Adolfo Diez-Perez M.D., Ph.D., Hospital del Mar, Autonomous University of Barcelona, Barcelona, Spain

Osteoporosis is defined as a decrease in bone strength, and this results from the integration of bone density and bone quality. Bone mineral density is a common surrogate used clinically although their performance in predicting the mechanical resistance of bone to fracture is limited. Bone quality is assessed in several ways but the different approaches only measure one of the elements (microarchitecture, geometry, microdamage, etc.) of this elusive concept. Moreover, these methods are not suitable for a wide use in clinical practice.

Bone tissue mechanical properties are deemed a key component of bone strength but their assessment requires invasive procedures. We have validated a new instrument, the Tissue Diagnostic Instrument (TDI), for measuring these tissue properties *in vivo*. The TDI performs Bone Microindentation Testing by inserting a probe assembly through the skin covering the tibia and, after displacing periosteum, applying 20 indentation cycles at 2 Hz each with a maximum force of 11 N. Recently we published the study of 27 women with osteoporosis-related fractures and 8 controls of comparable ages. Measured Total Indentation Distance (46.0 ± 14 vs. 31.7 ± 3.3 microns, p= 0.008) and Indentation Distance Increase (18.1 ± 5.6 vs. 12.3 ± 2.9 microns, p=0.008) were significantly greater in fracture patients than in controls. Areas under the Receiver Operating Characteristic, ROC, curve for the two measurements were 93.1% (95% CI: 83.1, 100) and 90.3% (95% CI: 73.2, 100) respectively. Interobserver CV ranged from 8.7 to 15.5% and the procedure was well tolerated.

Our method has several advantages. Measures the tibia because there is a wide flat bone surface in their anterior face that permits a quasi-perpendicular indentation. Periosteum is easily removable here and the procedure is totally painless by using local anesthesia. However, several questions need to be addressed in the near future. Since we measure the tibial diaphysis, we assess a purely cortical bone. Whether their microindentation properties are representative of bone tissue mechanical strength in other bone compartments or anatomical areas needs to be explored. We need normal reference values and the assessment of the technique performance in other populations and clinical conditions. Predictive ability of the TDI has to be evaluated in longitudinal cohort studies. The response of bone to different treatments or pathological situations, one of the main limitations of bone densitometry, has to be measured. Finally, if TDI is able to demonstrate precision, reproducibility, discriminant ability, sensitivity to change and a good prediction of future fracture, either in basal condition or, more importantly, after exposure of the bone tissue to a drug, TDI might be the main surrogate for fracture occurrence. In this way, we could assess individual fracture risk with high predictive ability. Furthermore, expensive studies on bone response to treatment, requiring large population samples and long periods of follow up with clinical fractures as the main outcome, might be replaced by shorter studies in a limited number of individuals.

As of today, we hypothesize that Bone Microindentation Test, by inducing microscopic fractures, directly measures bone mechanical properties at the tissue level. The technique is feasible for use in clinics with good reproducibility. It discriminates precisely between cases with and without fragility fracture and may provide clinicians and researchers with a direct *in vivo* measurement of bone tissue resistance to fracture.