Biomechanical Mechanisms: Resolving the Apparent Conundrum of Why Individuals With Type II Diabetes Show Increased Fracture Incidence Despite Having Normal BMD

Karl J Jepsen and Stephen H Schlecht

Department of Orthopaedic Surgery, The University of Michigan, Ann Arbor, MI, USA

The article in this issue of the *Journal of Bone and Mineral Research* by Farr and colleagues[1] highlights how clinical technologies enable our ability to identify biomechanical mechanisms contributing to musculoskeletal health and disease. Given that fractures are a mechanical event, establishing biomechanical mechanisms is as important as establishing molecular mechanisms to advance our understanding of how a disease condition ultimately leads to increased risk of fracturing.

As noted by Farr and colleagues,[1] many investigators consider the increased fracture risk of type II diabetic (T2D) patients to be a conundrum, given that these individuals tend to show normal or higher bone mineral density (BMD). This would be considered a conundrum if one believes there is only a single pathway leading to increased risk of fracturing. However, we now know that reduced fracture resistance can arise through many different pathways (Fig. 1). The most familiar pathway to reduced strength is through low bone mass resulting from an imbalance between bone resorption and formation. However, there are pathways that are less well recognized but equally important, and these come through alterations in bone morphology (eg, neck shaft angle, cortical thickness, trabecular bone volume fraction [BV/TV], trabecular connectivity) or tissue-level mechanical properties (eg, strength, brittleness, toughness, fatigability). BMD will continue to be an important screening tool for fracture risk. However, it is too much to ask that any one technology capture all biological and biomechanical pathways leading to fracture risk. As such, it is important to continue developing new tools and scientific approaches that advance our ability to differentially diagnose fracture risk on an individualized basis.

The systematic evaluation of morphological and tissue-level mechanical properties presented by Farr and colleagues[1] allows for a more precise and expanded definition of fracture risk. Differentiating among these pathways is critical for developing the treatment options needed to best improve bone strength for a particular disease condition. For example, some individuals may fracture because of excessive bone loss leading to measurable decreases in bone strength, whereas other individuals may fracture because changes in the extracellular matrix lead to decreases in tissue-level toughness; these individuals would need to be differentially diagnosed and treated: one to slow bone loss and the other to improve tissue-quality. As a field, we have not yet developed the tools and scientific background to differentially diagnose and treat individuals. However, the article by Farr and colleagues[1] certainly moves the concept of personalized medicine one step forward.

Farr and colleagues[1] studied 30 postmenopausal women who had T2D for 10 or more years and 30 age-matched postmenopausal nondiabetic controls. The study cohort showed no difference in BMD at the hip, wrist, and spine, and no difference in fracture history. They found substantial changes (32% to 38%) in cortical porosity at the distal radius, consistent with other studies.[2] However, the study by Farr and colleagues[1] was not powered to detect a difference in this particular parameter, which is also a major contributor to tissue-level mechanical strength.[3] They found no deleterious changes in bone morphology, but did find a 10.5% change (adjusted for body mass index [BMI]) in tissue-level mechanical properties. Thus, by systematically evaluating multiple imaging and materials testing modalities, they were able to arrive at a biomechanical mechanism explaining why individuals with T2D may be at increased risk of fracturing. For T2D, the biomechanical mechanism is thought to be a consequence of reduced tissue toughness resulting from changes in collagen cross-linking.[4] The in vivo results of Farr and colleagues[1] thus confirmed prior animal and ex vivo human research showing that T2D is indeed associated with matrix-level alterations that appear to make the bone more damageable and brittle.

