Linking a Mechanistic Model of Bone Mineral Density to a Time-To-Event Model of Fracture

Rena J. Eudy[1], William R. Gillespie[3], Matthew M. Riggs[3], Marc R. Gastonguay[1,2,3]
(1) Department of Biomedical Engineering, University of Connecticut, (2) Metrum Institute, (3) Metrum Research Group, LLC

Objectives

1. To predict regional changes in bone mineral density (BMD) in patients with osteoporosis on three classes of osteoporosis drugs, using a multiscale systems model (MSM)[1] of bone metabolism.

2. To implement a time-to-event (TTE) model of fracture in order to examine the effect of mono- or combination therapy on the probability of fracture during long-term (10-yr) treatment.

Methods

To develop the MSM, data were assembled from 27 documented clinical trials with teriparatide, denosumab and/or combination therapy. Parameters were optimized using the R package *minqa* and changes in BMD were simulated using R package *mrgsolve*. The final model was evaluated by sensitivity analysis.

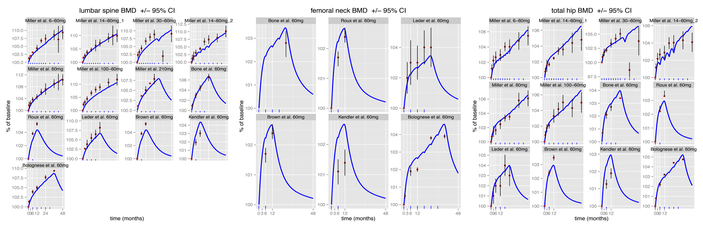


Figure 1: Trials with denosumab. Graphs show simulated (blue) overlaying data (red) and 95%CIs

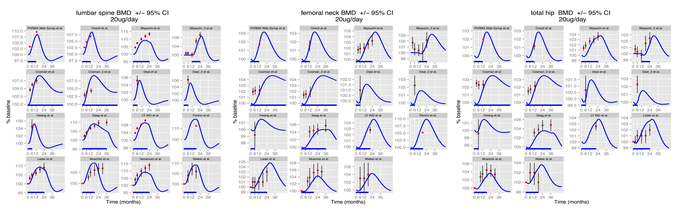


Figure 2: Trials with teriparatide. Graphs show simulated (blue) overlaying data (red) and 95%CIs

The data used to develop the hazard model for fracture was comprised of:

- A subset of **individual-level** data from the NHANES (2005-2008) database
- **Summary-level** BMD and fracture data from publications identified by specific search criteria (39 trials in total involving various treatments). The BMD timecourse used by the fracture model was simulated by the MSM.
  Candidate models were evaluated by DIC and PPC.

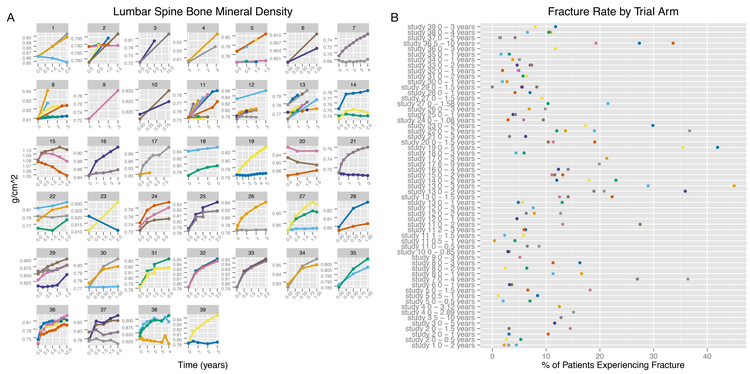
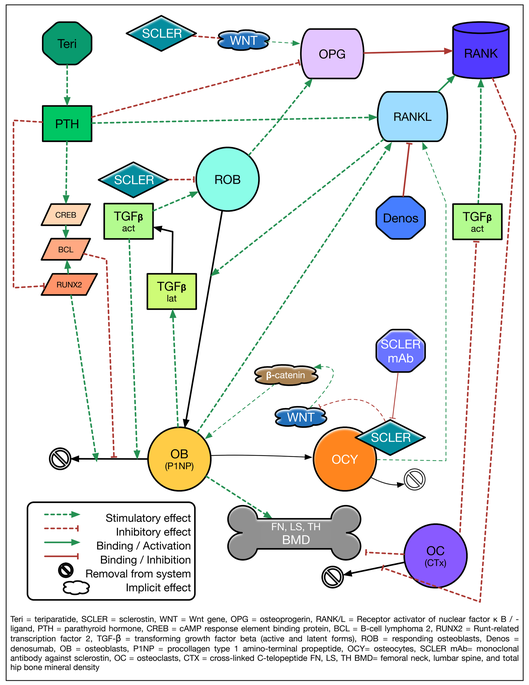


