Citation: BoneKEy Reports **5**, Article number: 813 (2016) | doi:10.1038/bonekey.2016.40
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REVIEW

In vivo evaluation of bone microstructure in humans: Clinically useful?

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In vivo **evaluation of bone microstructure with high-resolution peripheral quantitative tomography (HRpQCT) has been used for a decade in research settings. In this review, we examine the value this technique could have in clinical practice. Bone microstructure parameters obtained with HRpQCT are associated with prevalent fracture in men and women. In postmenopausal women, some parameters also predict incident fracture, independently of areal bone mineral density. In specific population groups including patients with diabetes, chronic kidney disease, glucocorticosteroid therapy and rheumatic diseases, abnormal microstructure parameters from HRpQCT have been reported. Findings from HRpQCT studies may also explain ethnic differences in bone fragility. Treatment monitoring has been challenging in the various clinical trials with available HRpQCT data. The improvements were of small magnitude but tended to be proportional to the potency of antiresorptive agents. Microfinite element analysis was a better predictor of treatment efficacy than the microarchitectural parameters. In conclusion, HRpQCT remains a valuable research tool, but more work is needed to be able to use it in clinical practice.**

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Introduction

The measurement of areal bone mineral density (aBMD) by dual-energy X-ray absorptiometry (DXA) is currently the reference procedure for the diagnosis of osteoporosis and prediction of fracture risk. This technique, however, has important limitations. Specifically, half of fragility fractures have been observed in postmenopausal women whose T-score is above the World Health Organization-defined diagnostic threshold for osteoporosis (that is, -2.5 s.d.), and this has been noticed in several different cohort settings.[1–3] In men, this proportion of captured individuals probably does not exceed 25%.[3,4] Furthermore, the proportion of the reduction in vertebral fracture risk after osteoporosis therapy that is explained by changes in BMD has been controversial.[5] It may be important only with the most potent antiresorptive drugs.[6,7]

Because osteoporosis is characterized both by low bone mass and microarchitectural deterioration, it has been suggested that *in vivo* assessment of bone microarchitecture may improve the prediction of fracture risk and the ability to monitor the response to therapeutic intervention. The gold standard technique for evaluation of bone microarchitecture is the histomorphometric analysis of a transiliac bone biopsy. This is not feasible in large-scale epidemiologic studies or in clinical practice. This limitation has led to the development of non-invasive imaging techniques. Magnetic resonance imaging (MRI) can measure trabecular bone microarchitecture, and finite element analysis (FEA) can be performed with good quality MRI images. The performance of the technique for the evaluation of cortical bone, however, is less satisfactory. Also, MRI machines are not easily available for large research projects and population screening, and, measurements may be costly, limiting research efforts with this technique.

In vivo assessment of bone microstructure became available about 15 years ago using high-resolution peripheral quantitative tomography (HRpQCT), and, most clinical studies published so far have used this technique, with the XTreme CT machine (Scanco, Bruttisellen, Switzerland). This system uses a two-dimensional detector array in combination with a 0.08-mm point-focus x-ray tube, allowing for the simultaneous acquisition of a stack of parallel CT slices with a nominal resolution (voxel size) of 82 μm. One hundred ten slices are obtained at the distal radius and tibia during a 3 mn time scan, thus delivering a three-dimensional representation of approximately 9 mm in the axial direction. The entire volume of interest is automatically separated into a cortical and trabecular region using a threshold-based algorithm. The total, trabecular and cortical volumetric bone densities are measured, along with the number and distribution of trabeculae and the cross-sectional area. The trabecular bone volume, the trabecular thickness and separation are calculated with the standard formulae from histomorphometry. Cortical porosity can also be assessed.

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Received 22 December 2015; revised 13 February 2016; accepted 22 February 2016; published online 15 June 2016

In this narrative review, we will focus on two potential clinical applications of *in vivo* measurement of bone microarchitecture—that is, the evaluation of fracture risk and the treatment monitoring.

Assessment of Fracture Risk: What is the Evidence?

