Reference Point Indentation (RPI) Instrument

Laboratory and Clinical Case-Control Studies

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Introduction

In addition to bone loss, the deterioration of tissue level bone mechanical properties due to aging and/or disease plays a significant role in bone fracture. The Reference Point Indentation (RPI) instrument is designed to measure these tissue level mechanical properties in bone – even the bone of living patients [1]. Here we review and extend five published laboratory case-control studies and present the most recent data from an ongoing clinical case-control study with this instrument (previously known as the Bone Diagnostic Instrument [2-4], Osteoprobe [3], and Tissue Diagnostic Instrument [6]).

By the time of the second paper [3], the protocols for bone had converged on using 20 cycles of indentation at 2 Hz and this has remained constant in subsequent work [1, 4, 5]. The nature of the precycles to find the bone surface [3] and the magnitude of the loading forces during the 20 cycles of indentation have continued to evolve, but we now believe that, except for very delicate bone, such as mouse bone, the measurement cycle of the Hospital del Mar Protocol is suitable and should be used to enable direct comparisons between future studies. We propose adding subscripts to measured parameters to indicate which protocol is used. Thus, for example, the Indentation Distance Increase (Figure 4a) measured with the Hospital del Mar Protocol would be abbreviated IDI_H.

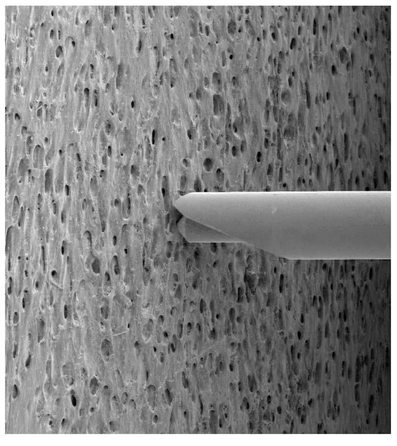

Figure 1 The RPI probe assembly consisting of a reference probe (a modified 22 gauge hypodermic needle) that rests on the surface of the bone to establish a reference point from which the indentation distances of an inner test probe into bone can be measured.

Methods

The general testing procedure is as follows: (1) Attach a new sterile probe to the RPI instrument. (2) Administer local anesthesia. (3) Insert probe through skin covering tibia until it rests on bone. (4) Displace periosteum. (5) Actuate measurement cycle which first begins a series of precycles at 4 Hz, then runs 20 indentation cycles at 2 Hz, each of which penetrate to a maximum force of 11N. (6) Repeat steps 3-6 in five or more locations.

Detailed methods and protocols for the five laboratory case-control studies (figures 4b-f) are in the previously published references: baked bovine [2], irradiated bovine [3], fluoride treated human [5], young and old human [3] and young and old mouse bone [4].

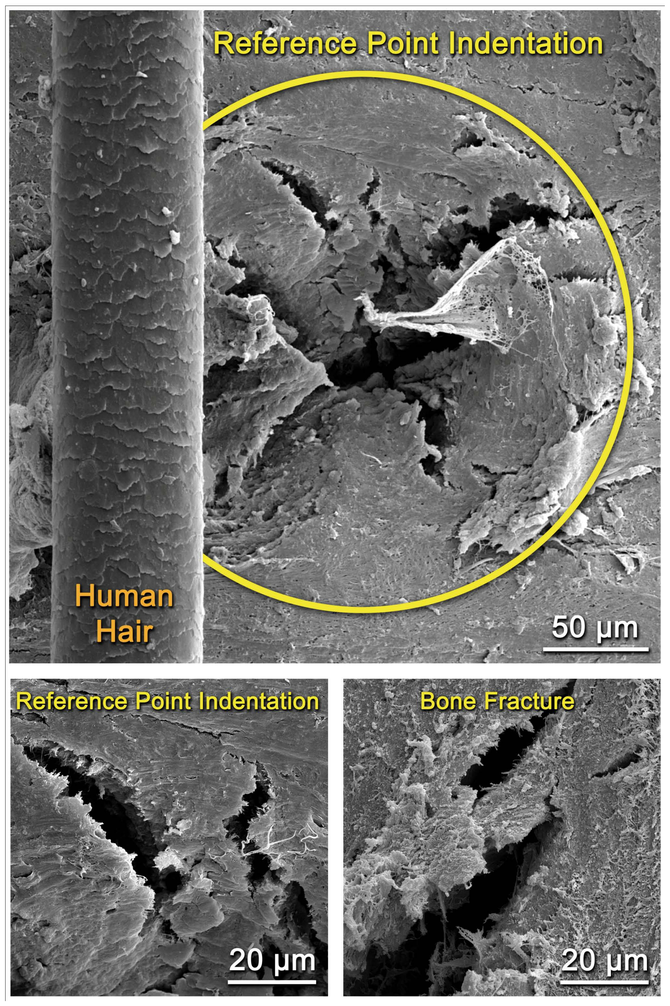

Figure 2 Top A stereoscopic scanning electron microscope image of an indentation created during RPI testing. **Bottom** Comparison of crack formation in actual bone fracture and RPI testing. As you can see RPI testing clearly replicates the same fracturing process.

