Tension Increases Teriparatide-Induced Bone Formation More Than Compression in the Human Femoral Neck

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Introduction: Most treatments for osteoporosis, such as bisphosphonates, preserve existing bone by inhibiting bone remodeling. Parathyroid hormone (PTH) and its analogs, including teriparatide (TPTD), provide an alternative mechanism. TPTD increases the remodeling rate and the amount of bone formed during each remodeling cycle. Iliac crest biopsies have demonstrated that PTH increases cortical and cancellous bone formation in humans.

To more fully understand the mechanisms behind PTH-related treatments, dynamic histomorphometric analysis has been used to measure cellular activity and the rates at which they occur. New bone is marked by fluorescent labels that are integrated into forming bone. By providing two doses to patients over a known time interval, the rate of formation and the extent of formation over that time period can be determined. Because this method requires the administration of these labels to a live subject, biopsy tissue has been the main source of data, limiting the site of analysis.

While mechanical loading may amplify the benefits of PTH, little is known about how the type of mechanical loading influences its role. No study to date has compared PTH treatment under tensile versus compressive loading in humans. The femoral neck is subject to bending, thereby providing a unique opportunity to study tensile and compressive loading at a single anatomical site from the same subject. Total hip replacements (THR) offer an ethical platform to obtain labeled femoral neck tissue. This study aimed to demonstrate a difference in histomorphometric indices between the tensile and compressive sides of the human femoral neck with TPTD treatment.

Methods: This study was approved by the Institutional Review Boards of Hospital for Special Surgery and Helen Hayes Hospital. All subjects gave informed consent. Thirty-eight postmenopausal men and women aged 60-89 with severe hip osteoarthritis requiring THR were randomized into two treatment groups, TPTD (n=21) and placebo (PBO) (n=17). Demographics were not different between the two groups. Treatments consisted of 20 µg of TPTD or identically appearing placebo, and were administered subcutaneously on a daily basis for an average of 6 weeks (range 4.6-11.8 weeks). Preoperative fluorescent labels were administered 4 times daily on the following schedule: 250 mg tetracycline for 3 days, 10 days off, 150 mg demeclocycline for 3 days, and 5-10 days off before THR. During surgery, a section of the femoral neck was removed then later fixed, sectioned, and stained with toluidine blue or mounted unstained as previously described.

The samples were divided into octants following the protocol established by Bell et al (Fig. 1). Superior (S) and superior-posterior (S-P) octants were categorized as tense, and inferior (I) and inferior-anterior (I-A) octants were categorized as compressive. The endocortical (Ec) and peristoeal (Ps) surfaces were analyzed for mineral apposition rate (MAR), mineralized surface (MS/BS), number of osteoclasts (Oc.N/BS), and eroded surface (ES/BS).

Data are presented as mean ± SEM. Comparisons between tensile and compressive data within a treatment group were evaluated using a paired t-test, and comparisons between treatment groups within a mechanical loading environment were evaluated using a two-sample t-test assuming equal variances. Significance was defined by a p-value of less than 0.05. Data with matching letters are statistically significantly different.

Results: Dynamic histomorphometric indices were compared across loading condition and treatment group. Ec-MS/BS and Oc.N/BS were greater on the tensile side than the compressive side in the TPTD group but not in the PBO group (Fig. 2). Ec-MS/BS also increased with TPTD treatment on the compressive side, and just missed significance on the tensile side (p=0.058). Ec-ES/BS showed no significant change across treatment and loading condition, although there was a trend toward greater values on the compressive side in the PBO group (p=0.08). Ps-MS/BS was greater on the compressive side than the tensile side for the PBO group but not for the TPTD group (Fig. 2). Ec- and Ps-MAR were similar across treatment and loading condition.

Discussion: TPTD treatment affected the tensile and compressive sides of the femoral neck differently. Within the Ec surface, TPTD led to greater values of MS/BS and Oc.N/BS on the tensile side than the compressive side. Within the Ps surface, the difference in MS/BS present in the PBO group was equalized with TPTD. This effect was most likely due to an increase on the tensile side even though statistical significance was not reached (p=0.12 tensile, p=0.92 compressive). All three of these measurements indicate that TPTD causes a greater increase of cortical bone formation parameters under tension than under compression. Data from four-point bending in rat tibiae with PTH showed similar increases in new bone formation to our results, with Ps formation suggesting greater increases in regions of tension. Our data show that TPTD changes the extent of bone forming surfaces rather than the rate of matrix apposition on the Ec and Ps surfaces in the human femoral neck, and leads to greater stimulation of bone formation on the tensile cortex than the compressive cortex.

Significance: Our study revealed that tensile and compressive loads influence TPTD differently. This knowledge furthers our mechanistic understanding of TPTD, and will help lead to future osteoporosis treatment plans that take advantage of the synergistic effects of mechanical loading and TPTD.

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