Advanced CT bone imaging in osteoporosis

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Non-invasive and/or non-destructive techniques can provide structural information about bone, beyond simple bone densitometry. While the latter provides important information about osteoporotic fracture risk, many studies indicate that BMD only partly explains bone strength. Quantitative assessment of macro- and microscopic features may improve our ability to estimate bone strength. Methods for quantitatively assessing macrostructure include (besides conventional radiographs) DXA and CT, particularly volumetric quantitative CT (vQCT). Methods for assessing microstructure of trabecular bone non-invasively and/or non-destructively include high-resolution CT (hrCT), microCT (μCT), high-resolution magnetic resonance (hrMR) and microMR (μMR). vQCT, hrCT and hrMR are generally applicable in vivo; μCT and μMR are principally applicable in vitro. Despite recent progress made with these advanced imaging techniques, certain issues remain. The important balances between spatial resolution and sampling size, or between signal-to-noise and radiation dose or acquisition time, need further consideration, as do the complexity and expense of the methods vs their availability and accessibility. Clinically, the challenges for bone imaging include balancing the advantages of simple bone densitometry vs the more complex architectural features of bone or the deeper research requirements vs the broader clinical needs. The biological differences between the peripheral appendicular skeleton and the central axial skeleton must be further addressed. Finally, the relative merits of these sophisticated imaging techniques must be weighed with respect to their applications as diagnostic procedures, requiring high accuracy or reliability, compared with their monitoring applications, requiring high precision or reproducibility.

KEY WORDS: Osteoporosis, Computed tomography, Micro computed tomography, Bone imaging, Bone quality, Bone structure, Bone mineral density, Quantitative computed tomography, Dual X-ray absorptiometry.

Introduction

The current clinical standard of diagnosing osteoporosis and assessing the risk of sustaining an osteoporotic bone fracture is DXA for the measurement of BMD at the spine and hip, the two skeletal locations most prone to fracture. Age, low bone density and prevalence of fractures are the most important risk factors for future fractures, but the predictive power of these variables is still insufficient to predict who eventually will have a fracture or to unambiguously identify high-risk groups. The structure or spatial arrangement of bone at the macroscopic and microscopic levels is thought to provide additional, independent information and may help to better predict fracture risk and assess response to drug intervention. This notion is supported by the large overlap of BMD values of people with and without fractures, and by in vitro mechanical strength differences that appear to be driven by variations in structure [1, 2]. While many of the parameters that were developed to capture macro- and microstructural properties can be easily assessed in vitro, non-destructive and non-invasive techniques for in vivo use are at the forefront of research in radiology of osteoporosis.

A large variety of different modalities from plain X-rays and DXA-based hip structural analysis (HSA) to CT and MRI have been developed to assess bone structure at the macro- and microlevels. However, the most dynamic development can be observed in the field of CT. Therefore, advances in this field are the topic for this overview. Figure 1 visualizes a range of CT-based images and Table 1 gives an overview of various CT techniques and applications. Compared with other modalities CT-based techniques have several advantages. In contrast to DXA, volumetric quantitative CT (vQCT) offers three-dimensional (3D) information and cortical and trabecular bone can be separately analysed. In contrast to MRI, vQCT acquisition is much quicker and technically less demanding. Also standard whole body clinical CT scanners can be used for acquisition. These are more widely available and easier to operate than MRI equipment. Dedicated peripheral CT scanners are available for assessing BMD in the radius and tibia as well as for measuring trabecular structure of the forearm. The imaging of specimen, bone biopsies and small animals for the investigation of bone structure currently is almost exclusively done with microCT (μCT) scanners. Over the past decade, several commercial companies have been offering an increasing variety of μCT scanners for different applications. In addition, active research in μCT is going on at several academic institutions.

vQCT

Originally QCT focused on measurement of trabecular BMD in single transverse CT slices at the lumbar mid-vertebral levels and at the forearm. The determination of BMD is still an application of the new spiral QCT acquisition protocols, [3–6] (Fig. 2). However, these new 3D data acquisition schemes raise challenges and promises for the analysis. A particular challenge is the reproducible location of a given analysis volume of interest (VOI) in longitudinal scans. One approach is to position the VOI relative to an anatomic coordinate system that can be reliably determined [6, 7]. As an alternative, a matching of baseline and follow-up scans has been suggested [8]. Most analysis software is experimental and only a few commercial programs are available.