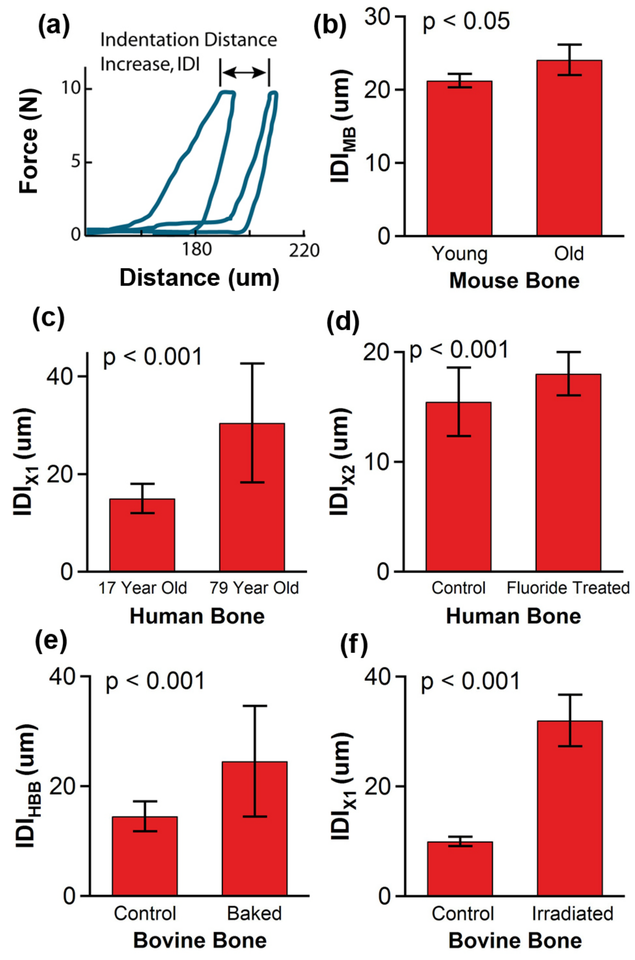

Figure 4 (a) Definition of Indentation Distance Increase, IDI
(b) - (e) IDI Results from laboratory studies. Subscripts refer to the protocol used. More easily fractured bone has higher IDI.

Results

In the five laboratory studies (Figure 4) the bone that was more easily fractured, as determined by conventional mechanical testing [2-5], had a higher Indentation Distance Increase. In the clinical study [7] (Figure 3) patients with osteoporotic fractures had significantly higher IDI_H than patients without osteoporotic fractures.

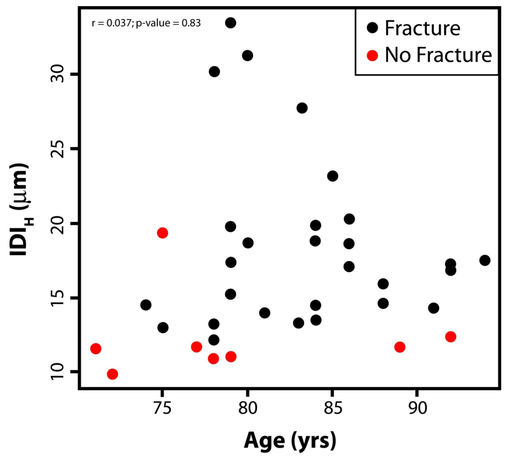

Figure 3 Indentation distance increase (IDI) measurements from clinical trials in Barcelona. Patients with fractures exhibited higher IDI.

Discussion

The Indentation Distance Increase, IDI, is greater for more easily fractured bone in five laboratory studies and in one clinical case-control study. It will be important, in the future, to standardize testing protocols for comparisons between studies because the IDI depends on protocol. IDI_H may be a suitable surrogate marker for the component of bone fracture risk due to tissue mechanical properties. This is very different from, and probably complementary to, current diagnostic tools and therapies that focus on mitigating or reversing bone loss. Thus the RPI may be a tool for the development of new pharmaceuticals: specifically a whole new class of drugs focused on improving bone's tissue level mechanical properties to decrease bone fracture risk.

References

[1]Hansma PK et al. The tissue diagnostic instrument. Rev Sci Instrum. 2009 May;80(5):054303. [2] Hansma PK et al. Bone diagnostic instrument. Review of Scientific Instruments, 2006. 77(7): p. 075105. [3] Hansma PK et al. The bone diagnostic instrument II: indentation distance increase. Rev Sci Instrum. 2008 Jun;79(6):064303 [4]Randall C et al., The bone diagnostic instrument III: testing mouse femora. Review of Scientific Instruments, 2009. 80(6): p. 065108. [5] Thurner PJ et al. Adv. Mater. 2009, 21, 451–457 [6] Hansma PK et al. The tisue diagnostic instrument. Review of Scientific Instruments, 2009. 80(5): p. 054303. [7] Diez Perez, A et al. Microindentation for in vivo measurement of bone tissue mechanical properties in humans. JBMR, in press. [8]Diez Perez, A et al. ASBMR abstract 1106. [9] Active Life Technologies, Santa Barbara, CA