

Advanced CT bone imaging in osteoporosis

H. K. Genant^{1,2}, K. Engelke^{3,4} and S. Prevrhal⁵

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 microstructural 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 (μ CT), high-resolution magnetic resonance (hrMR) and microMR (μ MR). vQCT, hrCT and hrMR are generally applicable *in vivo*; μ CT and μ MR 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 (μ CT) scanners. Over the past decade, several commercial companies have been offering an increasing variety of μ CT scanners for different applications. In addition, active research in μ CT 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 μ m are encountered frequently, especially in the elderly.

¹University of California, ²Synarc, Inc., San Francisco, CA, USA, ³Department of Medical Physics, University of Erlangen-Nürnberg, Erlangen, ⁴Synarc, Inc., Hamburg, Germany and ⁵Department of Radiology, University of California, San Francisco, CA, USA.

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Correspondence to: H. K. Genant, 7 Tara Hill Rd., Tiburon, CA 94920, USA.
E-mail: harry.genant@ucsf.edu

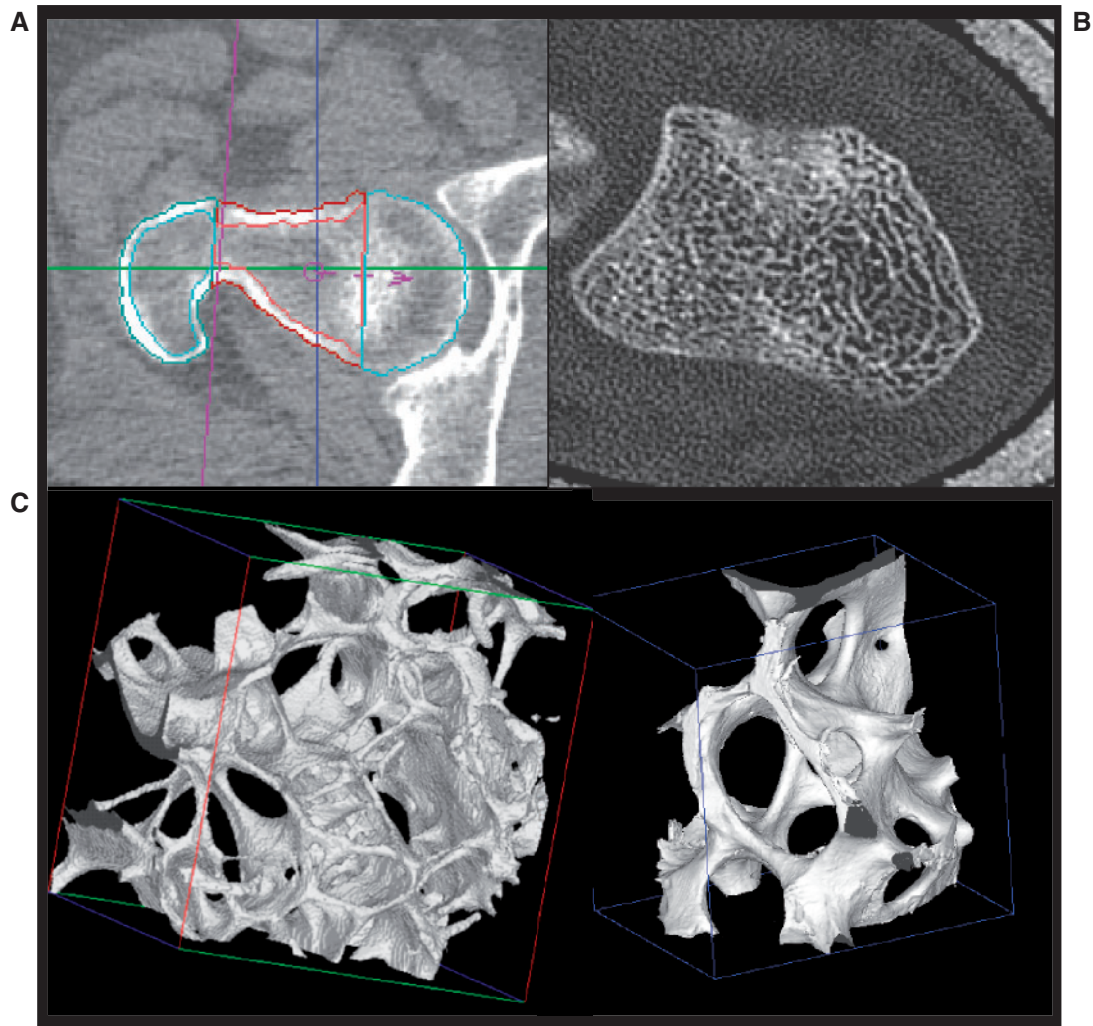


FIG. 1. CT imaging techniques to assess bone density and architecture. Top left: vQCT of the femur (in plane pixel size $350\ \mu\text{m}$, slice thickness $1\ \text{mm}$) to determine BMD and macrostructure; top right: hrCT of ultra-distal forearm (in plane pixel size $200\ \mu\text{m}$, slice thickness $0.5\ \text{mm}$) to determine texture and structure of the trabecular network; bottom: μCT of vertebral spongiosa (isotropic voxel size: left $30\ \mu\text{m}$, right $10\ \mu\text{m}$) to determine structure of the trabecular network.

TABLE 1. Overview of CT techniques to determine BMD and bone architecture

	vQCT	hrCT	μCT
In plane pixel size	$>0.3 \times 0.3\ \text{mm}^2$	$0.1 \times 0.1\text{--}0.3 \times 0.3\ \text{mm}^2$	Isotropic $1\text{--}100\ \mu\text{m}^3$
Slice thickness	$>1\ \text{mm}$	$0.2\text{--}1\ \text{mm}$	
Equipment	Whole body clinical scanners; dedicated peripheral scanners	Whole body clinical scanners; dedicated peripheral scanners	Dedicated μCT scanners
Skeletal location	Spine, hip, forearm, tibia	Spine, forearm	Human biopsies: iliac crest Animals and specimen: various
Subjects/samples	Human <i>in vivo</i>	Human <i>in vivo</i> /human biopsies/bone specimen	Laboratory animals <i>in vivo</i> and <i>in vitro</i> , bone specimen
Applications	BMD/bone macrostructure/FEM	Bone macrostructure/trabecular microstructure	Trabecular and cortical microstructure/ μFEM

Techniques with a voxel size $<1\ \mu\text{m}$ are typically called microscopy.

The limited spatial resolution also results in an underestimation of cortical BMD on the order of 1030%. 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

