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REVIEW

Osteoporosis drug effects on cortical and trabecular bone microstructure: a review of HR-pQCT analyses

Eric Lespessailles[1,2], Ridha Hambli[3] and Serge Ferrari[4]

[1]University Orleans, Orleans, France. [2]Rheumatology Department, Orleans Hospital, Orleans, France. [3]Prisme, University Orleans, Orleans, France. [4]Hospital University Geneve, Geneve, Switzerland.

With the development of new non-invasive analytical techniques and particularly the advent of high-resolution peripheral quantitative computed tomography (HRpQCT) it is possible to assess cortical and trabecular bone changes under the effects of ageing, diseases and treatments. In the present study, we reviewed the treatment-related effects on bone parameters assessed by HRpQCT imaging. We identified 12 full-length articles published in peer-reviewed journals describing treatment-induced changes assessed by HRpQCT. The design of these studies varied a lot in terms of duration and methodology: some of them were open-labelled, others were double-blind, placebo-controlled or double-blind, double-dummy, active controlled. In addition, the sample size in these studies ranged from 11 to 324 patients. Motion artifacts occurring during data acquisition were sometimes a real challenge particularly at the radius leading sometimes to exclude the analysis at the radius due to the uninterpretability of microstructural parameters. Responses to therapies were treatment-specific and divergent effects in cortical and trabecular bone with antiresorptive or anabolic agents were observed. Standardization of bone microarchitecture parameters (including porosity) and bone strength estimates by finite element analysis (FEA) are mandatory. The additional value of microarchitecture and FEA estimates changes with therapies in terms of improvement in fracture outcomes which have to be adequately assessed in clinical trials with fracture end point. Data from these reviewed studies advance our understanding of the microstructural consequences of osteoporosis and highlight potential differences in bone quality outcomes within therapies.

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Introduction

Osteoporosis treatments have proven efficacy in reducing the risk of vertebral fractures and improving bone mineral density (BMD) at spine and hip.[1] However, due to their different mechanisms of action, anti-resorptives and bone-forming agents may exert different effects on bone microstructure and strength.[2,3] In turn, their effects on the reduction of non-vertebral fractures, including hip, is quite variable.[4–6] Until recently, the evaluation of drug effects on trabecular and cortical bone microarchitecture was made by histomorphometric analysis and micro-computed tomography of bone biopsy specimen.[7] Although dynamic histomophometric analysis of iliac crest bone biopsies is still necessary to assess bone mineral apposition rate and cellular activities,[8] the development of high-resolution peripheral quantitative computed tomography (HR-pQCT) allows non-invasive assessment of volumetric density and some parameters of bone microstructure at peripheral sites *in vivo*.[9] Hence, HR-pQCT enables us to evaluate trabecular number and thickness,[10] as well as non-metric measures of the plate and rod-like spongious structure such as degree of anisotropy, structural model index, connectivity density and individual trabecular segmentation,[11] although not with the standard analysis.[12] In addition, cortical parameters like cortical thickness and cortical porosity can be assessed, although it remains a challenging task.[13,14] The intracortical porosity is considered a highly relevant parameter as it independently contributes to the age-related decrease in bone strength[15] and highlights gender and age differences in bone strength;[16] it has also been shown to be significantly and independently associated with prevalent hip fractures.[17] Furthermore, the mechanical significance of these trabecular and cortical parameters can be assessed from HR-pQCT images by using estimates of bone strength at the radius[18] and tibia[19] by micro finite element analysis (FEA). HR-pQCT is therefore a promising new technique with a high potential for improving our

Correspondence: Dr E Lespessailles, Rheumatology Department, Orleans Hospital, 1 rue Porte Madeleine Cedex 1, Orleans BP2439 45032, France.
E-mail: eric.lespessailles@chr-orleans.fr

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understanding of the osteoporosis drug-related effects at the microarchitectural level with separate analyses of cortical and trabecular compartments. Our objectives were to review the published manuscripts with the following key terms in the search through Medline (April 2005–2015): osteoporosis, microarchitecture, high-resolution peripheral quantitative computed tomography, anti-osteoporotic treatment.

