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MEETING REPORT

Proceedings of the first musculo-skeletal imaging by clinical micro CT symposium

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Meeting Report from the Proceedings of the First Musculo-Skeletal Imaging by Clinical Micro CT Symposium, Orléans, France, 26–27 June 2015

Introduction

The first international seminar of musculoskeletal imaging by clinical microCT has been held during 26—27 June 2015 in Orleans, France.

This meeting has gathered around 60 people coming from Europe and North America having special interest and/or expertise in the scientific or clinical use of High-Resolution peripheral Quantitative CT (HR-pQCT).

During the past decades, diagnostic imaging in rheumatology has used conventional radiography in the field of chronic inflammatory rheumatism (CIR) and areal dual-energy X-ray absorptiometry (DXA) in osteoporosis (OP). But over the past 10 years, recent technical advances in imaging with MRI, ultrasonography and HR-pQCT have constituted new assessments tools that permit new understanding in the pathophysiology of CIR and OP.

The rationale for the initiation of this meeting was the preliminary use of HR-pQCT in clinical research since 2005. Its first application in rheumatology was the non-invasive assessment of three-dimensional (3D) microarchitecture that has permitted to improve our understanding of the respective role of trabecular and cortical bone in sex differences and age-related changes. Other applications in the field of OP are now considered: prediction of fracture, assessment of treatment-related effects and heritability of microarchitecture.

New fields of investigation using HR-pQCT imaging became now possible and are illustrated in the various abstracts presented at this congress: measurement of systemic and localized bone loss (erosion) in CIRs (Rheumatoid Arthritis (RA), Psoriatic Arthritis…) assessment of arterial calcification and soft tissue analysis…

Considering the wealth of the subjects treated in this meeting, we do believe that this event will be a new annual scientific appointment in the field of rheumatology.

HR-pQCT in Osteoporosis

Genetic influences on human bone microarchitecture

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Background: Additive genetic factors contribute to almost 80% of the population variance for areal bone mineral density (aBMD) and genome-wide association study have started to delineate the multiple single-nucleotide polymorphisms (SNPs) associated with aBMD and/or fracture risk. Bone microarchitecture is the other main constituent of bone strength/fragility; however, its genetic constitution remains unknown.

Methods: The heritability (*h2, %)* of bone microarchitecture was derived from the parents–offspring correlations for trabecular (Tb) and cortical (Ct) traits measured at distal radius and tibia using HR-pQCT in 84 subjects (88% women) drawn from the Geneva Retirees Cohort (GERICO, mean age 65.3 ± 1.5 years) and 96 of their descendants (51% women, 37.9 ± 5.7 years). The contribution of serum periostin and sclerostin, two molecules directly implicated in the regulation of cortical bone adaptation to mechanical loading, to the inheritance of bone microstructure was similarly evaluated. Eventually, periostin gene (*Postn*) polymorphisms as well as more than 600 other SNPs in genes previously associated with osteoporosis were studied for their association with microstructural traits in an extended sample of 665 women from GERICO.

Results: H^2 values for bone microstructural traits ranged from 22 to 64%, with maximal values observed for Tb thickness and Ct perimeter at both sites, radius Ct porosity and tibia Ct thickness. Serum levels of periostin and sclerostin were also partly inherited (*h2,* 50% and 40%, respectively). After adjustment for serum periostin levels, but not for sclerostin, h^2 values decreased for several trabecular and cortical bone parameters, suggesting that genetic factors influencing circulating periostin levels also contribute to bone microarchitecture. Subsequently, several *Postn* SNPs were found to be significantly associated with Tb and/or Ct traits. Association analyses with other gene polymorphisms are ongoing.

Conclusion: Additive genetic effects account for a substantial proportion of the individual variance of bone microstructure. Moreover, serum periostin contributes to the

heritability of bone microstructure, particularly cortical porosity. Identification of gene polymorphisms associated with microstructural traits may provide further insights into the inherited mechanisms of bone fragility.

Disclosure: The authors declare no conflict of interest.