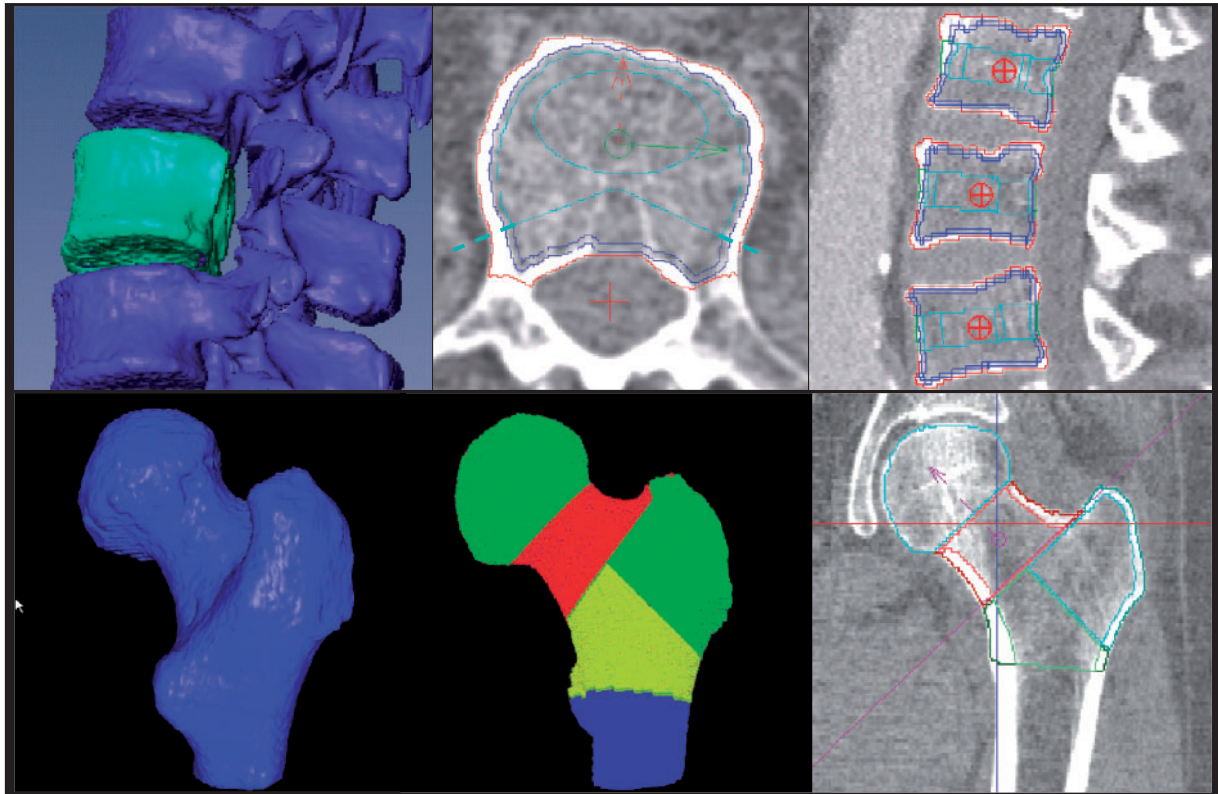


FIG. 2. The vQCT of the spine (top panel) and hip (bottom panel) may be used to analyse BMD in various bone compartments and to accurately measure BMD and geometry. Top left: segmented vertebral body selected for analysis with removed processes. Top centre and right: integral (red) and peeled trabecular volumes of interest (dark blue) along with the traditional elliptical and Pacman VOIs (light blue). Bottom left: segmented proximal femur. Bottom centre and right: analysis VOIs in the hip.

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 $\sim 100\text{--}1000\ \mu\text{Sv}$ and for the radius a dose

$<10\ \mu\text{Sv}$. These radiation doses compare favourably, however, with the average annual background effective dose of $2500\ \mu\text{Sv}$ in the United States and Europe, and the effective dose of $50\ \mu\text{Sv}$ 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 $\sim 0.5\text{ mm}$. 