1. Abstract

The use of physiologically based middle-out models, where the level of complexity incorporated in the model comes from the specific demands of the decisions required, is growing fast in the pharmaceutical industry. In this work we present an innovative model we developed for investigating the effect on bone remodeling of osteoporosis treatments. An imbalance in the activity of osteoclasts (cells that resorb bone matrix) and osteoblasts (cells that form new bone) can cause osteoporosis, wherein there is a net and progressive loss of bone. A better understanding of the molecular pathways regulating their activity in bone remodeling can guide the development of novel osteoporosis treatments. We have developed a semi-mechanistic model of bone remodeling that incorporates, integrates, and extends available physiological information on bone remodeling. The mechanistic basis of the model establishes a unified structure, wherein it can include multiple novel (e.g. calcilytics), and existing (e.g. bisphosphonates, PTH) treatment options, administered sequentially or simultaneously. We show some of the results of the model simulations in response to the common treatment strategies and compare them with published clinical data. Our model agrees with the data and elucidates on a long-standing puzzle: the key pathways governing the switch between the anabolic and catabolic action of the PTH. We think that our model is a first step in understanding the bone remodeling processes, enabling the testing of new hypotheses and the development of treatment strategies including combination therapies for osteoporosis.

2. Background

2.1 Bone Remodeling & Osteoporosis

- Continuous formation and resorption of bone via osteoblasts and osteoclasts

- A balance between the activity of bone resorbing agents (osteoclasts) and bone formation activity (osteoblasts) determines bone health

- Bone health chiefly measured by measuring Bone Mineral Density (BMD)

- The balance between osteoblast and osteoclast activity is tightly regulated by hormones and molecules: e.g. PTH, Ca, etc.

2.2 Osteoporosis Treatment Strategies

- Several different treatment options available:
  - Bisphosphonates (e.g. Alendronate) act on the osteoclasts ability to resorb bone cells
  - Direct Parathyroid Hormone (PTH) (e.g. Forteo) on preferably increasing the activity of osteoclasts.
  - Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g. Denosumab) act on RANKL, controlling their role in bone resorption

3. Model Development

- Model Features
  - The transparency, modular structure, based on simple mechanisms of action and can include multiple treatment strategies and drug interventions to common biomarkers of bone health
  - Incorporates available literature information and experimental observations relevant to bone remodeling. Model parameters and initial conditions are taken/estimated from available literature and/or animal data
  - Model Structure: 28 ODEs, ~40 parameters. Parameters/initial conditions are constrained to ensure steady state corresponding to homeostasis

4. Results

4.1 Effect of Alendronate Treatment

As part of a study of various treatments, Miller and co-workers [8] treated postmenopausal women with low lumbar spine T-scores (scores between -4 and -1.0) with Alendronate. The authors used the data they obtained as a starting point for their calculations to simulate the BMD over two years. The treatment was given for 2 years, and then stopped. The yellow dots in the graph represent the data acquired by Miller and co-workers. The two graphs, here, along with the one that appears in Miller’s article, show the results of the simulation. The black curve represents the CTX profile in our simulation of Miller’s Alendronate trial, the solid curve in B represents the BMD results from our simulation. The model incorporation indicates that the opening to CTX accompanies a compatible opening to osteoporosis population.

4.2 Effect of PTH

- Continuous formation and resorption of bone via osteoblasts and osteoclasts

- A balance between the activity of bone resorbing agents (osteoclasts) and bone formation activity (osteoblasts) determines bone health

- Bone health chiefly measured by measuring Bone Mineral Density (BMD)

- The balance between osteoblast and osteoclast activity is tightly regulated by hormones and molecules: e.g. PTH, Ca, etc.

5. Conclusions

- We have developed a mathematical model of dynamics of bone remodeling based on available physiological observations/data. The model, in form of ODEs, quantifies the relationship between the key molecular pathways governing bone remodeling, and links, via reasonable assumptions, the cell and molecular concentrations to the biomarkers measured in the laboratory.

- The results presented here show the utility of the unified model that we have developed, in understanding the effect of various interventions for osteoporosis mitigation. Model results are consistent with the known effects of PTH, Bisphosphonates and anti-RANKL on the bone remodeling process, and also agrees with available clinical data on BMD.

- The model allows the comparison of osteoporosis therapies already on the market and new, innovative therapies in different stages of development. The model is a platform for evaluating potential new therapies under various administration protocols to characterize their efficacy and ease of implementation by comparing them with alternatives. The model also enables the generation of testable hypotheses and predictions of the possible outcomes of clinical trials.

6. Acknowledgements/Key References

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References:
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