Calcium Homeostasis and Bone Remodeling: Development of an Integrated Model for Evaluation and Simulation of Therapeutic Responses to Bone-Related Therapies

M.C. Peterson[1], M.M. Riggs[2]

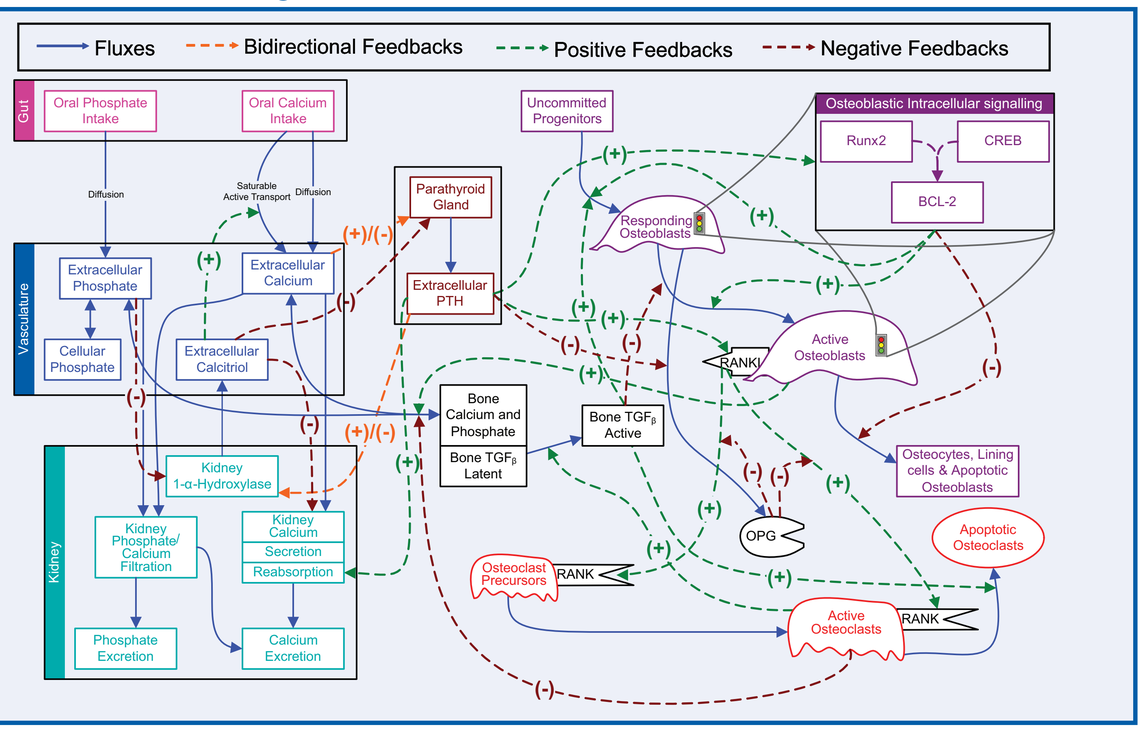
[1]Amgen Inc., Thousand Oaks, CA USA, [2]Metrum Research Group, LLC, Tariffville, CT USA

INTRODUCTION

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration with a subsequent increase in bone fragility and susceptibility to fracture. It affects an estimated 75 million people worldwide. In addition to the increased fracture risk, patients with osteoporosis may have spinal kyphosis, potentially leading to disfiguration, respiratory and digestive complications, and pain. Osteoporosis affects men and women: 1 in 3 women over 50 will experience osteoporotic fractures, as will 1 in 5 men.[1]

In osteoporosis, there is often an increase in bone turnover rate, and an imbalance resulting from bone resorption exceeding bone formation. Therefore, a model that characterizes and subsequently predicts expected rates of bone turnover, due to both natural disease progression and therapeutic intervention, would allow for evaluation of various affecting mechanisms. Such a model could provide *a priori* insight into previously unexplored pathways (or combinations of explored and unexplored pathways) to identify targets suitable for therapeutic exploration. It could provide a quantified magnitude of effect (e.g., % inhibition or stimulation of each pathway) needed to elicit therapeutic benefit, as well as the expected time course of on- and off-set of the effect. The model also could be explored for plausible mechanisms to explain clinical observations of therapeutic effects. Specifically, it may help to explain possible mechanisms for the anabolic effect of intermittent PTH administration versus its catabolic effect following continuous administration, or evaluation of the time-course of bone turnover marker (BTM) changes following discontinuation of therapy.