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 ($100\text{--}400\ \mu\text{m}$) and trabecular spaces ($200\text{--}2000\ \mu\text{m}$) 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

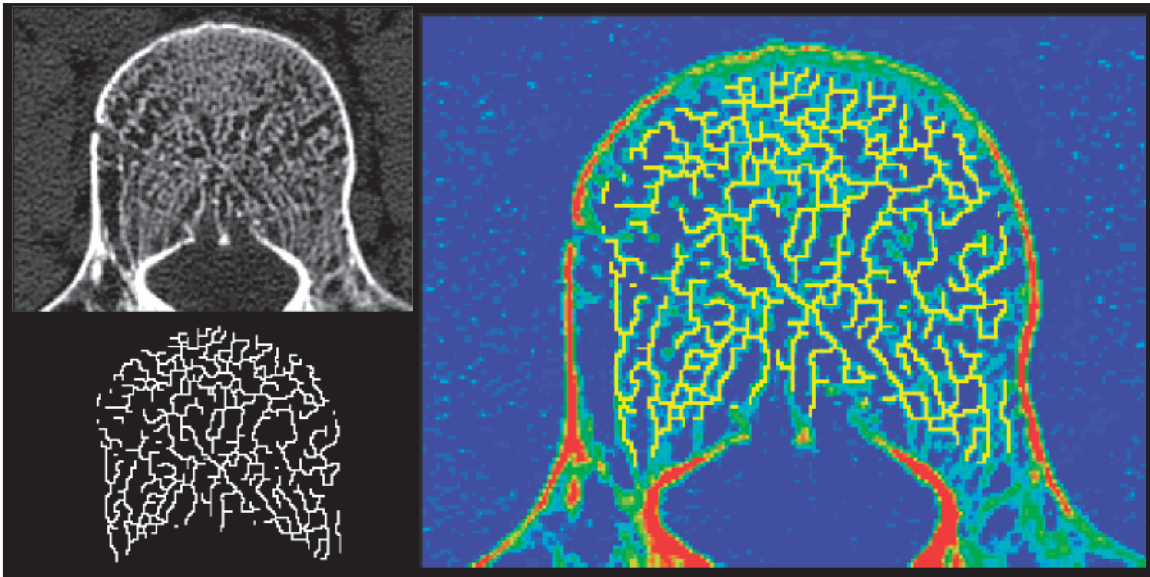


FIG. 3. Example of image processing of hrCT images. Trabecular structure can be approximated if individual trabeculae are well separated. The upper left shows the original hrCT spine image, followed on the lower left by the 'binarized' and 'skeletonized' image processed into single-pixel-thick trabeculae displayed in white against black of the surrounding marrow and followed on the right by a 'colourized' version for which quantitative image processing can be undertaken.

