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Perspective Article

Architecture and trabecular bone – Toward an improved understanding of the biomechanical effects of age, sex and osteoporosis

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Abstract

From an engineering perspective, trabecular bone is a highly complex material, being anisotropic with different strengths in tension, compression, and shear and with mechanical properties that vary widely across anatomic sites, and with aging and disease. While mechanical properties depend very much on volume fraction, the role of architecture and tissue material properties remain uncertain. In the context of osteoporosis, there is wide interest in the biomechanical role of architecture since this should lead to improved understanding of the disease and ultimately better diagnosis and drug treatment assessment. This study reviews what is known about architectural changes in trabecular bone associated with age, gender and osteoporosis and the role of these changes in the mechanical properties of bone. Recent development of three-dimensional high-resolution imaging technologies has provided more accurate measures of quantitative metrics of architecture, thereby providing new data and raising questions about earlier conclusions. Focusing on the hip and spine, this literature is synthesized and outstanding issues are identified. In addition, the changing paradigm of biomechanical research on trabecular architecture is addressed. Because of the complexity of the trabecular micromechanics, the prevailing approach to date can be classified as an inverse one, whereby candidate metrics of architecture are developed and tested for efficacy in an empirical trial-and-error fashion. In this approach, the biomechanics is treated only as an assay since it is not used to guide development of the candidate metrics. By contrast, a more forward approach is to study the associated micromechanics using engineering analysis and from that identify the metrics that in theory most affect mechanical properties. The latter approach, facilitated by the new high-resolution imaging techniques and increased computational power, is discussed in an attempt to direct attention to new types of architectural metrics that are independent of bone density and that should improve the ability to explain how age, gender and osteoporosis affect the mechanical properties of trabecular bone.

Keywords: Bone Strength, Biomechanics, Spine, Cancellous Bone, Aging

One important motivation for investigating sex differences in age-related changes in trabecular bone volume fracture and architecture is to understand the higher rate of osteoporotic fractures in females. If sex differences exist in age-related changes in trabecular bone mass or architecture, the added insight thus provided could lead to improved diagnostics and treatments that address specific attributes of the sex-related age changes.

It should be clear, however, that unless new approaches are taken to characterize changes in trabecular architecture and determine their biomechanical effects, little improvement is likely in terms of patient-specific fracture risk prediction. Bone density can explain up to 83%[1-4] and 92%[3,5] of the variation in mechanical properties of machined specimens of vertebral and proximal femoral trabecular bone, respectively, and quantitative computed tomography can currently provide excellent estimates of these properties.

With this in mind, we attempt to synthesize the literature on architectural changes in trabecular bone associated with age and sex and the role of these changes in the mechanical properties of bone. We will focus on vertebral trabecular bone.

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Age and sex effects on trabecular bone architecture

In general, trabeculae can be lost by two mechanisms. The first is biological, in which some trabeculae become so thin

from age-related reduction in bone formation rates that normal osteoclastic resorption breaks through the entire trabecula. This interrupts the trabecular network, effectively removing a surface upon which osteoblasts can subsequently replace the resorbed bone. In addition, if the depth of osteoclastic resorption is increased, due for example to an estrogen reduction as occurs at menopause, thicker trabeculae can be perforated, leading to early loss of trabeculae. The second mechanism is by mechanical overload, in which a trabecula is fractured due to high local stresses, resulting again in an interruption of the trabecular network and the same sequellae as with the first mechanism. For both mechanisms, which are not mutually exclusive, it is fundamental to understand how trabeculae lose thickness and number with age and if this differs between the sexes.

Based on our review of the literature, we therefore provide answers to some fundamental questions:

Do age-related reductions in vertebral trabecular bone volume fraction depend on sex?

From the available histomorphometry studies[6-10], it appears that the age-related reduction in vertebral trabecular bone volume fraction depends little, if at all, on sex.

How much vertebral trabecular bone is lost with age?

Pooling data for the sexes[8,9,11,12], all studies so far have reported linear type reductions of vertebral trabecular bone volume with age, with no obvious trend of non-linearities. The reported percentage reductions in trabecular bone volume fraction from ages 20 to 90 varies in the range of about 50-70%, which probably reflects differences in sample sizes, cohorts, and measurement regions within and between vertebra.

Is there hypertrophy of vertical trabeculae?

The concept that the vertical trabeculae in the aging spine increase their thickness is not supported by any quantitative data. However, the literature[6,8,12-14] suggests that there is hypertrophy of vertical trabeculae in the central region of the vertebra which results in maintenance of thickness with age for these trabeculae, compared to substantial age-related reductions in thickness for the adjacent horizontal trabeculae.

Does mean trabecular thickness decrease with age?

If horizontal and vertical trabeculae are pooled, as is done with traditional bone histomorphometry, the issue of age-related changes in mean trabecular thickness for vertebral bone is not controversial: there is a significant decrease with age[8,9,11,12,15,16]. Trabecular thickness for vertebral bone is highly and linearly correlated with bone volume fraction. Since bone volume fraction decreases with age in the normal lumbar vertebra, it is not surprising to find that mean trabecular thickness for vertebral bone decreases with age.

Are age changes in mean trabecular thickness different between the sexes?

The available evidence[8,9,12] suggests there is only a subtle sex effect on age-related changes in mean trabecular thickness. The only difference reported is for vertical trabeculae, where thickness can be lower by about 20% for females at about age 65. At all other ages, there are no reports of differences in either vertical, horizontal, or pooled trabeculae.

Does trabecular spacing (and number) change with age and sex?

