Dr. Thomas Nickolas [Multiple PI award with Dr. Michelle Denburg (Children's Hospital of Philadelphia)]

Children and adolescents with glomerular disease have unique and potentially modifiable risk factors for compromised bone health, but our current understanding of skeletal fragility in glomerular disease is lacking. In the first large population-based cohort study, we recently found that primary glomerular disease was independently associated with a >45% increased risk of incident spine and hip fracture, and that hip fracture risk was >1.5-fold greater in patients younger vs. older than 40 years of age. Mechanisms that drive increased fracture risk in glomerular disease are not clear but likely multifactorial. Our prior work in the Neptune cohort demonstrated that glomerular disease is associated with disturbances in vitamin D and mineral metabolism, and patients with glomerular disease are also exposed to medications which may negatively impact bone health. Identifying modifiable factors that compromise bone strength will facilitate the development of strategies to reduce fractures and other skeletal complications across the lifecourse. The primary objectives of this study are to: (1) determine the impact of glomerular disease on bone strength and (2) investigate the pathophysiologic underpinnings of impaired bone strength in glomerular disease. The proposed multi-center study will leverage the infrastructure of the NIH-funded CureGN prospective cohort study and the resources of two health systems [Children's Hospital of Philadelphia (CHOP)/University of Pennsylvania (Penn) and Columbia University Medical Center] with expertise in state-of-the-art high-resolution bone imaging and biopsy methods, to conduct the first prospective, longitudinal study to assess determinants of impaired bone quality and strength in glomerular disease. 150 CureGN participants (100 adults/50 children) and 120 age-, sex-, race-, and body mass indexmatched healthy reference participants will be evaluated at baseline and 12 months. The new 2nd generation high-resolution peripheral quantitative computed tomography (HR-pQCT) device will be used to assess bone microarchitecture and generate micro-finite element analysis (μFEA) estimates of bone strength. We will also determine the DXA measures of areal BMD and bone mineral content (whole body, spine, hip and radius) that reflect bone deficits captured by HR-pQCT. Tetracycline double labeled transiliac crest bone biopsy specimens will be collected from a subset of 40 adult CureGN participants and analyzed by 2D histomorphometry; by microCT for 3D cortical and trabecular microarchitecture and estimated strength by finite element analysis; and by Nanoindentation/Raman spectroscopy for bone mechanical and matrix-level characterization. Concurrent clinical and biochemical profiling will allow for assessment of predictors of prospective changes in biomechanical competence and cortical and trabecular microarchitecture by HR-pQCT as well as tissue-level bone matrix and mechanical properties. The results of this study will serve specifically to inform future multicenter clinical trials of interventions to mitigate the effects of glomerular disease on bone health and fracture risk in children and adults with glomerular disease.