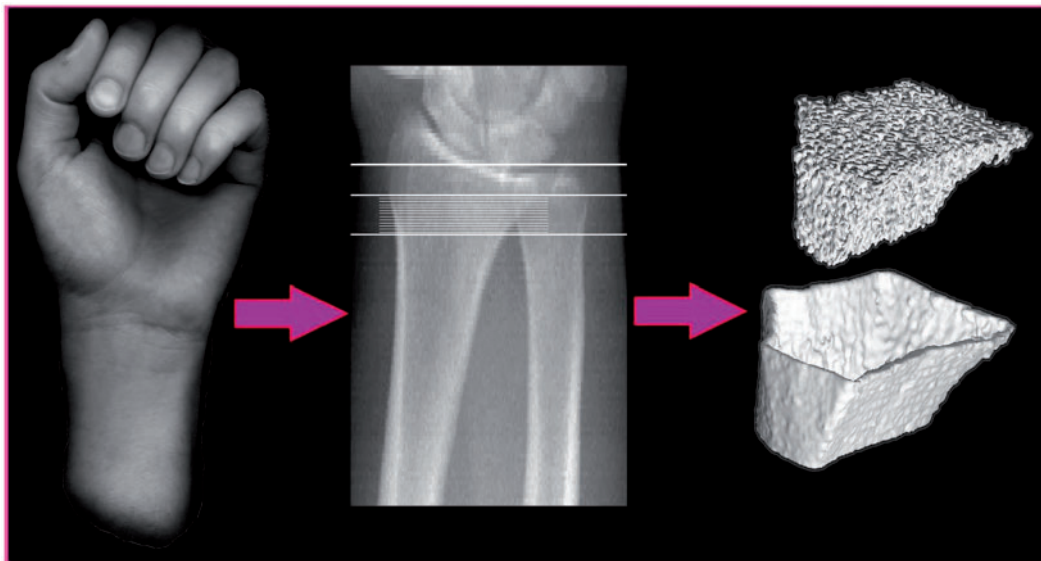


FIG. 4. *In vivo* μ CT of the distal radius using the XtremeCT system, with images showing the region of the distal radius imaged (centre) and the resulting 3D trabecular and cortical envelopes (right). Courtesy Bruno Koller.

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 R uegsegger [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 $\sim 1\%$ achieved by careful registration of the acquired 3D data sets. When *in vitro* pQCT structure measurements were compared with μ CT, 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 μ CT 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 R uegsegger 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