Heterogeneity of the Studies

Our search found 12 published articles describing the treatment-related effects on bone parameters assessed by HRpQCT imaging: Bisphosphonates (BPs) were tested in eight of these studies,[20–27] strontium ranelate (SR) in two,[22,23] denosumab (DMAB) in two,[21,27] teriparatide (TPTD) in four,[25,28–30] PTH 1–84 in two[25,27] and odanacatib in one study,[31] sometimes in head-to-head comparisons, sometimes in combination. Most of these studies included postmenopausal women with some level of low BMD, with one exception concerning a TPTD study where premenopausal women with idiopathic osteoporosis were enrolled.[29] The number of patients and the design of these studies varied quite substantially (**Table 1**). Some of these clinical trials were multicentric;[21–24,26,31] other studies were performed in a single center.[20,25,27–29] None of these studies considered fracture incidence as an end point due to their relatively short duration and limited size. Hence the observed changes in microstructure have to be interpreted in light of parallel studies with fracture end points for a full understanding of their clinical significance.

Anti-resorptives

In a pilot, double-blind, placebo-controlled trial, 53 early postmenopausal women were randomly allocated to receive either alendronate (ALN) or placebo over 24 months.[20] The only significant improvements with respect to baseline with ALN were on tibia cortical thickness (Ct.Th), area and load fraction, whereas no significant changes vs baseline were observed on radius Ct.Th. In this study, the only significant differences in densitometric measurements between the PBO and ALN were observed at 12 months, that is percent change in distal radius trabecular volumetric BMD (Tb.vBMD) and distal tibia cortical volumetric BMD (Ct.vBMD). Trabecular microarchitecture measures did not change significantly at the radius or at the tibia. However, a subregion analysis of the distal radius and tibia usual site of interest identified a significant treatment effect in the lateral quadrant of the radius for both trabecular number (Tb.N) and trabecular spacing (Tb.Sp). Due to a high and unexpected attrition rate in this study, the statistical power was limited (only 13 PBO and 20 ALN subjects completed the second year).

In a double-blind, double-dummy, placebo-controlled study, 247 postmenopausal women were randomized to ALN, DMAB or placebo for 12 months.[21] In this phase 2 pilot study, ALN prevented the decline in Ct.vBMD at the distal radius at one year observed in the placebo group. DMAB increased Ct.vBMD relative to baseline, and these longitudinal changes significantly exceeded those observed with ALN. At 1 year, Ct.Th decreased in the placebo group, whereas both DMAB and ALN prevented this decline. However, there were no significant differences between groups for trabecular microarchitecture parameters (trabecular separation, thickness, number) at either the distal radius or at the distal tibia at 6 or 12 months.

In the largest study including 324 postmenopausal women, patients were enrolled in two similarly designed double-blind, placebo-controlled studies.[26] In the first group, women were in their early phase of menopause with age $\leqslant 55$ years; in group 2, women were older with age >55 years. All these women were randomly allocated to receive either risedronate or placebo once a week, for 1 year. At 12 months, no between-arms differences were observed either for cortical or trabecular parameters at the distal radius. In this study, a new method of quantification of cortical porosity and segmentation of the compact-appearing, transitional and trabecular compartments was applied.[30] At the distal radius in the younger women group, a significant decrease in compact-appearing cortical porosity was observed in the placebo group, but this was prevented in the risedronate group. In the group 2, a significant decrease in the compact-appearing cortical porosity was observed. At the distal tibia, results were globally comparable, but in the older postmenopausal women group, significant differences were observed for compact-appearing cortex porosity, inner transitional zone porosity and total vBMD between the placebo and the risedronate groups.

Treatment with ibandronate was examined in a double-blind, placebo-controlled trial.[24] Postmenopausal women with osteoporosis ($n=148$) were recruited from four centers and were randomly allocated to receive either 150 mg ibandronate

Table 1 Heterogeneity in design and sample size in studies assessing treatment-related effects using HRpQCT

