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REVIEW ARTICLE

Bone microarchitecture as an important determinant of bone strength

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ABSTRACT. Structure and microarchitecture are determinant aspects of bone strength and essential elements for the assessment of bone mechanical properties. The main structural determinants of bone mechanical strength include width and porosity in the cortical bone; shape, width, connectivity, and anisotropy in the trabecular bone. There are several methods to assess bone architecture, particularly at the trabecular level. Two different approaches can be identified. The first is based on the use of optical microscopy and on the principles of quantitative histology, which evaluate microarchitecture two-dimensionally. The second applies the most modern diagnostic techniques, employing computed tomography and magnetic resonance to obtain and analyze three-dimensional images. From a clinical point of view, microarchitecture is an interesting aspect to study and define specific patterns, such as glucocorticoid-induced osteoporosis, or to evaluate bone alterations in transplanted patients. Microarchitecture seems to be a determinant of bone fragility independent of bone density. Moreover, bone microarchitecture seems to be important to understand the mechanisms of bone fragility as well as the action of the drugs used to prevent osteoporotic fractures. Several *in vivo* studies (on animals and humans) showed important findings on the effects of different treatments on microarchitecture. Bisphosphonates and parathyroid hormone seemed to preserve or even improve microarchitecture. These observations can provide an additional interpretation for the anti-fracture effect of drugs from a structural viewpoint. The challenge for the future will be to evaluate bone quality *in vivo* with the same or better resolution and accuracy than the invasive methods in use today.
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INTRODUCTION

The increasing use of densitometric devices for assessing bone fragility has progressively strengthened the assumption that mass is by large the most important property determining bone mechanical competence. However, numerous observations indicate that bone strength is only partially explained by bone density. Bone shape and internal structure, which are influenced by load and different stimuli and stresses, are crucial elements that contribute to the definition of bone distinctive characteristics.

Key-words: Bone density, bone strength, fractures, histomorphometry, microarchitecture, μCT.

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The interaction between the genetic species-specific elements and the environmental individual-specific stimuli occurs through a structure that can provide the best resistance to load, stress or compression, on account of the spatial orientation of the trabecular network as well.

The main structural determinants of bone mechanical strength include width and porosity in the cortical bone; shape, width, connectivity, and anisotropy in the trabecular bone. Structure and microarchitecture are therefore determinant aspects of bone strength and essential elements for the assessment of bone mechanical properties and changes. For instance, it has been observed that during age-related bone involution the loss of entire trabeculae would result in higher loads and consequently in the thickening of the remaining elements. In particular, the number of horizontal trabeculae decreases throughout life, whereas vertical trabeculae are resorbed more slowly and tend to increase in width with age

(1). This is probably due to the fact that the load in vertebral cancellous bone is mainly placed on the vertical elements, thus the compensatory hypertrophy or thickening effect is only to be expected in the vertical trabeculae.
From another point of view, it has also been observed (2) that the increases in bone mass recorded after drug therapies for osteoporosis can just partly explain the decrease in fracture incidence after these treatments. Therefore, other aspects, such as microarchitecture, may contribute to the determination of bone mechanical competence. In addition, the effect of some of these therapies on microarchitecture contributes to explaining their efficacy and rapidity of action.
Consequently, there is growing interest in the quantitative assessment of this particular morphological aspect of the bone.

METHODS TO ASSESS MICROARCHITECTURE

There are several methods to assess bone architecture, particularly at the trabecular level, that is, to detect the organization of bone in space and to measure the complexity of its structure quantitatively. Two different approaches can be basically identified. The first makes use of optical microscopy and is based on the principles of histomorphometry (that is, quantitative histology inspired to stereology), which evaluates microarchitecture on two-dimensional (2-D) bone sections. The second applies the most modern diagnostic techniques, employing computed tomography (CT) and magnetic resonance (MR) to obtain three-dimensional (3-D) images on which bone microarchitectural organization can be assessed. Various techniques have been used to create 3-D imaging of bone. The most significant among them are based on the rebuilding of 3-D size from 2-D serial sections of bone biopsies, using stereo- and scanning microscopy, volumetric and micro-CT, and micro-MR (3, 4). High-resolution tomography and MR are interesting new approaches employed *in vivo*, which can evaluate microarchitecture, but at present with lower spatial resolution.
The study of microarchitecture is based on the measure of width, number, and separation of trabeculae as well as on their spatial organization. The latter, defined as connectivity, is a 3-D property that describes the typology of the various connections between the so-called nodes (the structural units that represent the confluence of two or more trabeculae) and the connecting segments (struts and termini). From a quantitative standpoint, connectivity is an index of the variety of links among the trabeculae and can be defined as the major number of connections that can be broken before structure integrity is completely lost (5).