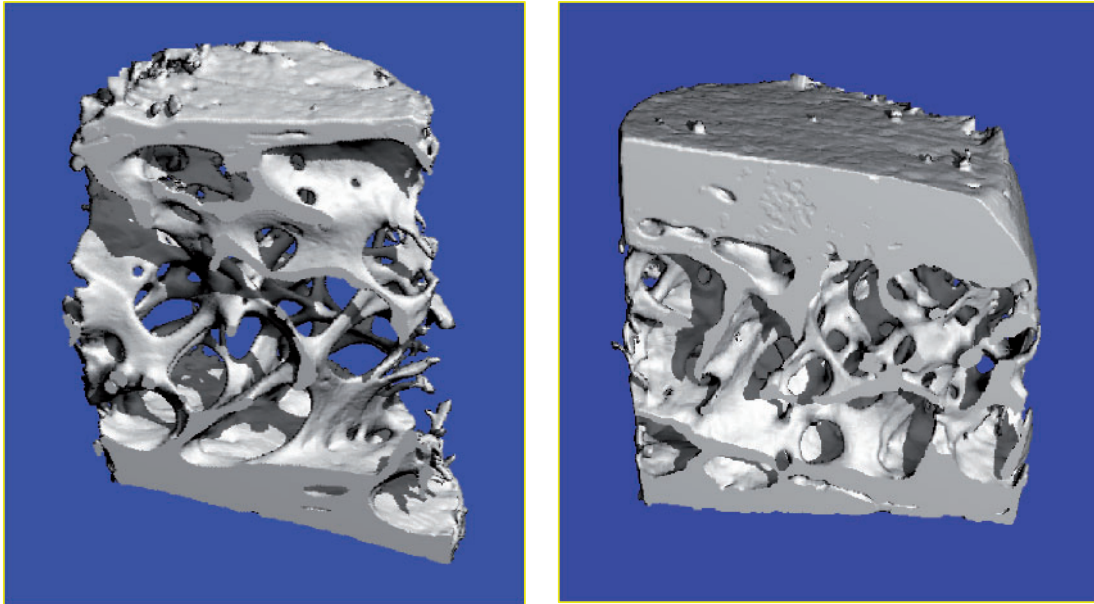


FIG. 5. 3D μ CT: microstructure of transiliac bone biopsies from two post-menopausal women after 36 months of strontium ranelate therapy. Left: placebo; right: strontium ranelate therapy [45].

the order of $100\ \mu\text{m}$. 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 ($r^2 > 0.8$) using the XtremeCT.

μ CT

μ CT denotes a CT technique with a spatial resolution of $1\text{--}100\ \mu\text{m}$. The techniques described below are typically termed microscopy. The μ CT 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 μ CT 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 μ CT 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, μ CT 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 μ CT [43]. In a study in ovariectomized baboons, bisphosphonates improved 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 $2\ \text{g/day}$ ($n=20$), were examined with μ CT at isotropic resolution of $20\ \mu\text{m}$. 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 μ CT, 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

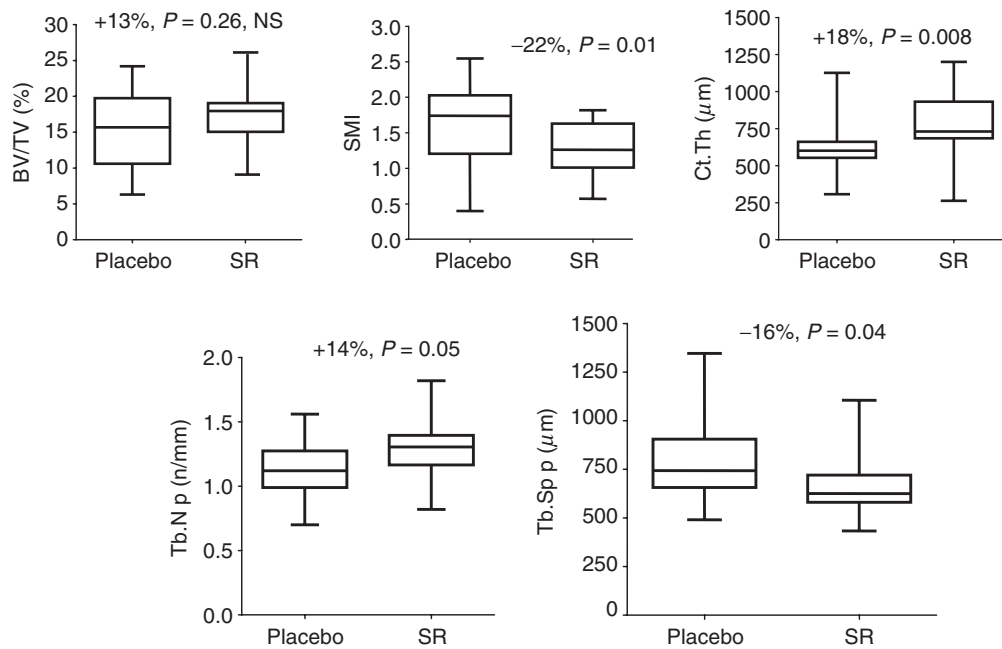


FIG. 6. Analysis of BV/TV, SMI, Ct.Th, Tb.N and Tb.Sp in transiliac bone biopsies from post-menopausal women after 36 months of strontium ranelate therapy [45]; placebo: $n=21$, strontium ranelate: $n=20$.