Treatments	*Duration (months)*	*Design*	*Number of patients*	*Authors year (reference)*
ALN vs PBO	24	DB, PC	53	Burghardt[20]
ALN vs DMAB vs PBO	12	DB, DD Pc	247	Seeman[21]
ALN vs SR	12	DB, DD, AC	88	Rizzoli[22]
ALN vs SR	24	DB, DD, AC	83	Rizzoli[23]
TPDT	18	Open-label	11	MacDonald[29]
IBN vs PBO	24	DB, PC	148	Chapurlat[24]
PTH 1-34 vs PTH 1–84-ZOL	18	Open-label	71	Hansen[25]
RIS vs PBO	12	DB, PC	324	Bala[26]
TPTD (pre MP)	18	Open-label	20	Nishiyama[30]
TPTD vs DMAB vs TPTD + DMAB	12	Open-label	94	Tsai[28]
PTH 1–84 + IBN	24	Open-label	43	Schafer[27]
ODN vs PBO	24	DB, PC	214	Cheung[31]

Abbreviations: AC, active controlled; ALN, alendronate; DB, double blind; DD, double dummy; DMAB, denosumab; IBN, ibandronate; ODN, odanacatib; PC, placebo controlled; RIS, risedronate; SR, strontium ranelate; TPTD, Teriparatide; ZOL, zoledronic acid.

or placebo once a month for 24 months. After 1 year, the trabecular bone volume at the radius, which was the primary end point, was not significantly different in the placebo group as compared with the ibandronate group. After 2 years, no differences were found in cortical and trabecular microarchitecture parameters at the distal radius, but at the distal tibia, total and cortical vBMD, associated with greater Ct.Th and area were significantly higher in the ibandronate group compared with the placebo group.

In an open-label, non-randomized study, 33 postmenopausal women with osteoporosis received zoledronic acid (ZOL; 5 mg infusion at baseline and al 12 months), and that group was compared with two others: one treated with PTH 1–34 (20 μg sc daily; $n = 18$), the other received PTH 1–84 (100 μg sc daily; $n = 20$).[25] HR-pQCT examinations of the distal radius ($n = 28$) and distal tibia ($n = 30$) were assessable. After 18 months, treatment with ZOL was associated with significant increases in BV/TV and Tb.N of both sites and significant increases in cortical thickness and density and in total density at the tibia with significant decreases in trabecular area and spacing also at the tibia. Intracortical porosity, measured at both sites as void cortical volume divided by total cortical volume, did not significantly change over 18 months in respect with baseline. FEA estimated bone strength was maintained with ZOL.

Teriparatide and PTH

HR-pQCT has been used to assess the effects of TPTD on bone microarchitecture and estimated bone strength.[25,27–29] In that head-to-head study against zoledronate (above),[25] the percent change in Ct.Th measured at the end of the study was significantly higher for PTH 1–34 vs PTH 1–84 at both sites. Percent change in Ct.Th was significantly lower in the PTH 1–84 group compared with the ZOL group at the tibia. Percent changes in cortical porosity were significantly higher in the two PTH groups compared to the ZOL group at both sites. Finite element estimates of bone strength were maintained with ZOL and PTH 1–34 but were significantly lower in the PTH 1–84 group as compared with the PTH 1–34 and ZOL groups at the tibia.

From a single clinical site, 11 postmenopausal women received TPTD in a open label 18-month longitudinal study.[28] In this small study, despite a significant decrease in total BMD and Tb.Th at the radius and a significant decrease in cortical BMD at the distal tibia, estimated bone strength (ultimate stress) was preserved over the 18-month follow-up. Note that 10/11 patients received BP therapy prior starting on TPTD. Using an automatic segmentation of cortical and trabecular compartment procedure previously introduced by Buie et *al.*[30] and a previously validated analysis of cortical porosity,[31] the authors found a trend for increased cortical porosity (+3–4%) at both sites.

TPTD therapy was also used in a pilot study including premenopausal women with idiopathic osteoporosis.[29] In this open-label study 20 premenopausal women received TPTD for 18–24 months according to the preference of the patients. By 18 months, there were significant increases in trabecular and total vBMD both at the distal radius and tibia. However, no significant changes were observed in cortical BMD or thickness at either site. Significant changes in cortical porosity were found at the radius (+17.8%) but not at the tibia, but the absolute change in cortical porosity observed at the radius was only 0.1%. In addition, there were significant increases in scaled stiffness and failure load at both sites and significant increases in homogeneous stiffness and failure load at the tibia only. A further detailed trabecular network analysis was provided by the individual trabecular segmentation.[11] This more detailed study of the trabecular bone microstructure showed significant improvements in trabecular plate microarchitecture.