Farr and colleagues[1] reported changes in a parameter called bone material strength (BMS), which is the name given to the outcome measure by the manufacturer of the in vivo micro-indentation device. This outcome measure requires some clarification, because the BMS parameter seems to be more related to tissue toughness rather than tissue strength, as measured through traditional mechanical testing procedures.[5] The device used by Farr and colleagues[1] (OsteoProbe) and its predecessor (BioDent), both marketed by ActiveLife Scientific, Inc. (Santa Barbara, CA, USA), were designed to assess cracking of
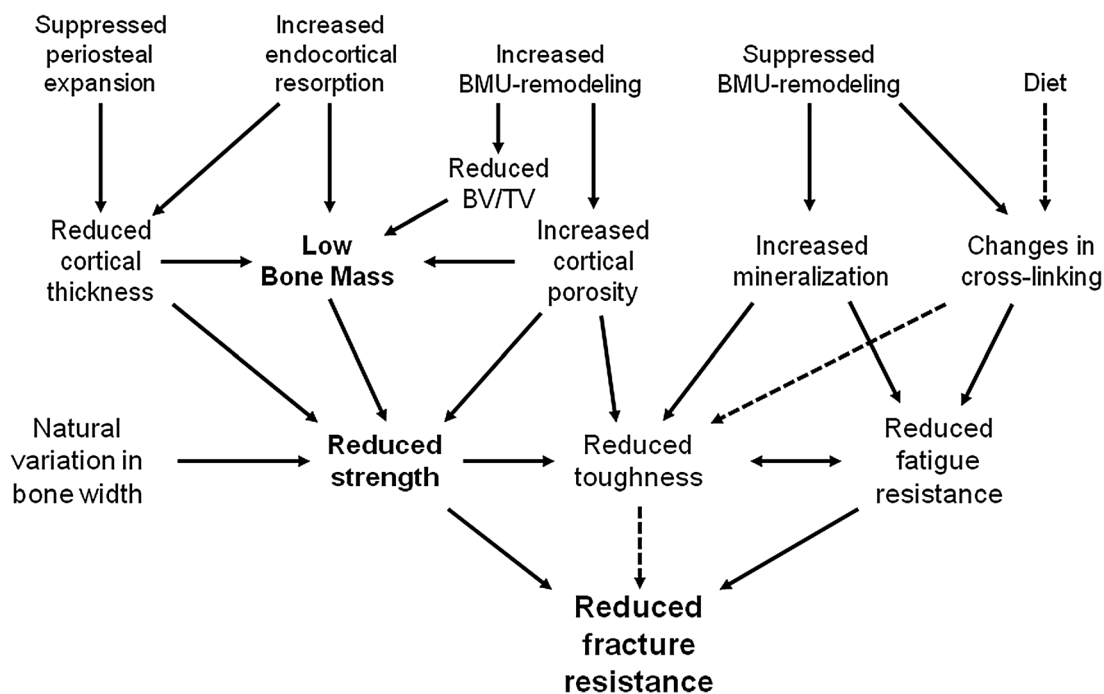
Fig. 1. Examples of different biomechanical pathways (mechanisms) leading to the reduced fracture resistance of aging bone relative to applied loads. Most investigators are familiar with the low bone mass path (bold). The article by Farr and colleagues[1] highlights the existence of other known paths (eg, diet → cross-link → reduced toughness; dashed arrows) that also compromise fracture resistance and which may help explain the increased fracture risk of T2D patients.

the matrix based on the premise that variation in the separation of mineralized collagen fibrils contributes to crack initiation and bone toughness.[6] BMS is a measure of how the indentation depth of the indenter tip compares to that of plastic. The system measures the indentation depth after a 40-N load and then converts this measure to BMS, which is 100 times the average indentation distance increase from the impact into a calibration phantom made of polymethylmethacrylate (PMMA) divided by the indentation increase from the impact into the bone sample. In other words, if a person has a BMS value of 100, their bone has the same resistance to indentation as PMMA. PMMA has a Young's modulus of elasticity of 1.8 to 3.1 GPa and a fracture strength of 48 to 76 MPa (http://www.engineeringtoolbox.com/young-modulus-d_417.html), which are much lower than the Young's modulus (15 to 20 GPa) and strength of bone (205 MPa in compression).[7] As such, it is important to recognize that the parameter provided by the manufacturer does not appear to be a measure of bone tissue strength.

