

Reduced Bone Tissue Heterogeneity with Bisphosphonate Treatment in Postmenopausal Women with Fractures

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INTRODUCTION

Bisphosphonate therapy reduces fracture incidence in osteoporotic patients, and the safety and efficacy of alendronate is generally preserved with treatment durations as long as 10 years [1]. Although no significant association between bisphosphonate use and subtrochanteric (ST) fracture risk was detected in recent analyses of datasets from large trials [2], identification of a rare atypical ST fracture pattern specifically associated with long-term bisphosphonate treatment [3] suggests that bisphosphonate use may alter bone quality and fracture resistance in a subset of patients. Therefore, our objective was to investigate the effect of bisphosphonate treatment on bone tissue composition near femoral fracture sites.

METHODS

Cortico-cancellous biopsies were removed from the lateral aspect of the proximal femur, adjacent to the fracture site, of postmenopausal women admitted for repair of intertrochanteric (IT) and ST fractures. All procedures were IRB-approved. Specimens were allocated to the bisphosphonate-naïve group (-BIS, n=14, age 86 ± 7y; fracture morphology: 13 IT, 1 ST, 0 atypical) if the patient had no history of bisphosphonate use; all others were allocated to the bisphosphonate group (+BIS, n=18, age 81 ± 11 y, duration 6 ± 5 y; fracture morphology: 13 IT, 1 ST, 4 atypical). Three 1-µm-thick sections from each biopsy were analyzed, and 3 cortical and 3 trabecular Fourier transform infrared (FTIR) images (400 x 500 µm²) from each section were collected over the spectral range 800-2000 cm⁻¹ at 6.25-µm spatial resolution [4]. The images were analyzed to determine the following parameters at each pixel: the mineral:matrix ratio (M:M, area ratio of the phosphate and amide I peaks), the carbonate:phosphate ratio (C:P, area ratio of the carbonate and phosphate peaks), the collagen maturity (XLR, intensity ratio of 1660 cm⁻¹/1690 cm⁻¹ bands), and the mineral crystallinity (XST, intensity ratio of 1030 cm⁻¹/1020 cm⁻¹ bands). For each image, the pixel histograms of each parameter were characterized by their mean and full width at half maximum to assess average composition and compositional heterogeneity, respectively. The FTIR properties for each group were compared with t-tests with significance levels of 0.05.

RESULTS

The mean tissue properties were similar across treatment groups for all of the parameters examined (Fig. 1a). In contrast, the distributions of tissue mineral properties were narrower in the +BIS group (Fig. 2). In particular, the distribution widths of the trabecular mineral:matrix ratio (-24%) and cortical crystallinity (-19%) were reduced in the +BIS group relative to those of the -BIS group (Fig. 1b). A trend toward a treatment-based effect in the +BIS group was also evident in the distribution width of the cortical collagen maturity (-19%, p=0.08) but did not reach statistical significance. All other properties were similar across groups.

DISCUSSION

The composition of cortical and trabecular tissue near fracture sites in the proximal femur was altered in postmenopausal women treated with bisphosphonates relative to that from bisphosphonate-naïve patients. While the mean tissue properties were similar across treatment groups, the distributions of tissue mineral properties were narrower in the +BIS group. In particular, the distributions of trabecular mineral:matrix ratio and cortical crystallinity were respectively 24% and 19% narrower in the +BIS group relative to those of the -BIS group. The trends observed here are consistent with previous reports of loss of compositional heterogeneity with bisphosphonate treatment in iliac crest biopsies from perimenopausal women without fractures [5] and in normal beagles [4].

Although loss of heterogeneity has not yet been directly related to fracture risk, it is associated with fragility: osteoporotic bone is characterized by reduced compositional heterogeneity relative to normal bone [6,7]. Tissue heterogeneity may confer increased mechanical integrity because spatial variations in tissue material properties hinder crack growth [8]. Indeed, a recent study of microdamage accumulation in iliac crest biopsies from patients with severely suppressed bone turnover (SSBT) showed that the SSBT tissue was characterized by

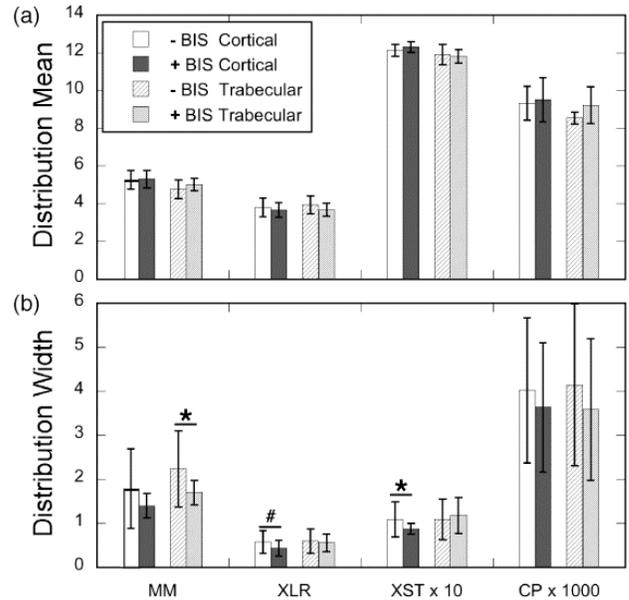


Figure 1. FTIR tissue properties for bisphosphonate-naïve (-BIS) and bisphosphonate-treated (+BIS) groups reported as image pixel distribution (a) means and (b) full widths at half maximum. (MM= mineral:matrix ratio; XLR=collagen maturity; XST=crystallinity; CP= carbonate:phosphate ratio; * p<0.05, # p=0.08)

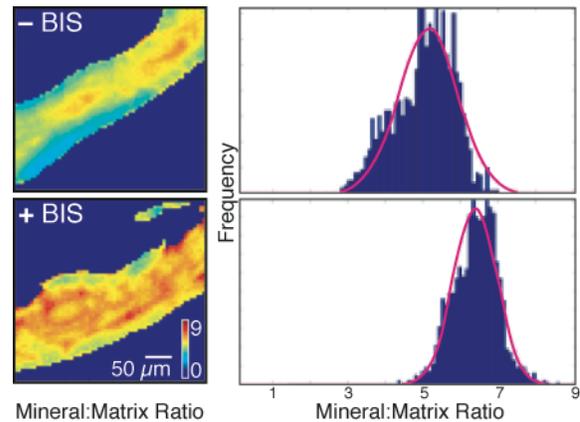


Figure 2. Representative mineral:matrix ratio images and associated pixel histograms with Gaussian fits for bisphosphonate-naïve (-BIS) and bisphosphonate-treated (+BIS) trabeculae.

reduced tissue mineral heterogeneity and altered microcrack propagation characteristics relative to healthy control tissue [9]. Because reductions in compositional heterogeneity may reduce tissue-level resistance to crack propagation, our data preliminarily suggest that oversuppression of bone turnover may alter bone quality and contribute to the increased risk of subsequent fractures in a subset of patients.

REFERENCES

[1] Bone+ 2004 [2] Black+ 2010 [3] Neviaser+ 2008 [4] Gourion-Arisquaud+ 2009 [5] Boskey+ 2009 [6] Roschger+ 2008 [7] Boskey+ 2005 [8] Fratzl+ 2007 [9] Tjhia+ 2010.

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