

A Theoretical Analysis of the Contributions of Remodeling Space, Mineralization, and Bone Balance to Changes in Bone Mineral Density During Alendronate Treatment

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In patients with osteoporosis, alendronate treatment causes an increase in bone mineral density (BMD) and a decrease in fracture incidence. Alendronate acts by changing the bone remodeling process. Changes in bone remodeling resulting in decreased remodeling space, increased bone balance per remodeling cycle, and increased mineralization (ash mass/bone mass) have all been associated with alendronate treatment. Understanding the relative contributions of these parameters to BMD increases could help predict the utility of long-term (>10 years) or intermittent treatment strategies, as well as treatment strategies in which another pharmaceutical is administered concurrently. We have developed a computer simulation of bone remodeling to compare the contributions of focal bone balance and mineralization on BMD by simulating alendronate treatment using a bone balance method (decreased remodeling space, increased focal bone balance, uniform bone mineralization) and a mineralization method (decreased remodeling space, neutral focal bone balance, varying bone mineralization). Although both methods are able to predict BMD increases caused by alendronate over short periods, our findings suggest that the mineralization method may be more descriptive of long-term alendronate treatment. This implies that mineralization may be a larger contributor to BMD changes caused by alendronate than the focal bone balance. Based on this finding we offer a hypothesis to describe how remodeling space, focal bone balance, and mineralization each contribute to alendronate-induced BMD changes. Future analyses with this method could be used to identify improved dosing regimens and to predict which osteoporosis treatments would best complement each other. (Bone 29:511–516; 2001) © 2001 by Elsevier Science Inc. All rights reserved.

Key Words: Alendronate; Osteoporosis; Computer simulation; Bisphosphonates; Bone mineral density (BMD).

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Introduction

Osteoporosis patients treated with alendronate experience increased dual-energy X-ray absorptiometry (DXA)-derived areal bone mineral density (BMD) and reductions in vertebral fracture incidence of up to 50%.²² The increase in BMD caused by alendronate has been attributed to decreased bone turnover, increased focal bone balance, and increased degree of mineralization of the bone tissue (expressed here as the ash fraction, ash mass/bone mass). Although decreases in bone turnover have been described quantitatively, it is not currently known how much focal bone balance and ash fraction contribute to BMD increases relative to each other. Understanding the relative importance of these factors can be important for understanding the changes in bone mechanical properties caused by alendronate. It could also be important for predicting which osteoporosis treatments would be most effective when combined with alendronate. In this work we summarize the findings of alendronate studies and use them, in combination with a computer simulation of bone remodeling, to compare the influences of focal bone balance and ash fraction during alendronate treatment.

Bone remodeling is a focal phenomenon involving groups of osteoclasts and osteoblasts known as basic multicellular units (BMUs). Each BMU resorbs a small portion of bone and, soon after, forms new bone. Net changes in bone mass can occur when either the focal bone balance (a measure comparing the bone volume formed to that resorbed by each BMU) is modified or the rate of bone turnover changes (the size or number of BMUs is modified). Alendronate treatment causes a significant decrease in bone turnover and a possible increase in the focal bone balance.⁴ An increase in the focal bone balance causes more bone volume to be formed at each remodeling site than is resorbed, increasing the total bone mass. A decrease in bone turnover has two important consequences with regard to bone mass. First, a decrease in bone turnover causes a reduction in the remodeling space and a corresponding increase in bone volume.¹⁵ The remodeling space represents the voids and osteoid that appear temporarily due to the fact that resorption and osteoid formation precede mineralized bone formation.¹⁴ When the rate of bone turnover is decreased fewer of these temporary voids are present, decreasing the size of the remodeling space but increasing the bone volume and bone mass.