2-D METHODS

The first approaches to quantitative evaluation of trabecular bone structure were based on the direct and indirect measure of trabecular width, separation, and number (6-8). The direct measurement of trabecular width was initially obtained by using a microscope with an ocular equipped with a special grid. The trabecular number and separation describe the basic relationship between space and trabecular network. The trabecular number is defined as (BV/TV)/Tb.Th, where BV is Bone Volume, TV is the volume of the examined tissue, and Tb.Th is the thickness of the trabeculae. Conventionally, all these parameters are expressed as volume instead of area, even if they are evaluated in 2-D sections, because they offer an inferred estimation of the spatial organization of the trabecular network. Similarly, the trabecular separation, defined as the distance between the edges of the trabeculae, is expressed in 3-D units (9).
More recently, new computerized methods that allow the acquisition of more sophisticated measurements by means of a digitizer have been introduced to integrate the use of the microscope (10, 11). These methods supply information on trabecular width as well as on its distribution and on the organization of the different trabeculae in a bone section. For instance, through the process of "skeletonization" of the trabecular bone on 2-D sections by a computed analysis, it is possible to obtain a network of 2-D components, called struts, which reproduces the trabecular distribution in space (12, Fig. 1). The link between two or more struts constitutes a node. When one side of a strut is not joined to a node it is referred to as "free end" or "termini", which represents an interruption in the trabecular network (13). The ratio between nodes and termini in a section is an index of spatial connectivity.
Other parameters that allow an indirect evaluation of the trabecular connectivity, through the assessment of the marrow connectivity, are:
- The marrow star volume (MaSV), i.e. the mean volume of all the parts of an object that can be unobscured in all the directions from a point inside the object (14, Fig. 2);
- The trabecular bone pattern factor (TBPf), i.e. the relation between convex and concave elements, considering a concave element as the expression of a well connected structure (15);

Strut analysis

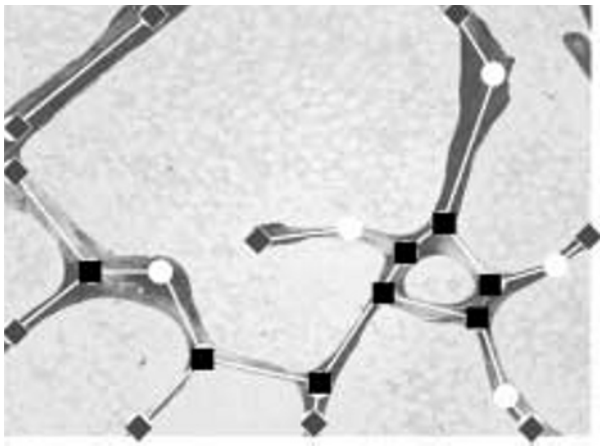

Fig. 1 - *Strut analysis. Black squares represent the nodes, that is, the connection between three or more struts (segments representing a trabecula, white points). Grey rhombi represent the free-ends or termini, which are ends of trabeculae or broken, interupted elements of the trabecular network.*

- The index of interconnectivity (ICI), after skeletonization of the bone marrow, defined as (NxNN)/[Tx(NF+1)], where N is the number of nodes, NN is the number of node-to-node branches, NF is the number of node-to-terminus branches, and T is the number of "trees", a tree being an independent portion of the medullary space totally enclosed by a trabecular structure (16);
- The Euler number, expressed per tissue volume (E/TV), i.e. the number of holes minus the number of connected components, which can be interpreted as the maximum number of branches that could be removed without breaking the network into different parts (17);
- The "fractal" analysis, which describes how an object fills space with relation to its structure (18). This parameter allows an evaluation of bone structural anisotropy, too.

Each of these parameters gives a distinctive analysis of the trabecular bone architecture. All the abovementioned 2-D approaches are limited by the necessity to infer 3-D information from a 2-D evaluation. Nevertheless, there are several pieces of evidence confirming that measurements on 2-D sections are well correlated to the 3-D structure and properties of bone (17).

3-D METHODS

Since the structural determinants of trabecular bone strength are 3-D features, their evaluation on conventional histological sections offers only indirect information on these properties. 3-D images are therefore necessary to obtain the direct measurement of trabecular connectivity, anisotropy, and shape. These approaches enable the measurement of the structural indices corresponding to width, number, and "apparent" trabecular separation, which are parameters that define microarchitecture at a 3-D level. They also make it possible to confirm the anisotropic structure of the trabecular bone, allowing the 3-D analysis of connectivity.