Figure 1: Schematic of Integrated Model to Describe Calcium Homeostasis and Bone Remodeling



METHODS

General Model Design (Figure 1) Predicated on 3 Manuscripts:[2-4]

- Calcium (Ca) homeostasis[2] = physiologic requirement to maintain extracellular Ca balance, regulated by Ca influx from gut and bone, and efflux to bone and urine (kidney). Each flux is regulated through a series of feedback and signaling mechanisms.
- Bone remodeling[3] = osteoblast function relates to bone formation and osteoclast function to bone resorption. Regulation is maintained through parathyroid hormone (PTH), receptor of NF-Kappa B (RANK)-RANK Ligand (RANKL)-Osteoprotegerin (OPG) system and transforming growth factor beta (TGF-β).
- PTH intracellular signaling[4] = continuous PTH administration leads to bone catabolism, once-daily (QD) PTH administration leads to bone anabolism. PTH-mediated anti-apoptotic signaling can account for these kinetic differences.

Data Sources

- Extensive PubMed literature research (1960-2007), Amgen® clinical data
- Specific disease states/therapeutics: renal insufficiency[5], QD PTH administration[6], Forteo® (teriparatide)[7], anti-RANKL therapeutic (Amgen® internal data)
- Parameters fixed or estimated where appropriate based on literature reported values and Amgen® internal data

Model Expansion and Feedback Integration

- Calcium and phosphate compartments added to incorporate oral administration, bioavailability, and absorption rates
- Incorporation of generalized cell signaling concepts, e.g., TGF-β mediated osteoblast/osteoclast homeostasis distinct from osteoclast numbers
- Positive and negative feedbacks parameterized as hyperbolic (E_{max}) relationships, with physiologically relevant maximums (or minimums). Sigmoidicity terms incorporated as needed to provide responses consistent with observed data.

Modeling Software

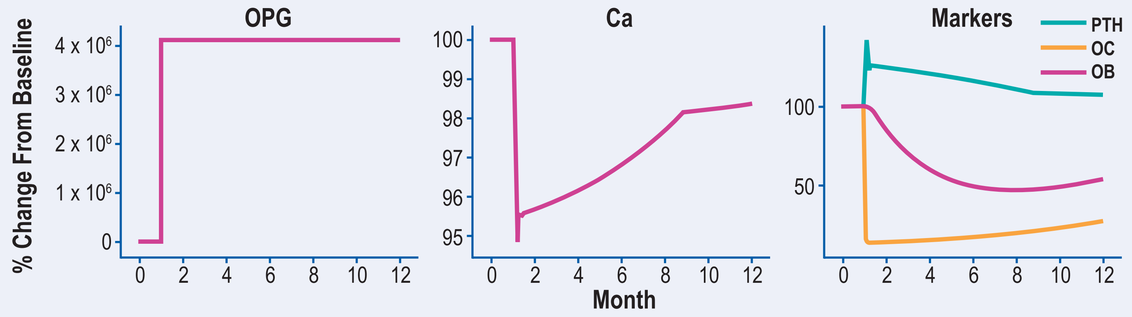
- Berkeley-Madonna 8.0 (Berkeley, CA)

Model Applied to Evaluate Therapeutic Scenarios:

