A PHYSIOLOGICALLY-BASED, MULTISCALE MODEL USED TO PREDICT PROGRESSIVE BONE MINERAL DENSITY LOSS DUE TO CHRONIC RENAL DISEASE

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Abstract

Purpose: *Extend an existing physiologically-based model of calcium and bone homeostasis to enable prediction of changes in bone mineral density (BMD) observed during the progression of renal failure.*

Methods: *The underlying physiologic model has been published and is described in Bone 46 (2010) 49–63.[1] Clinical data (plasma calcium, phosphate, parathyroid hormone (PTH), calcitriol, bone remodeling markers and bone mineral density (BMD)) measured at various degrees of renal function were digitized from Rix et al. (Kidney Int 56 (1999) 1084–93).[2] A mathematical expression describing progressive renal function loss as an exponential decrease in glomerular filtration rate (GFR) from a baseline of 100 mL/min to approximately 16 mL/min 10 years later was constructed and invoked in the model as: GFR = 10 + 90*exp(-0.27*time(yrs)). The model appropriately predicts the evolution of secondary hyperparathyroidism (HPT) caused by diminished renal phosphate clearance and increased plasma phosphate associated with GFR loss. Since an important sequelae of HPT is marked elevations in bone resorption and loss of BMD, a differential equation linking the prior description of bone remodeling markers was developed to predict longitudinal BMD changes during chronic worsening renal function.*

Results: *A differential equation model linked bone remodeling markers to elimination and formation rates of BMD. BMD was described with first order elimination ($0.000145\ h^{-1}$) and formation and elimination rates scaled by percentage of resorption and formation markers. The composite model predicted lumbar spine BMD losses from baseline at Month 28 (GFR = 58 mL/min), 50 (GFR = 39 mL/min) and 120 (GFR = 16 mL/min) of approximately –0.98%, –3.0%, and –6.5%, respectively, compared to the observed BMD values in corresponding renal function groups, scaled to a baseline of 100 mL/min, of –0.5%, –4.0%, –8.1%, respectively.*

Conclusions: *The extended multiscale model is able to predict changes in BMD during the progression of renal impairment. This model provides a platform for evaluating therapeutics and interventions targeted at underlying causal mechanisms, as well as symptomatic treatments.*

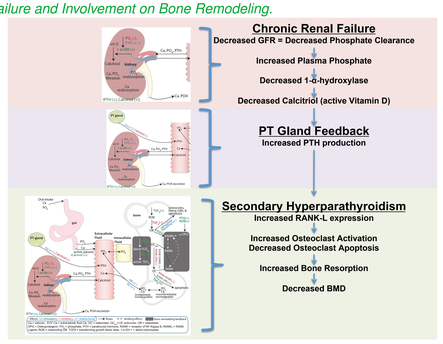
OBJECTIVE

- Link pathophysiology of secondary hyperparathyroidism due to chronic renal failure through to longitudinal changes in bone mineral density (BMD).
  - Explore effects of secondary hyperparathyroidism on bone remodeling markers.
  - Link changes in bone markers with BMD changes using turnover model.

BACKGROUND

- Calcium (Ca) homeostasis and bone remodeling (*Figure 1*)
  - Multiscale involvement: intracellular signaling, endocrine feedbacks, and multiple organs.
  - Maintains tight control of extracellular fluid (ECF) Ca concentration.
  - Regulates bone remodeling: maintain bone structure/quality.
- Chronic renal failure and secondary hyperparathyroidism.[2]
  - Loss of renal function manifests into PT gland hyperplasia[3] and, secondarily, hyperparathyroidism.
  - Clinical observations: plasma PTH increased 7- to 15-fold.[2,4]
  - Secondary hyperparathyroidism leads to increased net bone resorption and bone loss (renal osteodystrophy).
  - Therapeutic intervention includes calcitriol (infusion)[5] and calcimimetic (oral, e.g., cinacalcet[6]) treatments.

Figure 1: Etiology of Secondary Hyperparathyroidism Due to Chronic Renal Failure and Involvement on Bone Remodeling.



