

# A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis

C.J. Hernandez · G.S. Beaupré · D.R. Carter

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**Abstract** Factors that determine a post-menopausal woman's bone mineral density (BMD) include her mass at the time of skeletal maturity (peak BMD), menopause and the rate of loss she experiences as she ages. Understanding the relative influence of each of these factors may help identify important preventive treatments and provide new ways to identify women at risk for osteoporosis. In this analysis we utilize a computer model of the bone remodeling process to predict the relative influences of peak BMD, menopause and age-related bone loss on the development of osteoporosis. The delay in the onset of osteoporosis (defined as BMD < 2.5 SD from the young adult mean) caused by modifying peak BMD, age-related bone loss or the age at menopause is quantified. A 10% increase in peak BMD is predicted to delay the development of osteoporosis by 13 years, while a 10% change in the age at menopause or the rate of non-menopausal bone loss is predicted to delay osteoporosis by approximately 2 years, suggesting that peak BMD may be the single most important factor in the development of the disease.

**Keywords** Aging · Bone mineral density (BMD) · Computer simulation · Menopause · Osteoporosis

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C.J. Hernandez (✉) · G.S. Beaupré · D.R. Carter  
Rehabilitation Research and Development Center,  
VA Palo Alto Health Care System,  
Palo Alto, Calif, USA

C.J. Hernandez · G.S. Beaupré · D.R. Carter  
Biomechanical Engineering Division,  
Mechanical Engineering Department,  
Stanford University, Stanford, Calif, USA

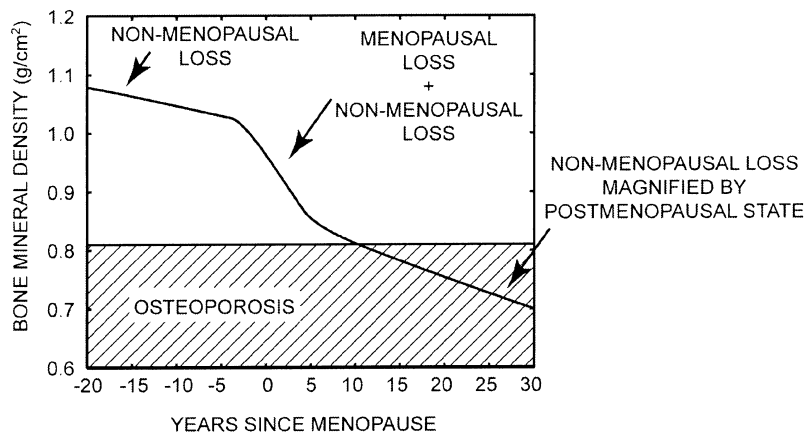
*Present address:* Orthopaedic Biomechanics Laboratory,  
Department of Mechanical Engineering,  
University of California, 2166 Etcheverry Hall,  
Berkeley, CA 94720-1740, USA

## Introduction

Adult bone mass is equal to the peak bone mass achieved in early adulthood minus the amount of bone lost afterward [1]. In women, bone mass declines during aging with an accelerated rate of bone loss occurring during the menopausal transition (Fig. 1). In many women this bone loss leads to osteoporosis. Osteoporosis is clinically defined by the World Health Organization as areal bone mineral density (BMD, g/cm<sup>2</sup>) more than 2.5 SD below the young adult average. One consequence of this definition is that diagnosis of osteoporosis is not related to fracture incidence or bone fragility. There is no single reason why one woman develops osteoporosis while another does not. Some women develop osteoporosis because they acquire a lower than normal peak bone mass that, when combined with normal rates of bone loss in adulthood, reduces bone mass to osteoporotic levels. Other individuals who experience normal peak bone mass may develop osteoporosis because adult bone loss is greater than normal. The large decline in bone mass associated with menopause is also a major factor contributing to the development of osteoporosis. As a result, women experiencing early menopause have an increased risk of developing osteoporosis (National Osteoporosis Foundation, <http://www.nof.org>). Although these factors are known to influence osteoporosis, it is not known whether reduced peak bone mass is a more influential factor in osteoporosis development than an increased rate of age-related bone loss or early menopause. Effective administration of preventive treatment to populations at risk for developing osteoporosis in many ways depends on understanding the relative influence of factors involved in the development of the disease.