One advantage of QCT compared with DXA, already advocated for the original 2D single slice applications, is the separate analysis of BMD of the trabecular and cortical compartments. Whereas trabecular bone in particular at the spine is metabolically more active and may therefore serve as an early indicator of treatment success, cortical bone, in particular at the hip, may be more important to estimate fracture risk [9]. Almost isotropic spatial resolution of ~0.5 mm significantly improves the 3D assessment of the cortex. Still the spatial resolution is not high enough to give accurate results of cortical thickness (Ct.Th) below values of ~1.5–2 mm. However, as shown by the authors [10] even below these values a 10–20% change of thickness can still be measured accurately. In general, it is easier to measure Ct.Th in the femur than in the spine where thicknesses of 200–500 μm are encountered frequently, especially in the elderly.
The limited spatial resolution also results in an underestimation of cortical BMD on the order of 10% to 30%. In addition to measuring the cortex, vQCT is a sophisticated tool to determine geometrical parameters of mechanical relevance such as cross-sectional moments of inertia.

At the spine, the cross-sectional area of the vertebral bodies is a macrostructural parameter of interest, since it is likely that larger vertebrae can sustain load better than smaller ones. Periosteal apposition, which may occur at the spine and the femur, has the potential to offset the increase in fragility caused by loss of bone mass by increasing cross-sectional area. A cross-sectional vQCT study by Riggs et al. [11] showed that women not only start out with smaller vertebrae and lose bone mass faster but also increase cross-sectional area slower than men. Although the magnitude of the changes reported by vQCT is inconsistent with DXA findings [12], the study indicates that spinal cross-sectional area measurement with vQCT may provide additional predictive power for fracture risk. Another parameter potentially of interest is the polar mass moment of inertia, which one measures to characterize the bone mineral distribution within the vertebral body.

Since the geometry of the proximal femur is much more complicated than that of the vertebral body, macrostructural parameters of interest include cross-sectional areas at the neck and greater trochanter, hip axis length and simple mechanical
measures such as cross-sectional moment of inertia and section moduli at various cross-sections along the femoral neck axis. As in the spine, periosteal apposition causes the cross-sectional areas of the femoral neck and shaft to expand with age [11]. The large Osteoporotic Fractures in Men Study (MrOS) confirmed this and also found cortical thinning with age. However, whereas the neck seemed to exhibit net cortical bone loss, periosteal expansion seemed to offset shaft cortical thinning to maintain cortical cross-sectional area [13]. This study also showed ethnic differences with higher femoral neck and lumbar spine volumetric BMD but lower cross-sectional areas in African Americans, which might contribute to some of the ethnic difference in hip and vertebral fracture epidemiology. Lang and colleagues [14] showed in a specimen study using vQCT that these parameters explain femoral strength partially independently of BMD.

Only a few treatment studies have so far used vQCT. The first one to do so, the effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis (PaTH) study, investigated PTH and alendronate treatment alone or in combination and found that femoral cortical volume increased with a 1-yr treatment with PTH followed by 1 yr with alendronate [15, 16]. CT examination also showed a substantial increase in volumetric trabecular BMD at total hip and femoral neck in PTH-treated post-menopausal osteoporotic women (n = 62) after 1 yr as well as after 2 yrs. Similar results were observed in another PTH study [17].

The overall advantages of this vQCT technique include high precision, on the order of 1–2% for BMD of the spine, hip and radius; nearly instant availability of data, in a matter of seconds to minutes; widespread access, with many thousands of systems available worldwide; and minimal user interaction. The major disadvantages for volumetric BMD are the use of modest radiation exposures, which for the spine and hip require an effective dose of ~100–1000 μSv and for the radius a dose <10 μSv. These radiation doses compare favourably, however, with the average annual background effective dose of 2500 μSv in the United States and Europe, and the effective dose of 50 μSv for a roundtrip transatlantic flight between the United States and Europe.

