Theoretical consideration of the effect of drug holidays on BMD and tissue age

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Abstract

Summary It has been suggested that some patients undergoing prolonged treatment for osteoporosis with anti-resorptive agents may benefit from discontinuing treatment. Here we use a computer simulation of bone cell activity to estimate changes in bone mineral density (BMD) and tissue age when treatment is discontinued.

Introduction Although anti-resorptive agents are effective at reducing fracture risk, questions remain regarding how long patients should continue treatment and how long treatment should be discontinued. Suspending treatment as part of a drug holiday may reduce the risk of adverse effects, but may also lead to reduced BMD.

Methods We use a computer simulation of the bone remodeling process to estimate how BMD and mean tissue age are changed after treatment is suspended. Mean tissue age is studied because increased tissue age has been associated with impaired bone quality and has been linked to the risk of adverse effects.

Results Our simulations suggest that BMD gains from anti-resorptive therapy can be lost over time, especially with anti-resorptive agents that have little residual effects. With regard to mean tissue age, the simulations suggest that increases in tissue age from anti-resorptive treatment are long lasting; increases in mean tissue age caused by treatment may remain for as long as 15 years after treatment is suspended. After stopping treatment, reductions in BMD are expected to occur long before mean tissue age returns to normal.

Conclusions Our simulations suggest that, when using a long-lasting anti-resorptive agent, 1- to 5-year drug holidays may have little effect on BMD in most patients but that drug holiday intervals that maintain BMD are unlikely to reverse alterations in tissue age caused by treatment. Our analysis echoes recent reviews suggesting patient selection and monitoring when anti-resorptive treatment is discontinued.

Keywords Atypical femoral fracture · Bisphosphonate · Bone remodeling · Computer simulation · Drug holiday

Introduction

Anti-resorptive agents are effective at reducing the risk of osteoporosis-related fractures. However, there have been concerns that long-term treatment with anti-resorptive agents (more than 5 years) increases the risk of adverse effects and it has been proposed that some patients consider suspending treatment for a period of time known as a “drug holiday,” although little evidence is available regarding recommended timing and lengths of drug holidays [1–4].

Reductions in bone turnover associated with anti-resorptive treatment cause increases in bone mineral density (BMD) and bone volume (by modulating the remodeling space [5]) but also increased tissue age. Bone tissue age is the amount of time a region of bone tissue has been present in the body and should not be confused with the age of an individual. For example, a 60-year-old individual will have regions of bone tissue that formed during bone remodeling in the past year (bone tissue age <1 year) as well as regions of primary interstitial bone that have been present throughout adulthood (bone tissue age >40 years). There is evidence that increases in bone tissue age impair the ability of bone to resist fracture by impairing bone tissue quality. Specifically, increases in collagen cross-linking (such as non-enzymatic

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glycation mediated cross-links) [6], increases in bone tissue degree of mineralization [7], reduced heterogeneity of bone tissue degree of mineralization [8] and alterations in the accumulation of microscopic cracks and other tissue damage [9] are all associated with increased tissue age and have been implicated in the pathogenesis of atypical femoral fractures [10] (Table 1). Mean bone tissue age will increase with age in most individuals, but is expected to increase more rapidly in individuals with reduced rates of bone turnover such as those taking anti-resorptive agents. Alterations in tissue age cannot be measured in patients but can be implied based on measures of bone remodeling achieved using histomorphometry [11].

As there are few clinical studies of the discontinuation of antiresorptive treatment, very little evidence-based guidance is available regarding appropriate lengths of a drug holiday and expected effects on BMD and tissue age. Computer simulation is a useful tool for addressing questions when clinical data is limited or difficult to obtain. In the current study, we use a computer simulation of the bone remodeling process to estimate: (1) the changes in BMD and tissue age following suspension of anti-resorptive treatment; and (2) how the changes in BMD and mean tissue age are altered by specified drug holidays. We expect changes in BMD and mean tissue age to be related to the length of the drug holiday and the length of residual effects of the anti-resorptive agent.

Methods

Estimates of changes in BMD and tissue age are performed using a computer simulation of the bone remodeling process. The model has been described thoroughly in a series of papers [5, 12–14] but has been modified to report changes in mean tissue age. We provide a brief description of the model here and refer the reader to the original publications for further details. The primary assumptions in the model are that changes in bone described in the model are caused entirely by bone

remodeling in the form of basic multicellular units (BMUs). The model uses indices of dynamic bone histomorphometry (Table 2) to calculate the origination, progression and termination of individual BMUs within a representative volume of bone tissue. Once a BMU originates in the model, it progresses over time initiating new bone resorption and formation cycles. The volume of bone tissue resorbed and formed by each BMU at each time step of the simulation is recorded, making it possible to calculate the age of each discrete volume of bone within the simulation. The mean tissue age is calculated in the model as the sum of i discrete volumes of bone with volume BV_i and Age_i such that:

