to the issue, as authors, reviewers, advisors, and funding sources.

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