Abstract 98: Orthopaedic Research Society; Vol. 37. 2012.

Osteon Morphotypes and Predominant Collagen Fiber Orientation are Adaptations for Habitual Medial-Lateral Bending in the Human Proximal Diaphysis: Implications for Understanding the Etiology of Atypical Fractures

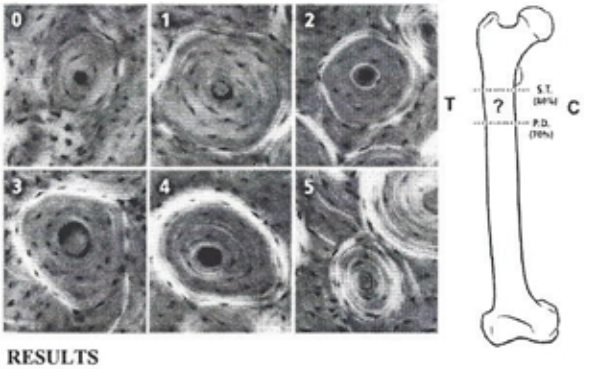
+[1]Skedros, JG; [1]Keenan, KE; [1]Halley, JA; [1]Knight, AN; [1]Bloebaum, RD
+[1]Bone and Joint Research Laboratory, Department of Veterans Affairs SLC Health Care System, Salt Lake City, UT
Corresponding Author: jskedros@utahboneandjoint.com

INTRODUCTION

Bisphosphonates are associated with atypical fractures in the human proximal femoral diaphysis [1]. It is theorized that these fractures are influenced by the accumulation of microdamage in this region because bisphosphonates block the remodeling process. However, little is known about the actual/natural strain history of this region, and how the microstructure of bone is adapted for this strain history and modulates the normal microdamage production that would be expected. This knowledge is important because it is plausible that atypical bisphosphonate-related fractures progress in a spatial/temporal manner similar to the "two-stage" fracture process that is thought to occur in human femoral neck fractures [2] and equine third metacarpal fractures [3]. Here, the "first stage" represents the accumulation of microdamage in a strain mode (e.g., tension or compression) to which the cortical region is not adapted, and cannot adapt quickly enough because the remodeling process is naturally slow. The "second stage" represents a fall or miss-step, that overloads the region that is compromised (during the "first stage" process) and fracture occurs. In this perspective we asked the question: "what are the patterns of microstructural adaptation across the proximal femur in the general diaphyseal location where these atypical fractures occur." We consider this study as an essential first step in better understanding the histological "environment" in which microdamage might occur and accumulate in this region during bisphosphonate treatment.

METHODS:

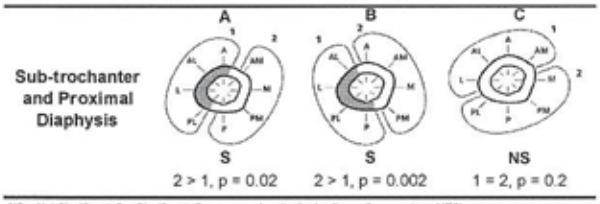
Five-millimeter-thick segments were cut transversely from the sub-trochanter and proximal diaphysis (70% diaphysis; see figure) of 12 human adult femora (2 males, 10 females: 22-64 years) and were embedded in polymethyl methacrylate (PMMA). A one-millimeter-thick section was obtained from each PMMA-embedded segment, mounted onto a glass slide, and ultramilled to achieve an overall thickness of 100±5 µm [4]. 50X images were obtained in octants for each sectioned bone. Regional differences in predominant collagen fiber orientation (CFO) were expressed as differences in weighted mean gray-level (WMGL) in circularly polarized light images. For each image, secondary osteon morphotype scores (MTSs) were assigned using the six-point method of our recent study [5] (see figure below). ANOVAs and Pearson correlations were used for statistical analysis.