Treatment-related effects on bone parameters assessed by HR-pQCT imaging: a review

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Background: For many years, sole invasive procedure, that is, bone biopsy at the iliac crest, allowed the assessment of the bone microstructure changes associated with anti-osteoporotic drugs with separated analyses of the trabecular and cortical bone. With the development of new non-invasive analytical techniques and particularly the advent of HR-pQCT it is possible to assessed cortical and trabecular bone changes under the effects of ageing, diseases and treatments.

Methods: In the present study, we reviewed the treatment-related effects on bone parameters assessed by HR-pQCT imaging.

Results: We identified 10 full-length articles published in peer-review journals describing treatment-induced changes assessed by HR-pQCT. 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. Response to therapies were treatment specific and divergent effects in cortical and trabecular bone with antiresorptive or anabolic agents were observed.

Conclusion: Larger controlled clinical trials that use HR-pQCT to compare and monitor the anti-osteoporotic drugs-related effects on bone microarchitecture are needed. 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 have to be adequately assessed in clinical trials with fracture end point. Data from these reviewed studies advances our understanding of the microstructural consequences of osteoporosis and highlight potential difference in bone quality outcomes within therapies.

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Fracture risk prediction using HR-pQCT

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Background: Current screening of individuals at risk of fracture is suboptimal because of the inadequate predictive value of aBMD and the calibration of the FRAX tool is not satisfactory in all countries.

Methods: We review the association between fragility fracture among postmenopausal women, men and in groups at high risk of fracture, such as patients with chronic kidney disease (CKD), and microarchitecture parameters that can be assessed with HR-pQCT.

Results: Bone microarchitecture parameters are greater in men than in women. Specifically, cortical thickness and trabecular thickness is greater in men. With aging, trabecular thickness declines in men, whereas this was the trabecular number decreases in women. Trabecular and cortical parameters are deteriorated in postmenopausal women with prevalent fracture compared with those without fracture, whereas aBMD does not necessarily distinguish those individuals. Cortical parameters were also more affected in those women with severe osteoporosis. In older men, trabecular parameters are also associated with vertebral and, to a lesser extent, to non-vertebral fracture. In the first analysis regarding the prediction of incident fracture from the OFELY Cohort, the trabecular parameters at the radius were significant predictors of fracture, independently of hip aBMD. In women with CKD stages 2–4, bone microarchitecture is also impaired at both compartments. In men, the cortical compartment is also affected. In patients on dialysis, a marked decrease in both compartments has been observed, but with a lesser decline in those on peritoneal dialysis. In the first prospective analysis in individuals with CKD stages 2–4, the predictive value of microarchitecture parameters was comparable to that of DXA.

Conclusion: HR-pQCT is a promisive technique to explore bone fragility in individuals with secondary osteoporoses. In postmenopausal women, the predictive value of HR-pQCT is independent of aBMD. This clinical use remains to be explored.

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Cortical bone segmentation in HR-pQCT images

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Because of its ability of capturing the microarchitecture of both cortical and trabecular compartment, HR-pQCT is becoming an important imaging tool for studies of bone disease and treatment assessment. However, an accurate volume segmentation remains a challenging task because of the complex structures of trabecular and cortical bone compartments and the noise characteristics. In this presentation, we will compare the performance of different recently published techniques. We will also present a novel HR-pQCT image segmentation method: a two step approach to extract the periosteal and endosteal surfaces of the cortex, respectively using a region-based model of active contours, followed by a new filling algorithm without any loss of precision.

Disclosure: The authors declare no conflict of interest.

HR-pQCT in Chronic Inflammatory

Precision and sources of variability in the assessment of rheumatoid athritis (RA) erosions by HR-pQCT

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Background: Initially developed for the study of bone diseases like osteoporosis, imaging by HR-pQCT is being evaluated for assessment of hands bone structure in RA, psoriatic arthritis or osteoarthritis (OA). The aim of our study was to assess the precision and the sources of variability with repositioning of the manual measurement of erosions located on the metacarpophalangeal joints (MCP) with HR-pQCT in RA.

