Introduction

- Intermittent parathyroid hormone (PTH) and PTH related peptide (PTHrP)
  - FDA-approved anabolic agents for osteoporosis
  - Induce modeling- and remodeling- based bone formation
- Modeling-based bone formation (MBF)
  - Bone formation on quiescent bone surface without prior activation of bone resorption
  - Only naturally occurring during growth, healing, and with external mechanical loading in adult skeleton
- Remodeling-based bone formation (RBF)
  - Bone resorption followed by new bone formation over resorbed surfaces
  - Constantly occurring to maintain a healthy skeleton
- Objective: To compare the efficacy of PTH and PTHrP by assessing their effects on trabecular bone microarchitecture and their ability to induce MBF and RBF
- Hypothesis: Different levels of MBF and RBF induced by PTHrP vs. PTH may lead to different degrees of improvement in bone microarchitecture

Materials and Methods

- Animal protocol: Sprague-Dawley (SD) rats received bilateral OVX surgery at 4 months of age and developed osteopenia for 12 weeks
- Treatment: 40μg/kg/day for μCT study and 20μg/kg/day for histomorphometry study; 5x/wk for 3 weeks
  - VEH: n=15/6 for μCT/histomorphometry, saline
  - PTH: n=36/6 for μCT/histomorphometry, PTH 1-34
  - PTHrP: n=17/6 for μCT/histomorphometry, PTHrP 1-36
- In vivo μCT: Metaphysis of the right proximal tibia (Fig. 1A)
  - 10.5 μm voxel size by Scanco vivaCT 40 at wk 0 & wk 3
  - Trabecular bone volume fraction (BV/TV), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), trabecular number (Tb.N), connectivity density (Conn.D), structural model index (SMI)
- Multicolor fluorochrome injections for histomorphometry: (calcine/green/G, alizarin complexone/red/R, tetracycline/yellow/Y)
  - Sequence of G-R-Y-G at days -2, 5, 12, 19
  - Euthanasia at day 21

Cryohistomorphometry and imaging: 8μm cryosections of the proximal tibia underwent multiple rounds of imaging
- Darkfield and fluorescent microscope → Trabecular structure and multi-color fluorochrome labels (Fig. 2A-C)
- Polarizing microscope (decalcified sections) → Cement line and surrounding collagen fibers

Identification of MBF and RBF sites
- MBF: Smooth cement line and uniform surrounding collagen fibers (Fig. 2D)
- RBF: Scalloped cement line with interrupted collagen fibers (Fig. 2E)

Dynamic histomorphometry analysis: mineralizing surface (MS/BS), mineral apposition rate (MAR), and bone formation rate (BFR/BS)

Results

In vivo μCT (Fig. 1B-G)
- Effects of VEH treatment
  - Reduction in BV/TV, Tb.N, Conn.D, and plate-like trabeculae (increased SMI)
  - Increase in Tb.Th and Tb.Sp
- Effects of PTH/PTHRP treatment
  - Improvements in BV/TV, Tb.Th, and plate-like trabeculae (decreased SMI)
  - Less reduction in Tb.N and Conn.D and attenuated increase in Tb.Sp compared to VEH
- Effects of PTHrP vs. PTH, respectively
  - Greater improvement in BV/TV (68% vs. 44%) and Tb.Th (54% vs. 45%)
  - Less reduction in Conn.D (-12% vs. -14%)
  - Greater increase in plate-like trabeculae (0.9 vs. -0.6 in SMI)
  - No difference in % reduction of Tb.N between PTH (-14%) and PTHrP (-9%)

Histomorphometry (Fig. 2F-H)
- Effects of PTH/PTHRP treatment
  - Greater MBF- and RBF-induced MS/BS, MAR, and BFR/BS compared to VEH treatment
  - Effect of PTHrP vs. PTH treatment, respectively
    - 55% and 50% greater MBF-induced MS/BS and BFR/BS
    - No difference in MAR
    - Similar increase of RBF-induced MS/BS, MAR, and BFR/BS

Discussion

- VEH treatment → Decreased structural integrity of trabecular bone microarchitecture, despite increase in MBF and RBF
- PTH and PTHrP → Enhanced structural integrity of the trabecular network by inducing greater MBF and RBF compared to VEH
- More effective improvement in trabecular bone volume and microarchitecture with PTHrP vs. PTH due to activation of more MBF surfaces
- Rate of mineral deposition not a contributing factor to improvement in trabecular bone
- Clinically, PTHrP administered at 4x the dose of PTH [4] → Expect further improvements in trabecular microarchitecture and greater induction of MBF

Conclusions

- Both MBF and RBF contribute to the improved trabecular bone microarchitecture in response to anabolic agents
- PTHrP (clinically abaloparatide) is more efficient at stimulating MBF and improving trabecular bone microarchitecture than PTH (clinically teriparatide) in OVX rats
- More work is needed to confirm this result in humans

References


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