Because bone loss occurs throughout adult life, most adults are, to some degree, in the process of developing osteoporosis. Therefore, any individual, given a sufficiently long lifespan, would be likely to develop the disease. This fact makes predictions of the age at which osteoporosis first develops (based on BMD) an indicator

**Fig. 1** A theoretical plot illustrating how menopausal bone loss occurs in addition to non-menopausal or age-related bone loss is shown. Before menopause only non-menopausal bone loss is present. Changes in BMU activity associated with menopausal bone loss are superimposed on this bone loss around the time of final menses. Long after menopause, the non-menopausal bone loss continues and is magnified by any changes in BMU activity that are maintained after menopause



of the likelihood that a patient will experience the disease and the associated increased risk of fracture. In women, bone loss leading to osteoporosis can be divided into a portion directly related to menopause and another portion that is not. We refer to bone loss directly associated with menopause as menopausal bone loss (Fig. 1). Menopausal bone loss consists of the accelerated loss of bone mass during perimenopause (including a few years before and after the final menses) [2]. All other bone loss is referred to as age-related or non-menopausal bone loss. By this definition, age-related or non-menopausal bone loss includes that caused by decreased physical activity, changes in nutritional intake and requirements and any effects secondary to menopause [3,4]. In this study, we perform a thought experiment to ask how small changes in peak BMD, average rates of non-menopausal bone loss and age at menopause influence the age of osteoporosis development.

## Materials and methods

A computer simulation of bone remodeling in a representative volume of cancellous bone is used in this analysis. The model is conceptually similar to previous modeling methods [5,6], but includes a quantitative description of basic multicellular units (BMUs) like that presented by Hazelwood and colleagues [7]. The model accounts for the birthrate of BMUs, the progression of each BMU through bone, the resorption and formation of bone performed by each BMU and variations in the degree of mineralization of the bone tissue associated with changes in remodeling. Initial input parameters for the model are taken from dynamic bone histomorphometry measures in healthy young individuals (Table 1). An equilibrium state based on these parameters is used as the initial condition for all simulations. The results from each simulation include the bone volume fraction (BV/TV) and the degree of mineralization (expressed as ash mass/total mass), which together are used to calculate changes in bone mineral density from an initial value. Changes in BMD in the simulated cancellous bone are compared to clinical changes in the lumbar spine. For a more thorough derivation of the computer model we refer the reader to previous work [8].

In the current analysis, the computer model is used to simulate bone remodeling over a period of 50 years. Each simulation is started at 30 years of age with bone mineral density at its lifetime peak and the bone remodeling system at equilibrium (no net bone loss). From this initial condition bone loss caused by both menopausal and non-menopausal factors is applied. Bone loss associated with menopause is simulated by increasing the birthrate of new

**Table 1** Initial remodeling parameters used in the analysis are presented. The values are based on clinical studies in young healthy individuals. The values are modified to account for menopausal and non-menopausal bone loss during bone loss simulations

Remodeling parameter	Nominal value
Origination frequency <sup>a</sup>	0.00585 BMU/mm <sup>2</sup> per day
Local resorption rate <sup>b</sup>	1.78×10 <sup>-6</sup> mm <sup>3</sup> /site per day
Local formation rate <sup>b</sup>	5.75×10 <sup>-7</sup> mm <sup>3</sup> /site per day
Resorption period <sup>c</sup>	42 days
Reversal period <sup>c</sup>	9 days
Mineralization lag time <sup>c</sup>	15 days
Formation period <sup>c</sup>	130 days
BMU lifespan of progression <sup>d</sup>	100 days
Secondary mineralization period <sup>e</sup>	6 years

<sup>a</sup>Based on an activation frequency of 9×10<sup>-4</sup> days<sup>-1</sup> found by Han et al. [17]

<sup>b</sup>Based on BMU geometry measured histologically [18]

<sup>c</sup>Value based on measures from young healthy individuals [19]

<sup>d</sup>Value based on estimates by Parfitt et al. [20]

<sup>e</sup>Based on previous simulations [8]

BMUs at a linear rate over the perimenopausal period (to a maximum increase of 120% greater than the original value), a method that has been shown to produce bone loss patterns similar to those observed clinically [2]. Changes in bone remodeling associated with menopause are assumed to be the same for all individuals. Bone loss associated with non-menopausal factors is simulated by applying a steady focal imbalance to bone remodeling so that less bone is formed than is resorbed at each remodeling site. Such a modification in bone remodeling activity is consistent with the reduction in wall thickness at remodeling sites that has been well documented in the histomorphometry literature [9]. This steady rate of non-menopausal bone loss is meant to represent the average rates of non-menopausal bone loss after 30 years of age.

The initial values for the peak BMD and the average rate of non-menopausal bone loss are taken from cross-sectional studies (Hologic database). The initial age at menopause is taken to be 50 years. Three different parametric analyses are performed varying the peak BMD (simulation method I), the age at menopause (simulation method II), and the rate of non-menopausal bone loss (simulation method III, see Table 2) from the initial values. The delay in the onset of osteoporosis as compared to that predicted with the initial values is used to determine the relative influence of the three factors.