Prevalent fracture and bone microstructure

The largest body of evidence comes from case–control and cross-sectional studies. Thus, in a case–control analysis from the population-based cohort OFELY, women with osteopenia with fragility fracture had lower trabecular density and more heterogeneous trabecular distribution than non-fractured women with the same aBMD at the spine and hip.[8] Similarly, in a case–control study enrolling women with recent wrist or hip fracture, HRpQCT measures—especially the cortical parameters at the distal tibia—were able to distinguish fractured and non-fractured women.[9] The measurement of cortical porosity was able to distinguish the postmenopausal women with osteopenia who did or did not have a history of wrist fracture.[10] Also in postmenopausal women, although all vertebral fractures were associated with low volumetric BMD and architectural alterations of both trabecular and cortical bone, severe and multiple vertebral fractures were further associated with impairment of cortical bone.[11] Most of these results observed in retrospective studies were obtained after adjustment for aBMD at the radius and hip for radius and tibia HRpQCT measurements, respectively.

In microFEA (μFEA), using linear models, the proportion of load carried by cortical bone compared with trabecular bone was associated with wrist fracture independently of aBMD and microarchitecture.[12] Non-linear μFEA models provide important additional information on the risk of wrist fracture, specifically a yield load-based factor of risk, bone ductility (yield deformation) and the cortical plastic volume.[13] Much greater computer performance is necessary to perform non-linear compared with linear μFEA models. The linear μFEA parameters evaluated at distal sites such as the tibia and radius were also associated with all types of prevalent fractures, including the vertebra.[14,15] The magnitude of this association was similar at the tibia and radius.[14] Thus, tibia and radius mechanical properties are relatively representative of those of other distant bone sites. The main limitation of μFEA is the access to powerful computers and the duration of the analysis (around 30 min per bone site with a linear model on a regular computer). With the rapid increase in computer performance, this duration could be significantly reduced.

Prediction of incident fracture

To determine the possible clinical role of HRpQCT in the prediction of fragility fracture risk, we need results from prospective studies showing that the prediction of fracture can be improved by HRpQCT, compared with current paradigms including aBMD or FRAX. Thus, the microstructure parameters must remain predictive of fracture after accounting for the reference for fracture prediction, that is, the aBMD or the area under the curve must be statistically significantly different. Another way to approach the microarchitectural contribution to incident fracture risk is to assess whether they can distinguish specific extreme phenotypes of bone fragility, using principal component analysis or cluster analyses.

So far, only one analysis of the prediction of incident fracture in postmenopausal women has been released but only in abstract form.[16] Thus, in a prospective cohort of French postmenopausal women, after adjustment for hip aBMD, the total vBMD, the trabecular vBMD, the trabecular number and the connectivity at the distal radius remained predictive of incident fracture, along with age-adjusted estimated failure load.

Specific populations

Differences between ethnicities. Compartment-specific analyses may be helpful to clarify discrepancies between fracture prevalence and risk prediction provided by aBMD. Indeed, Asian men and women have smaller bones; hence, aBMD underestimates their bone density. Nevertheless, Asians also sustain fewer fractures. Using HRpQCT, it has been observed that premenopausal Asian women had thicker cortices and thicker but fewer trabeculae than Caucasians,[17] with higher estimates of bone stiffness/strength in μFEA.[18] In Chinese American pre- and postmenopausal women, cortical porosity has been found lower than in Caucasian women,[19] possibly accounting for some of the differences in fracture incidence between Chinese and Caucasian women.

Diabetes. Patients with type 2 diabetes generally have normal-to-high aBMD, but they sustain more fractures than non-diabetic controls, especially at non-vertebral sites. Cross-sectional studies conducted so far among post-menopausal women with type 2 diabetes[20–22] have shown that the peripheral trabecular bone is relatively preserved. The greater fracture risk in diabetic patients may stem from the increased cortical porosity that has been observed in those diabetic postmenopausal women with prevalent fracture when compared with non-fractured diabetic women.[20–22] This finding was consistent with an impairment in estimated bone strength.[22] It remains to be determined whether this measurement of impaired peripheral cortical bone can improve the prediction of incident fracture sufficiently over aBMD to be clinically meaningful.

In a cross-sectional analysis of patients with type 1 diabetes, no significant difference has been found between a small group ($n = 55$) of middle-aged men and women (45 years) in those without microvascular disease and the non-diabetic controls.[23] In contrast, those patients with microvascular disease had impaired trabecular microarchitecture.

Bone fragility in men. HRpQCT has also been used to address bone fragility in men, because the limitations of the use of aBMD by DXA are even more important in men than in women. Khosla *et al*, have observed that the trabecular bone volume (BV/TV) and thickness were significantly greater in young men than in young women.[24] The rate of age-related decline in trabecular BV/TV seemed independent of gender, whereas in aging healthy men trabecular thinning seemed to predominate over loss of trabeculae, contrasting to what is observed in women. Vertebral fractures and their severity are associated with impaired cortical bone, even after adjustment for aBMD.[25] The association between peripheral fractures and bone microarchitecture was weaker and nonsignificant after

adjustment for aBMD. In addition, μFEA estimates of bone strength at the distal radius and tibia have been associated with prevalent fracture at distant sites,[26] reminiscent of what has been observed in postmenopausal women.

