Increased Endocortical Formation and Periosteal Resorption in Premenopausal Women with Idiopathic Osteoporosis Treated with Intermittent Parathyroid Hormone

[1]Mary Beth Tribble
[2]Adi Cohen, MD
[1]Chantal M. de Bakker
[2]Kyle Nishiyama, PhD
[2]Elizabeth Shane, MD
[1]X. Sherry Liu, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Columbia University, New York, NY, USA

Introduction

Idiopathic osteoporosis (IOP) in premenopausal women is characterized by low bone mineral density (BMD) and/or low trauma fractures, abnormal bone microarchitecture, and reduced bone strength, without an underlying secondary cause.[1] While intermittent parathyroid hormone (PTH) has been shown to be an effective treatment for osteoporosis in men and postmenopausal women, the response of premenopausal women with IOP to PTH remains unclear. We recently reported that daily injection of 20 μg of PTH 1-34 for 18-24 months improves bone density and quality at central skeletal sites.[2] Recently, using high-resolution peripheral quantitative computed tomography (HR-pQCT), we found that daily PTH injection also improves trabecular microarchitecture at the distal radius and tibia. However, little work has been done to determine how PTH affects cortical bone. Based on a standard cortical bone analysis, we observed no changes in cortical bone geometry at both the distal radius and tibia, and a significant increase in cortical porosity at the radius, but not at the tibia.[3] However, previous studies suggest that PTH causes significant changes in bone remodeling at cortical bone surfaces.[4,5,6] To further study the effect of PTH on cortical bone remodeling, we aimed to delineate the local bone resorption and formation activities in different envelopes of cortical bone over time. Therefore, in this study we developed an image analysis framework based on longitudinal HR-pQCT scans to quantify changes in BMD at cortical surfaces. We hypothesized that significant bone remodeling occurs at both the periosteal surface (PS) and endosteal surface (ES) in IOP patients in response to PTH.

Methods

Premenopausal women (n=17, age ± years) with a history of fragility fractures and/or low areal BMD received 20 μg of PTH 1-34 daily for 18 months. The distal tibia was scanned using HR-pQCT (XtremeCT, Scanco) at baseline and 18 months. A 110-slice region at a voxel size of 82 μm was scanned 22.5 mm proximal to the endplate of the nondominant distal tibia. Standard HR-pQCT 2D-area matching image registration may limit the detection of changes in structure or density near cortical surfaces. Therefore, landmark-initialized mutual information-based 3D image registration (ITK, NLM) of the trabecular compartment was used to align the grayscale baseline and follow-up scans. During image registration, the image from one time point (moving image) is resampled and transformed to align with the image from another time point (fixed image). Resampling the moving image leads to a reduction in image quality, while the fixed image is unaffected. Unequal amounts of artifact in the images may affect results obtained during image analysis. Thus, mutual moving registration (MMR) was developed. Briefly, the amount of 3D rotation needed to align the moving image with the fixed image is determined, divided equally, and used to mutually transform the images into a new coordinate system. By using MMR, comparable artefacts are induced, reducing the imbalance in image quality which occurs with standard image registration. Subsequent registration of a subvolume ensured precise alignment of the trabeculae (Figure 1), allowing for localized mineralization changes to be quantified. Once registered, contours were drawn semi-automatically to identify the PS and ES at both time points. The PS and ES voxels were isolated and then dilated to create surface masks which capture bone remodeling occurring adjacent to the cortical surfaces. The registered scans were subtracted to generate a BMD differential map (Figure 2), and the masks were used to isolate envelopes corresponding to the PS, ES, and intracortical area. Regional differences in bone mineral density (ΔBMD), and total mineral content (TMC) were derived from the BMD differential map. Based on the thresholded baseline and 18-month scans, structural parameters such as cortical thickness (Ct.Th),

Poster No: 2006
2014 Annual Meeting
Orthopaedic Research Society
xiaoweil@mail.med.upenn.edu

