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Perspective Article

Hylonome

Architectural changes independent of bone mineral in osteoporosis

H. Weinans

Department of Orthopaedics, Erasmus University Rotterdam, Rotterdam, The Netherlands

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Background

High resolution micro-CT scanning offers a wide perspective of possibilities for evaluating bone tissue. It is well described that bone mineral density correlates well with bone stiffness and strength and therefore this parameter is used as the gold standard in clinical practice to evaluate bone quality and fracture risk. The contribution of architecture to bone quality is also well recognized, however there exist many quantitative parameters of architecture and in 2-D many of those are biased. In particular, the possibility to accurately determine the 3-D architecture of the bone now gives the opportunity to determine the particular effects of architecture on bone mechanical properties independent of bone mineral density. This requires analysis of the bone architecture using the finite element method. When this method is combined with mechanical testing of bone specimens the combined data can provide additional information about the properties of matrix tissue, independent of architecture and bone mass.

Micro-CT and architectural measures

Interpretation of bone architecture from two-dimensional bone sections requires a model of the actual structure, usually the parallel plate model[1]. In fact, all architectural parameters can then be derived from the area fraction and perimeter. Using stereological principles Tb.Th., Tb.Sp. and Tb.N. can be determined. From micro-CT the complete three-dimensional architecture can be obtained in a computer and therefore it enables to more directly determine trabecular thickness, spacing and number. In addition, many other parameters can be obtained such as mean intercept length, structure model index, euler number, degree of anisotropy, volume orientation, fractal number, curvature etc. It is not always clear what the relevance is of these numbers, how the different parameters are related and whether they are uniquely defined. Besides, software may vary between research groups, which makes it even more difficult to compare the results of different studies. When the different parameters are compared it appears that many of the parameters are more or less related to volume fraction, thereby emphasizing the importance of bone mineral density. Only a few parameters, such as degree of anisotropy, are clearly independent of volume fraction. As such, these parameters are therefore more useful than others.

An additional problem is related to the transfer of the raw data from the micro-CT scan to the smoothed representation of the architecture. This transfer requires thresholding of the data that can be executed in different ways. Different thresholding algorithms can make an enormous difference between the quantitative outcome of the parameters, in particular when the resolution is above 10 microns. For example when volume fraction derived with micro-CT scan is compared with an Archimedes' test, differences will occur. Unbiased thresholding is a considerable problem in micro-CT scanning of bone tissue, which is not always acknowledged. Improved thresholding methods are a prerequisite for the further applications and success of micro-CT. In addition a more uniform way of deriving the three-dimensional architectural parameters is required to make 3-D parameters from micro-CT a standard in the sense as previously existed in sectional data using the parallel plate model of Parfitt[1,3].

Micro-CT and finite element models

What many studies attempt related to three-dimensional bone architecture parameters is to elucidate something related to a status of the bone or a disease. In particular, the mechanical properties or strength of the bone is important since osteoporosis is a major field of research in this area. It is well recognized that volume fraction/ BMD has its short-

Corresponding author: Harrie Weinans, Ph.D., Erasmus Orthopaedic Research Laboratory, Erasmus University Rotterdam, Room EE1614, P.O. Box 1738, 3000 DR, Rotterdam, The Netherlands
E-mail: weinans@ortho.fgg.eur.nl

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comings, however it is not clear what additional information we need to perfectly predict bone strength from architectural information. According to the definition of osteoporosis, fragility and architecture are important, but it is not clear how to quantify it. For architecture however there is a clear solution. Strength is a well-defined mechanical parameter, however the criterion on how the material fails is debatable. Different strength criteria are therefore defined, e.g. based on deformation or energy. For bone we are able to estimate stiffness quite well and we know that stiffness correlates well with strength. Under the assumption that the bone matrix properties (also called bulk properties as opposed to apparent properties) are uniform and isotropic we can fully calculate the stiffness of a piece of bone, even with a very complex architecture.

