INTRODUCTION AND AIMS: Decreased kidney function, as seen in CKD patients, has a profound effect on a multitude of interlinked secondary pathophysiological abnormalities, including metabolic acidemia, mineral and bone disorder (CKD-MBD) which comprise secondary hyperparathyroidism (SHPT) and extraskeletal calcification. These disorders contribute to increased morbidity and mortality. The aim of this study is to develop a comprehensive mathematical model describing bone remodeling and mineral homeostasis that enables in silico exploration of the ramifications of disease- and therapy-induced disturbances, with the goal of expanding knowledge and providing a rationale for new therapeutics.

METHODS: A mechanistic model describing bone remodel activities is developed to quantify the interrelations of the basic multicellular unit (BMU), namely osteoclasts, osteoblasts, and osteocytes. The synchronized activities of these BMUs are mediated by cell-cell (RANK-RANKL-OPG) and intracellular (Runx-2-CREB-Bcl-2) signaling pathways, cytokines (MCSF, TGFβ), PTH, sclerostin, and endocrine and paracrine feedbacks. The applicability of the resulting model is demonstrated by comparing model predictions of different pathologies (e.g., PHPT and SHPT, chronic metabolic acidemia, uremia) to clinical observations.

RESULTS: Our model qualitatively predicts clinically observed responses to induced PHPT and SHPT and acidemia, and their effects on extracellular calcium (Ca) and phosphate (PO4) levels and bone mineral density (BMD). We accurately predict differential responses of osteo-anabolic and catabolic effects of continuously and intermittently elevated level of PTH, respectively. In addition, the model also predicts the catabolic effect of metabolic acidosis on bone remodeling, including decreased BMD, and increased efflux of Ca and PO4. Using the model, short- and long-term in silico...
study of disease-induced primary, secondary or combination of disturbances can be undertaken to understand and investigate the effectiveness of different therapeutic interventions.

CONCLUSIONS: The model can be used to simulate bone remodeling homeostasis and to explore therapeutic and pathophysiological states of the various diseases through (1) in silico assessments of effect of therapeutic modality for CKD patients and other patients with metabolic bone diseases, (2) understanding intended and unintended disease-specific variations and alterations, (3) optimizing and personalizing dosing regimens to achieve acceptable target goals (e.g., maintenance of BMD), (4) simulation of infeasible clinical tests, and (5) generation of predictions of unmeasurable physiological variables. The in silico assessment can serve as a complementary tool for gaining further insights into the hierarchically complex dynamic features of bone and mineral metabolism.