Methods: We included RA patients with at least one erosion on the second, third or fourth MCP on conventional radiographs. We acquired two scans for each patient with repositioning. The main outcome was to calculate the short-term precision of the width, depth and volume of erosions after repositioning. Secondary outcomes were intraoperator precision, the least significant change and the sources of variability of the measurement.

Results: 29 patients were included, allowing the study of 803 erosions showing predilection for the radial sides of second or third MCPs. Precision after repositioning expressed in root mean square coefficient of variation (RMS CV)/root mean square standard deviation (RMS SD) of width, depth and volume was 17.8%/0.25, 20.2%/0.30 and 21.8%/1.63 mm, respectively. Intraclass correlation coefficients (ICC) were 0.95, 0.97 and 0.99, respectively. Intraoperator precisions were 16%, 16.4% and 18.7% with ICC 0.92, 0.97 and 0.985, respectively. Least significant changes of width, depth and volume were 0.3 mm, 0.2 mm and 0.3 mm^3. Precision was better for the erosions between 1.9 and 3 mm of axial width, with RMS CV of 16.6%, 13.5% and 13.9%. There was no significant correlation with bone microarchitecture parameters.

Conclusion: HR-pQCT is a sensitive method to detect and assess erosions, without the effect of repositioning. However, we showed weak precision in manual measurement due to intraoperator variability. We need to develop automated techniques to quantify bone erosions precisely.

Disclosure: The authors declare no conflict of interest.

Prevalence and predictive factors of osteoporosis in systemic sclerosis patients: a case-control study

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Background: To investigate the prevalence of osteoporosis in patients with systemic sclerosis (SSc), to describe alterations of bone tissue with HR-pQCT and to identify specific factors influencing SSc bone disease.

Methods: We conducted a cross-sectional study, including consecutively SSc patients and healthy women, matched on age, body mass index (BMI) and menopause. BMD was measured at the lumbar spine (LS), femoral neck (FN) and total hip (TH) by DXA. Volumetric BMD (vBMD) and bone micro-architecture parameters were measured by HR-pQCT at tibia and radius.

Results: 33 patients and 33 controls were included. In patients, BMI was significantly lower than in controls ($P<0.029$). The prevalence of osteoporosis in postmenopausal patients was significantly higher than in controls (42.8% vs 10.7%, $P<0.05$). HR-pQCT analysis showed a significant alteration of the trabecular compartment in patients, with a decrease in trabecular vBMD on both sites ($P<0.01$). In multivariate analysis, a low lean body mass, presence of anticentromere antibodies (ACAs) and older age were identified as independent factors for decreased BMD at LS ($r^2=0.43$; $P<0.001$), at FN ($r^2=0.61$; $P<0.0001$) and at TH ($r^2=0.73$; $P<0.0001$). History or current digital ulcers were also identified as an independent factor for microarchitecture alteration.

Conclusion: An increased prevalence of osteoporosis was found in patients with SSc. The HR-pQCT showed impaired trabecular bone compartment in patients. Also, low lean body mass, high age, digital ulcers and ACAs were identified as independent risk factors for bone damage.

Disclosure: The authors declare no conflict of interest.

Negative effect of glucocorticoids persistence therapy on porosity in rheumatoid arthritis patients treated with TNF blockers

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Background: RA is the most common joint inflammatory disease associated with an increased risk of bone fractures. The standard of therapeutic strategy is to achieve remission, which may require a combination of treatment including tumor necrosis factor (TNF) blockers and glucocorticoids (GC). TNF blockers have already shown a beneficial effect on bone loss in RA patients. However, GC could have paradoxical effects: by reducing arthritis, it can reduce bone loss related to inflammation; it can also impair bone remodeling balance that results in bone loss. The objective of this study was to assess the effects of GC persistence in RA patients with TNF blockers on cortical porosity.

Methods: In this pilot study, we enrolled eight RA patients requiring TNF blocker due to an active RA disease despite methotrexate therapy. Porosity was assessed by HR-pQCT on radius at the diaphysis site before, 6 and, 12 months after introducing TNF blocker. At the same time, BMD was assessed at the radial distal site.