Bone fragility and chronic kidney disease. In patients with chronic kidney disease (CKD), a compartment-specific approach is possibly preferable to DXA, because the various forms of osteodystrophies may affect the trabecular and cortical compartments differently. Impairment in bone micro-architecture has been observed in patients with early CKD[27,28] and in patients on dialysis.[29] Alterations in bone structure appeared to be less in patients on peritoneal dialysis than in those on hemodialysis. The rapid cortical bone loss that is observed in correlation with secondary hyperparathyroidism among patients on dialysis can be detected by HRpQCT over a short period of time (18 months).[30]

In a small group of men and women ($n = 131$) with pre-dialysis CKD (stages 3 to 5), the cortical parameters measured with HRpQCT at the distal radius predicted incident fragility fractures.[31] The areas under the curve (AUCs), however, were not significantly different from those obtained with aBMD. Larger studies in various patient settings are necessary to draw conclusions about the clinical significance of microarchitectural assessment among patients with CKD, in pre- and dialysis stages.

Corticosteroid-induced osteoporosis. Patients taking corticosteroids are at higher risk for fracture at a given aBMD level than those who do not take these drugs, suggesting that changes not captured by DXA might be detectable by the *in vivo* evaluation of bone microarchitecture. In a small case–control study ($n = 90$) conducted in an academic hospital, glucocorticosteroid-treated women had abnormal cortical and trabecular vBMD and microarchitecture at both the radius and tibia, including fewer trabecular plates, a less axially aligned trabecular network, lower trabecular connectivity, thinner cortices and lower whole-bone stiffness, despite similar aBMD by DXA compared with the controls.[32] This needs to be replicated in larger groups, and the association of these abnormalities with fragility fracture has to be established.

Bone fragility associated with rheumatic diseases. Rheumatic diseases such as rheumatoid arthritis, lupus and spondyloarthritis (SpA) are associated with an increased risk of fragility fracture that is not only due to the use of corticosteroids but also to the effects of chronic inflammation on bone remodeling. For example, the bone microarchitecture has been found impaired in men with SpA, at the distal radius and tibia, proportionally to the spine syndesmophyte score, which can be considered as roughly proportional to disease severity.[33] Whether the HRpQCT measurement in this special population can be used to screen individuals at risk for fracture more effectively than DXA, in an era of declining comorbidities of rheumatic diseases thanks to the use of biologics and treat-to-target strategies, remains to be established.

The Value of High-Resolution Peripheral Computed Tomography for Treatment Follow-Up

So far, the effect of antiosteoporotic drugs on HRpQCT parameters has been tested in randomized controlled trials with four classes of drugs: oral bisphosphonates, denosumab, strontium ranelate and odanacatib.

In a pilot trial comparing alendronate to placebo for 24 months,[34] HRpqCT measures showed improvement compared with baseline only at the distal tibia. Among postmenopausal women randomized to receive either placebo or risedronate 35 mg per week, there was no significant difference in trabecular and cortical parameters between groups at 12 months,[35] but compared with baseline risedronate tended to prevent vBMD and Ct.Th decline at the distal tibia. Among the youngest women (<55 years) enrolled in this trial, the prevention of bone microarchitecture decay was more important than in the oldest women. Similarly, in a trial examining the effect of oral ibandronate 150 mg/month compared with placebo,[36] no significant difference between groups appeared in either trabecular and cortical parameters at the radius, with up to 24 months of follow-up. At the tibia, however, cortical vBMD and Ct.Th were greater in the ibandronate group. In another double-blind trial, 247 postmenopausal women were randomized to denosumab (60 mg subcutaneous 6 monthly), alendronate (70 mg oral weekly) or placebo and treated for 12 months.[37] In the placebo group, microarchitecture variables declined, whereas in the alendronate group the decay was prevented.In the denosumab group, these HRpQCT parameters either were stable or were improved.

Strontium ranelate has been compared with alendronate within a randomized trial but not with placebo.[38] At the radius, most comparisons were not significantly different. At the tibia, microstructure parameters remained stable on alendronate, whereas they improved on strontium ranelate, including estimates of bone strength.