Quantitative CT (QCT) and, in particular, volumetric QCT (vQCT) are 3-D methods used to assess the macrostructure of bone quantitatively. With regard to trabecular bone microarchitecture, noninvasive and/or nondestructive 3-D methods include high-resolution CT (hrCT), micro-CT (μCT), high-resolution MR (hrMR), and micro-MR (μMR) vQCT, hrCT, and hrMR are generally applicable *in vivo*, whereas μCT and μMR are principally applicable *in vitro*. The potential ability of MR and CT to provide information on *in vivo* bone structure is an important and active research area, even if at present some applications are limited by the still reduced spatial resolution of methods and signal-to-noise ratio as well as by the complexity and cost of equipment.

In vivo, the use of standard QCT in the volumetric assessment (vQCT) can determine the bone mineral content or the bone mineral density (BMD) of the entire bone or subregion (vertebral body or femoral neck), as well as provide a separate analysis of the trabecular or cortical components. This method supplies a 3-D pool of densitometric measurements, each corresponding to one small volume. As the 3-D parameters of each volume are preserved, all the single units can be examined in every direction. In addition, using the accurate volumetric rendering al-

Marrow star volume

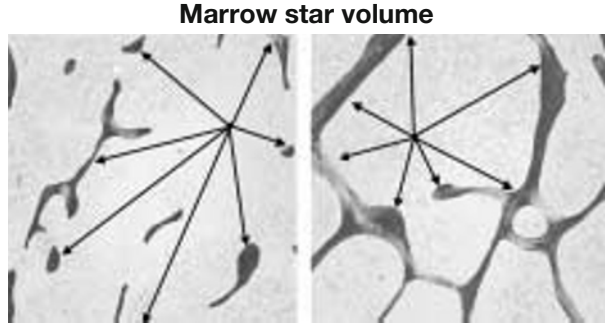

Fig. 2 - *Representation of marrow star volume. This parameter represents the mean volume of all the parts of an object that can be unobscured in all the directions from a point inside the object. By the analysis of marrow space distribution, we obtain an indirect evaluation of the trabecular network organization. The higher the mean of the segments, the lower the trabecular connectivity.*

lowed by this technique, important geometrical and biomechanical information can be obtained. For instance, in a study using this approach a good correlation between resistance to compression and apparent density was recorded (19).
Another method employing 3-D images *in vivo* is based on the use of hrMR, applied for instance to distal radius. It has recently been observed that this technique makes it possible to detect subjects with fractures on the basis of differences in microarchitecture parameters in a population of postmenopausal osteoporotic women (20).
3-D technology *in vivo* using high-spatial-resolution MR imaging (MRI) and multisection CT can also be applied to depict regional structural variations of trabecular bone in specific subregions of skeletal sites. This interesting approach seems to allow the evaluation of focal microarchitectural alterations (21).
As regards 3-D methods *in vitro*, μCT is based on the acquisition of 2-D serial images, which are then integrated by the computer to rebuild a 3-D image with resolution ranging from 10 to 70 μm. Binary images can be produced and connectivity and anisotropy can be assessed directly with the Euler number or another parameter by using 3-D reconstruction from a serial section.
This information cannot be obtained with a 2-D histological approach, even if in a recent study on an animal model evaluation of microarchitecture obtained from 2-D and 3-D approaches was consistent with glucocorticoid-induced osteopenia (22).