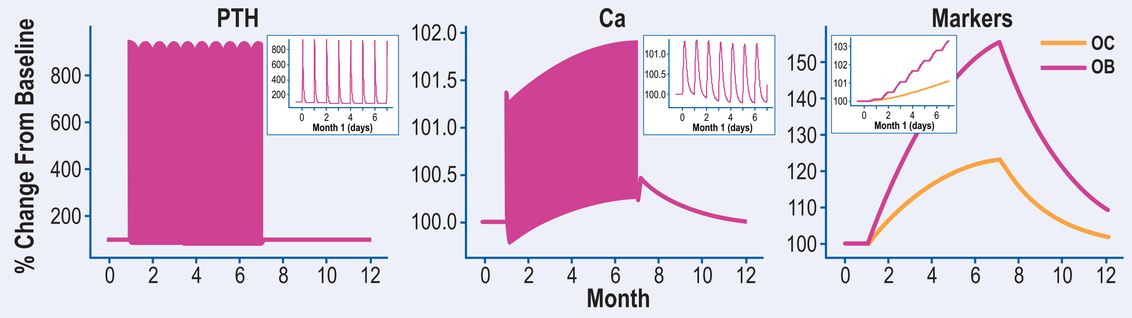
- (1) continuous OPG infusion, (2) once-daily- and (3) continuous-PTH administration, (4) hyper- and (5) hypo-calcemia, and (6) progressive renal insufficiency

RESULTS

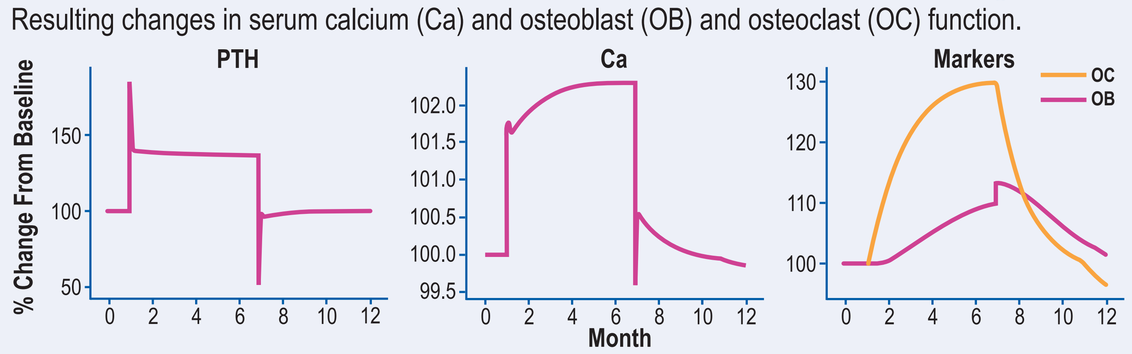
Scenario 1: Anti-RANKL effects via continuous OPG infusion from Months 1 through 12. Resulting changes in serum calcium (Ca) and PTH, and osteoblast (OB) and osteoclast (OC) function.



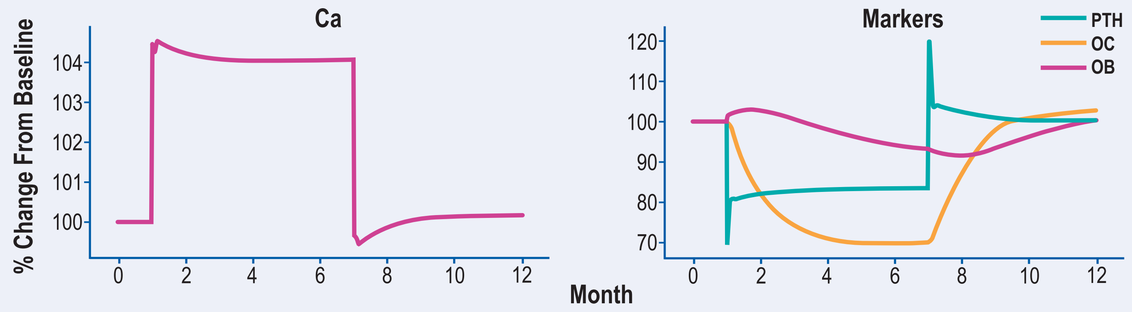
Scenario 2: Once-daily PTH administration from Months 1 through 7.
Resulting changes in serum calcium (Ca) and osteoblast (OB) and osteoclast (OC) function.