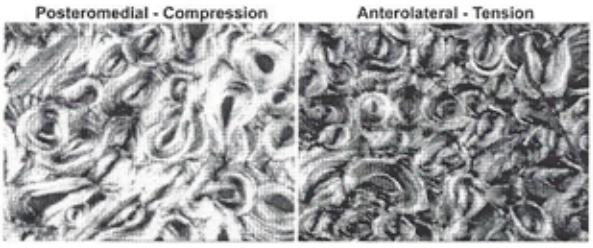
RESULTS

Significantly higher MTSs were present in the medial ("compression" = "C") cortex ($p < 0.05$) in both sections (sub-trochanter (ST) and proximal diaphysis (PD)). The table below shows three regional comparisons of the ST and PD where the grayed portions ("tension" side) represent relatively longitudinal CFO (lower osteon MTSs). This contrasts with the relatively brighter (i.e., greater gray levels/birefringence) in the medial "compression" cortex. Positive correlations exist between MTS and CFO (combined ST and PD, $r \sim 0.7$, $p<0.001$). The image below shows brighter osteons (i.e., higher MTSs, oblique/transverse CFO) in the "compression" cortex, and darker osteons (i.e., lower MTSs, longitudinal CFO) in the "tension" cortex.

Osteon MTSs in Biologically Relevant Groupings (A & B)



NS = Not Significant, S = Significant; Gray = more longitudinal collagen (lower osteon MTS)



DISCUSSION

Predominant CFO and osteon MTSs can be used as predictors of a bending load-history [5]. Osteon MTSs may have the ability to capture more information about the micro-structural organization of secondary bone than CFO alone. Finding sensitive and specific predictors of load-history is important because there is currently little data from direct measurements on the human femur (i.e., almost no in vivo strain data). When comparing the images above, it is evident that the brighter "compression" image has more osteons with oblique-transverse collagen across the entire osteon wall (MT score of 5), whereas, the osteons in the "tension" image more commonly exhibit longitudinal collagen with some degree of bright peripheral rings (MT scores 1-4) (see figure at left with 6 MT scores). Being able to distinguish these differences allows for a greater understanding of how bone can adapt for a regionally habitual strain mode. Experimental studies suggest that these different morphotypes modulate and optimize energy absorption for the locally prevalent strain mode [6,7]. In habitual "tension" and "compression" regions, the natural accumulation of strain-mode-specific microdamage likely also evokes the formation of specific secondary osteon morphotypes. Over time (months/years), cortical regions can become highly populated with different morphotypes [5]. If the natural remodeling process is perturbed (e.g., bisphosphonate treatment), then in some regions non-specific microdamage can accumulate in addition to the general reduction in the formation of 'beneficial' osteon morphotypes. This set of circumstances is substantially more deleterious than the simple accumulation of microcracks [8]. We hypothesize that these processes can occur in the proximal femoral diaphysis during this pharmacological treatment, which, when coupled with the high medial-lateral bending moment in this region, makes it prone to atypical fractures when the remodeling process is perturbed.

SIGNIFICANCE

Osteon MTSs are important histomorphological parameters because they correlate with microstructural toughening (modulating microdamage formation) and are associated with habitual strain modes. Consequently, they can be helpful in understanding the etiology of fragility fractures such as the hypothesized bisphosphonate-related femoral proximal diaphyseal fracture — where fracture is initiated in a region where microdamage accumulates in a strain mode that is not seen in normal loading and to which the bone cannot microstructurally adapt.

REFERENCES

[1] Shane et al. 2010 JBMR 25:2267-; [2] Mayhew et al. 2005 Lancet 366:129-; [3] Skedros et al. 2006 J. Exp Biol 209: 3025-; [4] Skedros et al. 1996 Anat Rec. 246:47-; [5] Skedros et al. 2011 J Anat 218:480-; [6] Hiller et al. 2003 J Orthop Res 21:481-; [7] Bigley et al. 2006 J. Biomech 39:1629-; [8] Reilly and Currey 1999 J. Exp Biol, 202:543-.