Characterization of Subtrochanteric Bone Density in Patients with Atypical Femur Fracture

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INTRODUCTION: Chronic bisphosphonate therapy has been linked to atypical femoral fracture (AFF), a rare but serious subtrochanteric fragility fracture. The risk factors underlying AFF susceptibility remain poorly understood, and the use of minimally invasive medical imaging to characterize cortical properties at AFF-prone sites remains largely unexplored. The current standard clinical protocol for assessing osteoporotic fracture risk includes DXA-derived bone mineral density (BMD) and fracture risk assessment but is limited in evaluating AFF risk. Computed Tomography (CT)-derived bone mineral density, expressed in Hounsfield Units (HU), is a key biomarker for fracture risk and may characterize cortical changes that predispose patients to AFF. The purpose of this research is to identify clinically measurable factors associated with AFF risk in bisphosphonate-treated patients. Specifically, this study aims to characterize subtrochanteric properties in AFF patients with long-term bisphosphonate use.

METHODS: Pelvic CT scans from 30 AFF patients (3 male, 27 female) on bisphosphonates for 6.8 ± 3.9 years treated at Penn Medicine were retrospectively analyzed in this IRB-approved protocol. Digital Imaging and Communications in Medicine (DICOM) voxel dimensions were standardized to 0.5 mm^3 in 3D Slicer, and cortical HU measurements were obtained using ImageJ, utilizing 1-mm^2 region of interests (ROIs) placed in anterior, posterior, medial, and lateral cortical locations. HU values at each cortical location were recorded at 16 consecutive 1-mm intervals from the inferior border of the lesser trochanter and extending distally. Statistical analyses were performed using JMP Pro 17 (SAS Institute Inc., Cary, NC). One-way ANOVA was used to evaluate the effects of cortical location, sex, and race on bone mineral density (estimated by HU), and bivariate fits were used to assess associations between distance from the lesser trochanter, age, and BMI with respect to HU.

RESULTS: A one-way ANOVA demonstrated that cortical region had a significant effect on HU ($F(3, 2596) = 196.22$, $p < 0.0001$, $\eta^2 = 0.19$, $R^2 = 0.18$). Mean HU values varied across locations, as the lateral cortex (M = 1444.6, SE = 9.1) and medial cortex (M = 1438.2, SE = 9.2) were higher in density compared to the anterior cortex (M = 1338.1, SE = 9.1) and posterior cortex (M = 1168.4, SE = 9.2). Across 2600 cortical measurements, mean HU was 1348 ± 259, and HU increased distally ($r = 0.067$, 95% CI [0.029–0.105], $p = 0.0006$). Bivariate linear regression showed an average increase of 3.8 HU per millimeter ($F(1, 2598) = 11.75$, $p < 0.0001$, $R^2 = 0.005$), and an average decrease of 5.74 HU per one-point increase in BMI ($F(1, 2598) = 24.55$, $p < 0.0001$, $R^2 = 0.009$). One-way Anova highlighted that HU varied significantly by race ($F(3, 2596) = 55.15$; $p < 0.0001$; $R^2 = 0.060$), with African-American patients demonstrating the lowest HU (n = 6, 1226.8 ± 11.2), followed by Asian patients (n = 8; 1361.2 ± 9.7) and White patients (n = 14; 1371.4 ± 7.3), while Hispanic/Latino patients had the highest HU (n = 2, 1443.3 ± 15.7).

DISCUSSION: This study demonstrates that subtrochanteric cortical location contributes significantly to HU-derived cortical bone density patterns among chronic bisphosphonate users with AFF. Cortical location accounted for 18% of the variance in HU, whereas distance from the lesser trochanter explained less than 1% of the variance, indicating that cortical location has greater influence on HU than the distance distal to the lesser trochanter. The medial and lateral cortices demonstrated higher HU values compared to the anterior and posterior regions, which is consistent with previous literature that recorded lateral cortical thickening and bone heterogeneity as predictive factors for AFF in long-term bisphosphonate users.
The limitations of this study include limited sample size due to the rarity of AFF, which may have affected statistical power. Furthermore, variability in scan timing relative to fracture, scanner kVp and contrast parameters, and the presence of joint replacement artifacts may have impacted imaging results. Despite these limitations, this study offers novel insights through monitoring in vivo BMD estimates at sixteen incremental distances in 4 different cortical locations, creating a highly detailed characterization not previously reported in AFF research. Future research will standardize scan methodology and examine demographically matched bisphosphonate-treated patients without AFF to determine femoral traits associated with increased fracture susceptibility.

SIGNIFICANCE: Cortical location has greater influence in bone density measurement variation than distance from the lesser trochanter when assessing the risk of AFF in long-term bisphosphonate users. These findings underscore the need to standardize the methodology for determining AFF risk. Given that CT scans are performed for various reasons, opportunistic analysis of these scans can be used to identify patients at an elevated risk for AFF. Further studies are required to validate these observations and establish which cortical location best predicts AFF susceptibility.

Figure 1A

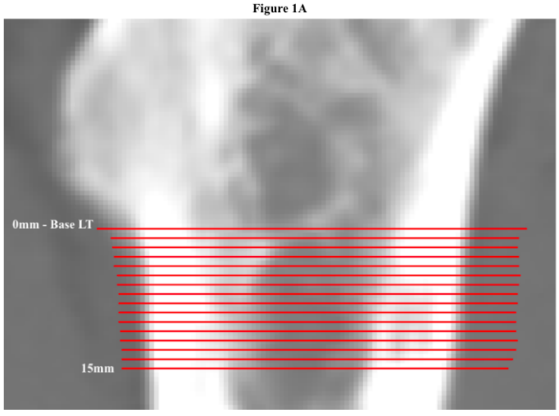

Figure 1B

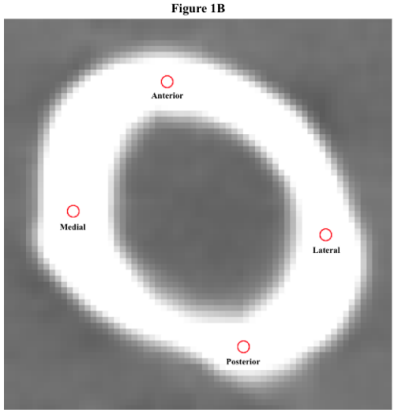

Figure 1. Method of conducting HU measurements: **1A.** Starting position for cortical HU measurements: from the base of the lesser trochanter distally at 1mm increments for 15 mm. **1B.** ROI placement by cortical location (Anterior, Posterior, Medial, Lateral).

Figure 2

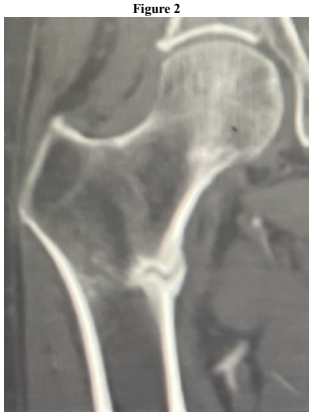

Figure 2. AFF at the level of the lesser trochanter in a patient on chronic bisphosphonate therapy