The device measures the resistance to penetration, which depends on how the bone gives way, or cracks, beneath the indenter tip. This may help explain why the measurements generated by the predecessor device (BioDent) tend to correlate with bone toughness.[8] As far as we are aware, similar validation studies have not yet been performed using the OsteoProbe and so it is unclear if the outcome measure of the OsteoProbe will also correlate with toughness. Nevertheless, it is important to clarify that tissue-level strength is a different mechanical property than tissue-level toughness. Just as we have to be precise in the definitions used in biology (eg, osteoblasts and osteoclasts are both cells, but they comprise very different cell populations), we also have to be precise in our definition of

mechanical properties. Tissue strength and toughness are both mechanical properties, but they mean different things, and changes in each property can be differentially related to the underlying biology in ways that are clinically meaningful. This device measures cracking of primary lamellar bone tissue located at the periosteal surface of the tibia. This measure does not take into account the bone microstructure (osteons, lamellae, cement lines, porosity, etc.), which also contributes to bone toughness.[9] As such, this device may be able to identify disease conditions that have a matrix-level defect, but may be more limited in its ability to detect defects arising at higher levels of microstructure. Changes in the outcome properties from the predecessor device have been reported for atypical fractures.[10]

Although Farr and colleagues[1] refer to prior studies conducted with the Biodent, much work remains to be done to determine whether the outcome measures of the two devices are comparable. It is important to note that the indentation distance increase (IDI) of the OsteoProbe results from a single load application, measured as the distance between the impact load (10 N = 2.25 lbs) and the peak load (40 N = 9 lbs). This is different from the IDI of the predecessor device (BioDent), which is a measure of the distance between the end of the first loading cycle and the end of the 20th load cycle, where each cycle consists of a 10-N peak load.[11] Because the BioDent and OsteoProbe use different loading profiles, it remains to be determined if the outcomes of the two devices are comparable. For the BioDent, the loading parameters are more similar to a creep test or a low-cycle fatigue test. For the OsteoProbe, the loading parameters are more like a microhardness test or a monotonic test. Thus, both load magnitude and the number of load cycles differ between the two devices. Although some readers may not appreciate the

subtlety in this comment, it should be noted that engineering tests are conducted with precision for a reason, just as molecular biologists use specific promoters in conditional knockout experiments to differentially perturb the system biologically. The details in load magnitude, loading mode, loading rate, cycle number, etc., differentiate one engineering test from another and each test provides unique insight into the material behavior of bone. Thus, comparing the results of the OsteoProbe to that of the BioDent should be done with caution, if at all. Thus, it remains unclear if extrapolating the 11.7% difference between T2D and controls measured with the OsteoProbe by Farr and colleagues[1] to a 33.4% change in toughness, based on prior work by others using the BioDent, was appropriate. Much basic science work remains to be conducted to fully understand what this device is measuring and how to interpret the changes in indentation depth in the context of disease.

Because the microindentation device is an invasive technology, extreme caution is warranted for the general use of this device as a screening tool for bone disease. Although no adverse consequences were reported by Farr and colleagues,[1] it will be important to document these when they do occur. Farr et al. conducted the microindentation tests in a circular pattern (personal communication) so the microcracks were not located close together, limiting their potential interactions. However, if the OsteoProbe is used inappropriately whereby multiple microcracks are placed too close together, this may adversely affect whole-bone strength in some patients given that the anterior tibial midshaft is generally loaded in tension and is a site where stress fractures occasionally occur.[12] It is also important to be aware that standardization of the sampling site is critical, because bone properties vary widely along the length of the tibia.[13] Small variations in the anatomical placement of the device could not only detrimentally damage the bone, but could also lead to increased interindividual variation and compromise the ability to identify a disease effect. Further, tissue-level mechanical properties also vary naturally relative to bone robustness.[13] These factors should be taken into consideration when conducting these tests. Farr and colleagues[1] standardized the location of their tests and consequently were able to detect a 11.7% (unadjusted) difference between diabetic and nondiabetic bone tissue. This article thus confirms prior cadaveric and animal research showing that an important factor contributing to increased fracture incidence in diabetic bone involves changes in the extracellular matrix that may lead to reduced tissue toughness. As the number of individuals with T2D steadily increases and the treatment of the primary disease for these individuals steadily improves, it will be important to address secondary effects of the disease such as fracture risk to develop treatments that target the matrix-level defect in order to improve the overall health of these individuals.

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