

## Quantifying the influences of menopause and age-related factors on the development of osteoporosis

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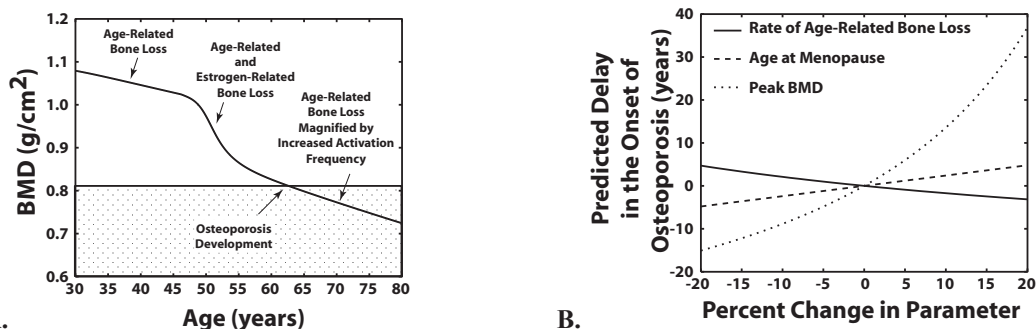
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**Introduction:** Computational and mathematical models have been used to predict BMD loss and fracture risk during aging<sup>1,2</sup>. These models are derived from statistics and do not detail the changes in cellular processes that cause bone loss. A model that accounts for the cellular processes behind bone loss could improve predictions of BMD loss and fracture risk. In this analysis we present a quantitative method for studying the influences of age-related and estrogen-related bone loss on the development of osteoporosis.

**Methods:** A computational simulation of bone remodeling in cancellous bone<sup>3</sup> is used to predict bone loss. The model utilizes a quantitative description of the activity of basic multicellular units (BMUs) similar to that used by Hazelwood et al.<sup>4</sup>. Simulations are initiated at peak BMD and account for bone loss caused by aging (due to inadequate nutrition or disuse) and estrogen depletion. Age-related bone loss is simulated by reducing the focal bone balance so that less bone is formed than is resorbed at each remodeling site. At menopause an increase in BMU activation frequency and a transient decrease in focal bone balance are applied to simulate the effects of estrogen depletion<sup>5</sup>. Mathematical relationships are developed to express the predicted age at which osteoporosis develops as a function of the age at menopause, the rate of age-related bone loss and peak BMD.

**Results:** Age-related factors influence bone loss throughout each simulation (Figure 1A). Around the time of menopause additional bone loss occurs due to estrogen depletion. In the postmenopausal years age-related bone loss is magnified by the increase in activation frequency caused by estrogen depletion. Equations are developed to relate the age of osteoporosis development to the age at menopause, the rate of age-related bone loss and peak bone mineral density. Based on the equations we predict that peak BMD has the most influence on the age of osteoporosis development, for example a 10% increase in peak BMD delays osteoporosis by 13 years while the same change in the age at menopause or the rate of age related bone loss is predicted to delay osteoporosis by approximately 2 years (Figure 1B).



**Figure 1. A.** A typical simulation of osteoporosis development. The shaded area indicates clinical osteoporosis (2.5 S.D. below the mean peak BMD). **B.** The delay in the development of osteoporosis caused by variation in peak BMD (from 1.08 g/cm<sup>2</sup>), the rate of age-related bone loss (from 0.25% of peak BMD/year), and the age at menopause (from 50 years) is presented.

**Conclusions:** The objective of this analysis was to quantitatively predict how peak bone mineral density, estrogen depletion and age-related bone loss contribute to the development of osteoporosis. The findings suggest that the delay in osteoporosis development caused by modification of peak BMD is much larger than that caused by a similar modification in the age at menopause or the rate of age-related bone loss. The importance of peak BMD has been known for some time<sup>2</sup>, but its importance relative to age-related bone loss and the age at menopause has never been quantified. Future studies with this computational model may improve predictions of fracture risk and help in the determination of new or more refined preventive treatments.

**References:** 1) He YF, et al. 1992 Bone 13: 243-7. 2) Wasnich RD 1999 in Primer of metabolic bone diseases and disorders of mineral metabolism 257-9. 3) Hernandez CJ, et al. 2001 Bone 29: 511-16. 4) Hazelwood SJ, et al. 2001 J Biomech 34: 299-308. 5) Hernandez CJ, et al. 2001 J Bone Min Res 16: S281.

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