Results: These eight RA patients (four men and three women) shared the usual characteristics of RA patients with a median age of 51.6 years (range: 35.8–62.4), median disease duration of 5.25 years (1–11) and a median DAS28 of 4.6 (3.9–6.1) with elevated biological inflammation (ESR 26 mm h^{-1} (9–68) and CRP 27.1 mg l^{-1} (3–68)). Rheumatoid factor and anti-citrullinated protein antibody (ACPA) were present in 83% of the cases. Four of the six RA patients received GC therapy at the inclusion. Although BMD remained stable under treatment, we observed an increasing of cortical porosity between baseline and 12 months ($P<0.05$). Interestingly, the increase in porosity over the last 6 months was correlated with GC daily dose ($P<0.02$; $r=0.87$).We observed no correlation between these parameters over the first 6 months ($P=0.42$; $R=0.105$).

Conclusion: Despite the small sample size of this pilot study, the strong difference between the two periods infers that the anti-inflammatory effects of GC participate to the beneficial effects of therapy on bone, while persistence of GC on the long term contribute to bone damage with increasing cortical porosity.

Disclosure: The authors declare no conflict of interest.

Relationship between bone loss and inflammation: What can HR-pQCT imaging add?

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Background: RA is a destructive autoimmune arthropathy causing periarticular demineralization, erosions and joint space narrowing. HR-pQCT is being applied to improve the longitudinal assessment of joint damage, and is studied in relationship to clinical disease activity.

Methods: Early inflammatory arthritis patients are recruited to undergo HR-pQCT scanning of the dominant hand MCP joints at diagnosis and at 1 year after treatment initiation. Disease activity measures and plain radiographs are similarly collected. HR-pQCT images are assessed for erosions using definitions and landmarks determined by the SPECTRA Collaboration, with the smallest detectable change calculated to assess for significant progression in erosion size. HR-pQCT standard evaluation scripts provide measures of bone densitometry and microarchitecture, and a custom script estimates joints space width parameters.

Results: At 1 year, significant reductions in disease activity are observed. The majority of subjects remain free of erosions, and relatively few have progression in erosion size. No significant changes were observed in bone densitometry or microarchitecture.

Conclusion: We have applied a high-sensitive imaging technology to characterize erosion development and regression, and quantify size differences, in early inflammatory arthritis. The majority of erosive lesions do not significantly progress when effective DMARD therapy is used.

Disclosure: The authors declare no conflict of interest.

Other Applications in Rheumatic Diseases

Advances in soft tissue analysis with HR-pQCT

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Background: Sarcopenia, the age-related loss of muscle mass, strength and function, may commonly co-exist in older adults with osteoporosis. Currently there is no standardized measure of age-related muscle loss over time.

Methods: This study accounted 45 women and 22 men from the Toronto cohort of the Canadian Multicenter Osteoporosis Study. Total body and lower limb lean tissue mass (TBLM, LLLM) were obtained from total body DXA scans (Hologic, Discovery A) using standard analysis protocols. Standard HR-pQCT scans (SCANCO Medical, XtremeCT) were acquired at the distal tibia. Muscle density (MD), volume (MV) and cross-sectional area (MCSA) were then calculated using a newly developed algorithm: muscle and fat seeds were identified using tight density thresholds, and were iteratively expanded until convergent segmentation of muscle volume. *T*-tests were used to examine sex differences and Pearson's correlations were calculated to assess relationships between DXA and HR-pQCT measurements.

Results: Women (age $= 68 \pm 9$ years) had TBLM (38 ± 6 kg) and LLLM (18 ± 3 kg) significantly lower than those of men (age $= 67 \pm 8$ years) (55 ± 7 kg, 22 ± 3 kg; respectively; $P < 0.05$). However, there was no sex difference in HR-pQCT-derived MD, MV and MCSA (13 ± 3 vs 13 ± 2mgHA cm^{-3}, $13\,224 \pm 3343$ vs $13\,405 \pm 3498$ mm^3 and 1521 ± 385 vs 1553 ± 418 mm^2; respectively; $P > 0.05$). There was no relationship between HR-pQCT-derived MD, MV and MSCA, and DXA, TBLM and LLLM ($r = -0.047$ to 0.031, $P = 0.7$–0.9).

