

Impact Microindentation Measure of Bone Quality Strongly Correlate with Whole Bone Strength Across Multiple Skeletal Sites and Tissue-Level Material Properties in Post-Menopausal Women

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INTRODUCTION: Post-menopausal women experience a significant incidence of hip, wrist, and spine fractures, with two-thirds of all fractures occurring in women without osteoporosis, as determined by DXA^{1,2}. While bone mineral density (BMD) is used to diagnose osteoporosis and predict fracture risk, it does not consider variations in bone composition and structure that influence bone strength³. Impact microindentation (IMI) evaluates bone quality at the tissue level and provides information beyond BMD⁴. Our objective is to investigate the relationship between IMI, BMD, and bone strength in a cadaver study to better understand the factors contributing to bone strength and improve fracture risk prediction. We hypothesize that incorporating impact microindentation measurements of bone quality, obtained from the tibia mid-diaphysis, will significantly enhance the prediction of bone strength and fracture risk compared to traditional bone mineral density (BMD) assessments alone.

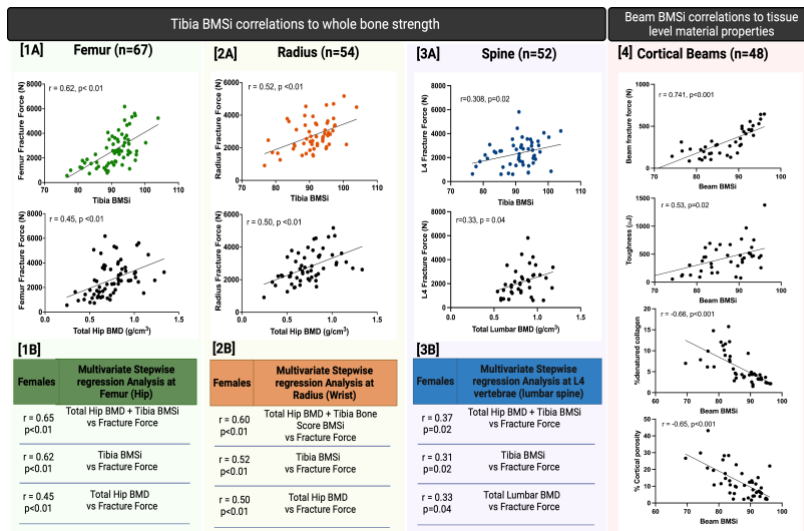
METHODS: We harvested femurs (n=67), radii (n=54), L4 vertebrae (n=52), and tibiae (n=67) bones from human cadavers of post-menopausal women with a mean age of 71±13 years. Dual energy X-ray absorptiometry (DXA) was used to measure BMD at different skeletal sites. IMI was performed at the FDA-approved tibia mid-diaphysis site and reported as Average Bone material strength index (BMSi). We mechanically tested the femurs, radii, and vertebrae to calculate fracture force (N) as a measurement of bone strength. We evaluated tissue-level mechanical properties using 3-point bending tests on rectangular beams from femoral midshaft sections and performed IMI measurements on regions outside the midspan to reduce bone heterogeneity effects. To assess changes in bone structure, we performed an α -chymotrypsin assay⁵ to quantitatively assess the extent of collagen denaturation and microCT scan (10 μ m voxel size, 70kVp x-ray tube potential, 57 μ A intensity, 500 projections, 700ms integration time) to measure cortical porosity of the beams. Pearson's correlation and stepwise multivariate regression were used to investigate the relationships between bone strength, BMD, and BMSi.

RESULTS: Our findings indicate that measuring bone quality at the tibia is predictive of bone strength at other skeletal sites, such as the femur, radius, and lumbar spine. At the femur, tibia BMSi shows a significantly higher correlation (r=0.62, p<0.05) with femur fracture force than total hip BMD (r=0.45, p<0.05), and adding tibia BMSi measurement to BMD increases the correlation to bone strength at the femur by 20% (Fig 1.1A,B). At the radius, tibia BMSi shows a strong correlation (r=0.52, p<0.05) with radius fracture force as total hip BMD (r=0.50, p<0.05), and adding tibia BMSi measurement to BMD increases the correlation to bone strength at the radius by 10% (Fig 1. 2A,B). At the spine, total lumbar BMD (r=0.33, p=0.04), show a stronger correlation with L4 fracture force, than tibia BMSi (r=0.30, p<0.01), however adding tibia BMSi to BMD significantly improves the correlation to bone strength than lumbar BMD or tibia bone score alone (Fig 1. 3A,B). We explored the relationship between beam-level BMSi and various parameters of bone mechanical and material behavior. Remarkably, beam BMSi demonstrated strong correlations with key measures of bone material behavior, including fracture force (r=0.741, p=0.01), toughness (r=0.53, p=0.02), as well as significant correlations with percent denatured collagen (r=-0.66, p<0.01) and cortical porosity (r=-0.65, p<0.001) (Fig 1.4).

DISCUSSION: Our study establishes a robust relationship between tibia BMSi, assessed through IMI, and bone strength across multiple skeletal sites, such as femur, radius, and lumbar spine. This correlation was consistently stronger than that observed with traditional BMD measurements. Incorporating tibia BMSi with BMD significantly enhances bone strength prediction, highlighting the value of assessing bone quality alongside BMD. Our findings highlight that BMSi assessments provide a comprehensive insight into bone's intrinsic material quality, its structural integrity, and its overall mechanical performance. This understanding carries substantial implications for advancing fracture risk assessment and guiding interventions aimed at improving bone health. We acknowledge certain limitations inherent to the study design, such as use of human cadaver specimens, which may not fully replicate the dynamic in vivo conditions. Despite these limitations, our study provides valuable insights into the potential of IMI to complement traditional assessments of bone health and fracture risk prediction.

SIGNIFICANCE/CLINICAL RELEVANCE: This study emphasizes the clinical significance of impact microindentation (IMI) as a complementary tool in fracture risk assessment for post-menopausal women. By revealing strong correlations between IMI-derived bone quality measurements and bone strength across key skeletal sites, this research highlights the potential for IMI to enhance personalized fracture risk prediction and guide targeted interventions to improve bone health in high-risk individuals.

REFERENCES: ¹Ruiz-Esteves, et.al, 2022; ²SY Joseph, et.al, 2022; ³FM Ulivieri, et.al, 2021; ⁴Schoeb, M,et.al, 2022; ⁵RA.Bank, et.al, 1997



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Figure 1: **1A.** Tibia BMSi is more strongly correlated with femur fracture force, than BMD. **1B.** Regression analysis shows addition of tibia BMSi to BMD increases the correlation to fracture force by 20%. **2A.** Tibia BMSi is as strongly correlated with radius fracture force, as BMD. **2B.** Regression analysis shows addition of tibia BMSi increases correlation to radius fracture force by 10%. **3A.** Tibia BMSi as well total lumbar BMD shows moderate correlation with L4 vertebrae fracture force. **3B.** Multivariate analysis shows addition of tibia BMSi increases correlation to L4 fracture force by 4%. **4.** Beam BMSi measurement strongly correlates with tissue level bone material properties such as fracture force, toughness, as well as % denatured collagen and % cortical porosity.