The second important consequence of reduced bone turnover involves the mineralization process in bone. A slower rate of bone turnover allows bone to accumulate more mineral before being resorbed in a succeeding remodeling cycle, thereby in-

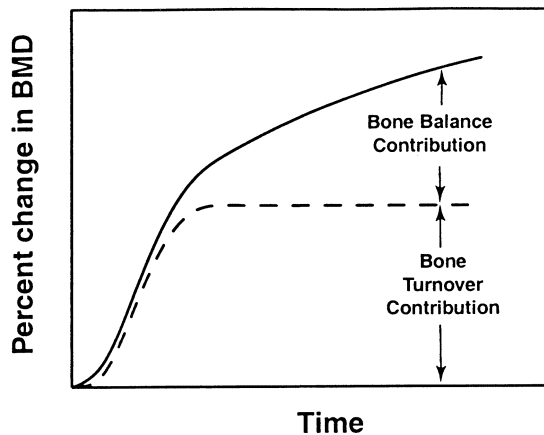


Figure 1. Conceptual illustration of the changes in BMD caused by alendronate treatment. The solid line represents the total BMD change caused by alendronate, whereas the dashed line represented the BMD changes attributed to changes in bone turnover. The difference between the two lines represents the BMD increase attributed to focal bone balance changes. Variation in the degree of mineralization (ash fraction) is considered to be part of the bone turnover contribution. Adapted from Heaney et al.¹⁰

creasing the average ash fraction of the bone tissue and the overall bone mass. Recently, it has been demonstrated that animals subjected to alendronate treatment have an increased ash fraction compared with placebo-treated controls.¹⁶ The magnitude of ash fraction changes occurring in response to decreased bone turnover is dependent on the length of the secondary mineralization period (P), a variable that has yet to be measured in humans.

Previously, Heaney and colleagues illustrated how alendronate treatment could be simulated as a decrease in bone turnover and an increase in focal bone balance.¹⁰ Using their method of simulating alendronate treatment they were able to attribute part of the BMD increase to changes caused by bone turnover and part to modification of the focal bone balance (**Figure 1**). Although their model could predict the BMD changes in a clinical study it accounted for only small variations in ash fraction because it used a short (approximately 6 month) secondary mineralization period. It is likely that a greater portion of the BMD increase that Heaney and colleagues attribute to bone turnover and part of the increase attributed to focal bone balance may actually be caused by increased ash fraction. To study this possibility we propose two methods of simulating alendronate treatment: a bone balance method, in which the ash fraction is maintained constant and alendronate causes a decrease in bone turnover and an increase in focal bone balance; and a mineralization method, in which alendronate treatment is simulated with a change in bone turnover and a resultant change in ash fraction, leaving the focal bone balance unchanged.

The primary objectives of this study are to compare the bone balance method and mineralization method with regard to their ability to predict BMD changes caused by alendronate. To meet this objective we develop a model of the bone remodeling process utilizing quantitative histologic measurements of BMU activity. The model is implemented in a computer simulation using both the bone balance method and the mineralization method. Each of these methods utilizes one influential parameter value that has not yet been measured definitively in humans (the change in focal bone balance caused by alendronate for the bone balance method and the length of the secondary mineralization period for the mineralization method). The unknown parameter

values are determined parametrically based on comparisons to the results of clinical studies. The two simulation methods are compared both by predictive ability (correlation with clinical results) and how they predict trends in BMD increases.

Materials and Methods

A BMU-based Model of Cellular Activity

A computer simulation of BMU activity in cancellous bone is used in this study. The model describes BMU activity in an arbitrary volume of cancellous bone defined by its bone volume fraction (mineralized bone volume/bulk volume). Nine independent remodeling parameters are used to describe the progression of BMUs and the resulting resorption and formation of bone (see Appendix). A feedback diagram illustrates how the model determines changes in bone volume fraction and osteoid volume fraction (**Figure 2**). The key remodeling parameters in the BMU model are those related to bone balance per remodeling cycle, bone turnover, and bone mineralization.¹¹ For this reason we concentrate our analysis on remodeling parameters associated with focal bone balance (local resorption and formation rates), bone turnover (origination frequency), and the secondary mineralization period.

