Linking a Mechanistic Model of Bone Mineral Density to a Time-to-Event Model to Evaluate Effects of Various Therapies on Fracture Risk in Postmenopausal Women with Osteoporosis

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Objectives: Predict regional changes in bone mineral density (BMD) in patients with osteoporosis on three classes of osteoporosis drugs by leveraging summary-level data from the literature, using a multiscale systems model of bone metabolism. Also implement a time-to-event (TTE) model of fracture events to evaluate mono- or combination therapy in terms of reducing probability of fracture during long-term (10-yr) treatment.

Methods: The BMD model was developed using data from 27 documented clinical trials with teriparatide, denosumab and 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.

The TTE model was developed using individual-level data from NHANES (2005-2008) database and summary-level BMD data from selected publications (17 trials involving various treatments). The BMD timecourse used by the fracture model was simulated by the BMD model. Candidate models were evaluated by DIC and PPC (posterior predictive check).

Results: Changes in BMD as a result of denosumab, teriparatide or combination therapy were described by ODEs with changes in formation activity (OB compartment) as the input and changes in resorption activity (OC compartment) as the output. The final BMD model structure is $rac{d\text{BMD}}{dt} = k_{in} \cdot \frac{\partial \text{OB}}{\partial \text{BMD}} - k_{out} \cdot \frac{\partial \text{OC}}{\partial \text{BMD}} \cdot \text{BMD}$, with estimated parameters $\delta = 0.102$ (mean; 95%CI: -0.666-0.869) and $k_{out} = 0.000137(-0.273-0.273)$, $k_{in}$ solved at steady state and initial conditions, and $Y$ fixed at original model value. The hazard model took the form

$h_{ij}(t) = h_{ij}(0)e^{(B_{\text{BMD}}) \cdot \log\left(\frac{\text{BMD}\_\text{spine}_{ij}(t)}{9.8}\right)+\beta_{\text{postMenoAge}}(\text{postMenoAge}_{ij}(t)-20)+\beta_{\text{radFracture}}I_{\text{radFracture},ij}+\beta_{\text{BMI}}(\text{BMI}_{ij}-27.1)},$

with $h_{ij} = 0.319$ (mean; 95%CI: 0.022-0.437), $\beta_{\text{BMD}} = -4.80(-8.98-0.733), \beta_{\text{postMenoAge}} = 0.0267(0.013-0.04), \beta_{\text{radFracture}} = 1.05(0.384;1.83)$ and $\beta_{\text{BMI}} = -0.0104(-0.0388-6.54E-5).$
Conclusions: The BMD model parameters were sensitive to perturbations around 20% of the typical value, and these estimates captured the central tendency within the 95%CI of the clinical BMD data. The median predictions of fracture occurrence by TTE model were also very close to clinical data.