**Does Long-term Bisphosphonate Therapy Cause Brittle Fractures?**

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**Introduction:** Every year over 2 million people suffer osteoporotic fragility fractures in the US [1]. Bisphosphonates (BP) are the frontline treatment. Clinical trials have shown that BP is highly effective at reducing fracture risk in the short term [2-4]. However, recently it has become clear that long-term (>5 years) therapy is associated with a new type of femoral fracture [5]. Paradoxically, BP may cause the fractures it was meant to prevent. This so-called Atypical Femoral Fracture (AFF) is poorly understood but have never the less caused the US Food and Drug Administration [6] (FDA) to request that manufacturers add warnings to BP medications.

Despite the concerns, there is consensus that BP is effective for many patients and will continue to play a key role in fracture management. As such, the FDA [6] and the American Society for Bone and Mineral Research have stated the urgent need for research into BP fracture mechanisms [7].

As yet no human studies have demonstrated that BP treated tissue has impaired mechanical properties in comparison to naive osteoporotic (OP) or normal elderly controls. Therefore, the aim of this study was to determine whether bone samples from patients treated with BP were weaker than OP and normal elderly controls. The specific hypotheses of the study are that: 1, BP treated human bones (>5 years) are weaker and more brittle than matched (age and sex) untreated controls; 2, despite improvements of bone mass and trabecular microstructure in BP treated human bones compared with matched untreated controls.

**Methods:** This study compared bone density and strength across age and sex matched femoral heads from BP treated (n=7), naïve OP (n=15) and normal elderly control (n=7) groups. BP and OP heads were collected from traumatic hip arthroplasties, whilst the elderly control heads were collected from cadavers. Five cylindrical cores (10mm in diameter x 7mm in height) were drilled from each femoral head (Figure 1a). Specimens were micro-CT scanned at the voxel size of 30 µm using a Nikon HMX-ST CT System (Figure 1b). Samples were mechanically tested till fracture under uniaxial compressive loading using an Instron 5565 mechanical test machine (Instron Engineering Corporation, US) (Figure 1c). The maximum load (which corresponded with fracture) divided by specimen cross-section, was used to compare the apparent strength of the cylindrical specimen among. After mechanical test, soft tissues were removed from samples and the bone mass were weighted to calculate apparent density. Finally micro-CT scans were used to quantify trabecular bone volume fraction (the bone tissue volume divided by the whole cylinder volume) using BoneJ [8] (Figure 1d).

**Results:** BP treatment increased the bone apparent density as well as the bone volume fraction compared with OP naïve patients (Figure 2a and 2b, respectively). However, the apparent strength of BP bones was weaker than untreated OP bones (Figure 2c). The tissue strength (normalizing the apparent
strength by the apparent density) in the BP treated bones were 20% weaker than untreated OP naïve bones and 48% weaker than elderly control bones (Figure 2d).

**Discussion:** BP therapy increased bone apparent density and volume fraction but lowered both the apparent strength and the tissue strength compared to untreated controls. Interestingly, although BP bone was denser it was never-the-less weaker than untreated osteoporotic bone (Figure 2c). When evaluating the tissue itself, the weakness of the BP bone was even more pronounced (Figure 2d). Together these results indicate that although BP increases the mass of tissue the bone quality is impaired in comparisons to OP and normal elderly controls.

**Significance:** Most current studies evaluating the effect of BP have been based on animal models. This is the first study to compare the mechanical strength of human bone treated with BP and naïve controls. The results suggest that in some patients long term (>5 year) BP therapy can impair bone strength and, presumably, increase fracture risk. A key point is that the effect of BP is seemingly not limited to AFF’s and the importance of the study is not limited to the association with AFFs, but to the effect BP may have on bone properties generally, and how these BP embrittled bones may possibly cause fractures whether ‘atypical’ or ‘typical’.

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**Figure 1.** (a) Five cores were drilled from femoral heads then (b) micro-CT scanned at 30 μm voxel size. (c) Cores were tested to failure in compression to calculate the mechanical strength. (d) Bone volume fraction was measured from the micro-CT scans.
Figure 2. Compared with OP naive samples, BP treated samples have significantly (a) greater apparent density, and (b) greater bone volume fraction, but (c) lower mechanical strength, and (d) lower tissue strength. Symbol denotations: * = one way statistically significant difference from Kruskal-Wallis test (p<0.05); ** = double way statistically significant difference from Kruskal-Wallis test (p<0.001). NF= comparable but not significant different (p>0.05).

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