**High-resolution CT**

Another area of active research is high-resolution CT (hrCT). As described above, modern CT scanners for measurements of the axial skeleton offer isotropic spatial resolution of ~0.5 mm. Although requiring increased radiation dose compared with vQCT, current spiral CT scanners can provide higher resolution, thin slice images, which allow better depiction of trabecular and cortical morphology, and provide improved assessment of skeletal fragility. However, given typical dimensions of trabeculae (100–400 μm) and trabecular spaces (200–2000 μm) this resolution is still borderline for a direct determination of trabecular architecture. Due to substantial partial volume artefacts, the extraction of the quantitative structural information is difficult (Fig. 3) and the results vary substantially according to the threshold and image processing techniques used. Instead of measuring structural parameters directly there is a tendency to use textural or statistical descriptors to characterize the trabecular architecture without requiring stringent segmentation of the individual trabeculae.

Older techniques used, for instance, the trabecular fragmentation index (length of the trabecular network divided by the number of discontinuities) [18], run-length analysis [19], a parameter reflecting trabecular hole area, analogous to star volume [20–22] and co-occurrence texture measures [22]. Newer approaches prefer grey-level analyses and use, for example, Minkowsky functionals [23] or Gabor wavelets [24] to quantify trabecular topology. Recently, structural parameters of the spine...
were analysed in a longitudinal in vivo study of PTH. In the treated group, all structural variables showed significant improvements with some independence from BMD [25]. In a different cross-sectional study, vertebral trabecular structure parameters measured with hrCT could better distinguish between fractured cases and non-fractured controls than BMD measurements with DXA [26].

Since the assessment of trabecular structure in vivo is rather difficult special-purpose peripheral CT scanners have been developed to assess the distal forearm, where trabecular thickness (Tb.Th) ranges from 60 to 150 μm and trabecular separation (Tb.Sp) from 300 to 1000 μm. The first to pursue this successfully were Durand and Rüegsegger [27] who built a thin-slice high-resolution laboratory peripheral quantitative computed tomography (pQCT) scanner for in vivo measurements with an isotropic voxel size of (170 μm)³. Using a scanner with further improved resolution, Muller et al. [28] reported a high in vivo reproducibility of ~1% achieved by careful registration of the acquired 3D data sets. When in vitro pQCT structure measurements were compared with μCT, the correlation of various 3D structural parameters between the two systems was $r^2 > 0.9$, despite the lower resolution of the pQCT system. Therefore, a dedicated segmentation threshold can be obtained for pQCT by calibrating the pQCT bone volume fraction to the μCT bone volume fraction [29].

This group also introduced a number of new parameters to quantify the trabecular network, like ridge number density [30] and the structure model index (SMI) [31]. The work of the group around Rüegsegger cumulated in the XtremeCT (Scanco, Switzerland), a commercially available in vivo pQCT scanner for the forearm and the tibia with specifications similar to that of the laboratory scanner described above (Fig. 4) [32]. A critical step in the analysis of follow-up scans in order to detect longitudinal changes of bone structure within a given subject is the registration of baseline and follow-up scans with an accuracy that should be in
the order of 100 μm. Thus, during the scans even slight motion of the forearm must be avoided, which is not an easy task given the scan time of several minutes. Compared with the manufacturer-provided matching, advanced 3D registration of scans could reduce the repositioning error by over 20% [33].

Apart from technical studies [32–34], some clinical studies using this device have already been reported. The first indication that peripheral trabecular structure assessment is indeed useful to differentiate women with an osteoporotic fracture history from controls better than DXA at hip or spine came from Boutroy and colleagues [32]. Khosla and colleagues [35, 36] examined age- and sex-related bone loss cross-sectionally and speculated as to the different patterns of bone loss in men and women. Finally, MacNeil and coworkers [37] reported a strong ability to predict bone apparent stiffness and apparent Young’s modulus for morphological and density measurements in the radius and tibia (r² > 0.8) using the XtremeCT.