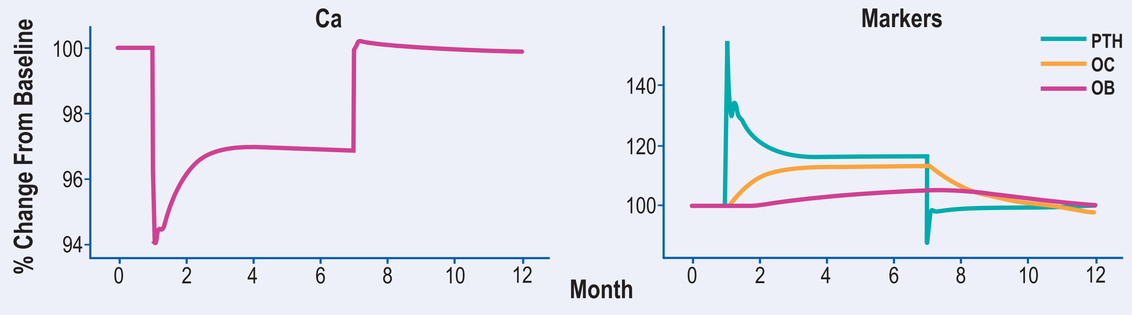
Scenario 3: Continuous PTH administration from Months 1 through 7.
Resulting changes in serum calcium (Ca) and osteoblast (OB) and osteoclast (OC) function.



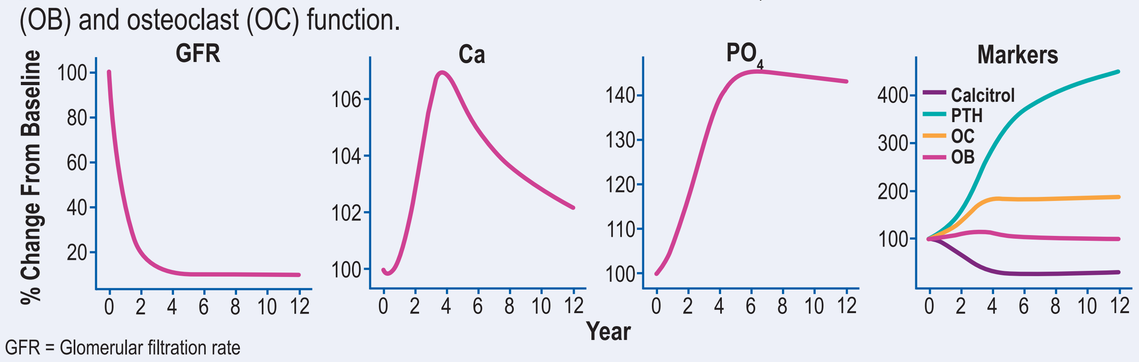
Scenario 4: Hyper-calcemia via increased Ca influx from Months 1 through 7. Resulting changes in serum PTH and osteoblast (OB) and osteoclast (OC) function.



Scenario 5: Hypo-calcemia via decreased Ca influx from Months 1 through 7. Resulting changes in serum PTH and osteoblast (OB) and osteoclast (OC) function.



Scenario 6: Progressive renal insufficiency (decreased GFR) over 12 years. Resulting changes in serum calcium (Ca), phosphate (PO_4), calcitriol, PTH, and osteoblast (OB) and osteoclast (OC) function.



GFR = Glomerular filtration rate

CONCLUSIONS

We have developed a robust physiologic model that adequately describes continuous changes in biomarkers and electrolytes including calcium, phosphate, PTH, and markers of bone turnover, consistent with literature and Amgen internal data.

This model may allow for investigation of therapeutics under development, prediction of cytokine mediators of bone homeostasis, and provide a platform for hypothesis testing prior to clinical investigations.

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