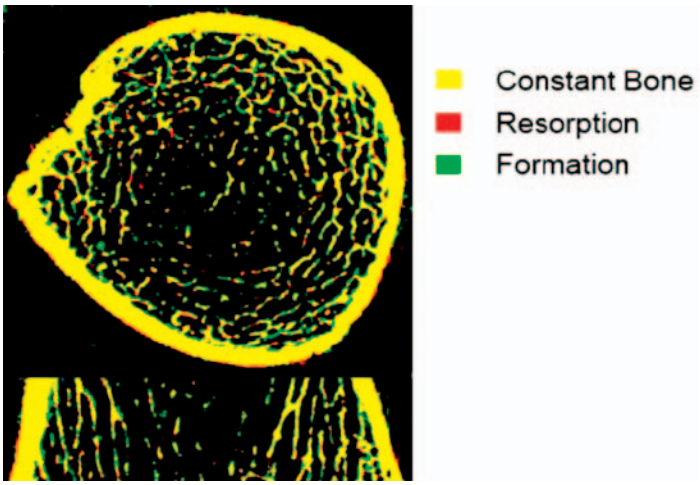

Figure 1. Registered segmented images indicating changes in bone over 18 months.

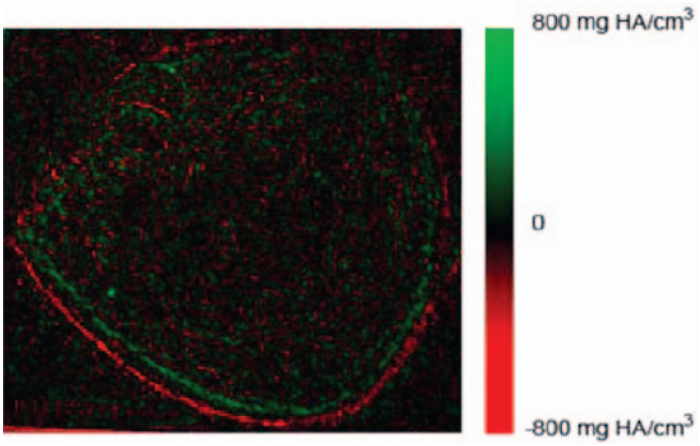

Figure 2. Differential map indicating ΔBMP at the PS and ES; there was minimal change at the intracortical area.

cortical area (Ct.Area), PS perimeter, ES perimeter, and polar moment of inertia (pMOI) were quantified. Paired student's *t*-tests were used for all comparisons, with $p<0.05$ considered a significant difference.

Results

After 18 months of PTH treatment, significant bone remodeling was observed. A 14% ($p<0.001$) decrease in TMC at the PS and a 6% ($p<0.001$) increase in TMC at the ES were observed over 18 months. There was no significant change within the intracortical area. Compared to ΔBMD of the intracortical area (-2.4 ± 19.8 mg HA/cm^3), ΔBMD at the PS (-53.9 ± 41.2 mg HA/cm^3) indicates significant mineral loss ($p<0.001$), and ΔBMD at the ES (44.6 ± 28.8 mg HA/cm^3) indicates significant mineral apposition ($p<0.001$, Figure 3)). While there was no significant change in pMOI over time, there were significant decreases in PS (0.2%, $p<0.01$) and ES perimeters (0.3%, $p<0.05$), a significant increase in Ct.Area (0.9%, $p<0.05$), and a 0.8% increase in Ct.Th trended towards significance ($p=0.1$).

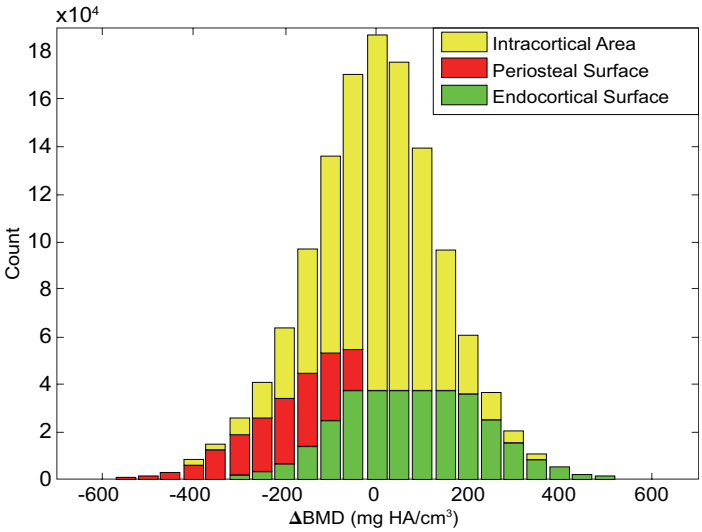

Figure 3. Histogram of ΔBMP within the three envelopes: periosteal surface, endosteal surface, and intracortical area.

