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Hylonome

Summary - Measuring "Bone Quality"

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Abstract

The idea of bone quality is well-established in the literature and represents a real conundrum in the treatment of osteoporosis. On the one hand, there are measurements for patients that predict fracture risk for the population as a whole, but between individual patients, one will fracture but another will not, despite the fact that all of the technical measurements we use to predict fracture risk are the same. There are, of course, many aspects of bone mechanical properties that cannot yet be measured in patients. The session began with a discussion of what bone quality is, then the speakers presented work on novel aspects of bone properties that could help explain why fracture prediction in vivo is inexact.

What is bone quality?

The observation underlying the concept of bone quality is that some patients *do* have osteoporotic fractures and others *do not* even though their expected risk of fracture is not different when examined using our current *in vivo* assessment techniques. The key to understanding what is meant by the term "bone quality" is to study how we predict expected fracture risk from the various technical measurements that can be made on a patient.

As an analogy, consider vertebral cancellous bone strength as a measure of bone quality. It is not ethical to measure human bone strength in the living (you have to break the bone to measure strength), therefore, we could choose to use bone volume fraction (BV/TV) as a predictor for bone strength. The failure of BV/TV to precisely predict bone strength (Figure 1) means that for any particular value of BV/TV there are individuals with bone strength that is higher or lower than expected – that is, the individuals have *high quality* or *low quality* bone compared to the expected strength predicted by the linear regression against BV/TV.

Defining quality as the excess or deficit of actual fracture risk compared to the expected (or predicted) fracture risk differs from the definition presented at the NIH Bone Quality Conference as reviewed by **Dr. G. Lester**. In that meeting, bone quality was presented as the sum total of characteristics *of the bone* that influence the bone's resistance to fracture. Although it may be idiosyncratic, Fyhrie argued that a good definition for bone quality comes from a generalization of the strength prediction analogy. His definition is that the term "bone quality" recognizes the *unpredicted* portion of fracture risk *with respect to the predicting variables.*

Speaking against the idea that bone quality should be defined solely with respect to bone mechanical properties, Fyhrie argued that it is not certain whether it is failure to predict bone mechanical loading, bone mechanical properties, or both that causes our inability to predict vertebral fracture risk. The absence of mechanical loading as a significant factor in the discussion was also brought up from the floor for discussion by Dr. R.T. Turner, Oregon State University and Dr. R. Recker, Creighton University, at separate times. It is clear that hip or Colles' fracture risk is very strongly related to the medical and environmental causes of falling. No amount of research on predicting bone mechanical properties could capture the "falls" portion of fracture risk for these sites. It is likely that a similar situation exists for the vertebrae, although we do not know to what extent unmeasured and unpredicted variability in loading affects osteoporotic spine fracture.

When the chosen variables are poor predictors of fracture risk then there is ample room for individual patients to be above or below the expected value and hence to have either unaccountably high or low quality bone. Since the measurements we can make on patients currently do not predict fracture risk as well as we might like, new measurement methods and new things to measure are interesting. The technical speakers of the session reported on novel measurements for bone that could be important to predicting the chances of fracture.

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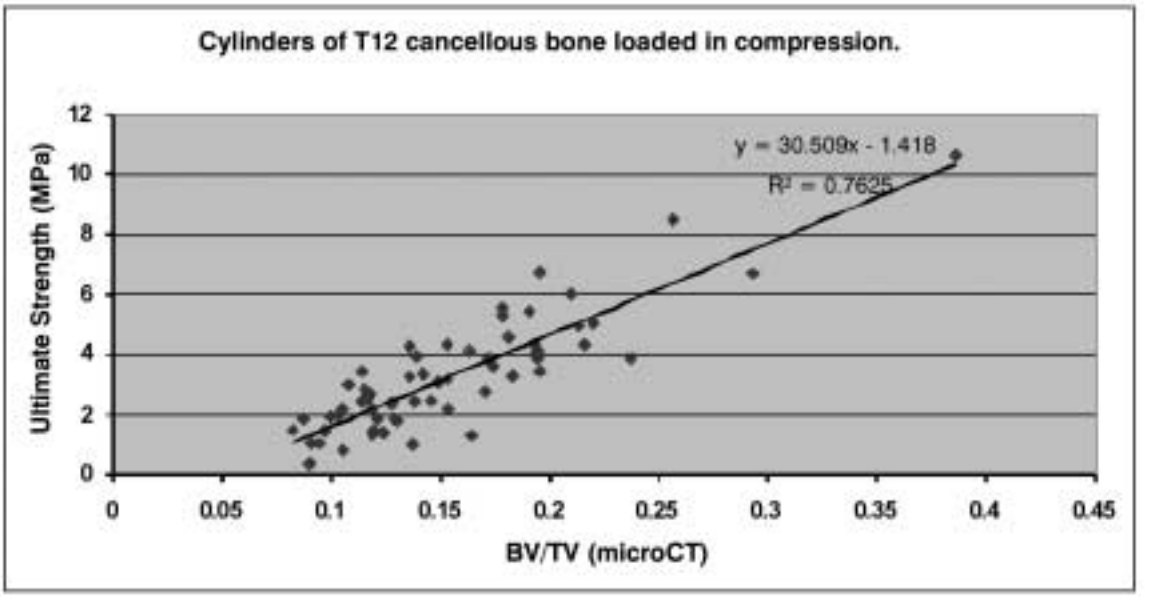

Figure 1. Bone strength (ultimate stress) is quite well predicted by microcomputed tomography measurements of bone volume fraction (BV/TV; unpublished data from Fyhrie.) However, there is still ample room for an individual data point to fall above the predicted (expected) value (to be high quality) or below the expected value (low quality). This illustrates the concept of bone "quality" as used in general conversation, where fractures do (or do not) occur as expected when predicted by a collection of clinically important variables.