We express the focal bone balance as the ratio of bone volume formed to that resorbed per remodeling site (the bone balance ratio, $\Delta\text{BMU.Rt}$). The bone balance ratio is therefore dependent on the total volume of bone resorbed and formed at each site (V_R , V_F in cubic millimeters per remodeling site):

$$\Delta\text{BMU.Rt} = V_F/V_R \quad (1)$$

If the volume resorbed (V_R) does not equal the volume formed (V_F) per remodeling site there is a net gain or loss of bone. In the present study changes in focal bone balance are modeled as decreases in the volume resorbed per remodeling site (corresponding to decreased osteoclast activity). An investigation of how these parameters are derived from histology measurements is found in the Appendix.

Bone turnover is evaluated experimentally using a two-dimensional histologic measurement known as the activation frequency (the rate of appearance of a BMU in a two-dimensional section, per day). In this model we use a more physiologic, three-dimensional descriptive parameter known as the origination frequency (number of new BMUs per square millimeter of bone surface/day) to represent the birthrate of new BMUs on the cancellous bone surface. Quantitative values for the origination frequency are calculated using a relationship between activation frequency and origination frequency that has been derived previously.¹³ The origination frequency is calculated using parameter values based on those measured in healthy postmenopausal women.⁷

The rate at which mineral accumulates in newly formed bone tissue is the final parameter that influences BMD predictions. A volume of osteoid becomes mineralized bone when small mineral crystals first appear within spaces between the collagen molecules. Over the first few days of mineralization, crystals appear throughout the mineralized bone, taking space that was previously occupied by water. This initial deposition of mineral occurs very quickly and is referred to as the primary mineralization phase. After the primary mineralization phase mineral continues to accumulate, most likely due to further increases in the number or size of crystals. During this secondary mineralization phase, mineral is added at an exponentially decreasing rate.¹⁷ Because mineral accumulates by displacing water present in the matrix there is a limit to the amount of mineral that can be

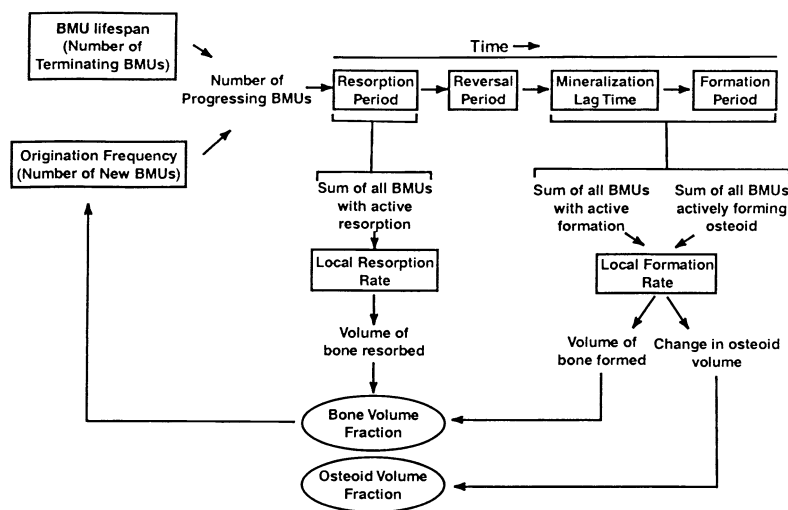


Figure 2. A diagram of the computational model is presented with remodeling parameters in boxes and model outputs in ovals. Starting at the left, the number of progressing BMUs at a point in time is modified by the number of new BMUs forming (based on the origination frequency) and the number of BMUs that are terminating (based on the BMU lifespan). Each progressing BMU begins a remodeling cycle that continues through a resorption period, reversal period, mineralization lag time, and formation period. The model tracks the BMU population history so that the total number of BMUs that are actively resorbing or forming bone can be identified at any point in time. The sum of all actively resorbing bone is used along with the local resorption rate to determine the volume of bone that is resorbed at any point in time. Likewise, the sum of all actively forming bone or osteoid is used, along with the local formation rate, to determine the volume of bone that is formed and the change in osteoid volume at any point in time. The difference between the volume of bone formed and that resorbed determines the change in bone volume fraction. The change in osteoid volume is used to determine the osteoid volume fraction. The bone volume fraction determines the surface area available for remodeling and therefore influences the number of new BMUs that originate in the next time step.