Modified from Figure 1 of Peterson and Riggs, 2010[1]

METHODS

- Prediction of clinical data using existing multiscale model (*Figure 1*)[1]
  - GFR chronic decline from 100 mL/min to approximately 16 mL/min 10 years later (GFR = 10 + 90*exp(-0.27*time(yrs)))
  - Phosphate (PO4), calcitriol and PTH changes affected by decreased GFR.
  - Associated effects on bone remodeling markers (predicted only, assuming no effect of renal function on marker clearance):
    - Bone resorption marker (osteoclast function): serum cross-linked C-telopeptide of type I bone collagen (CTx).
    - Bone formation marker (osteoblast function): bone specific alkaline phosphatase (BSAP).
- Extend model to link bone marker changes with BMD.
- Examine therapeutic intervention effects on Ca, PTH and BMD.
  - CaSR agonism (calcimimetic): investigated as constant 0.25, 0.5, 0.75 and 1 mM calcium equivalents.
  - Calcitriol infusion: 1.25 and 2.5 μg q.o.d.
- Equations (1–4): PTH and its dependencies on Ca and calcitriol feedback to PT gland

$$\frac{d(PTH)}{dt} = S_{\mathrm{PTH}} - 7.14 \cdot PTH$$

$$PTH_{t=0} = 53.9 \text{ pmol}$$
$$PTH_{conc} = \frac{PTH}{14 \text{ L}} \qquad (1)$$

$$S_{\mathrm{PTH}} = CaSR_{\mathrm{feedback}} \cdot \frac{PT_{\mathrm{pool}}}{0.5} \cdot PT_{\mathrm{hypertrophy}}$$

- $CaSR_{\mathrm{feedback}}$ represents feedback from the calcium sensing receptor on PTH production (385 at t=0)
- PT_{pool} represents the normal PT gland capacity to produce PTH (0.5 at t=0)
- $PT_{\mathrm{hypertrophy}}$ represents hypertrophy of the PT gland to increased PTH production capacity (1 at t=0)

$$CaSR_{\mathrm{feedback}} = 6249 - \frac{6153 \cdot (Ca_{conc} \pm \mathrm{agonist/antagonist})^{11.7}}{1.818^{11.7} + (Ca_{conc} \pm \mathrm{agonist/antagonist})^{11.7}} \qquad (2)$$

$$\frac{d(PT_{\mathrm{pool}})}{dt} = (1 - PT_{\mathrm{pool}}) \cdot (\mathrm{Effect}_{\mathrm{calcitriol},-}) - PT_{\mathrm{pool}} \cdot (\mathrm{Effect}_{\mathrm{calcitriol},+})$$

$$\mathrm{Effect}_{\mathrm{calcitriol},\pm} = 0.01 \cdot (0.85 \cdot (1 \pm \mathrm{TANH}(PT_{\mathrm{feedback}}) + 0.15) \qquad (3)$$
$$PT_{\mathrm{feedback}} = 0.03 \cdot \left(Calcitriol_{conc} - 90 \cdot \left(\frac{2.35}{Ca_{conc}} \right)^{0.9} \right)$$

$$\frac{d(PT_{\mathrm{hypertrophy}})}{dt} = 1.604e^{-4} \cdot \mathrm{Effect}_{\mathrm{calcitriol,hyper}} - 1.604e^{-4} \cdot PT_{\mathrm{hypertrophy}}$$

$$\mathrm{Effect}_{\mathrm{calcitriol,hyper}} = 4.1 - \frac{3.2 \cdot (Calcitriol_{conc})^{12.5}}{68.38^{12.5} + (Calcitriol_{conc})^{12.5}} \qquad (4)$$

- Equation (5): Link bone markers with BMD

$$\frac{d(BMD)_{LS}}{dt} = k_{in,BMD} \cdot \left(\frac{\mathrm{BSAP}}{\mathrm{BSAP}_{\mathrm{baseline}}} \right)^{\gamma_{OB}} - k_{out,BMD} \cdot \left(\frac{CTx}{CTx_{baseline}} \right)^{\gamma_{OC}} \cdot BMD_{LS}$$

$$\gamma_{OB} = 0.0739$$
$$\gamma_{OC} = 0.0679 \qquad (5)$$
$$k_{\mathrm{out,BMD}} = 0.000145 \text{ h}^{-1}$$

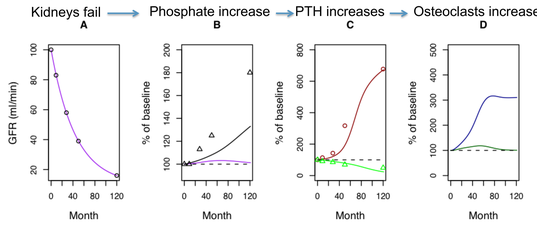
Rate constants and all other model parameters for each moiety (TGFβ, ROB, OB, osteoclasts [OC], PTH, extracellular and bone calcium, calcitriol, etc.) were fixed at previously reported values.[1]

- Software
  - Literature data digitized: Plot Digitizer 2.4.1 (http://plotdigitizer.sourceforge.net/)
  - Graphics and data management: R version 2.7.2 (http://r-project.org)
  - Model fitting and simulation: Berkeley Madonna 8.0 (http://berkeleymadonna.com)