The cathepsin K inhibitor odanacatib has also been evaluated in a randomized, double-blind placebo-controlled trial, using HRpQCT of the distal radius and distal tibia,[39] in 214 postmenopausal women treated for 2 years. Odanacatib increased cortical and trabecular volumetric density, improved cortical thickness of the distal radius and tibia and improved the estimated bone strength at the distal radius compared with placebo. Of note, the longitudinal evaluation of μFEA was more precise than that of the microarchitectural parameters.[40]

Taken together these data suggest that the distal tibia was more responsive to treatments than the distal radius, suggesting that the mechanical stimulus at this site might improve the response to treatments. The results of these interventions, however, should be interpreted with caution. Indeed, motion artifacts are common, especially when measuring the radius where the scan quality is often inadequate. In the trials, these scans have not been excluded, to avoid missing values and ensure the validity of the intent-to-treat analyses. This may have biased some of the results at the radius toward the null, contributing to the impression that the distal tibia site was more appropriate.

There are also technical limitations to the longitudinal evaluation of cortical thickness. The aforementioned analyses were limited to geometrical and microarchitectural response to

therapy but did not address the issue of effects on the bone material. Besides, the common regions of interest between baseline and follow-up scans are determined based on cross-sectional area matching, assuming a constant area over time. Therefore, when measured longitudinally, the total areas are necessarily the same. The increase in vBMD following the decrease in bone resorption can influence edge detection, thus increasing the cortical area and thickness artifactually. In fact, the increase in cortical bone density leading to apparent improvement in cortical thickness is probably due to filling of cortical porosity—that is, increasing the cortical area—because any actual thickening is beyond the resolution of HRpQCT. This reasoning is supported by our observation that the trabecular area decreased and the cortical area increased at the tibia in women on ibandronate compared with those on placebo, whereas the total area remained constant over time, suggesting that the greater Ct.Th was due to refilled endocortical porosity.[36] In the particular case of strontium ranelate, the higher X-ray attenuation of strontium ranelate than calcium can increase voxel density, even in the absence of new bone formation or mineralization. Indeed, when corrected with parameters less influenced by density, using a distance transformation method, differences between alendronate and strontium ranelate were no longer significant.[38]

One reason explaining that the results of treatment monitoring with HRpQCT parameters of microarchitecture were disappointing may be due to the poor reproducibility of the repeated measurements of the volumes of interest. This issue may be overcome by a three-dimensional registration that has been found to improve the common region of interest retained for longitudinal evaluation, improving the reproducibility of the cortical bone parameters.[40] The repeated measurement of bones with HRpQCT can also evaluate the variation in local bone remodeling and link it to tissue loading.[41] This could be used as a surrogate imaging marker of the variation of bone fragility in response to therapy.

Conclusion

The most convenient current method to assess bone microstructure *in vivo* is HRpQCT. The various parameters representing the trabecular and cortical bone compartments are associated with estimated bone strength and prevalent fragility fracture. They are also associated with incident fragility fracture, independently of aBMD. The increment in fracture detection compared with aBMD, however, is modest. Therefore, a wide use of this technique as a screening tool for bone fragility is unlikely.

It remains to be determined whether HRpQCT could be used in specific subgroups of secondary osteoporosis or individuals who have extreme microstructural phenotypes of male and postmenopausal osteoporosis. Hence, longitudinal studies of patients with secondary osteoporoses are necessary, along with the use of new statistical approaches—eg, cluster analyses—to identify special phenotypes of postmenopausal osteoporosis that may be better detected by HRpQCT.

Conflict of Interest

The author declares no conflict of interest.

