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

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ABSTRACT

• Prediction of clinical data using multiscale model (Figure 1):
  - GFR chronic decline from 100 mL/min to approximately 15 mL/min 10 years later (GFR = 10 - 0.98% time) [1]
  - Phosphate (PO4) concentration in plasma 

METHODS

- Progression of Renal Osteodystrophy During Chronic Renal Failure
  - Panel A: Progressive decrease in GFR (panel B): + increase in PO4 (black) and mineral change in total Ca (purple).

RESULTS

- Bone formation marker (osteoblast function): increase in CTX (blue)
  - Bone formation marker (osteoblast function): increase in BSAP (red)

DISCUSSION

- Model parameters: incorporate physiology, pathophysiology and pharmacologic intervention associated with chronic renal failure and secondary hyperparathyroidism.

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 functional models

BACKGROUND

- Biology of Calcium (Ca) homeostasis and bone remodeling
  - Multiple involvement: intestine, kidney, and bone
  - Maintain tight control of extracellular fluid (ECF) Ca concentration
  - Regulates bone remodeling: maintain bone structure and functionality
  - Chronic renal failure and secondary hyperparathyroidism
  - Loss of renal function manifests into PT challenge
  - Secondary hyperparathyroidism leads to increased bone resorption and bone loss
  - Treatment: includes calcitriol (Calcifediol) and calcimimetic (oral e.g., cinacalcet) treatments

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

- Calcium (Ca) homeostasis and bone remodeling
- Multiscale involvement: intestinal signaling, endocrine feedbacks, and multiple organs
- Maintain tight control of extracellular fluid (ECF) Ca concentration
- Regulate bone remodeling: maintain bone structure and functionality
- Chronic renal failure and secondary hyperparathyroidism
- Loss of renal function manifests into PT challenge
- Secondary hyperparathyroidism leads to increased bone resorption and bone loss
- Treatment includes calcitriol (Calcifediol) and calcimimetic (oral e.g., cinacalcet) treatments

Figure 2: Chronic Renal Failure and Changes in Bone Mineral Density

SUMMARY

- Multiscale Model of Calcium Homeostasis and Bone Remodeling
  - Extension provides a link between bone marker and BMD in patients with chronic renal failure
    - Provides simultaneous (multiscale) description of multiple known pathophysiologic effects of chronic renal failure and the effects of therapeutic interventions
  - Extension preserved the structure and parameter estimates 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 interventions
  - Serves as platform for incorporating these changes within the context of other therapeutic, disease, genetic, and system changes

REFERENCES

- [4] Progression of Renal Osteodystrophy During Chronic Renal Failure
- [7] The model underestimates the net increase in phosphate as renal function declines.
- [8] The observed markers may not provide for a direct accounting of bone metabolism changes as renal function declines.
- [9] The model underestimates the net increase in phosphate as renal function declines.
- [10] Therefore, the observed markers may not provide for a direct accounting of bone metabolism changes as renal function declines.

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