Combination Therapy

In the recent study by Tsai et *al.*,[28] the combined and separate effects of TPTD and DMAB were reported.[27] In this randomized study, postmenopausal women with osteoporosis were randomly allocated to receive DMAB 60 mg every 6 months ($n = 33$), TPTD 20 μg daily ($n = 31$) or both ($n = 30$) during 12 months. Total volumetric BMD increased in the DMAB and combined treatment groups whereas it was stable in the TPTD group at both sites. At the tibia, the increase in total BMD, cortical BMD and Ct.Th was significantly higher with combination therapy compared with the two other groups. In the TPTD group although intracortical porosity increased by 20.9 and 5.6% for the radius and tibia, respectively, mean percent change in stiffness and failure was stable vs baseline. These last bone strength estimates increased significantly in the other groups at both sites with once again a significantly higher failure load at the tibia in the combination group compared to the other groups. These data suggest that combining DMAB and TPTD may produce the most favorable charges in cortical microarchitecture parameters and in cortical density.

Another combination therapy has been evaluated in a randomized trial of two novel combinations of PTH (1–84) and IBN. Postmenopausal women ($n = 43$) were randomly allocated to receive either 6 months of daily PTH (1–84) (100 mg per day) and IBN 150 mg once a month followed by IBN for 18 months or two sequential courses of 3 months of daily 100 mg per day PTH (1–84) followed by 9 months of IBN. An interaction between the treatment group and scan type (tibia vs radius) was preplaned. The two treatment arms were pooled due to the lack of statistical difference between the groups regarding the microarchitectural parameters at 2 years. Changes in response to this combination therapy were differed at the radius and the tibia. Indeed, at the tibia, cortical, trabecular, total BMD and Ct.Th were increased and bone strength estimates were preserved whereas there were decreases in cortical and total BMD, and decreases in cortical thickness and biomechanical parameters vs baseline at the ultradistal tibia.

Strontium Ranelate

ALN was also used in a randomized, double-blind, double-dummy, active-controlled study compared with SR[22,23] in which 88 women with postmenopausal osteoporosis received either SR 2 g per day or ALN 70 mg once a week over 2 years. A pre-planned, interim, intention-to-treat analysis reported increases in cortical area and thickness and in trabecular bone volume fraction at the distal tibia with SR after 1 year. In contrast, no significant changes were observed in the Ct.Th nor cross-sectional area of the cortical bone in the ALN-treated group. Significant between-group differences were observed in favor of SR with respect to BV/TV, Ct.Th, Tb.vBMD, and cortical area.[22] Only 72% of the population had assessable distal radius

examinations. ALN treatment during one year was associated with a decline in Tb.Th and Tb.Sp and an increase in Tb.N with respect to baseline.[22] After two years of treatment,[23] changes already detected at one year were confirmed. In addition to the increase in Ct.Th and BMD and BV/TV, there was a significant increase in the estimated failure load (+2.1%) compared to baseline with SR (+2.1%) but not with ALN (−0.6%), resulting in a significant between-group difference ($P<0.01$). As strontium has an atomic number twice that of calcium, it cannot be excluded that the greater increase in Ct.Th observed with SR than with ALN might be due the effect of beam hardening, although SR has been shown to improve Ct.Th by other methods including analyses of iliac crest bone biopsies.[32]

Cathepsin K Inhibitors

Odanacatib therapy has been studied in a 2-year treatment trial including 214 postmenopausal women who were randomly allocated to receive either a placebo or ODN 50 mg weekly for 2 years.[31] There was a significant decline in total vBMD and cortical vBMD at both sites in the placebo group whereas this decrease was prevented by ODN. In addition, treatment differences from PBO were also significant. Some trabecular microstructure parameters were significantly improved in the ODN group compared with the placebo group either at the radius or at the tibia. Ct.Th and area changes were significantly different between the placebo and the ODN group. FEA estimated bone strength observed in this trial confirmed the positive influence of ODN in these postmenopausal women.