Figure 3: Metadata summary by trial of longitudinal changes in BMD (A) and fracture rate (B). Colors identify corresponding treatment arms in plots A & B

Mechanistic Model Results



Teri = teriparatide, SCLER = sclerostin, WNT = Wnt gene, OPG = osteoprogerin, RANK/L = Receptor activator of nuclear factor κ B / - ligand, PTH = parathyroid hormone, CREB = cAMP response element binding protein, BCL = B-cell lymphoma 2, RUNX2 = Runt-related transcription factor 2, TGF-β = transforming growth factor beta (active and latent forms), ROB = responding osteoblasts, Denos = denosumab, OB = osteoblasts, P1NP = procollagen type 1 amino-terminal propeptide, OCY= osteocytes, SCLER mAb= monoclonal antibody against sclerostin, OC = osteoclasts, CTX = cross-linked C-telopeptide FN, LS, TH BMD= femoral neck, lumbar spine, and total hip bone mineral density

Figure 4: MSM schematic. Changes in OB and OC, described by changes in turnover markers P1NP and CTx, directly influence regional changes in BMD. Figure adapted from Fig 2 in Ref 1

- Anabolic therapies (teriparatide and sclerostin mAb) are described by a two compartment disposition to enforce a time-delay for modeling activity:

$$\frac{\mathrm{d}}{\mathrm{dt}} DELAY = kin_{DELAY} \cdot \left(\frac{OB}{OB_{\mathrm{baseline}}}\right)^{\lambda_{OB}} - kout_{DELAY} \cdot DELAY$$

$$\frac{\mathrm{d}}{\mathrm{dt}} BMD = kin \cdot DELAY - \left(\frac{OC}{OC_{\mathrm{baseline}}}\right)^{\lambda_{OC}} \cdot kout \cdot BMD$$

$$kin_{DELAY} = kout_{DELAY} \qquad \text{and} \qquad kin = kout \cdot BMD_{\mathrm{baseline}}$$

- Denosumab and combination therapy effects described by a single compartment:

$$\frac{\mathrm{d}}{\mathrm{dt}} BMD = kin \cdot \left(\frac{OB}{OB_{\mathrm{baseline}}}\right)^{\lambda_{OB}} - \left(\frac{OC}{OC_{\mathrm{baseline}}}\right)^{\lambda_{OC}} \cdot kout \cdot BMD$$

$$kin = kout \cdot BMD_{\mathrm{baseline}}$$

	$kout$ (1/hrs)	$gamOC$ (unitless)	$gamOB$ (unitless)	$kout_{DELAY}$ (1/hrs)
LUMBAR SPINE				
SCLER	0.000145	0.065	0.758	0.00246
DENO	0.0000740	0.0791	0.0793	-
TERI	0.000554	0.0169	0.271	0.00100
COMBO	1.86 · DENO	1.28 · DENO	1 · DENO	-
TOTAL HIP				
SCLER	0.000145	0.0653	0.225	0.00246
DENO	0.000108	0.0552	0.0793	-
TERI	0.000139	0.131	0.298	0.00100
COMBO	0.971 · DENO	1.28 · DENO	1 · DENO	-
FEMORAL NECK				
SCLER	0.000145	0.0653	0.131	0.00246
DENO	0.000119	0.0515	0.0793	-
TERI	0.0000663	0.212	0.496	0.00100
COMBO	1.08 · DENO	1.30 · DENO	1 · DENO	-

Table 1: Estimated BMD Parameters

TTE Model Results

The candidate model with the lowest DIC value had the structure:

$$\begin{aligned} h_{ij}(t) \;=\; & h_{0j} \exp\Big(\beta_{BMD_{0,j}} \log\Big(BMD_0/\widehat{BMD_0}\Big) + \\ & \beta_{BMD_{\mathrm{cfb,j}}}\left(BMD_{\mathrm{cfb,ij}}(t)\right) + \\ & \beta_{\mathrm{postMenoAge}}\Big(\mathrm{postMenoAge}_{ij}(t) - \widehat{\mathrm{postMenoAge}}\Big) + \\ & \beta_{\mathrm{radFracture}} I_{\mathrm{radFracture},ij} + \beta_{\mathrm{BMI}}\Big(BMI_{ij} - \widehat{BMI}\Big) + E_{\mathrm{drug},ij}\Big) \end{aligned}$$

$$\log\left(h_{0j}, \beta_{BMD_{0,j}}, \beta_{BMD_{\mathrm{cfb,j}}}\right) \sim N\left(\left(\log\left(\widehat{h_0}\right), \widehat{BMD_0}, \widehat{\beta_{BMD_{\mathrm{cfb}}}}, \Omega_{h0}, \Omega_{\mathrm{BMD0}}, \Omega_{\mathrm{BMD\ CFB}}\right)\right)$$

for the i *th* trial and j *th* treatment arm.