Conclusion: These preliminarily findings suggest that MD, MV and MCSA obtained from HR-pQCT may not be predictive of DXA, TBLM and LLLM. HR-pQCT showed no sex differences in derived muscle parameters. Later it will be essential to relate muscle functions with HR-pQCT muscle parameters.

Disclosure: The authors declare no conflict of interest.

Description of new parameters developed to assess bone and articular changes on osteoarticular diseases with HR-pQCT

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Background: This study is a review of parameters developed to assess bone and articular changes on osteoarticular diseases with HR-pQCT. The main concerns are to detect early signs of arthritis and monitor their changes using 3D assessment of joint.

Results: Bone volumetric density as well as trabecular and cortical microstructure are impaired in patients with osteoarticular diseases. Bone erosion is defined as a cortical break in at least two consecutive slices in two orthogonal planes; it is associated with a loss of underlying trabecular bone and is non-linear in shape, in order to differentiate from physiological vessel channel. The shape of bone erosion and the localization of bone spurs, as well as their sizes, may be disease-specific.

Conclusion: HR-pQCT offers limited region of interest but high-resolution images (82 μm isotropic). It provides a sensitive method in the assessment of structural bone and articular damages, with parameters correlating with disease activity. Although a consensus has been reached for the definition of bone erosion and standardization of joint space morphology measurement is in progress, consensus definition and quantitative algorithms are needed for parameters such as bone spurs, osteosclerosis… Newly developed parameters such as cortical microchannel or surface irregularities have been discussed, while keeping in mind that segmentation is of particular importance and is a continuing challenge. The clinical relevance of some imaging abnormalities

observed in arthritis patients remains to be evaluated in larger studies.

Disclosure: The authors declare no conflict of interest.

Diagnostic imaging by CT of joint and enthesis: insights into pathogenesis

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Background: Pathogenesis of OA is complex. Recently, it has been suggested that subchondral bone remodeling has a role in the progression of OA. To test this hypothesis, we characterized the 3D microarchitecture of the subchondral bone and thickness of the subchondral plate, as measured by microCT, will differ among the distinctive level of degeneration within the tibial plateau subregions.

Methods: 10 tibial plateau harvested during TKA (Lille hospital) were used. MicroCT images were obtained from Skyscan1076 at IPROS clinic. In the microCT cross-section images of entire plateau, subregions for analysis were created via software (sw CTAn, Skyscan). Subchondral bone and plate were extracted in four quarters (antero medial, antero lateral, postero medial and postero lateral). We measured the plate thickness, bone volume fraction (BV/TV) and morphological parameters: Tb thickness (TbTh), Tb spacing (TbSp) and Tb number (TbN).

Results: BV/TV and morphological parameters showed significant differences between the four regions. BV/TV and TbTh were significantly higher at the medial region compared with the lateral. Note also that BV/TV was higher at the anterior side compared with the posterior region. Similarly, the medial compartment showed highest plate thickness compared with the lateral.

Conclusion: MicroCT could be used to distinguish subchondral bone from subchondral bone plate and quantify regional differences in entire human tibial plateau without coring the bone. Our 3D mapping confirmed differences between the medial and lateral compartment. The medial compartment showed highest bone volume in both subchondral bone and plate.

Disclosure: The authors declare no conflict of interest.

Correlations between 2D texture and 3D microarchitecture of the trabecular bone

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Background: This study presents the feasibility of imaging *ex vivo* knees in both X-rays standard radiography and HR-pQCT in order to study the correlations between the texture parameters and the Parfitt's ones.