present in the bone (this would occur if all water was displaced by the mineral and is referred to as the theoretical maximum mineralization). We define the secondary mineralization period (P, years) as the time between the end of the primary mineralization phase and the point at which the mineral content reaches 95% of the theoretical maximum mineralization (where the theoretical maximum ash fraction is 0.70; **Figure 3**). The length of the secondary mineralization period has been estimated to be >6 months,¹⁸ but could last many years.⁸

Simulations of Alendronate Treatment

All model simulations were performed on a Silicon Graphics O2 workstation (SGI, Mountain View, CA) using functions defined for use with MATLAB (Mathworks, Natick, MA, USA). An initial equilibrium state for the model was determined by starting the

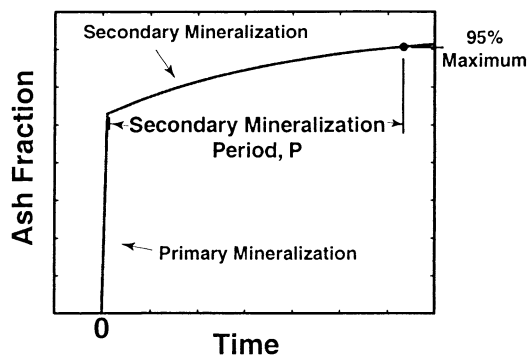


Figure 3. Primary and secondary mineralization phases. The secondary mineralization period is defined as the time required for bone to mineralize from 70% to 95% of the theoretical maximum ash fraction (a value of 0.70 in this model).

simulation with a neutral focal bone balance, no initial remodeling activity (no osteoid), and a bone volume fraction (0.20) typical of cancellous bone in the lumbar vertebrae. After the simulation was initiated, new BMUs originated, and resorption and formation occurred, removing and replacing bone volume and bringing the system to an equilibrium state. The equilibrium state was used as the initial state from which model parameters were modified to simulate alendronate treatment. Results are expressed in terms of percent change in BMD from the equilibrium state.

Alendronate’s effects on BMU activity were modeled using both the bone balance method (decreased remodeling space, increased focal bone balance, and uniform bone mineralization) and the mineralization method (decreased bone remodeling space, neutral focal bone balance, and varying bone mineralization). Chavassieux et al. showed that the activation frequency decreases by 87% after 2 years of daily treatment with 10 mg oral alendronate.⁴ In our model we assume that a similar change in the origination frequency occurs in each simulation method (since the activation frequency is directly related to the origination frequency¹³). Comparison of the two methods was performed using values for the unknown parameters (secondary mineralization period and focal bone balance) that predict the BMD changes found in clinical studies administering 10 mg/day of oral alendronate.^{3,6,21,22} The sum-of-squares for error (SSE) was used to determine how well the model predicts the results of clinical studies:

$$SSE = \sum (BMD_m - BMD_p)^2 \quad (2)$$

where BMD_m is the measured change in BMD, and BMD_p is the predicted change. The SSE and trends in the model predictions were used to evaluate the two methods.