**μCT**

μCT denotes a CT technique with a spatial resolution of 1–100 μm. The techniques described below are typically termed microscopy. The μCT promises to replace tedious serial staining techniques required by histomorphometric analysis of thin sections and the possibility of longitudinal in vivo investigations in small animals such as mice and rats. Many of the early μCT approaches used synchrotron radiation [38], which is still the method of choice for ultra high-resolution applications. Obviously, the use of desktop laboratory scanners equipped with X-ray tubes is much more convenient than setting up an experiment at one of the few synchrotron facilities available. Thus, after initial and still ongoing university-based research during the last decade a variety of X-ray tube-based commercial μCT scanners have been developed. Some of them include sophisticated software for the 3D analysis of bone structure [31, 39, 40] including finite element modelling (FEM).

One area of research is the investigation of trabecular bone structure in human iliac crest biopsies. For example, iliac crest bone biopsy specimens were analysed from women participating in a placebo-controlled risedronate trial. After 1 yr in the control group percentage of bone volume (BV/TV) decreased by 20% and trabecular number (Tb.N) by 14% compared with baseline. Tb.Sp increased by 13% and star volume of the marrow by 86%. In the same period, lumbar spine BMD as measured by DXA decreased by only 3.3%. In the risedronate-treated group, the architectural parameters did not significantly change during the same period [41]. In another study of paired biopsies taken before and after treatment with human PTH, μCT showed increased 3D connectivity density and confirmed the preservation of 2D histomorphometric BV/TV, Tb.N and Tb.Th [42]. Similar results for PTH were reported recently in a third biopsy study. After 19 months of PTH treatment compared with placebo, BV/TV increased by 44%, Tb.N by 12%, Tb.Th by 16% and connectivity density by 25%. Tb.Sp decreased by 10% and SMI by 50% demonstrating the usefulness of 3D parameters obtainable from μCT [43]. In a study in ovariectomized baboons, bisphosphonates preserved the microarchitecture in thoracic vertebrae [44].

Arlot and coworkers [45] investigated the 3D bone microstructure of post-menopausal osteoporotic women treated with strontium ranelate (SR). Transiliac bone biopsies (Fig. 5) were obtained in a subset of two large randomized double-blind multicentre studies, SOTI (Spinal Osteoporosis Therapeutic Intervention, 1649 patients, for incident vertebral fracture) and TROPOS (Treatment of Peripheral Osteoporosis, 5091 patients, for non-spinal fractures). A total of 41 biopsies of the iliac crests, obtained after 3 yrs of treatment with placebo (n = 21) or SR at 2 g/day (n = 20), were examined with μCT at isotropic resolution of 20 μm. Compared with placebo, SR treatment significantly improved trabecular structural model index (−22%, P = 0.01) shifting trabeculae from rod-like structure to plate-like pattern, decreased Tb.Sp (−16%, P = 0.04) based on a plate model assumption, increased Ct.Th (18%, P = 0.008), increased trabecular bone volume fraction (+13%, not significant) and increased Tb.N (+14%, P = 0.05) based on a plate model assumption (Fig. 6). SR treatment stimulates 3D trabecular and cortical bone formation, which is not at the expense of intra-cortical porosity. These changes in 3D trabecular and cortical microstructure, shown by μCT, enhance bone biomechanical competence and help explain the decreased fracture risk observed after SR treatment.

As it is rather difficult to obtain human bone biopsies, studies investigating drug and disease effects are often performed during the pre-clinical phase using laboratory animals. In an investigation of rat tibiae, 16 weeks after ovariectomy (OVX) BV/TV...
decreased by 69% and Tb.Th by 30% compared with a sham-operated control group. Tb.Sp increased by 100% and SMI by 48%. This showed that with oestrogen deficiency the trabecular network consisted of more rod-shaped trabeculae [46]. Treatment of OVX rats with risedronate maintained the plate-like trabecular structure and network connectivity [47]. A study with either cathepsin K- or rolipram-treated OVX BALB/c mice showed that, compared with the sham-operated control group in both treatment arms, a decrease in BV/TV and deterioration of trabecular structure were prevented [48]. Another study with ovariectomized rats showed that PTH and elcatonin (ECT), a synthetic derivative of eel calcitonin, preserved bone architecture by different means. After 12 weeks of treatment BV/TV was greater in the ECT and PTH groups than in the OVX group. The number of nodes per volume (N.Nd/TV) and Tb.N were significantly greater in the ECT group, whereas Tb.Th was greater in the PTH group [49]. A 3D μCT has also been used to quantify trabecular architecture in OA [50–55].