## Results

A simulation with the initial values of peak BMD, rates of age-related loss and menopausal age predicts the

**Table 2** Variations in peak BMD, age at menopause and the rate of non-menopausal bone loss for each simulation method are shown. The cross-sectional average peak BMD (pBMD) in the lumbar spine from clinical studies in women is used as the initial condition for simulations II and III and is varied with  $\pm 1.5$  SD in simulation I. The initial average rate of non-menopausal bone loss is also derived from the Hologic database and expressed as the percent of peak BMD lost per year (0.25% pBMD/year)

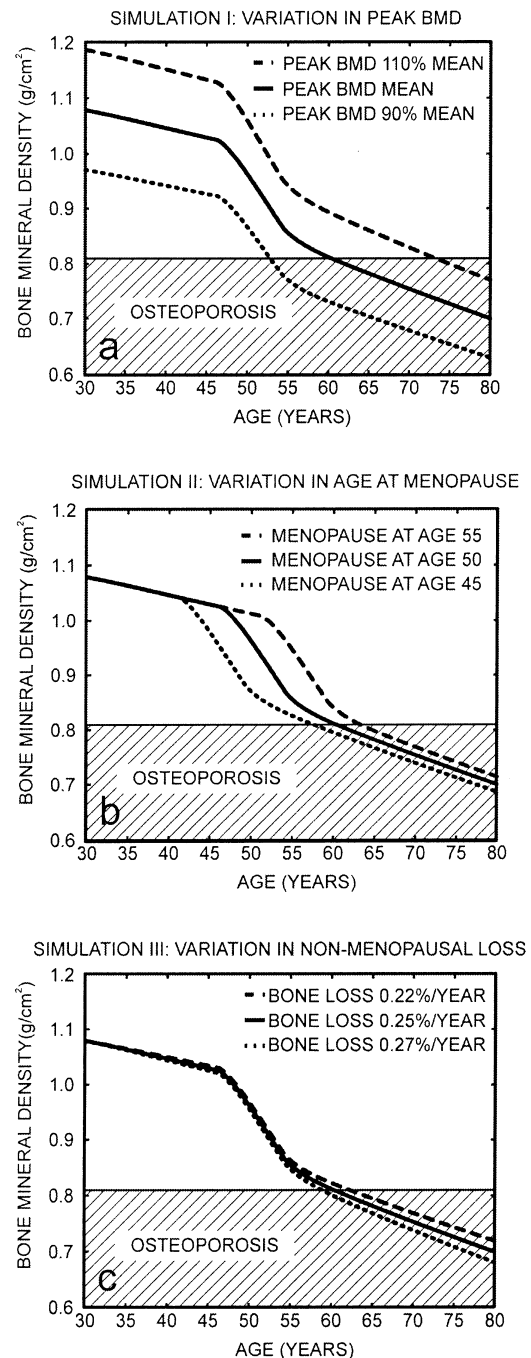
Simulation type	Peak BMD	Age at menopause	Rate of non-menopausal bone loss
I	0.92–1.25 g/cm <sup>2</sup>	50 years	0.25% pBMD/year
II	1.08 g/cm <sup>2</sup>	45–55 years	0.25% pBMD/year
III	1.08 g/cm <sup>2</sup>	50 years	0.00–0.70% pBMD/year

onset of osteoporosis to be near 60 years of age. Small changes in peak BMD are predicted to cause large changes in the age at which osteoporosis develops (Fig. 2a). Similar changes in the age at menopause and the rate of non-menopausal bone loss resulted in much smaller delays in the development of osteoporosis (Fig. 2b,c). The relative influence on the development of osteoporosis of each of the three parameters is shown in Fig. 3. A 10% increase in peak BMD is predicted to delay the development of osteoporosis by 13 years, while a similar change in the age at menopause or the rate of non-menopausal bone loss results in a delay of approximately 2 years.

## Discussion

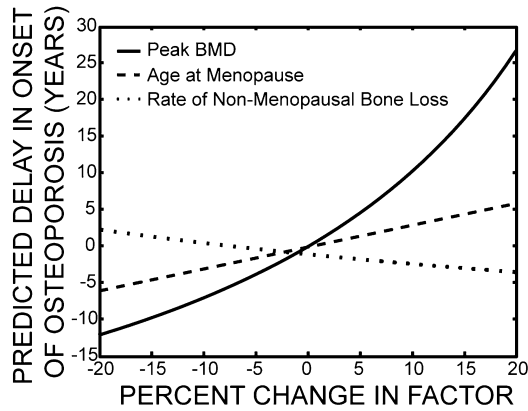
No computer model is capable of predicting when an individual will develop osteoporosis or an osteoporosis related fracture. The objective of this analysis was not to predict when an individual's BMD drops to levels low enough to result in a diagnosis of osteoporosis, but rather to compare how three factors involved in bone loss contribute to the development of osteoporosis. The current analysis places a quantitative estimate on the influence of peak bone mineral density, suggesting that a 10% change is approximately 6 times more influential on the development of osteoporosis than a similar change in the age at menopause or the rate of age-related, non-menopausal factors. Peak BMD has long been known to be a major factor influencing the development of osteoporosis [10]. This analysis provides further support for the theory that osteoporosis, as defined by the World Health Organization, is a disease caused primarily by failure to gain bone during development and maturation [10,11] and suggests that low peak BMD may be the single most important factor in the development of osteoporosis.