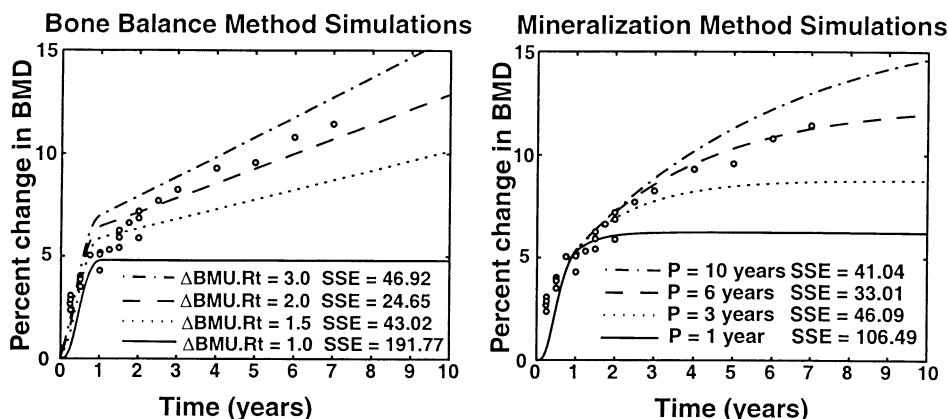


Figure 4. The results of initial alendronate simulations using both the bone balance method (left) and the mineralization method (right) are presented. Data from clinical studies of 10 mg/day of oral alendronate treatment in patients with low initial bone mass^{3,6,21,22} are plotted along with model predictions. For the bone balance method, the bone balance ratio ($\Delta\text{BMU.Rt}$) was initially unknown. A bone balance ratio of 2.0 gave good predictions of the clinical results (SSE = 24.65). Bone balance ratio values of 1.0, 1.5, 2.0, and 3.0 corresponded to focal increases in bone volume of 0.0, 2.48e-05, 3.73e-05, and 4.97e-05 mm³ per remodeling site. For the mineralization method, the secondary mineralization period (P) was unknown. A 6 year secondary mineralization period well described the BMD changes found clinically (SSE = 33.01).

Results

Alendronate simulations using the bone balance method predicted greater increases in BMD as the bone balance ratio became larger (Figure 4, left). Predicted BMD increases were sensitive to changes in the bone balance ratio, with changes after 10 years predicted to be 12.87% for a bone balance ratio of 2.0, and 10.12% for a bone balance ratio of 1.5. A bone balance ratio of 2.0 gave predictions of BMD increases similar to those found in clinical studies (SSE = 24.65). The bone balance method predicted that BMD would continue to increase as long as alendronate treatment was continued. The change in bone mass caused by a reduction in the remodeling space alone is presented in a simulation using the bone balance method with a neutral focal bone balance ($\Delta\text{BMU.Rt} = 1.0$; Figure 4, left). The increase in BMD caused by remodeling space after 10 years was predicted to be 4.78%.

Simulations using the mineralization method showed that longer secondary mineralization periods resulted in greater increases in BMD (Figure 4, right). A secondary mineralization period of 6 years resulted in good predictions of the results from clinical studies of alendronate (SSE = 33.01). The change in BMD predicted with a 6 year secondary mineralization period was 11.98% after 10 years, much greater than that predicted using a 1 year mineralization period (6.23%). Trends from the mineralization method simulations suggest that the rate of BMD increase was reduced after continued alendronate treatment.

Discussion

In this work we developed a computational model of bone remodeling and alendronate treatment. The model was designed to determine reasonable values for unknown parameters in the bone balance and mineralization methods and determine how well each model can predict the BMD increases measured clinically. We found that the bone balance method, using a bone balance ratio of 2.0, and the mineralization method, using a secondary mineralization period of 6 years, can each predict the BMD increases observed in clinical studies of daily alendronate treatment.

The model presented in this work is based on our current understanding of the process of bone remodeling and uses

parameter values based on histology data. It is therefore limited by the assumptions upon which those data are based.¹⁹ In addition, the focal bone balance was assumed to be neutral (the same amount of bone is formed as is resorbed with each remodeling cycle) in all of the pretreatment simulations (equilibrium states) used in this analysis. Individuals treated with alendronate may have a negative pretreatment focal bone balance (more bone is resorbed than formed with each cycle). A neutral pretreatment focal bone balance was used in our analysis because a number of placebo groups in alendronate studies^{3,21,22} have shown small or insignificant decreases in bone mass (most likely due to calcium supplementation and placebo effects) and a neutral pretreatment focal bone balance allows the simulations to reflect changes in bone mass caused by alendronate rather than those caused by pretreatment conditions.¹⁰