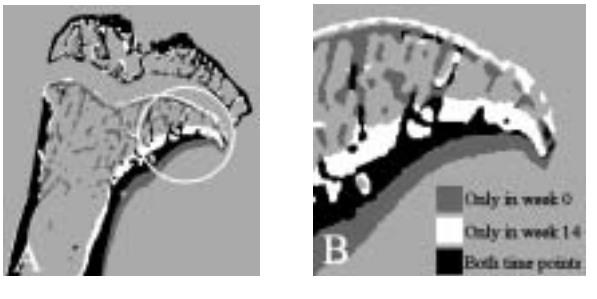
When a beam or a long bone bends, the stiffness depends on the bulk properties of the material (cortex) and the geometry of the cross-section. Therefore cross-section or moment of inertia is measured when the stiffness or strength of the beam is determined. For cancellous bone exactly the same can be done. However, the geometry of cancellous bone is much more complex and a finite element (FE) model is required to do the 'beam' analyses. Such FE-analyses have been done[2,3] and the finite element result should be interpreted with caution. The basic assumption is that the bulk property of cancellous bone is uniform and isotropic and we already know that this is not true in reality. However the result can also be interpreted in another way. The input for the finite element code is no more then the architecture of structure. There is no further information concerning matrix tissue properties or whatsoever. Hence, the input is no more than required for any other 3-D architectural parameter. The output, in this case the calculated stiffness or FE-stiffness of the specimen, is a number representing something which is only related to architecture! In that sense it can be interpreted as an alternative architecture parameter, similar to any other 3-D parameter. Though it is a nice one, since it represents the stiffness of the specimen exclusively as a consequence of the 3-D architecture, free of matrix (bulk) properties. However, it should not be interpreted as the true stiffness as measured from an experimental compression test with the true specimen. The difference being precisely related to the matrix bulk properties only!

Micro-CT and mechanical tests

It appears obvious that the bone matrix properties are important as well. Bone quantity is of course only important as long as the quality of the material itself is beneficial. This is the reason that, when diaphyseal bone is tested, it should be corrected for cross-sectional geometry. Again, we can do the same for a test with a piece of cancellous bone. The finite element model functions as the correction factor because it can provide us with the stiffness as a result of architecture only. The difference between a true stiffness from a mechanical test and the finite element model thus can provide us with exactly the matrix (bulk) stiffness of the trabeculae. It should be emphasized that this difference can only be determined as one number and thus the method can not give any information about variation in bulk stiffness e.g. related to micro-damage or mineralization variations in the individual trabeculae. Therefore the difference between 'FE-stiffness' and 'tested-stiffness' is related to what is called 'effective-stiffness' of the bulk material the trabeculae are made of. Such combined tests have been performed recently by a few research groups[2,4,5] and have shown novel information, e.g. about the strength and stiffness of trabecular bulk material (matrix). For example Day et al. have used this method to show that the trabecular bone tissue matrix of subchondral bone from patients with mild osteoarthritis is decreased by approximately 60%[5].

Future perspective of micro-CT

Micro-CT has been introduced to study and to evaluate bone tissue in great detail in its 3-D architecture. This requires sophisticated evaluation as well. The latest developments have enabled us to apply the micro-CT scan with *in vivo* experiments. Currently we have performed a series of *in vivo* micro-CT scans (Skyscan, Antwerp, Belgium) in a follow-up study with 9-month-old rats to evaluate the effects of OVX. We made scans of the proximal tibia with a resolution of 20 microns and radiation dose below 0.4 Gy, enabling us to do follow-up studies with individual rats. So far we have a 14-week follow-up of control and OVX treated rats. Since we have multiple scans of one animal the consecutive scans can be overlaid (registration or matching) on top of each other to determine architectural changes in time in individual rats. Precision and reproducibility have been tested. Using this method we can accurately determine architectural changes at the level of individual trabeculae in living animals. Preliminary results show a novel finding of additional growth and architectural changes in OVX rats relative to sham operated rats (Figure). These new developments of *in vivo* micro-CT scanning will greatly contribute to experimental studies in small animals concerning orthopaedic or pharmacological intervention and transgenic mouse models.



Overlaid identical cross-sections of registered data-sets of epi- and metaphysial parts of tibia of the OVX rat. At the right detail of lateral metaphysis of OVX rat showing growth of approximately 150 microns at the growth plate 14 weeks after OVX in a 9-month-old rat.

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