Discussion

By using longitudinal HR-pQCT imaging and advanced 3D image registration, we were able to delineate regional changes in cortical BMD over time. Premenopausal women with IOP treated with PTH experienced significant decreases in BMD at the periosteum and increases at the endosteum, possibly due to excessive bone resorption at the PS and net bone formation at the ES. The effect of PTH on cortical bone remodeling at the iliac crest has been studied previously in postmenopausal osteoporosis. Short-term (<6 months) administration of PTH has been shown to increase bone formation at the ES and PS of the iliac crest.[4,5] However, a study of the effects of 18 months of PTH treatment found increased bone formation at the ES and little formation at the PS, thus supporting our findings.[6]assessed by DXA, by different mechanisms of action, supported by changes in biochemical markers of bone turnover. The purpose of this cross-sectional study was to explore the differential effects of these two osteoporosis treatments at the bone tissue level by examining bone histomorphometric parameters of bone turnover after either 6 or 18 months of treatment.\nMATERIALS AND METHODS: Patients were a cohort from a randomized parallel double-blind study conducted to compare the effects of once-daily teriparatide 20 microg and alendronate 10 mg in postmenopausal women with osteoporosis. Transiliac crest bone biopsies were obtained after tetracycline double labeling from 42 patients treated for 6 months (n = 23 Several factors confound the interpretation of this study within the context of previous research. Since the levels of bone remodeling differ between the peripheral and central skeleton, conclusions drawn from studies of bone remodeling at the iliac crest may not be applicable to the distal tibia. Also, due to the differing pathologies between postmenopausal osteoporosis and premenopausal IOP in women, observations relating to bone remodeling for postmenopausal osteoporosis may not translate to premenopausal IOP. In summary, our results

indicate that after 18 months of treatment, PTH preferentially improves new bone deposition at the endosteum and accelerates bone resorption at the periosteum of the distal tibia in premenopausal women with IOP. Although both ES and PS perimeters decrease, there is a significant increase in cortical area and a trend toward an increase in cortical thickness. Taken together, these changes in cortical structure did not alter the cortex's mechanical resistance to bending, as indicated by the lack of change in pMOI. Moreover, the preferential mineral deposition at the endosteum may help to improve bone's resistance to endocortical trabeculation, a major bone loss mechanism after menopause.

Significance

By using HR-pQCT and advanced image registration, we noninvasively examined the effects of PTH on cortical bone remodeling at the distal tibia in premenopausal women with IOP. PTH causes significant endocortical formation and periosteal resorption. As mechanical function of the cortex was maintained and endocortical BMD was improved, we conclude that PTH is a viable treatment option for premenopausal IOP.

Acknowledgments

The work is partially supported by the Penn Center for Musculoskeletal Disorders (NIH/NIAMSP30AR050950).

References

1. Cohen A, et al. Bone microarchitecture and stiffness in premenopausal women with idiopathic osteoporosis. *J. Clin. Endocrinol. Metab.* 94, 4351–4360 (2009).

2. Cohen A, et al. Teriparatide for idiopathic osteoporosis in premenopausal women: a pilot study. *J. Clin. Endocrinol. Metab.* 98, 1971–1981 (2013).

3. Kyle Nisiyama. Marked Increases in Cortical Porosity After Kidney Transplantation Especially Near the Endocortical Surface: An HR-pQCT Study. *ASBMR* (2013).

4. Lindsay R, et al. Effects of a one-month treatment with PTH(1-34) on bone formation on cancellous, endocortical, and periosteal surfaces of the human ilium. *J. Bone Miner. Res.* 22, 495–502 (2007).

5. Ma YL, et al. Comparative effects of teriparatide and strontium ranelate in the periosteum of iliac crest biopsies in postmenopausal women with osteoporosis. *Bone* 48, 972–978 (2011).

6. Arlot M, et al. Differential effects of teriparatide and alendronate on bone remodeling in postmenopausal women assessed by histomorphometric parameters. *J. Bone Miner. Res.* 20, 1244–1253 (2005).