Ex Vivo Trabecular Bone Adaptation to Load is Predicted by Micro Finite Element Analysis

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INTRODUCTION: An estimated 12% of Canadians aged 40 and older were diagnosed with osteoporosis between 2015 and 2016 [1]. Further advancements in understanding the biomechanical behaviour of bone on both macro and micro scales could improve osteoporosis prevention, diagnosis, and treatment. Two methods for assessing bone behaviour include *ex vivo* and *in silico* [2]. *Ex vivo* experiments maintain and grow tissues in an environment that simulates *in vivo* conditions [3]. Using an *ex vivo* environment, live bones can be mechanically loaded to stimulate osteogenesis which is reflected by an increase in apparent elastic modulus (E_{app}) [4]. *In silico* refers to computer models that aim to predict natural processes. Many studies have used finite element analysis (FEA) to predict bone adaptation to mechanical stimuli. Three previously studied stimuli include strain energy density (SED) [5], von Mises stress (σ_{VM}) [6], and maximum compressive principal strain (ε_3) [7]. These studies, however, are often limited by assumptions of linearity, meshing accuracy, and lack of experimental validation. Therefore, this study aimed to predict bone adaptation from FEA modelled trabecular stress-strain fields. Trabecular bone adaptation to mechanical loading was measured in an *ex vivo* experiment and correlated against µCT-based FEA to predict the load response.

METHODS: Twenty-three viable bone cores were excised from an 18-month-old bovine sternum and stored in 3D-printed bioreactors with individual medium reservoirs at 37°C and 5% CO_2 for 21-days. Each bone core was tested in uniaxial quasi-static compression on day 0 with a Mach-1 mechanical testing apparatus (Biomomentum) using a -4000 µε displacement at 50 µε/s (Figure 1a). The apparent elastic modulus (E_{app}) was determined from the slope of the force-displacement curves. Bone cores were divided into "load" (n=12) and "control" (n=11) groups with equivalent day 0 mean E_{app}. The load group was stimulated with a cyclic load between -1000 and -5000 µε for 120 cycles at 2 Hz five days per week. Additional quasi-static tests were performed on day 8 and day 21 to track the change in E_{app} ($\%\Delta E_{app}$) over time. Following the 21-day experiment, the remaining bone cores (n=17) were µCT scanned at 20 µm voxel size (Vector^{4}CT, MILABS) and segmented (Mimics 23.0, Materialise). Compression loading of the load group cores (n=8) was simulated with µCT-based FEA (Abaqus 2017, Simulia) with contact between the bone and loading pistons. The resulting distributions for SED, σ_{VM}, and ε_3 were calculated and median values were recorded for each bone core. Linear regressions were completed between $\%\Delta E_{app}$ and the median value for each remodelling criteria. All data analyses were completed in MATLAB 2021b (MathWorks) and statistical analyses were completed in Origin 2021b (OriginLab Corporation). Mann-Whitney U tests were used to assess differences between the load and control groups, and a Friedman ANOVA with Dunn's multiple comparison post hoc test for differences within the same group (α=0.05).

RESULTS: The load group increased E_{app} by 63.4% between day 0 and 21 compared to 20.9% in the control group (p=0.010). Load group cores increased significantly between day 0 and 21 (p<0.001), whereas the control group increased significantly between day 8 and 21 (p=0.008). The median SED, σ_{VM}, and ε_3 averaged for the load group cores (n=8) were 739 J/m^3, 1.05 MPa, and -774 µε, respectively. Pearson R^2 values between the three mechanical stimuli and $\%\Delta E_{app}$ were 0.01, (p=0.806), 0.51 (p=0.046), and 0.72 (p=0.008), respectively.

DISCUSSION: The significant difference in $\%\Delta E_{app}$ between the two treatment groups highlighted the ability for *ex vivo* experiment to quantify bone adaptation when subject to mechanical strain for 21 days. When observing local mechanical stimuli using FEA, ε_3 best predicted the change in elastic modulus. Limitations of this study included a small sample size, variations in bone structure and cell viability, and assumed material homogeneity in FEA. Based on a power analysis from the 16 remaining bone cores from this study, a sample size of 24 per group is recommended for future *ex vivo* experiments to increase statistical power and account for lost specimens. Future work includes histology for cell viability and mineral apposition rate. µCT-based FEA will be improved with heterogeneous tissue moduli, and further validation including correlating measured local bone growth with the predicted FEA stress-strain field.

SIGNIFICANCE/CLINICAL RELEVANCE: The presented study demonstrated that *ex vivo* experimentation can be used to measure the load adaptation in trabecular bone, and that local stimuli, specifically ε_3, can predict trabecular bone adaptation. Understanding how trabecular bone adapts in response to load can aid clinicians in developing treatments for injuries and bone diseases such as osteoporosis. Additionally, design engineers can use FEA models to facilitate predictions regarding bone adaptation to improve total joint replacements.

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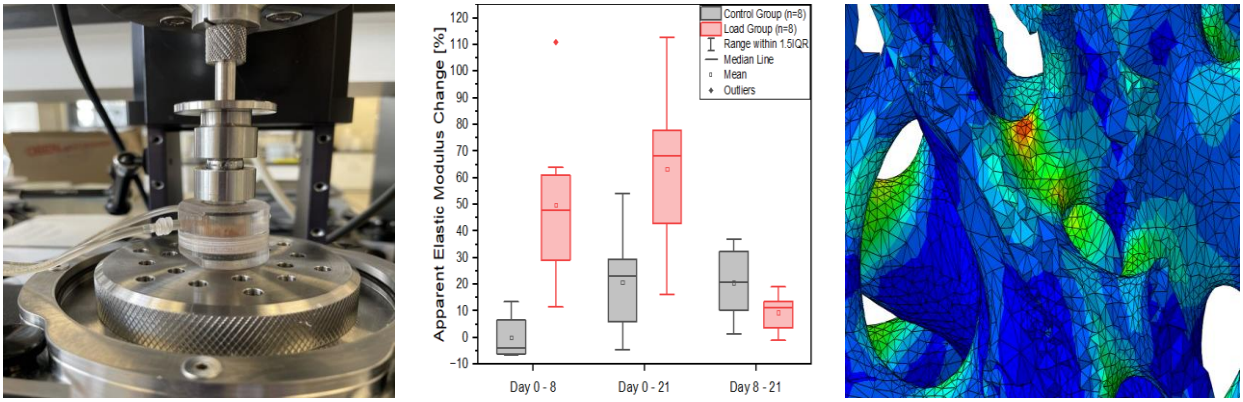

Figure 1: (1a) Mechanical testing and loading in bioreactor with Mach-1 apparatus. (1b) Percent change in elastic modulus for load and control groups. (1c) Example of local von Mises stress distribution in trabeculae from FEA compression load on core.