Special Issues

Differences between antiremodeling and anabolic agents
HRpQCT is now able to evaluate treatment effects on trabecular and cortical microarchitecture and, with FEA, on bone strength. Differing and contrasting effects of both antiresorptive and

Table 2 Main results in density, microstructural and FEA parameters in studies assessing treatment-related effects using HRpQCT

Treatment [ref]	*Volumetric bone density changes*	*Trabecular compartment structural changes*	*Cortical compartment structural changes*	*FEA parameters changes*
ALN vs PBO[20]	At Tib vs BSL in ALN : ↑ BMD, Ct BMD and Tb BMD SDBTG in ct BMD	SDBTG in Tb N at the lateral quadrant of the Rad	At Tib vs BSL in ALN ↑ Ct Th (+3 to 4%), Ct. Ar SDBTG in Ct.Th at the lateral quadrant of radius	Treatment effects NS
ALN vs DMAB[21] vs PBO	At Rad : SDBTG DMAB vs PBO and ALN in BMD and Ct BMD (12 months % change in BMD around 1% and 0% for DMAB and ALN, respectively)	Neither SDBTG at Rad nor at the Tib	At radius SDBTG DMAB vs and ALN vs pbo in Ct Th (12 Months % change in Ct Th around 3 to 4% for DMAB and 2 to 3% for ALN)	NR
IBN vs PBO[24]	No SDTBG at the Rad SDTBG in Ct BMD at the Tib for IBN vs PBO	No SDBTG in BV/TV at the radius (10.8 vs 10.5%)	No SDBTG at the radius SDBTG in Ct Th at the tibia	NR
RIS vs PBO[26]	SDBTG in BMD and Ct BMD at Tib RIS vs PBO	No SDBTG	SDBTG in Ct Po at Tib Ris vs PBO	NR
ALN vs SR,[22,23]	At Tib SDBTG in Ct BMD for SR vs ALN (1.4 vs 0.4 %)	At Tib SDBTG in BV/TV for SR vs ALN	At Tib SDBTG in Ct Th for SR vs ALN (6.3 vs 0.9%)	SDBTG in failure load for SR vs ALN
TPTD pre MPW[30]	↑ Tb BMD at both sites vs BSL	↑ Trabecular plate BV fraction at both Rad and Tib vs BSL	↑ Ct Po at the Rad	↑ Whole bone stiffness and failure load at both sites vs BSL
TPTD post MPW[29]	↓ BMD at the Rad vs BSL ↓ Ct BMD at both sites vs BSL	↑ Tb Th at the Rad vs BSL	Trends for ↑ Ct Po at both sites vs BSL (1.5% increase in Ct Th)	Bone strength maintained
PTH 1-34 vs PTH 1–84[25] vs ZOL	↓ Ct BMD for both PTH at both sites ↓ BMD for PTH 1–84 at both sites	↓Tb Th at the Tib vs BSL for PTH 1–84 vs ZOL	SDBTG in Ct Po at both sites for ZOL vs PTH 1-34 and PTH 1–84 SDBTG in Ct Th at both sites for PTH 1-34 vs PTH 1–84	SDBTG in failure load for ZOL and PTH 1-34 vs PTH 1–84 at Tib
TPTD vs DMAB vs TPTD +DMAB[28]	↑ BMD, Ct and Tb BMD at both sites for DMAB and combination vs BSL ↓Ct BMD at both sites vs BSL for TPTD SDBTG at both sites in BMD and Ct BMD for combination VS TPTD	NS changes at both sites vs BSL	↑ Ct Th at both sites for combination vs TPTD vs BSL SDBTG for combination vs TPTD in Ct Th	Bone stiffness and failure load maintened in TPTD SDBTG in failure load at both sites for combination vs TPTD
PTH 1–84 +IBN[27]	↑ BMD and Tb BMD (2.26 and 3.22 at Rad and Tib, respectively) vs BSL at both sites ↓ Ct BMD at Rad vs BSL	↑ Tb Th vs BSL at both sites	↑ Ct Po at Tib vs BSL ↓ Ct Th at Rad vs BSL	Stiffness and failure load decreased at the Rad, NS at Tib
ODN vs PBO[31]	↑ BMD vs BSL with ODN at both sites SDBTG for Ct and Tb BMD at both sites SDBTG for TvBMD (3.84 and 2.63 for Rad and Tib, respectively)	At the Rad, SDBTG for Tb Th and BV/TV vs PBO At the Tib, SDBTG for Tb Nb and BV/TV vs PBO	At both sites SDBTG for Ct Th (2.15 and 1.57% at the distal Tib and Rad respectively) and Ct Ar	SDBTG in failure load (2.64 and 2.66% at Rad and Tib, respectively)