Methods: Up to now two cadaver knees have been studied. They are imaged with the BMA (D3A Medical System) at first then scanned into the XTremCT (Scanco) with 75 μm and 42 μm resolution, respectively. ROI and VOI are placed in both lateral and medial compartments according to a standardized process based on Podsiadlo's work. The VOI produced by the HR-pQCT are averaged by the radiographs axes in order to provide a synthetic projection excluding any soft tissues interactions. Parfitt's parameters are computed on the VOI using the Mean Intercept Length algorithm. The fractal parameter H is computed using the Whittle estimator based on the power spectral density on both ROI (X-rays and synthetic projection).

Results: The first four measurements performed proved the feasibility of the study. For the synthetic projections, H seems correlated to the trabeculae thickness Tb.Th ($r = 0.92$), the ratio of bone surface and bone volume BS/BV ($r = -0.89$) and the trabecular number Tb.N ($r = -0.71$). For the X-radiographs, H is highly correlated with the bone volume BV/TV ($r = -0.99$) and seems linked to the trabeculae separation Tb.Sp ($r = 0.5$). The plot of the Parfitt's parameters versus H shows first order tendencies for all the parameters and with reverse orientations for BV/TV and Tb.Th. Also, the H parameter computed on the synthetic projections and the X-rays seemed to be not correlated ($r = -0.29$).

Conclusion: It is too early to talk about correlations considering the reduced number of samples. However, the feasibility of the measurements is proved and more knees will be included in the study. We also showed some tendencies indicating that H could reflect a mixture of several 3D parameters. For the confrontation with and without soft tissues, up to now we would say that they have some influence over the measurement.

Disclosure: The authors declare no conflict of interest.

Lower leg arterial calcification assessed by high-resolution peripheral quantitative computed tomography is associated with bone microstructure abnormalities in women

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Background: Here, we report the relationships of bone geometry, volumetric BMD and bone microarchitecture with LLAC as assessed by HR-pQCT.

Methods: We were able to study associations between measures obtained from HR-pQCT of the distal radius and distal tibia in 341 participants (162 women and 179 men) aged 72.1–81.4 years with or without LLAC; $n = 28$ (17.3%) vs $n = 134$ (82.7%) in women; $n = 83$ (46.4%) vs $n = 96$ (53.6%) in men, respectively. We used linear regression models to investigate the cross-sectional relationships between LLAC, and bone parameters for men and women.

Results: Women with LLAC had substantially lower cortical area (Ct.area; $P = 0.004$) and thickness (Ct.Th; $P = 0.014$) at the distal tibia than those without LLAC. Adjustment for confounding factors did not materially affect the relationship described for Ct.area ($P = 0.016$) at the distal tibia but differences in Ct.Th at the distal tibia were attenuated ($P = 0.083$). Regarding trabecular parameters, trabecular vBMD (Tb.vBMD) and trabecular number (Tb.N) were lower in women with LLAC ($P = 0.019$ and $P = 0.013$, respectively) at the distal tibia, while trabecular separation (Tb.Sp) was higher ($P = 0.008$). Adjustment for confounding factors did not materially affect the relationship described for Tb.N ($P = 0.013$) and Tb.Sp ($P = 0.012$) but differences in Tb.vBMD at the distal tibia were attenuated ($P = 0.087$). Similar results were found for Tb.vBMD ($P = 0.004$),

Tb.N ($P = 0.027$) and Tb.Sp ($P = 0.016$) at the distal radius with a lower trabecular thickness also observed (Tb.Th; $P = 0.009$) but results were attenuated after the adjustment for confounding factors, with only Tb.Th remaining significant ($P = 0.027$). Distal radial or tibial bone parameters analyses in men according to their LLAC status revealed no significant differences except for Tb.N at the distal tibia when adjusted ($P = 0.035$).

Conclusion: LLAC assessed by HR-pQCT was associated with bone microstructure abnormalities of the distal radius and tibia in women.

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Conflict of Interest

EL received speaker consultant fees from AMGEN (France) and ELI LILLY (France) and speaker fees from Expanscience, Novartis, Servier. HT declares no conflict of interest.