A Mathematical Model to Quantify Links Between Bone Mineral Density, Patient Factors and Therapeutic Interventions on Fracture Risk in Patients with Osteoporosis

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Objectives

Two datasets, one measuring fracture events at the individual patient level derived from NHANES, and another aggregated from clinical studies in a model-based meta-analysis (MBMA) approach, were used to build a combined hazard model of fracture in order to determine

1. The extent to which individual-level patient characteristics (BMI, years post-menopause, age) influence fracture risk
2. The degree to which different therapeutic mechanisms influence fracture rate, independent of their effects on BMD

Methods: Data Structure

NHANES

A subset of patient data were assembled from the NHANES database (2005-2008). Patients included in this dataset were post-menopausal women above 20 years of age and who were at least 2 years post-menopausal at screening. They also had accompanying bone mineral density (BMD) data at the spine and hip at screening (N=1925 total patients).

BMD measurements were imputed at the time of a fracture event using the following equation, for different cohorts of BMD reported at screening:

$$\begin{aligned} BMD_{pred,i} &= \beta_0 + \beta_1 (\text{postmenopausal age} - 20) + \\ &\quad \beta_2 (\text{age at last menopausal period} - 51.7) + \\ &\quad \beta_3 (BMI - 27.1) + \\ &\quad \beta_4 I_{african-american} \end{aligned}$$

for the i *th* individual.

MBMA

The MBMA was comprised of treatment-arm-level data from clinical trials published from 1995-2015 having fractures as a primary endpoint and lumbar spine BMD as a secondary endpoint. The resulting dataset included data from 21 studies, 79 treatment arms, representing 48241 individual patients.

For both datasets, if BMI was missing it was imputed using the following equation:

$$BMI_i = \beta_5 + \beta_6 (age_i - \widehat{age})$$

for the i *th* individual or treatment arm,
where β_5 and β_6 were estimated separately for each dataset.

Coefficients for both equations were estimated by multiple linear regression.

Metadata Summary

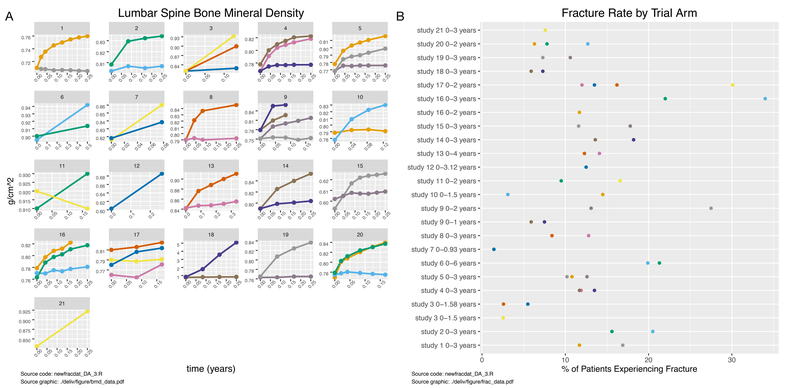


Figure 1: Metadata summary by trial of longitudinal changes in BMD (A) and fracture rate (B). Colors identify corresponding treatment arms in plots A & B

All data assembly and computation was performed in R®, v3.2.1.

References

1. Baron R, Ferrari S, Russell RGG (2011) Denosumab and bisphosphonates: Different mechanisms of action and effects. Bone 48:677692. doi: 10.1016/j.bone.2010.11.020
2. Sornay-Rendu E, Boutroy S, Munoz F, Delmas PD (2007) Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study. J Bone Miner Res 22:425433. doi: 10.1359/jbmr.061206
3. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, Kearns A, Thomas T, Boyd SK, Boutroy S, Bogado C, Majumdar S, Fan M, Libanati C, Zanchetta J (2010) Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res 25:18861894. doi: 10.1002/jbmr.81
4. Hansen S, Hauge EM, Beck Jensen JE, Brixen K (2013) Differing effects of PTH 1-34, PTH 1-84, and zoledronic acid on bone microarchitecture and estimated strength in postmenopausal women with osteoporosis: An 18-month open-labeled observational study using HR-pQCT. J Bone Miner Res 28:73645. doi: 10.1002/jbmr.1784

Methods: Model Structure

Two forms of the likelihood equation were defined, one for each dataset, but parameters were estimated simultaneously using a Bayesian approach implemented in OpenBUGS, v.3.2.2. A random effect was applied to the baseline hazard, h_0, allowing flexibility for differences between the study arms.