**FEM**

FEM is a computer-based simulation of the strains and stresses induced by mechanical loading of an object and is widely used in engineering. The object is described as a connected set of simple-shaped elements that are ascribed elastic properties. One of its goals is to better predict load conditions that lead to fracture and thus to improve fracture prediction. Currently, the models are typically derived from volumetric QCT scans, and element elastic properties are computed from bone density at the position of the elements (Fig. 7) [14, 56]. Finite element models incorporate mechanically all of the anisotropic, inhomogeneous and complex geometry of the bone structure examined.

At the spine, Silva et al. found that in healthy subjects the cortical shell does not transfer much of the load [57]. It has been claimed that voxel-based finite element model-derived estimates of strength are better predictors of in vitro vertebral compressive strength than clinical measures of bone density derived from QCT with or without bone size [58]. However, this advantage of FEM may not pertain if more sophisticated parameters than just mid-vertebral trabecular BMD and bone size are measured [6]. Though imaging resolution for FEM is not critical in cross-sectional studies using clinical CT scanners, longitudinal studies that seek to track more subtle changes in stiffness over time should account for the small but highly significant effects of voxel size [59].

In the femur, vQCT-based FEM applications for fracture prediction are still rare. One study in 51 women aged 74 yrs [60] showed different risk factors for hip fracture during single-limb stance and falls, which agrees with epidemiological findings of different risk factors for cervical and trochanteric fractures. In the in vitro arm of the European femur fracture study with finite element analysis and QCT (EFFECT) parameters predicted fractures load in fall and stance configuration as well as FEM [61]. Also, reproducibility may impose limits on the usefulness of finite element analysis.
With the vast increases of computer power of the last decade and the availability of μCT data, the application of FEM at spatial resolutions that allow modelling of individual trabeculae, which is computationally much more demanding than just using voxels containing average grey values, has become feasible. Full 3D models were first developed by van Rietbergen et al. [62]. Prediction of overall bone strength recorded during mechanical testing of small samples of trabecular bone with such models is indeed better than that with macroscopic bone density measurements [58, 63]. However, only recently has μCT scanning offered the resolution to allow conversion of the grey values of the individual pixels to elastic moduli to further improve the accuracy of fracture load prediction [64]. Using this improved technique for example, Homminga and colleagues [1] showed that while osteoporotic vertebrae can withstand daily load patterns comparatively with normal bone, loading as occurs during forward bending caused much higher stresses in the osteoporotic vertebra.

Challenges for bone imaging

Despite the considerable progress that has been made over the past two decades in advanced bone imaging for osteoporosis assessment, a number of challenges remains. Technically, the challenges reflect the balances and trade-offs between spatial resolution, sample size, signal-to-noise, radiation exposure and acquisition time, or between the complexity and expense of the imaging technologies vs their availability and accessibility. Clinically, the challenges for bone imaging include balancing the advantages of standard BMD information vs the more complex architectural features of bone or the deeper research requirements of the laboratory vs the broader needs of clinical practice. The biological differences between the peripheral appendicular skeleton and the central axial skeleton and their impact on the relevant bone imaging methods must be further clarified. Finally, the relative merits of these sophisticated imaging techniques must be weighed with respect to their applications as diagnostic procedures, requiring high accuracy or reliability, vs their applications as monitoring procedures, requiring high precision or reproducibility.

**Rheumatology key messages**

- Non-invasive and/or non-destructive imaging techniques can provide structural information about bone, beyond simple bone densitometry.
- Quantitative assessment of macro- and microstructural features may improve our ability to estimate bone strength.