Although in our analysis the age at onset of osteoporosis is most sensitive to variation in the peak BMD, the rate of non-menopausal bone loss still plays an important role. This is because the rate of non-menopausal bone loss probably varies much more than the



**Fig. 2** Simulations varying **a** the peak bone mineral density, **b** the age at menopause and **c** the rate of non-menopausal bone loss within 10% of the initial value are shown. The shaded area corresponds to the clinical definition of osteoporosis in the lumbar spine (BMD < 2.5 SD below the young adult mean)

peak BMD. A 10% change in peak BMD corresponds to almost 1 SD from the population mean. One standard deviation change in the rate of non-menopausal bone loss may be much greater than 10% of the initial value used in the current study. In addition, age-related bone loss in the lumbar spine may not be as steady as that simulated in the computer model. Some researchers have found very little age-related bone loss in the lumbar



**Fig. 3** The delay in the development of osteoporosis predicted in response to a percent change in peak BMD, age at menopause or the rate of non-menopausal bone loss is shown. A small percent change in peak BMD can generate a much larger delay in the development of osteoporosis than a similar change in the age at menopause or the rate of non-menopausal bone loss

spine of premenopausal patient populations [12,13], suggesting that age-related loss may be confined to older individuals. To consider this possibility, additional simulations in which non-menopausal bone loss was not applied until 50 years of age were performed. While these additional simulations resulted in different patterns of bone loss, similar predictions of the relative influence of peak BMD, age-related bone loss and menopause were achieved.

The primary limitation of our analysis is that changes in BMD of cancellous bone caused by remodeling are used to predict changes in the areal BMD of the entire lumbar spine. Such a comparison is limited because it does not account for differences in bone remodeling between cancellous and cortical bone in the lumbar spine. In addition, significant periosteal apposition (or bone modeling) has been documented to occur in the lumbar vertebrae with age [12,14], a process that could influence areal BMD measures in a manner that is not predicted by our simulations of bone remodeling in cancellous bone. Our results therefore have limited application between groups with different patterns of periosteal apposition or significant variation in whole bone size during aging. Lastly, our simulations begin to apply non-menopausal bone loss at 30 years of age, assuming that BMD is at its lifetime peak at that age. In many individuals, non-menopausal bone loss may begin at an earlier or later age. A change in the age when non-menopausal bone loss begins would result in a similar change in the age at which osteoporosis is predicted to develop but would not affect the relative influence of peak BMD, menopause or age-related bone loss.

In an attempt to better predict bone mass in elderly individuals, Hui et al. performed a cross-sectional analysis of bone mass in pre- and postmenopausal women [15]. They concluded that cortical bone mass in the radius of women soon after menopause is highly influenced by peak bone mass, but that in women in their 70s, peak bone mass and postmenopausal rates of loss

contribute equally to elderly bone mass. The current analysis provides a different perspective on this issue, one that suggests that, while peak BMD and rates of postmenopausal bone loss are both important for determining elderly BMD, any intervention that can cause even small increases in peak BMD may be much more effective at preventing or delaying the development of osteoporosis than an intervention that causes similar changes in other factors. One possible reason for this finding is that differences in peak BMD occur early in life and therefore influence bone mass for a longer period of time.

The current analysis was designed for understanding the development of osteoporosis in individuals based on declines in bone mineral density observed in the general population. It does not account for the effects of drug or hormonal treatments that may influence bone mass (including glucocorticoids, thyroxine and hormone replacement). Because it is based on bone mineral density, it is useful for understanding the factors that contribute to the development of osteoporosis as defined by the World Health Organization, but makes no predictions regarding bone fragility. Fracture risk prediction relative to lifespan has been calculated in previous studies based on the average rates of bone loss, age, ethnicity and other factors [16]. The current model is different in that it bases all changes in bone mass on modifications to bone remodeling, making it capable of describing interactions between factors, such as the amplification of age-related bone loss after menopause (Fig. 1). Computational approaches like that performed in this study have great potential for comparing the effectiveness of treatments and for developing clinical or experimental studies of new treatments or prevention techniques.

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