Osteoporosis International (2019) 30:411–421
https://doi.org/10.1007/s00198-018-4725-0

ORIGINAL ARTICLE

Associations between radius low-frequency axial ultrasound velocity and bone fragility in elderly men and women

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Received: 20 February 2018 / Accepted: 27 September 2018 / Published online: 10 October 2018
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Abstract

Summary An exploratory study in elderly women and men from the Geneva Retirees Cohort indicates that low-frequency quantitative ultrasound measurement at the radius captures aBMD, bone size, and cortical tissue mineral density and might be used for screening purposes prior to DXA to evaluate fracture risk.

Introduction The contribution of distal radius bone mineral density (BMD) and cortical microstructure to fracture risk has recently been demonstrated. In this exploratory study, we investigated whether low-frequency quantitative ultrasound measurement at the distal radius may capture the peripheral determinants of bone fragility assessed with dual-energy X-ray absorptiometry (DXA) and high-resolution peripheral quantitative computed tomography (HR-pQCT).

Methods Low-frequency velocity (V_{LF}) was measured at the radius using OsCare Sono®, a portable axial transmission ultrasonometer, in 271 community-dwelling postmenopausal women and men (age 71.5 ± 1.4 years) from the Geneva Retirees Cohort. Cortical (Ct) and trabecular (Tb) volumetric (v) BMD and microstructure at the distal radius were assessed by HR-pQCT, in addition to areal (a) BMD by DXA, at the same time point.

Results V_{LF} was highly correlated with aBMD at the distal third radius ($r = 0.72$, $p < 0.001$). For microstructure parameters, the highest correlation was observed with cortical area ($r = 0.59$, $p < 0.001$). V_{LF} also captured bone geometry (total area) and cortical tissue mineral density independently of aBMD. In models adjusted for age and sex, V_{LF} was significantly associated with prevalent low-trauma fractures [OR 95%CI for one SD decrease of V_{LF} 1.50 (1.05, 2.14), $p = 0.024$], with discrimination performance comparable to femoral neck or distal radius aBMD.

Conclusion Measurement of V_{LF} at the radius captures aBMD, bone size, and cortical tissue mineral density and might be used for screening purposes prior to DXA to evaluate fracture risk.

Keywords Bone microstructure · Bone mineral density · Fracture · Osteoporosis · Ultrasonic low-frequency velocity

Introduction

In addition to the decline in areal bone mineral density (aBMD), age-related bone fragility is associated with alterations in "bone quality," including trabecular bone loss, cortical thinning, and porosity [1, 2]. Impaired cortical bone microstructure has been associated with prevalent fractures in premenopausal and postmenopausal women [3, 4] and men [5], as well as with incident fractures [6–8]. While the World Health Organization (WHO) operational definition for osteoporosis [9] is based on the measurement of aBMD by central DXA (hip and spine), recent prospective cohort data indicate that aBMD and bone microstructure at peripheral bone sites, especially the ultra-distal radius which comprises of both trabecular and cortical bone compartments, predict incident fractures beyond central DXA and FRAX [6, 10]. These studies were, however, based on high-resolution peripheral

Study registration: ISRCTN11865958 (http://www.isrctn.com)

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00198-018-4725-0) contains supplementary material, which is available to authorized users.

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quantitative computed tomography (HRpQCT), a technology limited to some research centers and thus not largely applicable for routine clinical practice. The limited accessibility of DXA in several parts of the world leaves the door open to the development of devices which would be used to widely screen for bone fragility at peripheral bone sites, e.g., the radius. The wrist is a common site at which early fragility fractures are sustained and these are themselves a recognized risk factor for future major fractures including vertebral and hip fractures [11].