$$\text{Mean Tissue Age} = \frac{\sum Age_i \times BV_i}{\sum BV_i},$$

where $\sum BV_i$ is the total bone volume within the simulation. Mean tissue degree of mineralization is determined assuming rates of primary and secondary mineralization (as described by Hernandez et al. [5]). Bone resorption is assumed to be independent of tissue age in these simulations (i.e., resorption does not occur preferentially in older or younger tissue). Changes in BMD are calculated as a combination of bone volume fraction (BV/TV) and tissue degree of mineralization [5]. Anti-resorptive therapy is simulated by reducing the activation frequency by 85 % from pretreatment, mimicking histomorphometry studies of alendronate treatment (Fig. 1) [5].

Anti-resorptive treatment is simulated for a period of 5 years followed by suspension of treatment. Suspension of treatment is simulated by returning activation frequency to the

Table 2 Simulations of bone remodeling were performed using bone remodeling parameters derived from dynamic bone histomorphometry studies, as described previously [5]. The values are based on clinical studies of healthy postmenopausal women

Remodeling parameter	Nominal value
Activation frequency	6.0×10^{-4} per day ^a
Local resorption rate	1.24×10^{-4} mm ³ /site per day ^b
Local formation rate	4.27×10^{-7} mm ³ /site per day ^b
Resorption period	42 days ^c
Reversal period	9 days ^c
Mineralization lag time	15 days ^c
Formation Period	130 days ^c
BMU lifespan of progression	100 days ^d
Secondary Mineralization Period	6 years ^e

^a Based on an activation frequency in healthy postmenopausal women [15]

^b Based on BMU geometry measured histologically and is doubled for simulation of remodeling in cortical bone [12]

^c Value based on measures from young healthy individuals [16]

^d Value based on estimates by Parfitt [17]

^e Based on previous simulations [5]

Table 1 Possible contributors to the etiology of atypical femoral fractures identified by the ASBMR task force on atypical femoral fractures are listed [10]. All but one of the traits is associated with increased bone tissue age

Factor	Associated with increased bone tissue age?
Alterations in collagen cross-linking	Yes
Microdamage accumulation	Yes
Increased mineralization	Yes
Reduced heterogeneity of mineralization	Yes
Variations in rates of bone turnover	Yes
Reduced vascularity, antiangiogenic effects, altered stress fracture repair	No

Fig. 1 Changes in bone remodeling associated with anti-resorptive treatment were simulated by altering the activation frequency [4]. Suspension of treatment was simulated by returning activation frequency toward baseline using one of three different recovery simulations (Immediate, 5 year and 10 year)

pretreatment value (Fig. 1). The rate at which bone remodeling returns to baseline after suspension of anti-resorptive treatment likely varies among anti-resorptive treatments and among patients. We perform three different types of simulations to characterize the expected range in bone remodeling response to suspension of treatment: (a) Immediate Recovery; (b) 5-Year Recovery; and (c) 10-Year Recovery. In the Immediate Recovery simulations, the activation frequency is returned to baseline over the course of 1 day, in the 5-Year Recovery and 10-Year Recovery simulations activation frequency is returned to baseline over 5 or 10 years, respectively (Fig. 1). The three simulation methods may be interpreted as illustrating different anti-resorptive agents or as characterizing the experience of different types of patients. For example, the Immediate Recovery simulations are similar to what is expected from suspension of treatment with denosumab which shows little residual effect after treatment has ended [18], while the 5- and 10-Year Recovery simulations are more similar to what is expected from suspension of treatment with bisphosphonates which can have effects on bone remodeling years after suspension of treatment [19, 20]. Alternatively, the Immediate Recovery simulations may be interpreted as illustrating patients who respond rapidly to suspension of anti-resorptive treatments (fast responders) while the 5- and 10-Year Recovery simulations can be viewed as representing patients whose rates of bone remodeling change more slowly after suspension of treatment.

We first consider 5 years of anti-resorptive treatment followed by suspension of treatment for 15 years to estimate

the long-term effects of discontinuation of treatment. In the second set of simulations we consider drug holiday regimens in which anti-resorptive treatment is performed for 5 years, suspended for a period of time (1 year or 5 years) and then resumed. Simulations are performed for a region of cancellous bone mimicking that of the lumbar spine (as would be measured by DXA including cancellous bone and vertebral shell, $BV/TV=22\%$) and repeated for a representative region of cortical bone ($BV/TV=80\%$).