Abbreviations: ALN, alendronate; BMD, total BMD; BSL, baseline; BV/TV, trabecular bone volume/total volume; Ct Ar, cortical bone area; Ct BMD, cortical BMD; DMAB, denosumab; IBN, ibandronate; NR, not reported; NS, not significant; ODN, odanacatib Rad radius; PBO, placebo; RIS, risedronate; SDBTG, significant difference between treatment group; SR, strontium ranelate; Tb BMD, trabecular BMD; Tb N, trabecular number; Tb Th, trabecular thickness; Tib, tibia; TPTD, teriparatide; ZOL, zoledronic acid.

anabolic treatments were demonstrated in this review highlighting the potential differences in bone strength and microstructure outcomes within therapies. **Table 2** details these differences in HRpQCT parameters as reflected by the main results reported in this review. In summary, anabolic agents increased cortical porosity and decreased cortical density in both tibia and radius but estimated strength was preserved. Antiremodeling agents decreased porosity but did not result in an increase in estimated bone strength compared with baseline.

Differential responses at radius and tibia

Greater cortical and trabecular bone responses to treatment have been found at the distal tibia compared with the distal radius in most of the studies. Tibia was more responsive than radius to BPs in particular for the cortical bone parameters.[20,24–26] The weight-bearing nature of the distal tibia as compared with the distal radius suggests a possible interaction between BP treatment and the mechanical stimulus. Synergetic or additive effects between exercise and osteoporosis drugs have been clearly demonstrated in 2×2 factorial design trials in ovariectomized rats.[33] However, such a synergy between physical activity and BPs in postmenopausal women was not demonstrated for etidronate[34] or for ALN.[35] Better responses to TPTD and SR were also found at the distal tibia compared to the distal radius.[23,29] Indeed, discrepancy in the results between tibia and radius were shown particularly for rod appearance of bone volume fraction and cortical porosity in premenopausal women treated with TPTD.[29] With SR, an increase in Ct.Th was found at tibia but not at radius levels. In this context of differences in treatment effects at these two sites, it is noticeable that generally aBMD changes with treatments are smaller at the radius than at the lumbar spine or trochanter, bone sites that are associated with higher trabecular bone and bone remodeling activities than the radius.

Finally, technical limitations in the assessment of the distal radius parameters by HRpQCT compared with the distal tibia have to be underlined. The readability of radius images is often compromised by movement artifacts.[36] Difficulties in measurements were found in 28% of radius images in the SR vs ALN trial.[23] In the following BPs trials[20,21,24,26] to maintain the intent-to-treat analysis, despite variability in scan quality, inadequate scans were not excluded. As noticed by Chapurlat et *al*,[24] this may have biased the results toward the null and also contributes in these studies to wrongly consider the tibia as much an appropriate site as the radius for monitoring effects of therapies.

Issues in assessing drug effects on cortical thickness

Of note, the effects of ALN on Ct.Th in the three studies assessing its effects by HRpQCT are inconsistent.[20–22] At 12 months, relative change from baseline of Ct.Th. at the tibia varied from 1.3 up to 5% among the studies.[20–22] These discrepancies might be related to the segmentation process used in these studies. In the Burghard *et al.*[20] study both direct endosteal-periosteal three-dimensional (3D) measure and standard areal estimate of Ct.Th. were used. In the study by Seeman et *al*,[21] Ct.Th. was derived from an annular model where the measured cortical area was divided by the periosteal perimeter and in the Rizzoli *et al.*[22] study, Ct.Th. was the mean cortical volume divided by the outer bone perimeter. These differing results underscore the issues of accuracy in Ct.Th. assessment due to threshold effects in these evaluations and the need for a standardization process to measure cortical parameters.[37,38]