Alternative and non-invasive technologies are therefore needed to assess bone properties at peripheral bone sites. Quantitative ultrasound (QUS) methods represent a low-cost and readily accessible alternative to DXA or QCT measurements for the assessment of fracture risk. Previous ex vivo studies of femoral neck or radius demonstrated that QUS measurements are correlated with bone strength and reflect a combination of cortical and elastic properties, which are mainly affected by mineralization, porosity, and bone geometry [12, 13]. The use of QUS to identify subjects at low or high risk of osteoporotic fracture has not supplanted DXA because of several limitations. The majority of the evidence was obtained by heel QUS, with pretty good performance to predict fractures [14]. However, calcaneum QUS is not so easily practicable, does not measure bone properties at relevant fracture sites, and uses relatively high-frequency waves limiting the assessment to the periosteal region of the cortex. More recently, the development of low-frequency (LF) axial transmission ultrasound methods enabled the measurement of LF velocity (V_{LF}) that reflects cortical and subcortical BMD, cortical thickness, and elastic stiffness of bone [15–18]. Low-frequency velocity is more sensitive to cortical thickness than high-frequency velocity, and the ultrasound waves can propagate up to greater bone thickness than those of the radius, suggesting that it might reach the endocortical compartment [19]. A previous study comparing three axial transmission devices to measure distal radius speed of sound found that the low-frequency ultrasound velocity was correlated with failure load ($r = 0.51$) [20]. Whether these portable LF devices provide a better discrimination of fractures thanks to a better analysis of the cortex remains to be investigated. These devices are applicable to peripheral bone sites, making measurements easily realizable in clinical practice and directly relevant to potential fracture sites. A preliminary study in women suggests that this method would be of interest to discriminate subjects with and without fractures [21, 22]. Low-frequency signal velocity, measured at the tibia, has also been shown to reflect BMD and the geometry of proximal femur [23].

This is the first known study to measure radius V_{LF}, by QUS, in parallel with radius microstructure, using HRpQCT. In the context of the recent demonstration of the independent contribution of distal radius BMD and cortical microstructure to fracture risk, we conducted an exploratory study aiming to investigate to what extent V_{LF} might capture the determinants of bone fragility obtained by DXA and HR-pQCT at the distal radius, and therefore might be used as a screening tool for bone fragility. In addition, the associations with prevalent low-trauma fractures were assessed as a secondary outcome.

Subjects and methods

Subjects

GERICO (Geneva Retirees Cohort http://www.isrctn.com/ISRCTN11865958) is a prospective ongoing cohort study designed to identify predictive factors of fracture risk in retired workers from the Geneva area. The baseline characteristics of this cohort have been previously reported [6, 24]. The present analysis was conducted in 293 community-dwelling postmenopausal women and men aged 71.5 ± 1.4 years who attended the second follow-up visit of this cohort between 2015 and 2017, after 6.9 ± 0.5 years. Body weight and standing height were measured, and body mass index (BMI) calculated. Fracture history (after the age of 20 years) was recorded during face to face scheduled and structured interviews, in which details on fracture site, date, type and intensity of trauma, and modalities of treatment were recorded by the investigator. Low-trauma (LT) fractures were defined as any fracture resulting from a fall from standing height or less, with exclusion of fractures of fingers, toes, skull, and face. The study protocol received approval from the Geneva University Hospitals' Ethics Committee, and all participants provided written informed consent.

Low-frequency velocity assessment

Axial transmission speed of ultrasound was measured at the distal third of the radius at the non-dominant arm, or at the contralateral arm if a fracture was reported in the region of interest, using OsCare Sono® according to the manufacturer recommendations [18]. The OsCare Sono® is a portable axial transmission ultrasonometer which emits and receives pulses of ultrasound along the radius bone at low 200-kHz frequency and measures the speed of sound in the radius (low-frequency velocity, V_{LF}, m/s). The probe consists of an array of source and receiver elements operating according to a bidirectional principle so as to accurately correct for the effects of overlying soft tissue. The probe was centered on the radius at a distance from the distal end of the radius corresponding to one third of the forearm length measured with a ruler between the olecranon process and the styloid process of the ulna (easily identified anatomical landmarks). Ultrasound gel was used as the contact medium. Once the probe was positioned, firm pressure (approx. 1 kg) was applied against the skin. The gel and the pressure applied ensured that optimum acoustic coupling was

achieved so that soft tissue effects were minimized. Three trained investigators (EB, JP, and AdS) worked on V_{LF} assessments and performed three measurements on the participants they were in charge. For interobserver variabilities assessment (Supplemental Table 1), some participants ($n = 93$) were assessed by two operators (6 measurements for these participants). The quality of each assessment (signal curves and angle between pulse transmission and radius) was checked by the investigator using the user interface software as the measurement progressed. The median of all measurement was used for each participant in the analyses. V_{LF} T-scores were derived in the same manner as DXA results, by comparing the subject's measurement (for women and men) against the mean and standard deviation of measurements in a reference cohort of 173 healthy Caucasian women 20–40 years of age, collected in Germany and Finland in 2011 and provided by the manufacturer.