References

1. Siris ES, Miller PD, Barrett-Connor E, Faulkner KG, Wehren LE, Abbott TA *et al.* Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women: results from the National Osteoporosis Risk Assessment. *JAMA* 2001; **286**: 2815–2822.
2. Sornay-Rendu E, Munoz F, Garnero P, Duboeuf F, Delmas PD. Identification of osteopenic women at high risk of fracture: the OFELY study. *J Bone Miner Res* 2005; **20**: 1813–1819.
3. Schuit SC, van der Klift M, Weel AE, de Laet CE, Burger H, Seeman E *et al.* Fracture incidence and association with bone mineral density in elderly men and women: The Rotterdam Study. *Bone* 2004; **34**: 195–202.
4. Szulc P, Munoz F, Duboeuf F, Marchand F, Delmas PD. Bone mineral density predicts osteoporotic fractures in elderly men: The MINOS study. *Osteoporos Int* 2005; **16**: 1184–1192.
5. Delmas PD, Seeman E. Changes in bone mineral density explain little of the reduction in vertebral or nonvertebral fracture risk with anti-resorptive therapy. *Bone* 2004; **34**: 599–604.
6. Austin M, Yang YC, Vittinghoff E, Adami S, Boonen S, Bauer DC *et al.* Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and nonvertebral fractures. *J Bone Miner Res* 2012; **27**: 687–693.
7. Black DM, Vittinghoff E, Eastell R, Bouxsein M, McCulloch C, Cawthon PM *et al.* Hip BMD by DXA can reliably estimate eeduction in eip fracture risk in osteoporosis trials: a meta-regression. *J Bone Miner Res* 2015; **30**(Suppl):S49.
8. 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**: 6508–6515.
9. Vico L, Zouch M, Amirouche A, Frère D, Laroche N, Koller B *et al.* High-resolution pQCT analysis at the distal radius and tibia discriminates patients with recent wrist and femoral neck fractures. *J Bone Miner Res* 2008; **23**: 1741–1750.
10. Bala Y, Zebaze R, Ghasem-Zadeh A, Iuliano S, Atkinson EJ, Peterson JM *et al.* Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. *J Bone Miner Res* 2014; **29**: 1356–1362.
11. Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas PD. Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women. *J Bone Miner Res* 2009; **24**: 737–743.
12. Boutroy S, van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, Delmas PD. Finite element analysis based on *in vivo* HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res* 2008; **23**: 392–399.
13. Christen D, Melton III LJ , Zwahlen A, Amin S, Khosla S, Muller R. Improved fracture risk assessment based on microfinite element simulations from HRpQCT images at the distal radius. *J Bone Miner Res* 2013; **28**: 2601–2608.
14. Vilayphiou N, Boutroy S, Sornay-Rendu E, van Rietbergen B, Munoz F, Delmas PD *et al.* Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in postmenopausal women. *Bone* 2010; **46**: 1030–1037.
15. Nishiyama KK, McDonald HM, Hanley DA, Boyd SK. Women with previous fragility fractures can be classified based on microarchitecture and finite element analysis measured by HRpQCT. *Osteoporos Int* 2013; **24**: 1733–1740.
16. Sornay-Rendu E, Boutroy S, Duboeuf F, Chapurlat R. Bone microarchitecture assessed by HR-pQCT as predictor of fracture risk in postmenopausal women: The OFELY Study. *J Bone Miner Res* 2014; **29**(Suppl 1):S29.
17. Wang XF, Wang Q, Ghazem-Zadeh A, Evans A, McLeod C, Iuliano-Burns S *et al.* Differences in macro- and microarchitecture of the appendicular skeleton in young Chinese and white women. *J Bone Miner Res* 2009; **24**: 1946–1952.
18. Liu XS, Walker MD, McMahon DJ, Udesky J, Liu G, Bilezikian JP *et al.* Better skeletal microstructure confers greater mechanical advantages in Chinese-American women versus white women. *J Bone Miner Res* 2011; **26**: 1783–1792.
19. Boutroy S, Walker MD, Liu XS, McMahon DJ, Liu G, Guo XE *et al.* Lower cortical porosity and higher tissue mineral density in Chinese American versus white women. *J Bone Miner Res* 2014; **29**: 551–561.
20. Burghardt AJ, Issever AS, Schwartz AV, Davis KA, Masharani U, Majumdar S *et al.* High-resolution peripheral quantitative computed tomographic imaging of cortical and trabecular bone microarchitecture in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010; **95**: 5045–5055.
21. Shu A, Yin MT, Stein E, Cremers S, Dworakowski E, Ives R *et al.* Bone structure and turnover in type 2 diabetes mellitus. *Osteoporos Int* 2012; **23**: 635–641.
22. Patsch JM, Burghardt AJ, Yap SP, Baum T, Schwartz AV, Joseph GB *et al.* Increased cortical porosity in type 2diabetic postmenopausal women with fragility fractures. *J Bone Miner Res* 2013; **28**: 313–324.
23. Shanbhogue VV, Hansen S, Frost M, Jørgensen NR, Hermann AP, Henriksen JE *et al.* Bone geometry, volumetric density, microarchitecture, and estimated bone strength assessed by HR-pQCT in adult patients with type 1 diabetes mellitus. *J Bone Miner Res* 2015; **30**: 2188–2199.
24. Khosla S, Riggs BL, Atkinson EJ, Oberg AL, McDaniel LJ, Holets M *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**: 124–131.
25. Szulc P, Boutroy S, Vilayphiou N, Chaitou A, Delmas PD, Chapurlat R. Cross-sectional analysis of the association between fragility fractures and bone microarchitecture in older men: The STRAMBO study. *J Bone Miner Res* 2011; **26**: 1358–1367.
26. Vilayphiou N, Boutroy S, Szulc P, van Rietbergen B, Munoz F, Delmas PD *et al.* Finite element analysis performed on radius and tibia HR-pQCT images and fragility fractures at all sites in men. *J Bone Miner Res* 2011; **26**: 965–973.