CLINICAL IMPORTANCE OF MICROARCHITECTURE

From a clinical point of view, microarchitecture is an interesting aspect to study and define specific patterns. Some years ago, Grotz observed that the evaluation of bone architecture, performed by hrCT, showed differences between renal allograft recipients and patients with osteoporosis, despite similar bone density (23). More recently, it has been observed that hrMR structural measures of the calcaneous in combination with BMD of the lumbar spine can be used to characterize fracture incidence in kidney transplanted patients (24).
Another interesting pattern for the study of microarchitecture is corticosteroid-induced osteoporosis, since an important disproportion between the increase in fracture rate and the decrease in bone mass is observed. This suggests an effect of steroids on the bone structure independent of bone density. There is only little evidence in literature considering microarchitecture evaluation in this particular clinical condition. In a histomorphometric study on bone biopsies, Chappard et al. (25) reported a structural alteration in patients chronically treated with steroids, which is characterized by a decrease in the trabecular network organization with impairment of connectivity. When patients treated with steroids were divided into two groups according to trabecular bone volume (BV/TV>or<11%), microarchitecture parameters differed clearly. Trabeculae were well-connected in the group with BV/TV>11%, which also suggested a possible threshold for the appearance of structural alterations in that particular model.
Another aspect of the importance of microarchitecture assessment in understanding the pathophysiology of the different kinds of bone fragility was demonstrated in a study comparing corticosteroid-induced osteoporosis with idiopathic osteoporosis. In that case, it was observed that with the same bone mass loss idiopathic osteoporosis was characterized by an early increase in the trabecular perforations, while corticosteroid-induced osteoporosis was associated with progressive thinning of trabeculae without early perforation (26, Fig. 3).
As regards this aspect, we observed that microarchitecture assessment can provide peculiar information and that the cumulative dose of steroids plays an essential role in microarchitectural bone alterations. Patients treated with 10 g of prednisone showed a trabecular network dramatically and irreversibly impaired in comparison with patients treated with lower cumulative doses (27, Fig. 4 and 5).

MICROARCHITECTURE AND FRACTURES

With regard to the relationship between microarchitecture and fractures, some recent observations seem to confirm that microstructural alterations are important determinants of bone fragility, even independently of bone density. In a recent study on the evaluation of bone turnover, density, mechanical

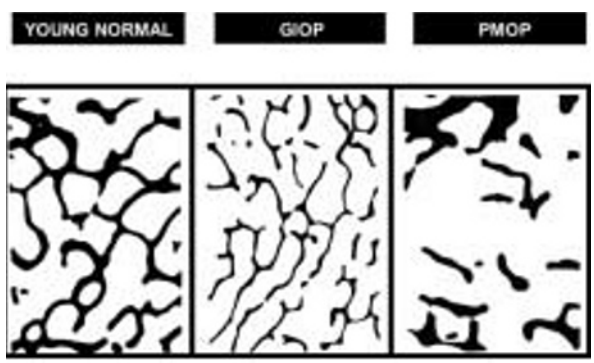

Fig. 3 - *Different pathways in idiopathic and glucocorticoid-induced osteoporosis (23).*

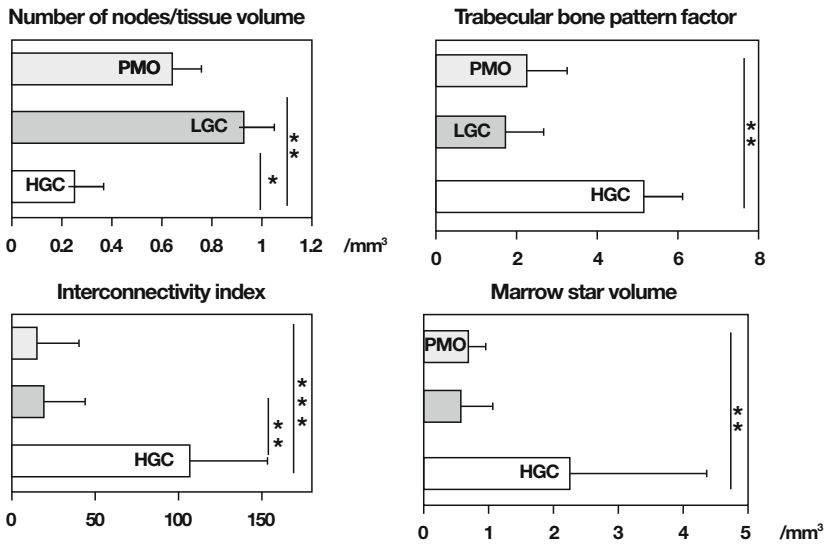

Fig. 4 - *Parameters of microarchitecture in patients after low glucocorticoid cumulative dose (LGC; <10 g) vs high dose (HGC; >10 g) and postmenopausal osteoporosis (PMO) (24).*
**: p<0.05; **: p<0.005; ***: p<0.0005.*

properties, and microarchitecture using MRI in osteopenic patients, the correlations between the measures of bone architecture, such as "apparent trabecular number and separation" and different elastic moduli (i.e. load and torsion), were higher than those between elastic moduli and BMD (28). In another study on orchidectomized rats, the evaluation of microarchitectural parameters such as MaSV, fractal dimension, and node count were dramatically affected, thus confirming that bone loss and fragility secondary to orchidectomy was associated with trabecular perforation and reduction of the complexity of trabecular network (29).
Finally, in another study on men affected by idiopathic osteoporosis, Legrand et al. (30) observed that the differences in bone microarchitecture parameters with the same mass and bone volume were the only discriminating factor between patients with or without vertebral fracture.
All these observations confirm that microarchitecture is an independent factor of bone fragility.