Results

The simulations suggest that discontinuation of anti-resorptive treatment results in reductions in BMD much more rapidly than reductions in mean tissue age (Fig. 2). In the Immediate Recovery simulations, suspension of treatment leads to a rapid return of BMD to pre-treatment levels; half of the BMD gain associated with treatment in cancellous bone is lost within 1–2 years of suspending treatment (Fig. 2a). BMD is retained much longer in the 10-Year Recovery Models where half of the BMD gained from treatment is lost at 8–9 years after suspension of treatment. The patterns of reductions in BMD following suspension of treatment were similar in cancellous and cortical bone (Fig. 2).

The simulations suggest that mean tissue age increases steadily over time in both continuously treated and untreated individuals, although the rate of change in mean tissue age is greater when bone remodeling is suppressed (Fig. 2b, d). After suspension of treatment, mean tissue age approaches that of an untreated individual slowly. In the Immediate Recovery simulations, 8 years are required until half of the effect of treatment on tissue is removed, while in the 10-Year Recovery simulations, more than 15 years are required to remove half of the changes in bone tissue age caused by treatment. A patient who takes an anti-resorptive agent for 5 years is expected to display increased bone tissue age (relative to an untreated individual) 15 years after stopping treatment (Fig. 2b, d). Alterations in mean tissue age associated with treatment are larger in cortical bone than in cancellous bone, reflecting the reduced rate of bone turnover in cortical bone.

Simulations of drug holidays show oscillations in BMD and mean tissue age (Fig. 3). Reductions in BMD and tissue age are greatest during longer drug holidays and in simulations where remodeling recovers more rapidly (such as the Immediate Recovery simulations). Reductions in BMD from a drug holiday in the Immediate Recovery simulations were large; almost half of the BMD gained by the first 5 years of treatment is lost during a 1-year-long drug holiday. In contrast, reductions in BMD in 5- and 10-Year Recovery simulations are negligible during a 1-year drug holiday and modest in 5-year drug holidays. Cortical and cancellous bone followed the same patterns of BMD loss in drug holiday simulations.

Fig. 2 Simulations of five years of anti-resorptive treatment followed by 15 years of suspended treatment are shown for the three different Recovery models. Results are presented for both cancellous bone (**a, b**) and cortical bone (**c, d**). Data points in part **a** are average changes in lumbar spine BMD observed in clinical studies of continuous alendronate treatment [19, 20]

Regarding mean tissue age, longer drug holidays are associated with greater reductions in mean tissue age, although none of the simulations of drug holidays suggest that tissue age will ever match that of an untreated individual (Fig. 3). Reductions in mean tissue age are greatest in the Immediate Recovery simulations and smallest in the 10-Year Recovery simulations. Changes in mean tissue age during drug holidays are greater in cancellous bone than in cortical bone, but remain small in 5- and 10-Year Recovery simulations in both types of bone tissue.

Discussion

Our simulations suggest that suspending anti-resorptive treatment can lead to reductions in both BMD and mean tissue age, but that reductions in BMD occur much faster than reductions in mean tissue age. Increases in tissue age caused by a 5-year period of anti-resorptive treatment may be present more than a decade after suspension of treatment. Our findings support the idea that lengthy drug holidays (5 years) with a long-lasting

anti-resorptive agent can maintain BMD, but are unlikely to cause large reductions in mean tissue age.

When interpreting our results, it is important to keep in mind that it is not possible for a computer simulation to completely mimic bone cell activity throughout the skeleton. The current model considers only bone remodeling in the form of BMUs as described in iliac crest biopsies and does not include bone modeling (uncoupled bone formation and resorption) and periosteal apposition. The model simulates representative regions of cancellous and cortical bone and does not address variations in uptake of bisphosphonates at different regions of the skeleton or variations in rates of bone remodeling in different regions of the skeleton (spine vs. femur, etc.). Additionally, the model is deterministic and does not account for variability from patient to patient so our results should not be viewed as predicting the results in individuals but instead should be viewed as an estimate of a typical response within a population. A strength of the current study is that the model uses dynamic bone histomorphometry data from the literature to estimate changes in BMD and tissue age. Hence, the model is a simulation of the mechanisms involved

Fig. 3 Simulations of treatment for 5 years followed by a 1 year drug holiday (a–d) or a 5 year drug holiday (e–h) are shown. Immediate Recovery simulations showed large oscillations while 10 year recovery models showed only minor oscillations

in changing BMD and tissue age and can be viewed as an extrapolation from existing clinical data.