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**References**

1. Homminga J, Van-Rietbergen B, Lochmuller EM, Weinars H, Eckstein F, Huiskes R. The osteoporotic vertebral structure is well adapted to the loads of daily life, but not to infrequent "error" loads. Bone 2004;34:510–6.
2. Homminga J, McCreadie BR, Ciarelli TE, Weinars H, Goldstein SA, Huiskes R. Cancellous bone mechanical properties from normals and patients with hip fractures differ on the structure level, not on the bone hard tissue level. Bone 2002;30:759–64.
3. Kang Y, Engelke K, Kalender WA. A new accurate and precise 3-D segmentation method for skeletal structures in volumetric CT data. IEEE Trans Med Imaging 2003;22:586–98.
4. Lang TF, Guglielmi G, van Kuijk C, De Seno A, Cannissa M, Genant HK. Measurement of bone mineral density at the spine and proximal femur by volumetric quantitative computed tomography and dual-energy X-ray absorptiometry in elderly women with and without vertebral fractures. Bone 2002;30:247–50.
5. Lang TF, Li J, Harris ST, C. Lang M, Genant HK. Assessment of vertebral bone mineral density using volumetric quantitative CT. J Comput Assist Tomogr 1999:23:130–7.
6. Mastmeyer A, Engelke K, Fuchs C, Kalender WA. A hierarchical 3D segmentation method and the definition of vertebral body coordinate systems for QCT of the lumbar spine. Med Image Anal 2005;9:102–7.
7. Kang Y, Engelke K, Fuchs C, Kalender WA. An anatomic coordinate system of the femoral neck for highly reproducible BMD measurements using 3D QCT. Comput Med Imaging Graph 2005;29:333–41.
8. Li W, Sode M, Saeed I, Lang T. Automated registration of hip and spine for longitudinal QCT studies: integration with 3D densitometric and structural analysis. Bone 2006;38:273–9.
9. Bousson V, Le Bihan A, Roqueplan F et al. Volumetric quantitative computed tomography of the proximal femur: relationships linking geometric and densitometric variables to bone strength. Role for compact bone. Osteoporos Int 2006;17:855–64.
10. Prevrhal S, Engelke K, Kalender WA. Accuracy limits for the determination of cortical width and density: the influence of object size and CT imaging parameters. Phys Med Biol 1999;44:751–61.
11. Rigg BL, Melton L Jr 3rd, Robb RA et al. Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. J Bone Miner Res 2003;18:1766–74.
12. Duan Y, Beck TJ, Wang XF, Seeman E. Structural and biomechanical basis of sexual dimorphism in femoral neck fragility has its origins in growth and aging. J Bone Miner Res 2003;18:1766–74.
13. Marshall LM, Lang TF, Lambert LC, Zmuda JM, Ensrud KE, Orwoll ES. Dimensions and volumetric BMD of the proximal femur and their relation to age among older U.S. men. J Bone Miner Res 2006;21:1197–206.
14. Lang TF, Keyak JH, Heitz MW et al. Volumetric quantitative computed tomography of the proximal femur: precision and relation to bone strength. Bone 1997;21:101–8.
15. Black DM, Greenspan SL, Ensrud KE et al. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 2003;349:1207–15.
16. Black DM, Bleiziffer JP, Ensrud KE et al. One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med 2005;353:555–65.
17. Greenspan SL, Bone HG, Ettinger MP et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med 2007;146:326–39.
18. Chevalier F, Lavall-Jeantot AM, Lavall-Jeantot M, Bergot C. CT image analysis of the vertebral trabecular network in vivo. J Biomech 1995;28:1–8.
19. Chevalier F, Lavall-Jeantot AM, Lavall-Jeantot M, Bergot C. CT image analysis of the vertebral trabecular network in vivo. J Biomech 1995;28:1–8.
20. Gordon CL, Webber CE, Adachi JD, Christoforou N. In vivo assessment of trabecular bone structure at the distal radius from high-resolution computed tomography images. Phys Med Biol 1996;41:495–508.
21. Gordon CL, Lang TF, Augat P, Genant HK. Image-based assessment of spinal trabecular bone structure from high-resolution CT images. Osteoporos Int 1998;8:317–25.
22. Shawalter C, Clymer BD, Richmond B, Powell K. Three-dimensional texture analysis of cancellous bone cores evaluated at clinical CT resolutions. Osteoporos Int 2001;12:775–86.
23. Saparin P, Thomsen JS, Kurfiss J, Beiler G, Gwinn W. Segmentation of bone CT images and assessment of bone structure using texture features. Med Phys 2004;31:3857–73.
24. Xiang Y, Yingling VR, Malique R, Li CY, Schaffler MB, Raphan T. Comparative prediction of overall bone strength recorded during mechanical testing of vertebral microstructure by high-resolution CT in vivo: results from the EUROFORS Study. J Bone Miner Res 2002;17:1426–33.
25. Itto M, Ikhi M, Hayashi K, Yamada M, Uetani M, Nakamura T. Trabecular texture analysis of CT images in the relationship with spinal fracture. Radiology 1995;194:55–9.
26. Gordon CL, Webber CE, Adachi JD, Christoforou N. In vivo assessment of trabecular bone structure at the distal radius from high-resolution computed tomography images. Phys Med Biol 1996;41:495–508.
27. Durand EP, Rüegsegger P. High-resolution CT images for bone structure analysis. Med Phys 1992;19:589–73.
28. Muller R, Hildebrand T, Hauselmann HJ, Rüegsegger P. In vivo reproducibility of three-dimensional structural properties of noninvasive bone biopsies using 3D-qCT. J Bone Miner Res 1996;11:1745–50.
29. Müller R, Koller B, Hildebrand T, Laba A, Gianolli S, Rüegsegger P. Resolution dependency of microstructural properties of cancellous bone based on three-dimensional μ-tomography. Technol Health Care 1996;4:113–9.
30. Laba A, Hildebrand T, Hauselmann HJ, Rüegsegger P. Ridge number density: a new parameter for in vivo bone structure analysis. Bone 1997;21:541–6.
31. Hildebrand T, Rüegsegger P. Quantification of bone microarchitecture with the structure model index. CMBBE 1997;1:15–23.
32. Bousson S, Buxseux ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. Clin Endocrinol Metab 2005;30:6508–15.
33. Macneil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. Med Eng Phys 2007;29:1065–77.
34. Macneil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. Med Eng Phys 2007;29:1065–77.
35. Khosla S, Riggs BL, Atkinson EJ et al. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive in vivo assessment. J Bone Miner Res 2006;21:124–31.
36 Khosla S, Melton LJ 3rd, Achenbach SJ, Oberg AL, Riggs BL. Hormonal and biochemical determinants of trabecular microstructure at the ultradistal radius in women and men. J Clin Endocrinol Metab 2006;91:885–91.