Estimated parameter values (mean, 95%CI):

$\beta_{BMD_0}(\frac{1}{g/cm^2}) = 0.396(-2.40; 3.18)$, $\beta_{BMD_{cfb,ij}}(\frac{1}{g/cm^2}) = 4.83(-0.540; 10.2)$,
$\beta_{\mathrm{radFracture}}(unitless) = -0.200(-0.379; -0.0221)$ $\beta_{\mathrm{postMenoAge}}(\frac{1}{yrs}) = 0.0249(0.0117; 0.0376)$,
$\beta_{\mathrm{BMI}}(\frac{1}{kg/m^2}) = -0.199(-0.0509; 0.0111)$, $\beta_{\mathrm{bisphosphates}}(unitless) = -0.696(-0.833; -0.556)$,
$\beta_{\mathrm{PTH/teriparatide}}(unitless) = -0.894(-1.22; -0.578)$, $\beta_{\mathrm{denosumab}}(unitless) = -0.898(-1.21; -0.579)$,
$\beta_{\mathrm{calcitonin}}(unitless) = -1.73(-4.92; 0.333)$, $\beta_{\mathrm{MK\text{-}677}}(unitless) = -0.658(-2.62; 0.812)$,
$\beta_{\mathrm{strontium\ ranelate}}(unitless) = -0.764(-1.69; 0.0518)$,
$\Omega_{h0} = 0.746(0.562; 0.967)$, $\Omega_{\mathrm{BMD0}} = 3.34(0.0835; 8.99)$, $\Omega_{\mathrm{BMD\ CFB}} = 9.76(6.04; 15.2)$
and reference values of 0.8, 20, and 27.1 for BMD, post-menopausal age, and BMI, respectively.

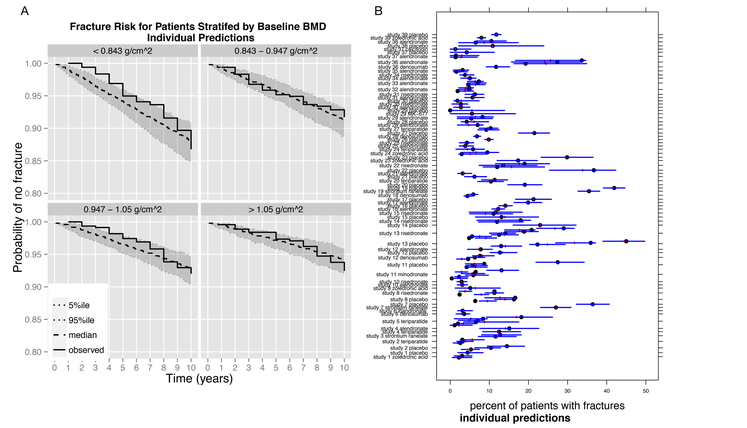


Figure 5: Posterior predictions for the NHANES dataset (A) and the metadataset (B). "Individual" predictions = prediction of hypothetical new observations within the same trial. For B, black = observed fracture; red = posterior median; blue = 90% credible intervals

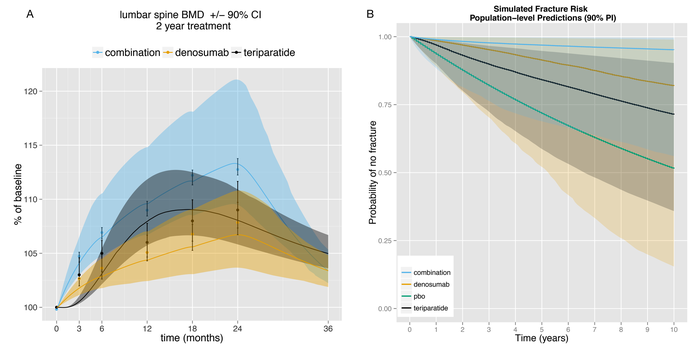


Figure 6: Simulations using MSM to model predicted changes in BMD (A). Solid lines represent the mean; shading represents simulated error around individual parameters in the model. The median posterior predicted fracture rate is shown (B); Shading represents 90% prediction intervals.

Conclusion

The MSM predicted regional changes in BMD within the range of clinical variability in most treatment arms. The candidate TTE fracture model that best described the metadataset was the model that included BMD expressed as change from baseline, baseline BMD and an additional drug effect as covariates.

1.) R. Eudy, M. Gastonguay, K. Baron, and M. Riggs. Connecting the Dots: Linking Osteocyte Activity and Therapeutic Modulation of Sclerostin by Extending a Multiscale Systems Model. CPT: Pharmacometrics & Systems Pharmacology, (Sept), 2015.

Presented at ACoP6; Arlington, VA; 07-October 2015; Copies available at: metrumrg.com/publications