We presented two different methods of simulating alendronate’s effects on bone remodeling. Both methods showed similar sum-of-squares for error (SSE = 24.65 for the bone balance method, and SSE = 33.01 for the mineralization method), suggesting that either method could be used to predict BMD changes over the treatment periods that have already been studied (up to 7 years). The two methods gave considerably different predictions for longer treatment periods. The bone balance method predicted a steady increase in BMD with alendronate treatment because the focal bone balance caused small increases in bone volume during each remodeling cycle. The mineralization method predicted that there is a maximum possible BMD increase because there were limits on the degree of mineralization of bone (Figure 3). Although alendronate treatment has not been studied for periods of >7 years, BMD increases caused by alendronate do not appear to be unlimited. In addition, the bone balance method required a bone balance ratio of 2.0 to predict the results of clinical studies. It is unclear whether such high values can occur for prolonged periods in humans. For these reasons it is likely that the mineralization method is a better description of the effects of alendronate on bone remodeling.

Our results support the findings of recent studies suggesting that the degree of mineralization contributes more to the BMD increases caused by alendronate than the focal bone balance. Chavassieux et al. showed that patients taking alendronate for 2–3 years do not show significant increases in bone volume fraction,⁴ a result that would be expected in response to changes

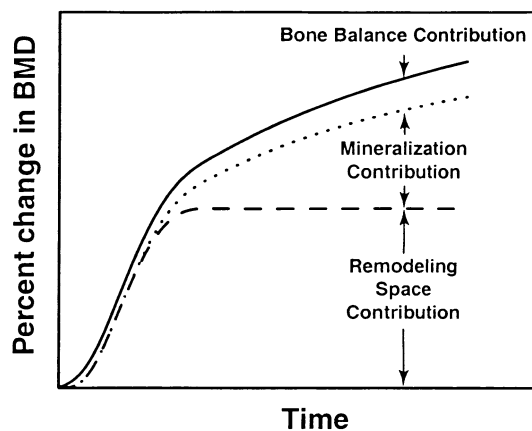


Figure 5. A theoretical description of the relative contributions of remodeling space, mineralization, and focal bone balance to BMD increases during alendronate treatment. The solid line represents the total change in BMD. The dashed line represents the contribution caused by changes in the remodeling space alone. The dotted line represents the BMD changes predicted to be caused by both the remodeling space and mineralization (ash fraction). As depicted, the focal bone balance contribution is smaller than the contribution caused by mineralization. It is possible that the BMD contribution caused by focal bone balance is negligible.

in the focal bone balance.¹⁶ In addition, the mean wall thickness of bone formed does not appear to increase in response to alendronate treatment.^{4,5} If the erosion depth reached during resorption also remains unchanged the focal bone balance would be neutral during alendronate treatment. Accurate measurement of the erosion depth and the focal bone balance is difficult, however. Trends in the focal bone balance have been observed, but it is still unclear whether modification of the focal bone balance truly occurs in response to alendronate.⁴ A more recent study of patients taking alendronate² found the changes in degree of mineralization to be similar to the changes in BMD. The investigators in this study concluded that changes in the degree of mineralization may account for a majority of the BMD increase caused by alendronate. These findings do not rule out the possibility that focal bone balance is changed in response to alendronate. They do imply that, with regard to alendronate treatment, the influence of focal bone balance on BMD increases is small compared to the influence of mineralization or the remodeling space.

Heaney and colleagues attributed part of the increase in BMD caused by alendronate to the remodeling space and another part to the focal bone balance (Figure 1).¹⁰ Our findings imply that changes in mineralization (ash fraction) not only contribute to BMD changes after alendronate treatment, but may explain most of the increase in BMD that was attributed to focal bone balance by Heaney et al. We therefore suggest that changes in remodeling space, changes in mineralization (ash fraction), and increased focal bone balance all contribute to alendronate-induced BMD increases, with the focal bone balance being the smallest contributor (Figure 5). Changes in bone turnover are responsible for the changes in remodeling space and ash fraction presented here, making bone turnover the single most important aspect of BMU activity that is modified by alendronate treatment. The importance of bone turnover has two consequences with regard to alendronate treatment. First, changes in bone mass caused by bone turnover are the result of a reduction in remodeling activity,⁹ implying that most of the benefits in bone mass