37 MacNeil JA, Boyd SK. Load distribution and the predictive power of morphological indices in the distal radius and tibia by high resolution peripheral quantitative computed tomography. Bone 2007;41:129–37.

38 Graef W, Engelke K. Microradiography and microtomography. In: Ebashi E, Koch M, Rubenstein E, eds. Handbook on synchrotron radiation. Amsterdam: North-Holland, 1991;361–405.

39 Hildebrand T, Rüegsegger P. A new method for the model independent assessment of thickness in three-dimensional images. J Microsc 1997;185:67–75.

40 Ogdaa A, Gundersen HJ. Quantification of connectivity in cancellous bone, with special emphasis on 3-D reconstructions. Bone 1993;14:173–82.

41 Dufresne TE, Chmielewski PA, Manhart MD, Johnson TD, Borah B. Risedronate preserves bone architecture in early postmenopausal women in 1 year as measured by three-dimensional microcomputed tomography. Calcif Tissue Int 2003;73:423–32.

42 Dempster DW, Cosman F, Kurland ES et al. Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. J Bone Miner Res 2001;16:1846–53.

43 Fox J, Miller MA, Recker RR, Bare SP, Smith SY, Moreau I. Treatment of postmenopausal osteoporotic women with parathyroid hormone 1-84 for 18 months increases cancellous bone formation and improves cancellous architecture: a study of iliac crest biopsies using histomorphometry and micro computed tomography. J Musculoskelet Neuronal Interact 2005;5:356–7.

44 Hordon LD, Iota M, Shore PA et al. Preservation of thoracic spine microarchitecture by alendronate: comparison of histology and microCT. Bone 2006;38:444–9.