Summary of technical speakers

Bone is commonly thought of as a two component composite of an organic matrix and mineral. Images and a novel interpretation of bone mechanical test results have led the **Hansma** group to conclude that a third organic component of bone—glue—is needed in order to explain the observed behavior of the tissue. The glue is proposed to be polymeric and to absorb the energy of fibril separation by the mechanisms of calcium bonding and entropic elasticity. The results were compelling and the data is largely reported in recent publications from the group[1,2]. Hansma has begun development of a patented device to measure bone toughness in a minimally invasive way. Preliminary tests were able to detect mechanical toughness differences between a 73 year old and 21 year old cadaveric male tibiae *in situ*.

Kinney and collaborators presented data consistent with an important role of hydrogen bonding in determining the fracture properties of bone. Their experiment substituted polar solvents of differing Hansen's solubility parameter (alcohol, acetone, methanol) for the water in the tissue. It is well known that dehydration radically changes the mechanical properties of bone[3] and dentin[4]; however, the interpretation here was in terms of the differing bonding properties of the polar solvents. The experiments showed similarities in the UV Raman signature for Amide I between aged bone and young bone imaged in the different polar solvents. Their results suggest that the idea that bone water content is highly significant to bone mechanical properties remains relevant. It might be fruitful to revisit this idea, paying particular attention to the role of hydrogen bonding in bone fracture. Kinney also presented preliminary results supporting a significant role for elastic trabecular buckling in the collapse of vertebrae[5]. This is an interesting concept, and supports the importance of measuring trabecular architecture *in vivo*, as small changes in trabecular geometry can cause large reductions in the critical collapse load.

The mineral of bone is often considered to be essentially a rigid component of the tissue. Results from the **Morris** group, however, show that the Raman signature of both matrix and mineral change significantly during loading[6]. It is not certain what structural changes are occurring in the mineral crystals during loading, but they were detectable during the loading process. The accuracy of the Raman method allows demonstration that the mineral phase is under compression when the bone is unloaded. This is consistent with many observations that bone matrix contracts when demineralized[7]. Morris also presented preliminary data to demonstrate that Raman measurements of bone were technically possible through an overlying soft tissue covering. It is not known, yet, whether the preliminary *in situ* measurements are reproducible *in vivo* in humans.

Damage to bone matrix is known to reduce the mechanical properties of bone tissue[8,9]. Changes in crosslinking, such as those caused by lathyrism, are also known to be associated with reduced bone strength[10]. The **Vashishth** group presented data supporting an hypothesis that naturally occurring nonenzymatic glycation (NEG)[11] doesn't change the

fracture initiation toughness of cortical bone but strongly affects the propagation toughness of the tissue. Data were presented supporting the existence of an *in vivo* effect of NEG on the fracture propagation toughness of cortical bone and upon the post-yield energy absorption by cancellous bone. NEG modified tissue had less capacity to form diffuse damage and formed fewer microcracks during failure, suggesting a mechanism for the observed effect of NEG on bone mechanical properties.

Weinans presented results from his microcomputed tomography method for the *in vivo* measurement of trabecular bone microstructure in small animals[12]. The method has resolution approaching the ability to resolve resorption pits as part of trabecular architecture and is the first method developed that can determine bone *loss* since individual trabeculae were tracked longitudinally in time. Radiation dose is a limiting factor, but trabecular loss and thickening were observable in the tibiae of ovariectomized rats. The method promises to be a powerful tool in the study of tissue microstructural reorganization during age and drug intervention. In humans, the potentially equivalent method could be analysis of high resolution MRI to determine cancellous bone structure[13]. Weinans' technique could provide the longitudinal animal experimental method necessary to understand fully any human *in vivo* methods for measuring trabecular architecture.

Summary

To predict bone quality *in vivo*, we need to know what microstructural, chemical, biological and load-related data predict osteoporotic fractures. The presentations made at this session support the idea that microstructure must be measured *in vivo* in order to understand cancellous bone collapse (Kinney and Weinans), that our mechanical understanding of bone as a two phase material is quite likely incorrect (Hansma), that bone fracture propagation toughness falls with age as a result of changes in the organic matrix that are invisible to X-ray analysis (Kinney and Vashishth) and, finally, that bone mineral is not a rigid component of bone, but measurably deforms under load (Morris). If we add our lack of understanding of bone loading into this mix, it is apparent that novel *in vivo* measurements will be necessary to accurately predict the risk of fracture of a patient. The preliminary work of the Hansma group on a minimally invasive method for measuring bone fracture toughness *in vivo* or that of the Morris group on performing Raman spectroscopy *in vivo* may be first steps towards the measurements we need.

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