Paget’s Disease Of Bone: Multi-scale Characterization Of The Structure And Fracture Resistance

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Disclosures:

Introduction: Patients with Paget’s disease of bone (PDB) experience bone reorganization leading to bone enlargement and deformity (1). The symptoms are due to a severely high bone turnover resulting in a positive bone balance (2), where large-sized osteoclasts resorb bone at an elevated rate and lead to rapid deposition of immature bone (3). Thus, with PDB, the bone formed during the remodeling process has a poorer quality and resembles a mosaic of woven bone. Despite the dramatic change in bone structure, the associated deformity of the Pagetic bone, as well as the occurrence of small incomplete fissure fractures, a substantial clinical increase in fracture risk has not been reported (4). Here, we study the structure and fracture resistance of bone with PDB at multiple length-scales. Indeed, bone’s toughness results not only from intrinsic mechanisms generating plasticity at small length-scales but also extrinsic toughening mechanisms at the microstructural level preventing crack growth. Thus, the hypothesis is that the negative consequences of the altered osteonal/lamellar pattern on the mechanical properties are compensated by the altered composition at small length-scales to maintain toughness.

Methods: The cohort consisted of iliac crest biopsies from 50 cases of PDB and 50 control cases from the Hamburg Bone Registry at the University Medical Center, Hamburg-Eppendorf, Germany; all biopsies were attained in accordance with the City of Hamburg Ethics Committee. The disease state was confirmed with histological analysis on toluidine blue or Giemsa-stained undecalcified sections. At small length-scales, the structure of the bone was investigated on all samples via quantitative backscattered electron imaging (qBEI) to quantify the bone mineral density distribution (BMDD). Additionally, polarized light microscopy and synchrotron micro-computed tomography were used to demonstrate the disorganization of the microstructure at larger length-scales. On a subset of the samples (n = 14 PDB and n = 14 control), nanoindentation and reference point indentation were performed to quantify the bone’s mechanical properties. Additionally, in situ fracture toughness tests (n=3 PDB and n=5 control) were measured in the scanning electron microscope to characterize the toughness as a function of crack extension and to observe crack growth. A p-value < 0.05 indicates statistical significance.

Results: Using quantitative backscattered electron imaging, our results show that the histologically proven PDB cases have a 19% lower degree of mineralization than controls, while at higher length-scales synchrotron computed x-ray tomography and polarized light microscopy indicate that healthy organized lamellar Haversian osteons are replaced with an unorganized mosaic of woven bone. The distinct alterations to the nano- and micro-structural features should influence the mechanical properties. However, while hardness and elastic modulus measured via nanoindentation are significantly lower in PDB cases, the toughness was not significantly different from controls.

Discussion: The rapid rate of remodeling in patients with PDB causes the newly deposited bone to have an altered structure at multiple hierarchical length-scales. At larger length-scales, PDB is known to produce a highly disorganized woven bone. In comparison to healthy lamellar bone, where major contributions to the toughness are made extrinsically through crack deflection and bridging toughening mechanisms resisting crack growth, an unorganized bone microstructure should reduce the toughness (5). However, a significant difference in toughness was not observed between the PDB and control cases. Indeed, our results indicate that the extrinsic toughness should deteriorate due to the loss of lamellar bone but this loss is compensated by a gain in intrinsic toughening mechanisms, where the lower mineral density promotes plasticity within the bone, which is consistent with the lower hardness and elastic modulus measurements for PDB cases.

Our toughness measurements are supported by clinical results, which do not indicate an increase in fracture risk with PDB (4). Additionally, studies on antler, which is another fast growing and low mineralized tissue, indicate a high plasticity (6) and toughness (7). Consequently, we conclude that the increased plasticity due to the lower mineral content with PDB maintains the bone’s toughness not through microstructural-based shielding mechanisms (i.e., crack deflection and bridging) but through increases in plasticity at the crack tip.

Significance: This study provides a mechanistic basis to explain why fracture risk does not significantly reduce in PDB. Indeed, many bone diseases result in changes to bone structure at both small length-scales (e.g., changes in composition or crosslinking) as well as at larger length-scales (e.g., changes in the osteon/lamellae organization). As healthy bone generates toughness intrinsically at small length-scales by promoting plasticity and extrinsically at large length-scales by shielding the crack tip, a
critical feature of understanding bone diseases is how changes to the structure relate to fracture risk.

Acknowledgments:

References: 1. Paget, J. Medico-Chir. Trans. 60, 37-64.9 (1877).

ORS 2014 Annual Meeting
Poster No: 0595