The likelihood for the time to first fracture in the i *th* patient in the **NHANES** dataset took the form:

$$\begin{aligned} &L(\theta | t_{frac,i}, \text{censor}_i, X_i) = \\ &\exp\left(-\int_0^{t_{frac,i}-1} h_i(u|\theta, X_i)\, du\right) - \exp\left(-\int_0^{t_{frac,i}} h_i(u|\theta, X_i)\, du\right), \\ &\quad \text{if the fracture was interval censored or} \\ &\exp\left(-\int_0^{t_{end,i}} h_i(u|\theta, X_i)\, du\right), \\ &\quad \text{if the fracture was right-censored.} \end{aligned}$$

where $t_{frac,i}$ is the end of a 1 year period during which a fracture occured and $t_{end,i}$ corresponds to the length of the observation period for the i *th* individual.

The hazard equation for the NHANES model took the form:

$$\begin{aligned} h_i(t) &= h_0 \cdot \exp\Big(\beta_{BMD} \log\left(BMD_{pred,i}/\widehat{BMD_0}\right) + \\ &\quad \beta_{\text{postMenoAge}} \left(\text{postMenoAge}_{0,i}(t) - \widehat{\text{postMenoAge}}\right) + \\ &\quad \beta_{\text{BMI}} \left(\text{BMI}_i - \widehat{\text{BMI}}\right)\Big) \end{aligned}$$

for the i *th* individual.

The probability of fracture in the **MBMA** dataset took the form:

$$p_{frac,ij} = 1 - \exp^{-\int_0^{t_{ij}} h_{ij}(u|\theta, X_{ij})\, du}$$

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

Four variant forms of the hazard equation were evaluated, having different structures for the drug effect (shown in red text, below).

$$\begin{aligned} h_{ijk}(t) &= h_{0i} \exp\Big((\beta_{BMD} + \beta_{E_{\text{drug},k}}) \log\left(BMD_{ij}(t)/\widehat{BMD}\right) + \\ &\quad \beta_{\text{postMenoAge}} \left(\text{postMenoAge}_{ij}(t) - \widehat{\text{postMenoAge}}\right) + \\ &\quad \beta_{\text{radFracture}} I_{\text{radFracture},ij} + \beta_{\text{BMI}} \left(BMI_{ij} - \widehat{BMI}\right) + \\ &\quad E_{\text{drug},k}\Big) \\ &\quad \log\left(h_{0ij} \sim N\left(\log\left(\widehat{h_0}\right), \Omega_{h0}\right)\right) \end{aligned}$$

for the i *th* trial, j *th* treatment arm, and k *th* drug treatment

The four model candidates were evaluated by visual predictive checks and deviance information criteria (DIC ; a calculation of -2log(likelihood) with a penalty term for the number of parameters in the model. When comparing models, generally the *lower* DIC indicates the more parsimonious model that better describes the data).

Results

The DIC values for each model candidate are shown to the right.
The model that resulted in the lowest DIC and best described the data included the drug interaction term and the additonal drug effect. This model yielded the following fracture predictions and parameter estimates:

Drug Effect Model	DIC
BMD + Drug Interaction ($\beta_{E_{\text{drug},k}}$)	1642.70
BMD + Drug Interaction ($\beta_{E_{\text{drug},k}}$) + Additional Drug Effect ($E_{\text{drug},k}$)	**1548.75**
Additional Drug Effect only ($E_{\text{drug},k}$)	1553.70
No Drug Effects	1654.35

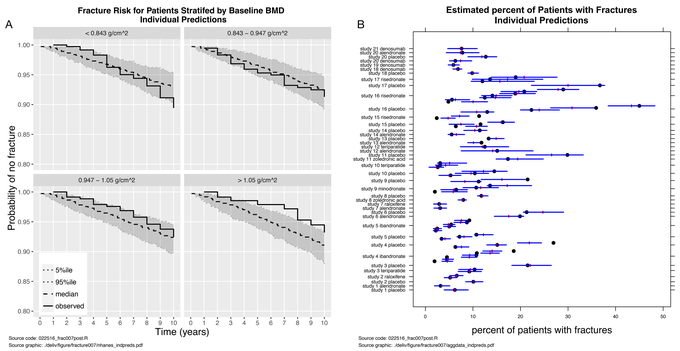


Figure 2: Posterior predictions for the NHANES dataset (A) and the MBMA dataset (B). "Individual" predictions = prediction of hypothetical new observations within the same trial. For B, black = observed fracture; red = posterior median; blue = 90% credible intervals

Parameter (units)	Mean (95% CI)
$\widehat{h0}$(1/years)	0.0405 (0.0294;0.0543)
β_{BMD}(1/gm/cm2)	−1.0400 (-2.16;0.113)
$\beta_{PostMenoAge}$(1/years)	0.0241 (0.00758;0.0409)
β_{BMI}(kg/m^2)	−0.0126 (-0.046;0.021)
ω_{h0}	0.7380 (0.62;0.888)