caused by alendronate may be lost if cellular activity returns to pretreatment levels. If changes in bone turnover account for most of the increases in bone mass, a patient who discontinues alendronate treatment may eventually lose most of the benefits of treatment. Second, the ash fraction is known to influence bone strength differently than the bone volume fraction (mineralized bone volume/bulk volume).¹² Areal BMD measurements do not differentiate between increases caused by ash fraction and those caused by increased bone volume fraction. Because focal bone balance changes modify the bone volume fraction, it is possible that BMD increases from ash fraction could change bone strength in a different way than the same BMD increase caused by focal bone balance. This may explain why the decreased rate of fracture after alendronate treatment (nearly 50% decrease after 3 years) appears to be so large compared to the observed change in BMD (~6%–8% after 3 years).²²

With proper validation the model used in this work could predict changes in bone mass caused by a number of different agents. What we have presented here, however, is a useful tool for comparing ideas of how alendronate affects bone mass. Future simulations based on this model could be used to identify improved dosing regimens and to predict which other osteoporosis treatments (hormone replacement, parathyroid hormone, and exercise) would best complement alendronate treatment.

Appendix

The BMU-based simulation examined here is adapted from a model presented previously.¹¹ The model uses nine independent parameters to describe BMU geometry and the resorption and formation process (Table A1). The volume resorbed and formed per remodeling site (V_R , V_F), shown in equation (1), are related to the local resorption and formation rates ($R_s.R$, FR) as follows:

$$V_R \text{ (mm}^3\text{/remodeling site)} = R_s.R \times R_s.P \quad (A1)$$

$$V_F \text{ (mm}^3\text{/remodeling site)} = FR \times FP \quad (A2)$$

The variables $R_s.P$ and FP represent the length of time in which resorption and formation occur during a remodeling cycle (resorption and formation periods in days) and $R_s.R$ and FR represent the rate at which bone volume is resorbed or formed (local resorption and formation rates in cubic millimeters per day per remodeling site). Initial values for the volume resorbed or formed per remodeling site (V_R , V_F) are calculated by defining the shape of a BMU in cancellous bone (semiellipsoidal in cross section with major radius equal to half the BMU width and minor radius equal to the erosion depth).¹¹ The BMU width (equivalent to the diameter of a cortical BMU, 0.152 mm)¹ and erosion depth (for healthy postmenopausal women, 0.049 mm)⁷ are based on clinical measurements.

The initial values for the local formation and resorption rates are calculated from equations (A1) and (A2). Changes in the local formation and resorption rates by the same factor represent changes in the BMU shape (width or depth). Changes in local formation and resorption rates by different factors result in changes in the focal bone balance. This method of representing the focal bone balance allow us to differentiate between modifications in focal bone balance caused by changes in resorption and those caused by changes in formation.

Table A1. Independent parameters of basic multicellular unit (BMU) bone remodeling

Remodeling parameter	Description	Nominal values
Origination frequency	Birthrate of BMUs on the bone surface	0.0039 BMUs/mm ² per day ^a
Local resorption rate	Volume of bone resorbed per remodeling site per unit time	1.24e-06 mm ³ /site per day ^a
Local formation rate	Volume of bone formed per remodeling site per unit time	4.27e-07 mm ³ /site per day ^a
Resorption period	Time during which resorption occurs at a remodeling site	60 days ^b
Reversal period	Time between osteoclast and osteoblast activity	57 days ^b
Mineralization lag time	Time between osteoid formation and the start of mineralization	22 days ^b
Formation period	Time during which formation occurs at a remodeling site	175 days ^b
BMU lifespan	Amount of time that a BMU progresses	100 days ^c
Secondary mineralization period	Time required for bone to mineralize from 70% to 95% theoretical maximum	Unknown ^d

^aInitial value calculated using histology data.

^bValue based on histologic data for healthy postmenopausal women.⁷

^cValue based on estimates by Parfitt et al.²⁰

^dEstimated values ranging from 6 months¹⁸ to many years.⁸

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