CHANGES IN BONE MINERAL DENSITY AFTER ALENDRONATE TREATMENT MAY BE CAUSED BY INCREASED DEGREE OF MINERALIZATION

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Introduction: In patients with low initial bone mass, alendronate treatment causes small increases in DXA derived areal bone mineral density (BMD) and large decreases in fracture incidence. An increase in bone balance (the difference between bone formed and that resorbed per remodeling cycle) is often cited as the primary cause of increased BMD in clinical trials. Although some evidence exists suggesting that bone balance can change during alendronate treatment, these changes are not seen in all patients taking alendronate[1]. Recent findings that alendronate treatment increases the degree of mineralization of bone tissue have led to a theory that the increase in BMD and decrease in fracture incidence in clinical trials is due to increases in the ash fraction (ash mass/dry mineralized bone mass) of the bone tissue[2].

Increased ash fraction occurs when bone accumulates more mineral before being resorbed during a subsequent remodeling event. This can occur when the rate of mineral accumulation is increased or the rate of bone turnover is decreased. Mineral accumulation occurs in two phases, a quick primary mineralization phase lasting only a few days and a secondary mineralization phase that is estimated to last from months to years[3, 4]. Bone turnover is commonly measured by the activation frequency, a parameter known to decrease in response to alendronate treatment[1]. The objective of this study is to determine whether the changes in ash fraction caused by alendronate treatment can account for the observed changes in BMD.

Methods: A computer model of basic multicellular unit (BMU) activity in cancellous bone is used to simulate the clinical study described by Chavassieux et. al.[1]. All input parameters in the model have values based on those found in healthy post-menopausal women[1, 5]. The mineralization process is simulated as follows (figure 1): the ash fraction rises to 70% of the maximum ash fraction after 5 days[3] (primary mineralization), and afterwards rises exponentially toward the theoretical maximum ash fraction so that 95% of the theoretical maximum is reached by the end of the secondary mineralization period, P.
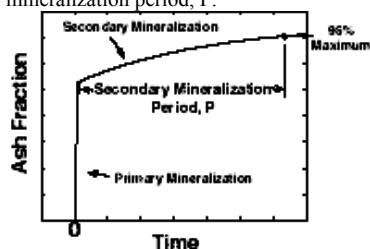

Figure 1. The secondary mineralization period is defined here as the time between the end of primary mineralization and the time when 95% of maximum mineralization occurs.

Each simulation is started in an equilibrium state where the bone balance is assumed to be neutral (the same amount of bone is formed as is resorbed with each remodeling cycle). Two different models of alendronate treatment are performed. In the first model (Ash Fraction Model) bone balance is assumed to be neutral, the ash fraction is a function of time (figure 1) and alendronate treatment is simulated by decreasing the activation frequency to that found in patients after two years of alendronate treatment (a 87% reduction)[1]. Additional simulations are performed using the Ash Fraction Model where the secondary mineralization period (P) is varied from 6 months to 10 years or with the ash fraction assumed constant. The second model (Bone Balance Model) is based on a previous study[6] where the ash fraction is assumed to be constant and alendronate treatment is simulated with a positive bone balance and decreased activation frequency. The results from both models are presented as percent increase in BMD from baseline.

Results: The results of the Ash Fraction Model simulations showed a large dependence on the mineralization process. When the ash fraction was constant, alendronate treatment showed an increase in BMD to a new equilibrium level. When a short mineralization period (1 year) was considered, equilibrium was reached at a slightly higher BMD. Longer mineralization periods (10 years) were associated with larger increases in BMD and did not reach equilibrium after 3 simulated years (figure 2A). A mineralization period of approximately 5 years gave good predictions of the

changes in lumbar spine BMD observed in four different clinical studies (Ash Fraction Model, figure 2B). The Bone Balance Model was also effective at predicting the changes in BMD observed in these studies.
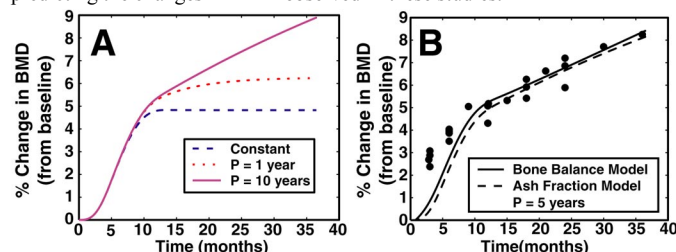

Figure 2. A. Simulations of alendronate treatment using the Ash Fraction Model are shown. Simulations with a constant ash fraction are compared to those with secondary mineralization periods (P) of 1 and 10 years. **B.** Both alendronate treatment models are presented along with data points from four clinical trials (Liberman 1995, Chesnut 1995, Pols 1999, Bone 2000) . The Bone Balance Model fits the data points approximately just as well as the Ash Fraction Model developed in the current study.

Discussion: This study shows that a positive increase in bone balance, an increase in ash fraction or some combination of the two may be responsible for the changes in BMD that are observed in patients undergoing alendronate treatment. Heaney et. al.[6] demonstrated how a positive bone balance could predict the BMD changes during alendronate treatment. The Ash Fraction Model simulations in the current study have demonstrated that variation in the ash fraction can lead to results that are indistinguishable from those caused by the bone balance. It is important to differentiate between these two processes because ash and bone volume fraction influence bone mechanics differently[7]. Since long-term changes in the bone volume fraction are caused by the bone balance, modification of the bone balance may result in mechanical properties strikingly different from those associated with changes in the ash fraction, even when the BMD is identical.

The contribution of ash fraction changes to BMD during treatment is dependent on the length of the secondary mineralization period. A short secondary mineralization period implies that changes in ash fraction caused by a reduction in activation frequency account for only a small amount of the increase in BMD seen during alendronate treatment. A long mineralization period implies that ash fraction changes could explain most or possibly all of the changes in BMD. Improved quantitative information regarding the secondary mineralization period in osteoporosis patients is needed to determine the contribution of ash fraction. An increase in BMD caused by ash fraction leads to a greater increase in bone strength than a comparable change in bone volume fraction, consistent with the theory of Meunier and Boivin[2]. Significant changes in ash fraction and not bone volume fraction may therefore explain why the decrease in fracture incidence during alendronate treatment appears to be large relative to the observed changes in BMD.

References: **1)** Chavassieux, et al. (1997) J Clin Invest 100: 1475-80. **2)** Meunier and Boivin (1997) Bone 21: 373-7. **3)** Parfitt (1983). Bone Histomorphometry: Techniques and Interpretation. **4)** Frost (1963) Bone Remodeling Dynamics. **5)** Eriksen, et al. (1990) J Bone Miner Res 5: 311-9. **6)** Heaney, et al. (1997) J Bone Miner Res 12: 1143-51. **7)** Schaffler and Burr (1988) J Biomech 21: 13-6.