RESULTS

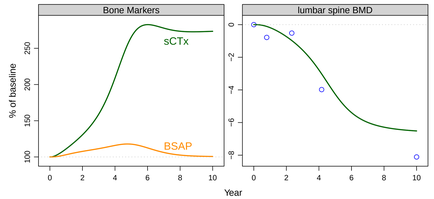
Progression of Renal Osteodystrophy During Chronic Renal Failure

Figure 2: Panel A = Progressive decrease in GFR; Panel B = increase in PO4 (black) and minimal change in total Ca (purple); Panel C = increase in PTH (red) and decrease in calcitriol (green); Panel D = increase in sCTx (dark blue) and only moderate change in BSAP (dark green)



Observed data (symbols) were scaled from Rix et al.[2] Modified from Figure 6 of Peterson and Riggs, 2010.[1]

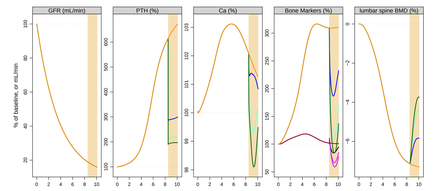
Figure 3: Predicted longitudinal changes in bone markers and corresponding change in BMD



Observed BMD data (symbols) were scaled from Rix et al.[2] Model predictions (solid lines) from multiscale model including Equation 5.

Model Simulation: Therapeutic Interventions

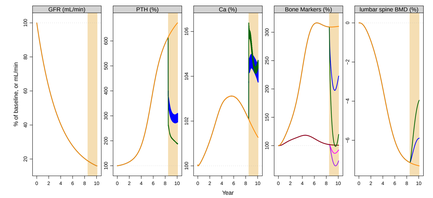
Figure 4: Ca sensing receptor agonism (as varying Ca millimolar equivalents) starting at Year 8.5 – Simulated effect in severe renal impairment on plasma PTH, Ca, sCTx (BSAP), and BMD



orange (dark red) = no intervention; blue (black) = 0.33 mmolar Ca Eq; aqua (magenta) = 0.67 mmolar Ca Eq; green (purple) = 1.0 mmolar Ca Eq

Treatment period depicted by shaded region.

Figure 5: Calcitriol infusion starting at Year 8.5 – Simulated effect in severe renal impairment on plasma PTH, Ca, sCTx (BSAP), and BMD



orange (dark red) = no intervention; blue (magenta) = 1.25 mcg QOD; green (purple) = 2.5 mcg QOD

Treatment period depicted by shaded region.

DISCUSSION

- Model quantifies and conceptually explains physiology, pathophysiology and pharmacologic intervention associated with chronic renal failure and secondary hyperparathyroidism.
- Model provides for *in silico* explorations of disease progression and evaluations of therapeutic intervention. Simulations provided mechanistic, multiscale accounting for:
  - Calcium sensing receptor agonism: beneficial effects on PTH and bone, but corresponding potential for *hypo*calcemia.[7]
  - Calcitriol administration: beneficial effects on PTH and bone, but corresponding potential for *hyper*calcemia.[8]
- A bone marker of bone metabolism is a measured enzyme or protein released during bone formation or during bone resorption (breakdown). The rate of production of this enzyme or protein is therefore considered to be proportional to the relative activity of either bone formation or bone resorption. Although some urinary markers are corrected by creatinine ratio, the effect of renal impairment on the clearance of these markers has not been reported.[9] Therefore, the observed markers may not provide for a direct accounting of bone metabolism changes as renal function declines. Development of this mechanistic model provides a link from renal function to PTH to bone metabolism to BMD markers without direct need for observed bone markers and so without concern for any assumption on formation versus removal rate of these markers during renal function decline.
- The model underestimates the net increase in phosphate as renal function declines (*Figure 2, Panel B*). The predicted increase in phosphate during renal function loss is currently driven solely by a net decrease in renal filtration. Recent evidence implicates the involvement of fibroblast growth factor (FGF-23) in renal phosphate handling (reduces expression of sodium-phosphate co-transporters in the proximal tubules) and FGF-23 inhibits 1α-hydroxylase.[10,11] The inclusion of these FGF-23 related effects along with FGF-23 production from osteocytes may warrant further model extension.

SUMMARY

Multiscale Model of Calcium Homeostasis and Bone Remodeling

- Extension provides a link between bone maker changes and BMD in patients with chronic renal failure thereby allowing for exploration of therapeutic effects on clinical outcome (BMD).
- Extension preserved the structure and parameter estimates[1] and so retains its ability to describe the previously described therapeutic interventions and disease states.
- Provides simultaneous (multiscale) description of multiple known pathophysiologic effects of chronic renal failure and the effects of therapeutic intervention.
- Serves as platform for incorporating these changes within the context of other (therapeutic, disease, genetic) system changes.

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