Non-invasive measurements of bone strength: Promise and peril

M.L. Bouxsein

Orthopaedic Biomechanics Laboratory, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA

Keywords: Bone Strength, Microarchitecture, QCT, DXA, MRI, μCT

In designing a trial to test whether it is possible to "cure" osteoporosis, it is necessary to develop appropriate outcome assessments. A reduction in incident fractures is the obvious desired outcome, yet trials with fractures as the primary outcome require a large number of patients, are long in duration and therefore, costly. Perhaps, depending on how an osteoporosis "cure" is defined, the objective could be to treat until fracture risk is normalized, as assessed by some surrogate measure of fracture risk. Thus, the following question was asked: what non-invasive measurements are accurate, practical and affordable for determining how "curative" osteoporosis therapy influences fracture risk?

To begin to address this question, one needs to define what the non-invasive measurement needs to accomplish. For example, should it predict bone strength, fracture risk, and/or treatment efficacy? While these are not mutually exclusive goals, the type of study required to validate a surrogate measurement will largely depend on the level of performance required. Thus, to validate the ability of a new non-invasive measurement to predict bone strength, one needs to conduct an in vitro cadaver study, whereas to validate the ability to predict treatment efficacy with regard to fractures, the measurement must be tested prospectively in a clinical trial with treated and untreated subjects and fractures as outcomes. In the latter case, it would be useful to solicit FDA guidance regarding incorporation of new non-invasive measurements into a clinical trial.

With these issues in mind, it is useful to review a few general principles regarding bone biomechanics, as they influence the development and evaluation of non-invasive imaging techniques. The response of a whole bone to an applied load depends upon the intrinsic properties of the material(s) of which the bone is comprised, how much of this material is present (i.e., the mass) and how this material is distributed (i.e., the geometry and microarchitecture). Thus, in theory, the ideal imaging methodology would reflect a bone’s geometry and microarchitecture, as well as characteristics of the bone matrix, such as the degree of mineralization, amount and nature of existing microdamage, amount of collagen, and extent of collagen cross-linking. Note that the hierarchical organization of bone infers that one may want to measure architecture at the macrostructural or whole bone level (i.e., on a centimeter-to-millimeter scale), at the microstructural level (i.e., on a millimeter-to-micron scale), or on the lamellar level (i.e., on the micron-to-nanometer scale).

The current gold standard for diagnosis of osteoporosis and prediction of fracture risk is areal BMD by dual-energy X-ray absorptiometry. Areal BMD reflects bone mass, the degree of bone matrix mineralization, and is partly influenced by bone size. Accordingly, several studies using human cadavers have shown that BMD is strongly correlated to whole bone strength. Yet, BMD measurements do not specifically reflect attributes of 3-D geometry, trabecular microarchitecture, or intrinsic properties of bone matrix, and appear to be only modest predictors of the anti-fracture efficacy of anti-resorptive drugs.

There are several alternative methodologies for assessing bone strength. Quantitative computed tomography (QCT) is capable of assessing bone macroarchitecture, as well as trabecular and cortical bone density. It has been used in several clinical trials, and as expected, appears to be more sensitive than DXA to changes in the trabecular bone compartment. The resolution of QCT (~ 500 μm to 3 mm) is not sufficient to measure trabecular microarchitecture. In comparison, several studies have demonstrated that high resolution magnetic resonance imaging (MRI) is able to reflect trabecular architecture at peripheral skeletal sites, such as the distal radius, calcaneus and distal tibia. Resolution of MRI images is approximately 150 to 200 μm in plane, and 300 – 500 μm slice thickness. One advantage to MRI measurements is that they do not involve ionizing radiation and can be performed using standard MRI equipment. Yet, disadvantages to this approach are that the measurements and subsequent image analysis techniques are technically demanding, scans cannot be performed on all patients, and scan acquisition is expensive. High-resolution micro-computed tomography is another technique that has recently been introduced for in vivo assessment of trabecular architecture at peripheral skeletal sites. The resolution of...
in vivo μCT is reported to be approximately 80-90 μm in all three directions. This technique requires specialized equipment and to date has only been tested in a few subjects.

Another promising approach that combines imaging and structural analyses for in vivo prediction of bone strength is QCT-based finite element analysis. This method uses the three-dimensional geometry and density measurements available from QCT (or peripheral QCT) to create a model of the bone, to which loads can be applied analytically and the mechanical response to those loads computed. In vitro studies using this technique indicate that it correlates with vertebral and distal radius strength better than DXA-derived BMD or QCT-derived volumetric BMD. It is important to note, however, that none of the aforementioned techniques has been tested prospectively for their ability to predict fracture risk either in untreated subjects or in those receiving therapy.

There are presently no non-invasive techniques that are able to assess specific properties of the bone matrix, such as the collagen composition and cross-linking, the degree of matrix mineralization, and the type and extent of pre-existing microdamage. Additional studies are also needed to define the utility of serum biochemical markers as indicators of bone matrix quality.

In summary, future studies are needed to validate currently available non-invasive measurements for their ability to predict fracture risk in untreated individuals and in particular, in individuals receiving "curative" therapy. Ultimately, a better understanding of the material and structural mechanisms that govern bone failure at different skeletal sites will lead to new imaging techniques and biomarkers.

References


13. Rehman Q, Lang TF, Arnaud CD, Modin GW, Lane NE. Daily treatment with parathyroid hormone is associated with an increase in vertebral cross-sectional area in postmenopausal women with glucocorticoid-induced osteoporosis. Osteoporos Int 2003; 14:77-81.