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 μ CT 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

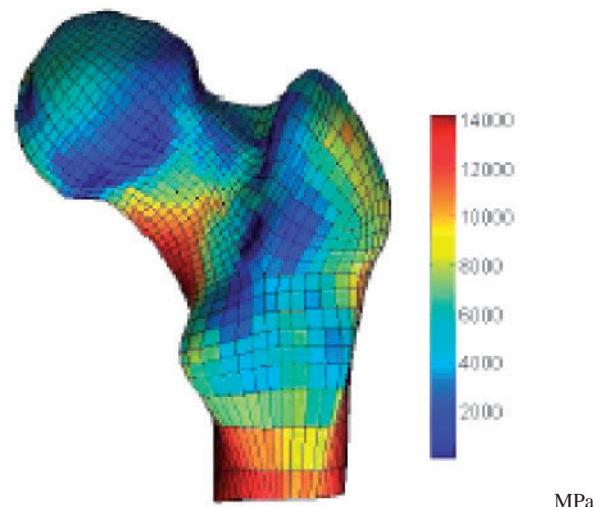


FIG. 7. Distribution of Young's modulus computed from BMD in the elements of the mesh using vQCT data. Young's modulus (MPa). Image courtesy of Dr David Mitton.

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 μ CT 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 μ CT 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 comparably 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, Weinans 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, Weinans 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 Serio A, Cammisa 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, 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* 2006;10:560–77.
- 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;29:533–41.
- 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 Bras 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 Prevhal 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 Bio* 1999;44:751–64.
- 11 Riggs BL, Melton LJ 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* 2004;19:1945–54.
- 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, Bilezikian 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, Laval-Jeantet AM, Laval-Jeantet M, Bergot C. CT image analysis of the vertebral trabecular network in vivo. *Calcif Tissue Int* 1992;51:8–13.
- 19 Ito M, Ohki 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.
- 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 Showalter C, Clymer BD, Richmond B, Powell K. Three-dimensional texture analysis of cancellous bone cores evaluated at clinical CT resolutions. *Osteoporos Int* 2006;17:259–66.
- 23 Saparin P, Thomsen JS, Kurths J, Beller G, Gowin W. Segmentation of bone CT images and assessment of bone structure using measures of complexity. *Med Phys* 2006;33:3857–73.
- 24 Xiang Y, Yingling VR, Malique R, Li CY, Schaffler MB, Raphan T. Comparative assessment of bone mass and structure using texture-based and histomorphometric analyses. *Bone* 2007;40:544–52.
- 25 Graeff C, Timm W, Nickelsen TN *et al.* Monitoring teriparatide-associated changes in vertebral microstructure by high-resolution CT in vivo: results from the EUROFOR Study. *J Bone Miner Res* 2007;22:1426–33.
- 26 Ito M, Ikeda K, Nishiguchi M *et al.* Multi-detector row CT imaging of vertebral microstructure for evaluation of fracture risk. *J Bone Miner Res* 2005;20:1828–36.
- 27 Durand EP, Ruegsegger P. High-contrast resolution of CT images for bone structure analysis. *Med Phys* 1992;19:569–73.
- 28 Muller R, Hildebrand T, Hauselmann HJ, Ruegsegger P. In vivo reproducibility of three-dimensional structural properties of noninvasive bone biopsies using 3D-pQCT. *J Bone Miner Res* 1996;11:1745–50.
- 29 Müller R, Koller B, Hildebrand T, Laib A, Gianolini S, Ruegsegger P. Resolution dependency of microstructural properties of cancellous bone based on three-dimensional μ -tomography. *Technol Health Care* 1996;4:113–9.
- 30 Laib A, Hildebrand T, Hauselmann HJ, Ruegsegger P. Ridge number density: a new parameter for in vivo bone structure analysis. *Bone* 1997;21:541–6.
- 31 Hildebrand T, Ruegsegger P. Quantification of bone microarchitecture with the structure model index. *CMBBE* 1997;1:15–23.
- 32 Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J Clin Endocrinol Metab* 2005;90:6508–15.
- 33 Macneil JA, Boyd SK. Improved reproducibility of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys* 2007;29:1096–105.
- 34 Macneil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys* 2007;29:1096–105.
- 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 Graeff 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, Ruegsegger P. A new method for the model independent assessment of thickness in three-dimensional images. *J Microsc* 1997;185:67–75.
- 40 Odgaard 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, Itoda 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;10:1153–8.
- 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 Wachsmuth L, Engelke K. High-resolution imaging of osteoarthritis using micro-computed 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, Odgaard 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, Kirkley A, Lavery 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, Kirkley A, Lavery 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, Bonnassie A *et al.* Subchondral bone micro-architectural alterations in osteoarthritis: a synchrotron micro-computed 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;33:909–14.
- 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, Ruegsegger 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, Ruegsegger P, Weinans H. Introduction and evaluation of a gray-value voxel conversion technique. *J Biomech* 2001;34:513–7.