Studies that used direct comparison between drugs may help to differentiate between their mechanisms of action and effects, however with some caveats. It can be observed that at the tibia, ALN maintained HRpQCT parameters whereas cortical BMD, Ct.Th and estimated failure load increased with SR.[23] In the pilot study comparing DMAB, ALN or PBO, the microstructural parameters decreased in the PBO group. The decline in these parameters was prevented in the ALN group, and the parameters were either stable or, in particular total and cortical BMD, increased with DMAB.[21] In a *post hoc* analysis of the head to head analysis of DMAB vs ALN, a detailed study of the compact-appearing cortex porosity has been done[39] A greater reduction in cortical porosity by DMAB vs ALN was observed, this finding was associated with earlier and more complete inhibition of remodeling by DMAB vs ALN[39] Contrasting treatment-specific effects were observed between two different PTH agents (that is, PTH 1–34 and PTH1–84) and zoledronate (**Table 2**). Once again, the limited sample size and the design of the protocol cannot lead to definitive and clear conclusions from this latter study.[25] The observed changes in Ct.Th with HR-PQCT could reflect profoundly different mechanisms of action with different drugs, that is, true bone apposition at the periosteal and/or endocortical envelopes with PTH. However, these effectscould paradoxically be underestimated when bone is new and relatively undermineralized, such as with TPTD and PTH, and, in contrast, be overestimated with SR due to the physical nature of the compound, and even with anti-resorptives, due to the higher degree of cortical bone mineralization and/or reduction of porosity that can influence the edge-detection threshold of the measurement.

FEA of bone strength

Several linear and non-linear isotropic and anisotropic FE models based on CT scans have been developed in the past by several authors.[40–46] In this case, the 3D FE models are generated from the set of slices driven by CT. Generally, the real microarchitecture of the trabecular bone is not considered and the obtained model models are partitioned into trabecular bone and cortical bone continuum regions with the Hounsfield (HU) scale: $HU > 600$ are taken as the cortical region.[47] For simplicity and due to the limited knowledge of the anisotropic behavior of bone, most FE models for bone organs fracture simulation (femur and vertebra mainly) considered the bone tissue as continuum inhomogeneous and isotropic material with empirical assigned material properties based on empirical density–elasticity relationships to every FE of the mesh driven by CT scans. The CT scan-based FE models generally require a reduced computation time than with HRpQCT and can simulate the response of a whole bone organ (proximal femur, vertebra). Nevertheless, partition of the bone into trabecular and cortical regions based on the empirical separation threshold may generate a certain inaccuracy in the assessment of cortical bone thickness which can have an important role in bone resistance to fracture.[48]

The application of FEA based on HR-pQCT images allows the estimation of biomechanical bone properties in a non-invasive way.[18,19,49] One of the main clinical applications of this method is in the investigation of the effects of therapeutic treatments for osteoporosis on bone strength. Generally, FE estimation

of the biomechanical factors changes were performed at different time intervals from baseline and compared to placebo groups.

After image segmentation obtained generally from volume of interests of the tibia and the distal radius, each bone voxel of the HR-pQCT is converted to hexahedral FE mesh having linear-elastic and isotropic material behavior, with a homogeneous Young's modulus and Poisson's ratio of 10 and 0.3 GPa, respectively. A linear isotropic iterative solver (Scanco FE Software, Scanco Medical) implemented in the HR-pQCT system allows for the calculation of apparent stiffness subjected to 1% apparent compressive strain and failure load based on the assumption that bone failure occurs if a greater number then 2% of the elements are strained beyond 0.7% strain.[49,50]

Most of the studies included in this review assigned the same material properties to bone tissue (Young's modulus and Poisson's ratio of 10 and 0.3 GPa) without accounting for the bone heterogeneity, patient-specific variation, mineralization and fatigue microcracks density. It is suggested by several studies[51–56] that mineralization may change the bone tissue mechanical properties due to several factors such as remodeling and decreased turnover generated by different treatments. Increased mineralization rate of bone has the combined effects of stiffening the tissue while making it more stiff and brittle and will require much less energy to fracture.[52,53,55,57] This may confound estimation of bone strength in typical FE analysis models. In addition, it has been proved that fatigue microcracks co-localize within highly mineralized regions of cortical bone tissue.[51,54]