The average spacing between both vertical and horizontal trabeculae increases with age, the latter being greater[6,8,9,12,14,17]. This increase in spacing is due mostly from loss of trabeculae since percentage changes in mean trabecular thickness do not account for the large changes in spacing. An exponential increase in spacing occurs at low trabecular bone volume fraction. Regarding any sex effects, while a number of studies have reported little or no effect, one study found that the major difference between the sexes was for greater increases in spacing between horizontal trabeculae for females, an effect that is manifested only in the very elderly[8]. Trends for trabecular number are usually the reciprocal of those for spacing.

Are there sex differences in the effects of age on trabecular bone strength?

There is no evidence of any clinically relevant sex differences in the effects of age on the compressive strength of vertebral trabecular bone[8,10].

Is osteoporosis a "disease" or just another manifestation of aging?

Weaver and Chalmers suggested in 1966[10] that osteoporosis might be thought of as "one of the normal manifestations of aging rather than a disease in the true sense of the word". In support of this concept, the accumulated evidence seems to suggest that because of the menopause, females might effectively age faster than males in terms of vertebral trabecular bone status, but that both sexes eventually reach the same state of advanced deterioration of the bone, the result of an otherwise normal aging process. As with any aging process, there will be substantial apparently random variations in the observable effects across the population. In the case of vertebral trabecular bone, this random variation appears to overwhelm any systematic sex effects. The numerical simulation described below illustrates this concept and lends support to the notion that osteoporosis may indeed be better considered as just another manifestation of aging than as a disease *per se*.

Statistical approaches – Intra-specimen variations in architecture

Almost all architecture studies to date, even if using the latest three-dimensional model-independent assays[18] of architecture, continue to adhere to the use of *averaged* architectural properties per specimen, all of which have turned out to be highly correlated with bone volume fraction. The measures themselves have mostly been derived from traditional histomorphometry. This results in an inverse approach in which investigators determine the efficacy of pre-selected architecture variables on mechanical behavior. Given the complexity of the micro-mechanics of trabecular bone and its

substantial heterogeneity, this empirical approach is overly optimistic and the insight gained thus far has been limited. In a more direct approach, knowledge of the appropriate micro-mechanics of the system would be used to dictate the biomechanically relevant measures of architecture, if any, that can complement information already contained within measures of bone volume fraction. As discussed next, such a direct approach does indeed suggest new measures of architecture.

Numerical simulation of bone loss with age

A finite element model of human vertebral trabecular bone was created[19] from the histomorphometric idealization of the trabecular network as a lattice of vertical and horizontal rods[10], each with their own length and thickness distribution. With thicker vertical trabeculae on average, 25 geometric variations of the model were created in which the distributions of trabecular spacing and orientation were identical but variations in thickness were different. Initial mean parameters (mean vertical and horizontal thickness; mean vertical and horizontal spacing) were the same in all models. To represent the time-averaged effects of depressed osteoblastic bone formation rates, ten microns of bone thickness per decade were removed from each trabecula. To represent normal osteoclastic resorption, trabeculae were removed if their thickness fell below 50 microns. To model the elevated osteoclastic resorption rates associated with the menopause, the rate of bone loss was increased by 50% between the ages of 45 and 60. Elastic modulus was computed for all cases.

As expected, across all ages and thickness distributions, there was a positive correlation between elastic modulus and bone volume fraction. However, within any single age group, increases in trabecular thickness variation resulted in an increase in bone volume fraction but a decrease in elastic modulus. At low volume fraction this effect was weak, indicating that after substantial bone loss the trabecular network is less sensitive to the effects of variations in thickness. The models with transient elevations in osteoclastic resorption rates showed the characteristics of advanced but normal aging. Consistent with the empirical observations, normal aging resulted in preferential loss of horizontal trabeculae (which were initially thinner), and by age 90, nearly one in four horizontal trabeculae were lost compared to one in eleven vertical trabeculae.

Although the model included no loss of trabeculae from mechanical effects, it did predict behavior highly consistent with the available empirical data on age and sex effects on vertebral trabecular bone architecture. The model suggests that variations in trabecular thickness within a specimen are important, and that knowledge of such distributions at an early age together with measures of remodeling rates may be predictive of later changes. Finally, the models illustrate how advanced bone loss during the menopause is morphologically and biomechanically equivalent to advanced but otherwise normal aging. These results therefore support the concept that osteoporosis – in terms of trabecular bone status – might best be considered as the ultimate manifestation of an otherwise normal aging process.

Outstanding issues, new directions

Because a number of issues remain in doubt, there is a need for larger scale studies to describe the morphological effects of age and sex for vertebral trabecular bone. Three-dimensional model-independent assays should be used to eliminate bias, and bone should be sampled in various regions within the vertebra, including the cortical shell. Vertical and horizontal trabeculae, as well as plates and rods, should be separated. Focus should be placed on ages 55-95 for both sexes.

Additional biomechanical studies should be performed to prescribe the most theoretically important architectural variables.

The same types of studies are required for the hip. In this case, mechanical assays should test the response of bone to multiaxial loads, which better represent the loading conditions during a sideways fall. Bone for the femoral neck and trochanter should be considered separately. Comparisons for the hip and spine should be made with the iliac crest in anticipation of clinical applications.

Parting questions: What determines trabecular bone morphology at skeletal maturity? Do substantial variations in thickness distribution exist across the population, and if so, why? Do rates of bone loss vary much across the population or over time or do initial conditions dominate? Can we predict trabecular bone changes over time with knowledge of current bone morphologic and biologic status?

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