Parameter (unitless)	Mean (95% CI)
$\beta_{radFracture_1}$	.5980 (0.0528;1.14)
$E_{\text{drug,bisphosphate}}$	− 0.3100 (-0.383;-0.238)
$E_{\text{drug,teriparatide}}$	− 0.9020 (-1.28;-0.544)
$E_{\text{drug,denosumab}}$	− 0.4500 (-0.615;-0.291)
$E_{\text{drug,SERM}}$	− 2.6500 (-12.4;3.65)

Parameter (unitless)	Mean (95% CI)
$\beta_{radFracture_2}$	0.1870 (-0.408;0.811)
$\beta_{E_{\text{drug,bisphosphate}}}$	0.9510 (0.165;1.72)
$\beta_{E_{\text{drug,teriparatide}}}$	− 0.7820 (-3.51;1.96)
$\beta_{E_{\text{drug,denosumab}}}$	3.8600(-0.213;8.14)
$\beta_{E_{\text{drug,SERM}}}$	56.3000 (-148;313)

Additional Results, Conclusion & Future Work

Hazard models with and without a drug-BMD interaction term and an additional drug effect covariate were compared. It was determined that there is an additional beneficial effect of some classes of therapies, which in most cases is independent of the contribution of changes in BMD elicited by the therapy, on fracture reduction.

Distributions of hazard ratios describing the probability of an event of any fracture type were calculated for each class of drug using the posterior estimates for the drug effects, approximated 1 year BMD after 1 year of treatment and using the placebo arms as reference. This analysis points to significant benefits of all classes of therapies in fracture reduction, compared to placebo.

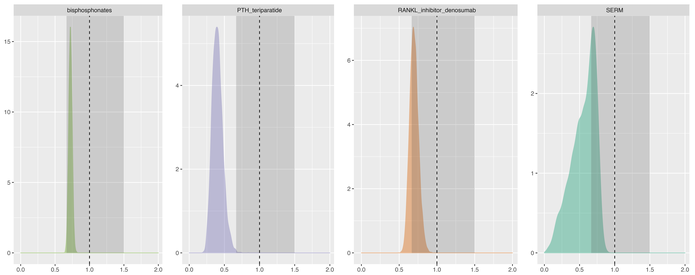


Figure 3: Hazard Ratios for each treatment relative to placebo are represented, for the model with both drug-BMD interaction and additional drug effect. The shaded region represents the alpha region (0.5log unit above and below unity).

Although there is a large amount of uncertainty in some classes (dependending on the richness of data for those respective arms in the dataset), every drug class analyzed showed reduction of hazard relative to placebo that accounted for both drug-BMD interaction and an independent drug effect.

Discussion

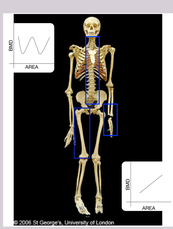
The improvement of hazard prediction using a model with a drug parameter independent of BMD may be highlighting the differential effects of therapy on regional areal BMD and bone microarchitecture. This model supports the widely held notion that BMD response to therapy only partially contributes to a reduction in fracture risk and does not represent the full benefit of therapy on fracture reduction.[1,2] Possible ways that mechanisms of action contribute to these differential effects on bone microarchitecture are discussed below.

Bisphosphonates

- affected by drug distribution[3]
- high affinity of bisphosphonates for hydroxyappetite may limit distribution.

  Osteoclasts may not stop remodeling until the entire matrix containing bisphosphonates is resorbed.

  This may lead to non-uniform mineralization throughout the skeleton.



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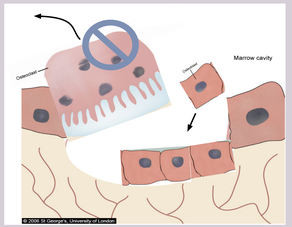
Teriparatide

- unlike bisphosphonates, has been shown to decrease cortical thickness in the tibia and radius[4]
- also increases cortical porosity and significantly increasing trabecular number in the tibia
- PTH is likely to accelerate intracortical and endosteal remodeling

Denosumab

- inhibits osteoclast synthesis so that there is a rapid reduction in newly excavated resorption cavities[3]
- simultaneous filling of existing cavities
- much higher CTX response than elicited by bisphosphonates, at comparable doses



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Future Work

Future development of the model may include investigation between the relationship between changes elicited by drug effects on BMD and microarchitecture and fractures at **specific sites**. The major limitiation to this is a lack of clinical data reporting site-specific fracture events. Additional clinical data at the level of the individual patient is also desired for more precise estimates of parameters relating patient characteristics to fracture outcomes.