The changes in BMD in our simulations show patterns that are consistent with clinical findings. The computer simulations of the first 5 years of treatment show increases in cancellous bone BMD similar to lumbar spine BMD changes observed in clinical studies [5] (Fig. 1a, c) and the changes in cortical bone BMD ($\sim 4\%$ increase at 5 years of treatment) of similar magnitude to changes in femoral neck BMD in clinical studies ($\sim 4\%$ at 5 years) [19, 20]. Our simulations of discontinuation of treatment for 5 years with a long-lasting antiresorptive agent (the 10-Year Recovery model) predict negligible changes in cancellous bone BMD, which is similar to lumbar spine BMD changes seen in clinical studies of discontinuation of alendronate (less than 1 % of baseline loss at 5 years) [19, 20]. However, clinical observations of reductions in BMD in regions of cortical bone (femoral neck and trochanter, $\sim 2\text{--}4\%$ of baseline) were greater than predicted by the computer simulations ($<1\%$ of baseline, 10-Year Recovery Model). Additionally, our simulations of discontinuation of an anti-resorptive treatment that has very little residual effects (the Immediate Recovery simulations) are consistent with rapid reductions in BMD within the first year of suspending denosumab treatment [18].

The causes of atypical femoral fracture are poorly understood but most of the proposed mechanisms of development of atypical femoral fractures involve increases in tissue age (Table 1). Increased cortical bone tissue age observed in older individuals is associated with reductions in bone tissue toughness that are much greater than reductions in tissue strength [21]. The causes of reduced toughness are likely due to alterations in bone tissue quality. Regions of older bone tissue have increased non-enzymatic cross-links among collagen molecules, which makes bone tissue less likely to resist crack growth [6, 22]. Regions of older bone tissue also have increased tissue degree of mineralization, which has long been associated with reduced ability to resist crack growth [7]. Reduced bone remodeling can also reduce tissue heterogeneity at the scale of 10–100 μm [23], which is also expected to reduce the ability of bone tissue to resist crack growth. Consistent with the above observations, microscopic tissue damage, formed in vivo or through mechanical loading in vitro, is more likely to form in regions of interstitial bone where bone tissue age is greater [24–26]. The effect of accumulation of microdamage on mechanical failure of bone tissue is complicated because there are multiple toughening mechanisms in bone around a microscopic crack [27]. Additionally, while the presence of microdamage is an indicator of previous loading it remains unclear how much microdamage in bone is required to influence fracture risk [28].

Retrospective clinical studies have found that the risk of atypical femoral fracture is reduced within 2–3 years of discontinuing bisphosphonate treatment [29, 30], yet our simulations suggest that there is relatively little change in mean tissue age 2–3 years after stopping treatment. One might therefore conclude from these studies that mean tissue age may not contribute to the pathogenesis of atypical femoral fracture. However, the morphology of atypical femoral fractures is indicative of impairment in bone tissue mechanical properties associated with tissue age [31] and only a small portion of bone tissue with impaired mechanical properties could be removed and replaced by remodeling over 2–3 years [11] (especially under the rates of bone turnover observed following suspension of bisphosphonate treatment [19, 20]). We therefore suggest two other possibilities: (1) atypical femoral fractures are related to alterations in tissue age other than the *mean* value that change more rapidly following discontinuation of treatment (heterogeneity, periosteal vs. intracortical differences, etc.); or (2) atypical femoral fracture occurs through a combination of increased mean tissue age and factors independent of tissue age such as impaired vasculature, angiogenesis and stress fracture repair (Table 1) [32]. There are limited experimental data on these last two possibilities, highlighting useful areas of investigation.

Our simulations suggest that a drug holiday is unlikely to reduce mean tissue age without first causing large reductions in BMD. Any agent that reduces bone turnover (alendronate, risedronate, SERM, denosumab, etc.) will contribute to increases in tissue age, suggesting that switching from one anti-resorptive agent to another is unlikely to greatly reduce tissue age or mediate alterations in bone quality related to tissue age. Replacement of anti-resorptive agents with an anabolic agent like parathyroid hormone has been proposed in case studies (reviewed by [32]). Increases in bone turnover caused by parathyroid hormone treatment are expected to cause remodeling of older regions of bone tissue thereby reducing mean tissue age. The current study does not include simulations of parathyroid hormone simulations due to the limited data on alterations in dynamic histomorphometry parameters associated with parathyroid hormone treatment (activation frequency, remodeling event size, etc.) and interactions between parathyroid hormone and anti-resorptive agents (which appear to be complicated [33, 34]).

Given variability among anti-resorptive agents and among patients, it is unlikely that a single drug holiday regimen will be appropriate for all patients. In our experience patient case history can include multiple factors influencing bone turnover (hormonal disorders, treatment history, etc.) leading to some individuals in which bone remodeling rapidly recovers after suspending a treatment (similar to the Immediate Recovery Model) while others may recover more slowly from the same treatment (similar to the 10-Year Recovery Model). It is possible that whole body biomarkers of bone turnover may

be useful to classify patients, helping to guide the length of a drug holiday [3], but it remains unclear what combination of bone turnover markers (formation, resorption) would be useful for such classifications. Computer simulations like the one performed here are useful for addressing questions where clinical data is limited or unlikely to be collected in large studies, as is the case with drug holidays.

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