45 Arlot ME, Jiang Y, Genant HK et al. Histomorphometric and micro-CT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. J Bone Miner Res 2008;23:215–22.

46 Yang J, Pham SM, Crabbe DL. High-resolution micro-CT evaluation of mid- to long-term effects of estrogen deficiency on rat trabecular bone. Acad Radiol 2003;10:1159–8.

47 Ito M, Nishida A, Aoyagi K, Uetani M, Hayashi K, Kawase M. Effects of risedronate on trabecular microstructure and biomechanical properties in ovariectomized rat tibia. Osteoporos Int 2005;16:1042–8.

48 Xiang A, Kanematsu M, Kumar S et al. Changes in micro-CT 3D bone parameters reflect effects of a potent cathepsin K inhibitor (SB-553484) on bone resorption and cortical bone formation in ovariectomized mice. Bone 2007;40:1231–7.

49 Washimi Y, Ito M, Morishima Y et al. Effect of combined humanPTH(1-34) and calcitonin treatment in ovariectomized rats. Bone 2007;41:786–93.

50 Wachschnuth L, Engelke K. High-resolution imaging of osteoarthritis using microcomputed tomography. Methods Mol Med 2004;101:231–48.

51 Patel V, Issever AS, Burghardt A, Laib A, Ries M, Majumdar S. MicroCT evaluation of normal and osteoarthritic bone structure in human knee specimens. J Orthop Res 2003;21:6–13.

52 Ding M, Ogdaa A, Hvid I. Changes in the three-dimensional microstructure of human tibial cancellous bone in early osteoarthritis. J Bone Joint Surg Br 2003;85:906–12.

53 Batiste DL, Kirkey A, Laverty S, Thain LM, Spouge AR, Holdsworth DW. Ex vivo characterization of articular cartilage and bone lesions in a rabbit ACL transection model of osteoarthritis using MRI and micro-CT. Osteoarthr Cartilage 2004;12:986–96.

54 Batiste DL, Kirkey A, Laverty S et al. High-resolution MRI and micro-CT in an ex vivo rabbit anterior cruciate ligament transection model of osteoarthritis. Osteoarthr Cartilage 2004;12:614–26.

55 Chappard C, Peyrin F, Bonnasse A et al. Subchondral bone micro-architectural alterations in osteoarthritis: a microcomputed tomography study. Osteoarthr Cartilage 2006;14:215–23.

56 Keyak JH, Rossi SA. Prediction of femoral fracture load using finite element models: an examination of stress- and strain-based failure theories. J Biomech 2000;33:209–14.

57 Silva MJ, Keaveny TM, Hayes WC. Load sharing between the shell and centrum in the lumbar vertebral body. Spine 1997;22:140–50.

58 Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. Bone 2003;33:744–50.

59 Crawford RP, Rosenberg WS, Keaveny TM. Quantitative computed tomography-based finite element models of the human lumbar vertebral body: effect of element size on stiffness, damage, and fracture strength predictions. J Biomech Eng 2003;125:434–8.

60 Ciarelli TE, Fyhrie DP, Schaffler MB, Goldstein SA. Variations in three-dimensional cancellous bone architecture of the proximal femur in female hip fractures and in controls. J Bone Miner Res 2000;15:32–40.

61 Engelke K, Bousson V, Duchemin L et al. EFFECT – The European femur fracture study using finite element analysis and 3D CT, in ASBMR 28th annual meeting. 2006. Philadelphia, Il: ASBMR.

62 van Rietbergen B, Weinans H, Huiskes R, Odgaard A. A new method to determine trabecular bone elastic properties and loading using micromechanical finite-element models. J Biomechanics 1995;28:69–81.

63 Ulrich D, Hildebrand T, Van Rietbergen B, Muller R, Rüegsegger P. The quality of trabecular bone evaluated with micro-computed tomography, FEA and mechanical testing. Stud Health Technol Inform 1997;40:97–112.

64 Homminga J, Huiskes R, Van Rietbergen B, Rüegsegger P, Weinans H. Introduction and evaluation of a gray-value voxel conversion technique. J Biomech 2001;34:513–7.