27. Bacchetta J, Boutroy S, Vilayphiou N, Juillard L, Guebre-Egziabher F, Rognant N *et al.* Early impairment of trabecular microarchitecture assessed with HR-pQCT in patients with stage II-IV chronic kidney disease. *J Bone Miner Res* 2010; **25**: 849–857.
28. Nickolas TL, Stein E, Cohen A, Thomas V, Staron RB, McMahon DJ *et al.* Bone mass and microarchitecture in CKD patients with fracture. *J Am Soc Nephrol* 2010; **21**: 1371–1380.
29. Pelletier S, Vilayphiou N, Boutroy S, Bacchetta J, Sornay-Rendu E, Szulc P *et al.* Bone microarchitecture is more severely affected in patients on hemodialysis than in those receiving peritoneal dialysis. *Kidney Int* 2012; **82**: 581–588.
30. Nickolas TL, Stein EM, Dworakowski E, Nishiyama KK, Komandah-Kosseh M, Zhang CA *et al.* Rapid cortical bone loss in patients with chronic kidney disease. *J Bone Miner Res* 2013; **28**: 1811–1820.
31. West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D *et al.* Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 2015; **30**: 913–919.
32. Sutter S, Nishiyama KK, Kepley A, Zhou B, Wang J, McMahon DJ *et al.* Abnormalities in cortical bone, trabecular plates, and stiffness in postmenopausal women treated with glucocorticoids. *J Clin Endocrinol Metab* 2014; **99**: 4231–4240.
33. Klingberg E, Lorentzon M, Göthlin J, Mellström D, Geijer M, Ohlsson C *et al.* Bone microarchitecture in ankylosing spondylitis and the association with bone mineral density, fractures, and syndesmophytes. *Arthritis Res Ther* 2013; **15**: R179.
34. Burghardt AJ, Kazakia GJ, Sode M, de Papp AE, Link TM, Majumdar S. A longitudinal HR-pQCT study of alendronate treatment in postmenopausal women with low bone density: Relations among density, cortical and trabecular microarchitecture, biomechanics, and bone turnover. *J Bone Miner Res* 2010; **25**: 2558–2571.
35. Bala Y, Chapurlat R, Cheung AM, Felsenberg D, Laroche M, Morris E *et al.* Risedronate slows or partly reverses cortical and trabecular microarchitectural deterioration in postmenopausal women. *J Bone Miner Res* 2014; **29**: 380–388.
36. Chapurlat RD, Laroche M, Thomas T, Rouanet S, Delmas PD, de Vernejoul MC. Effect of oral monthly ibandronate on bone microarchitecture in women with osteopenia-a randomized placebo-controlled trial. *Osteoporos Int* 2013; **24**: 311–320.
37. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E *et al.* Microarchitectural deterioration of cortical and trabecular bone: differing effects of denosumab and alendronate. *J Bone Miner Res* 2010; **25**: 1886–1894.
38. Rizzoli R, Chapurlat RD, Laroche JM, Krieg MA, Thomas T, Frieling I *et al.* Effects of strontium ranelate and alendronate on bone microstructure in women with osteoporosis. Results of a 2-year study. *Osteoporos Int* 2012; **23**: 305–315.
39. Cheung AM, Majumdar S, Brixen K, Chapurlat R, Fuerst T, Engelke K *et al. J Bone Miner Res* 2014; **29**: 1786–1794.
40. Ellouz R, Chapurlat R, van Rietbergen B, Christen P, Pialat JB, Boutroy S. Challenges in longitudinal measurements with HRpQCT: evaluation of a 3D registration method to improve bone microarchitecture ans strangth measurement reproducibility. *Bone* 2014; **63**: 147–157.
41. Christen P, Ito K, Ellouz R, Boutroy S, Sornay-Rendu E, Chapurlat R *et al.* Bone remodelling in humans is load-driven but not lazy. *Nat Commun* 2014; **5**: 4855.