PHT Reverses the Imbalance between Cortical and Trabecular Bone Compartments in Hypoparathyroidism: A Three-Year Longitudinal HR-pQCT Study

INTRODUCTION:

Hypoparathyroidism (HypoPT), a disorder of PTH deficiency, is associated with increased areal bone mineral density (aBMD) and microstructural abnormalities in association with markedly reduced bone turnover [1, 2]. In contrast, continuous excess secretion of PTH, as seen in primary hyperparathyroidism, causes preferential reduction of aBMD at the distal 1/3 radius (a cortical site) and relative preservation of aBMD at the lumbar spine (a trabecular site) [3]. These observations confirm the dual action of PTH to be anabolic at trabecular bone and catabolic at cortical bone, and suggest that PTH may serve as a regulator of the balance between cortical and trabecular bone.

By providing the hormone that is missing in the disease of hypoparathyroidism, PTH treatment should reverse the microstructural abnormalities associated with hypoparathyroidism. To address this hypothesis, we evaluated cortical and trabecular skeletal microstructure in hypoparathyroidism by high resolution peripheral quantitative computed tomography (HR-pQCT; Xtreme CT, Scanco Medical) before and after PTH treatment. This represents the first prospective longitudinal HR-pQCT study of a disorder of defective parathyroid function.

MATERIALS AND METHODS:

100 μg of hPTH(1-84) was administered every other day to 42 subjects with untreated hypoparathyroidism (9 male, 33 female, 46±13 yrs) for 36 months. HR-pQCT was performed on all participants at baseline and after 3, 6, 12, 24, and 36 months. The non-dominant forearm and distal tibia were immobilized in a carbon fiber shell and scanned as previously described [4]. The region of interest was defined on a scout view by manual placement of a reference line at the endplate of the radius or tibia: the first slice being 9.5 mm and 22.5 mm proximal to the reference line at the radius and tibia, respectively. The HR-pQCT measurement included 110 slices, corresponding to a 9.02 mm section along the axial direction, with a nominal voxel size of 82 μm. At each visit, the same forearm and distal tibia were scanned. Only the volume of interest that was common to both the baseline and follow-up scans was analyzed to obtain density and microstructural measurements.

According to the standard patient evaluation protocol, total, trabecular and cortical volumetric bone mineral density (Dvol, Dτ and Dcort) in mg HA/cm³ was calculated. Additionally, structural parameters, including cortical and trabecular area (Ct.Area and Tb.Area), cortical perimeter and thickness (Ct.Pm and Ct.Th), trabecular number, thickness, and spacing (Tb.N, Tb.Th, and Tb.Sp) were analyzed [3]. To assess the reproducibility of the HR-pQCT measurements, the Percent Coefficient of Variance was calculated based on the two separate baseline scans of 30 subjects within a 2-day period. Linear mixed model was utilized for repeated measures with fixed effects for age, sex, baseline measures, and time. In the presence of statistically significant effect of time, post-hoc comparisons between baseline and each time point was performed.

RESULTS:

In comparison to age- and sex-matched controls, subjects with untreated hypopPT had 13% higher Ct.Area and 12% greater Ct.Th at the distal radius (p<0.03), but not at the distal tibia. While Dcomp was similar to controls, Ct.Pm was 14% and 8% higher at distal radius and tibia (p<0.05). Tb.Area, Dvol, and trabecular microstructure measurements were similar between hypoPT and controls while Dcort tended to be higher in HypoPT at both the distal radius and tibia.

Reproducibility (%CV) of volumetric BMD (total, trabecular, and cortical), Ct.Th, and Tb.Area ranged from 0.8–1.5% at the distal radius, and 0.5–1% at the distal tibia. Reproducibility of Ct.Area and Ct.Pm were 4.8 and 3.2% at the distal radius, and 1.25 and 0.52% at the distal tibia. In comparison, the reproducibility for trabecular microstructural measurements Tb.N, Tb.Sp, Tb.Th, and Tb.Sp.SD were lower, ranging from 7.6–10.6% at the distal radius, and 3.7–4.0% at the distal tibia.

Measurements were made at 0, 3, 6, 12, 18, 24, and 36 months. Treatment-related reductions were found in Ct.Area at the distal radius (24 month, -2%, p=0.08) and the distal tibia (24 month, -2%, p=0.03), Dcomp at the distal radius (24 and 36 month, -1–-2%, p<0.01), Ct.Th at the distal radius (36 month, -3%, p=0.11) and the distal tibia (24 and 36 month, -2%, p<0.02). In contrast, Dtrab significantly increased at the distal radius (24 and 36 month, 2–3%, p<0.05) but remained unchanged at the distal tibia. As a result, at the distal radius, D100 remained unchanged with Dcomp and Dtrab changing in opposite directions; at the distal tibia, D100 significantly decreased (24 month, 1%, p=0.02). In addition, Tb.Area did not change with PTH. Other trabecular microstructure measures, such as trabecular number, thickness and spacing, showed no significant change.

DISCUSSION:

We found that PTH deficiency in hypoparathyroidism is associated with normal trabecular indices but abnormal increases in the cortical bone compartment in the peripheral skeleton as compared to matched controls. Previous findings based on aBMD measurements by dual energy X-ray absorptiometry (DXA) suggested that 24 months of PTH treatment caused a 3% increase at the lumbar spine (a trabecular site) and a 2% decrease at the distal 1/3 radius (a cortical site) [1]. By monitoring the longitudinal change of the cortical and trabecular bone compartment of the distal radius and tibia, our results showed that PTH treatment was associated with normalization in the area and thickness of the cortical compartment at both the distal radius and tibia, along with concomitant increases in trabecular bone density at the distal radius. These data suggest that PTH administration reverses microstructural skeletal abnormalities in hypoparathyroidism by restoring the balance between cortical and trabecular indices.

Our study also showcases the clinical utility of HR-pQCT for performing longitudinal studies on the effects of treatment on volumetric BMD and structure of cortical and trabecular bone. High reproducibility of integral, trabecular, and cortical BMD, bone area and cortical thickness make them excellent measurements for assessing longitudinal bone change.

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