MICROARCHITECTURE AND TREATMENT

Bone microarchitecture seems important to understand the mechanisms of bone fragility as well as the action of the drugs used to prevent osteoporotic fractures. The exact mechanism of the anti-fracture effect of drugs inhibiting resorption, such as alendronate, risedronate, and raloxifene has not yet been completely explained, and increases in bone mass alone cannot account for their efficacy. Therefore, more attention has been lately paid to microarchitecture evaluation as a peculiar feature of bone quality, which is one of the targets of the drugs currently in use. For instance, a histomorphometric study on patients undergoing 3-yr therapy with alendronate showed that bone lamellar architecture was preserved with no qualitative alteration after treatment (31).
More recently, in a study on animals using 3-D μCT it was observed that, compared to controls, risedronate could preserve bone microarchitecture. The maintenance of microarchitecture was associated with better bone strength, thus confirming the close correlation between structure and bone strength (32).
Based on the latter observations, a re-analysis of the data related to the vertebral efficacy with risedronate therapy - North America (VERT-NA) study on risedronate treatment has been made in order to verify its possible effect on human bone structure. Thirty-eight biopsies of the patients under investigation (21 of the treated patients and 17 of the con-

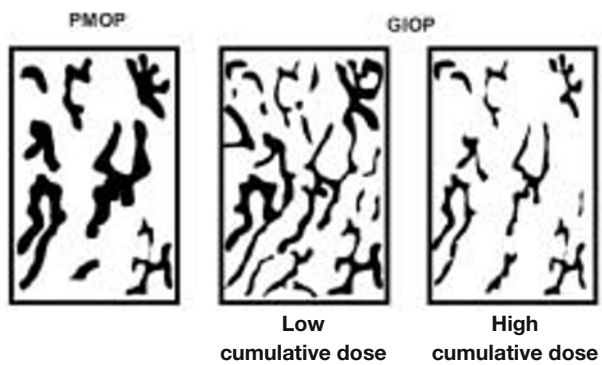

Fig. 5 - *Different models in postmenopausal and glucocorticoid-induced osteoporosis, based on cumulative dose.*

trol group) were therefore re-analyzed by 3-D rebuilding using μCT (33). In this case too, the analysis showed the preservation of microarchitecture in patients treated with risedronate for 3 yr.
Other recent studies on dogs showed that trabecular microarchitecture evaluated with μCT on the lumbar vertebral specimen was improved both after short and long-term treatment with bisphosphonates (34, 35).
The studies on the use of parathyroid hormone also confirm its action on microarchitecture, which can provide an interpretation for its anti-fracture effect from a structural viewpoint. Analysis of cancellous bone structure in 3-D by μCT showed maintenance of cancellous bone volume, particularly in women. Through this approach with μCT, it has also been observed that this treatment exerts an increase in the trabecular connectivity and induces an anabolic effect at the cortical level in the treated subjects. In these subjects there was evidence of an anabolic effect, particularly on the endosteal surface, where an increase in the packet wall width was observed (36). This anabolic effect on cortical bone was consistent with increased mechanical strength (37). In addition, the evaluation of microarchitecture in rats treated for a long time with PTH showed that its skeletal effects are a complex function of dose and duration. On the other hand, in the rat model, short-term treatment seems to be more effective than near-life treatment, because PTH stimulates skeletal growth throughout life, resulting in abnormal architecture (38).
Undoubtedly, further studies will be necessary to confirm and thoroughly investigate these acquisitions. We will then be able to understand the exact pathophysiologic mechanisms leading to bone fragility and find new therapeutic strategies to face the serious consequences of osteoporosis and other metabolic bone diseases.

CONCLUSIONS

Microarchitecture is an important element of bone quality and its integrity contributes to bone mechanical competence. The assessment of microarchitecture may be useful to evaluate the risk of fracture as well as the drug mechanism of action.
In the last decade several methods, from the traditional quantitative histology improved by computed analyses, to the recent applications of CT and MR, have been devised and applied to assess this specific bone property.
The challenge for the future will be to evaluate bone quality *in vivo* with the same or better resolution and accuracy than the invasive methods in use today. This goal would be essential to introduce the evaluation of such an important determinant of bone strength as microarchitecture in the routine diagnostic approach to skeletal diseases inducing fragility.

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