Combined Treatment with Dietary Inulin and a Calcimimetic Agent Improves Cortical Bone in a Rat Model of Chronic Kidney Disease

Daniel J. Stephen[1], Corinne E. Metzger[2], Emily K. Matter[2], Shruthi Srinivasan[3], Kalisha O'Neill[3], Neal X. Chen[3], Sharon M. Moe[3], Matthew R. Allen[2]

Indiana University School of Medicine[1], Department of Anatomy, Physiology, and Cell Biology[2], Department of Medicine[3]

Background: Chronic kidney disease (CKD) leads to an increased risk of fractures. The increased skeletal fragility is partly due to secondary hyperparathyroidism commonly seen in CKD patients, which leads to cortical bone deterioration. Pharmacological lowering of parathyroid hormone (PTH) via calcimimetics is a key treatment, but fracture risk is not altered in clinical trials. Previous preclinical work has shown dietary inulin reduces PTH levels potentially through alterations of the gut microbiome to reduce gut-derived uremic toxins, but bone mechanics did not improve. Due to the complex nature of CKD, combination therapy with a PTH lowering pharmacotherapy, like etelcalcetide, and dietary inulin may better mitigate skeletal fragility.

Methods: Male Cy/+ rats were treated with either 10% dietary inulin, 3x/week KP injections (a rat analog of etelcalcetide), or combination for 10 weeks. Bone mechanical properties were tested via three-point bending of femora. Microstructural cortical bone parameters of the midshaft femur were assessed via micro-computed tomography. Bones were analyzed via histomorphometry to evaluate bone turnover, and serum PTH and kidney biomarkers were obtained.

Results: Both treatments significantly lowered PTH independently and in combination, with the combined treatment demonstrating a 60-fold lower PTH compared to untreated CKD. Bone mechanical properties, including ultimate force, stiffness, total work, and toughness, were significantly improved in combination treatment compared to untreated CKD. Combined treatment had the greatest effect on bone microarchitecture, displaying 10.6% higher cortical bone area than untreated CKD. Additionally, untreated CKD had an average of 7.4% cortical porosity while combined treatment had approximately 0.1% cortical porosity. Combined treatment lowered bone turnover compared to untreated CKD.

Conclusions/Implications: These data demonstrate that combined treatment was the most effective at improving bone structure and mechanical properties. This indicates combined treatment with dietary inulin and a calcimimetic could be a promising treatment option for treating the bone complications of CKD.