Nishiyama *et al.*[30] developed an HR-pQCT-based study to determine whether TPTD treatment was associated with improvements in compartmental volumetric BMD, bone microarchitecture and estimated bone strength of the distal radius and tibia. The FE calculations were performed using custom FE solver (FAIM Solutions Ltd, Calgary, AB, Canada, version 6.0; Numerics88). To account for tissue mineral changes due to TPTD, the authors used both homogeneous and scale FE models to estimate bone strength. The scale models assigned material properties based on the various tissue densities within the bone rather than on homogeneous material properties for all bone tissue based on a fixed segmentation threshold. The authors showed that scale models may be a more sensitive means of detecting the changes in bone strength, given that greater heterogeneity in mineralization would be expected with TPTD treatment. To investigate the changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of TPTD therapy in postmenopausal women with osteoporosis, Macdonald *et al.*,[29] estimated apparent ultimate stress using FE analysis based on HR-pQCT images. In order to account for possible treatment-related changes in tissue density, the authors used scale models in which the CT attenuation values were converted to tissue moduli according to previously established relationships.[58,59]

These results suggest that bone mechanical properties assessed by FE based on HR-pQCT may provide information about effects of bone treatments. Nevertheless, the results predicted from the FE based HR-pQCT simulations should be interpreted in accordance with the limiting assumptions of the model. The first limitation to be considered is that it applies linear isotropic behavior with homogeneous material properties assignment to estimate the load fracture. However, failure behavior of bone is non-linear by nature as reported by several authors.[40,57,60] Realistic prediction of bone fracture pattern, fracture force and ultimate apparent stress at fracture requires the simulation of the initiation and subsequent progressive propagation of damage within the bone that take place during the fracturing process. The force at fracture can be assessed as the maximum of the predicted force-displacement curve. The second limitation is associated with the limited boundary conditions (compressive load at the static regime).

These limitations do not detract from the importance of the FE-based HR-pQCT simulations. The system provides the means for a biomechanical estimation of bone strength, which is a more physical way compared to current applied statistical correlations based on BMD measurements. Nevertheless, the FE simulation may be enhanced by (i) considering non-linear material behavior coupled to damage and fracture criteria, (ii) inclusion of bone heterogeneity, patient-specific variation, mineralization and fatigue microcracks density and (iii) implementing dynamic (rate dependent) model to account for the effect of the bone response subjects to dynamic load (impact). Furthermore, future challenging applications with HR-pQCT may concern the development of enhanced bone biomechanical factors FE models coupling separated models including remodeling and fracture into a full multiscale one. Such FE models would allow clinicians to directly predict bone strength, estimate the risk of fracture and implement relevant preventative treatments for patients.

Moving Forward

Standardization of bone microarchitecture and bone strength estimates should be the next task in order to permit direct comparison of treatment effects. In addition, there are still a number of technical limitations and pitfalls of HRpQCT including matching of the region of interest in longitudinal studies, segmentation, effects of thresholding and hypothesis-based statements in the measurement of both densitometric, microstructural and FEA parameters. The divergent treatment-specific effects reported in this review have to be reproduced in larger clinical trials using HRpQCT to allow head to head comparisons of current and future osteoporosis therapies which in turn will help the choice of treatment in the management of postmenopausal osteoporosis. The use of HRpQCT might also have a significant potential to become an important treatment end point in regulatory clinical trials, but this will require validation that changes in density, microstructural and μFE simulations from HRpQCT images correlate with antifracture efficacy in clinical studies with fracture end points. Fracture risk assessment in individual patients can be envisaged using HRpQCT if the following statements can be achieved:

- Development of normative databases and standardized quality control criteria.
- New prospective longitudinal studies assessing the relationship between porosity or other structural parameters or μFEA estimated bone strength and fracture.
- Adaptation of the fracture prediction tools such as FRAX to include HRpQCT parameters.

Conclusion

This review confirms that HRpQCT provides insight into the mechanism of action of current or novel therapies for osteoporosis. HRpQCT use advances our understanding of potential differences in microarchitectural and μFEA outcomes of the treatments for osteoporosis.

Conflict of Interest

EL received speaker consultant fees from AMGEN (France) and ELI LILLY (France) and speaker Fees from Expanscience, Novartis, Servier. The remaining authors declare no conflict of interest.

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