BMD and bone microstructure assessment

Lumbar spine, proximal femur, and distal radius aBMD were determined by DXA using a Hologic QDR Discovery W instrument (Hologic Inc., Waltham, MA, USA). Using the WHO classification and female references for all participants, subjects were classified as osteoporotic if they had at least one T-score ≤ 2.5SD at the lumbar spine, total hip, or femoral neck (central DXA). Additional data were also provided with inclusion of 1/3 radius aBMD in osteoporosis definition. Volumetric BMD and microstructure variables, for total (Tt) bone and the Ct and Tb compartments separately, were determined at the distal radius by HR-pQCT (XtremeCT1, Scanco Medical, Brüttisellen, Switzerland), as previously described [25]. The measurements were performed on the non-dominant limb or at the contralateral forearm if a previous fracture had occurred at the non-dominant site. Scan quality was assessed according to the image grading of motion artifact suggested by the manufacturer and scans with severe motion artifacts (grade 5) were excluded (20 radius scans). Recorded variables were Tt, Ct, and Tb vBMD (Tt.vBMD, Ct.vBMD, and Tb.vBMD, mg/cm^3) and areas (Tt.Ar, Ct.Ar, and Tb.Ar, mm^2); Tb number (Tb.N, mm^{-1}) and thickness (Tb.Th, mm); Ct thickness (Ct.Th, mm); and tissue mineral density (TMD, mg/cm^3) and Ct porosity, quantified with two different methods, a morphological assessment using an automated segmentation technique which identifies the periosteal and endosteal margins of the Ct compartment of the distal radius (Ct.Po), and a density assessment method using StrAx1.0 software within the total cortex (Tt Ct.Po) or the cortex segmented into compact-appearing cortex (Comp Ct.Po), outer transitional zone (Out Ct.Po), and the inner transitional zone (Inn Ct.Po) [26, 27]. All BMD and microstructure variables were measured both on the same day of V_{LF} assessment and at the baseline visit of the cohort (6.8 ± 0.3 years earlier), except Ct porosity quantified with density method only on the baseline scans.

Statistical analysis

All data were reported as means and standard deviations (SD), and percentages. Spearman correlations were used to assess the associations between V_{LF} and BMD or HR-pQCT parameters. The Shapiro–Francia W test and Skewness/Kurtosis tests were used to test the normality of the distributions and non-Gaussian variables were normalized using simple mathematical transformations before using it in linear models. Independent predictors of V_{LF} among BMD and microstructure variables were selected from multivariate regression analyses. Since there are high correlations between several HR-pQCT variables, a selection based on the variance inflation factor (VIF) was performed to detect independent variables and avoid multicollinearity. Microstructural variables entered into the final model were Ct.Th, Ct.TMD, Ct.Po, Tt.Ar, Tb.N, and Tb.Th. Additional models, defined a priori and including aBMD at radius 1/3 distal (same bone site as V_{LF}) and ultra-distal (same bone site as HR-pQCT) ± age and BMI, were performed to further investigate independent microstructural predictors of V_{LF}. Effects sizes for these models were estimated using Eta squared (total variance of the dependent variable explained by the model) and partial Eta squared (percentage of the variance explained by the effect of the dependent variable and unexplained by effects or interaction of the other dependent variables). Regarding the associations with fractures, we used logistic regression models adjusted for age and sex to estimate the odds ratios (OR) for prior low-trauma clinical fracture per one SD impairment of V_{LF} or of BMD or microstructure parameters. For these models, controls were subjects without prior fracture (subjects with traumatic fractures were excluded from controls, except those with fractures of fingers, toes, skull, and face). Subgroups analyses by sex and fracture site were also performed. To assess the ability of BMD, microstructure, or V_{LF} to discriminate between women with or without prevalent fractures, receiver operating characteristic (ROC) curve analyses obtained from logistic regressions were performed. A p value of ≤ 0.05 was considered to be significant for all analyses. The data were analyzed using STATA software, version 14.0. (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the study participants

Of the 293 participants who attended for the study visit, 19 participants were excluded as their forearm soft tissue thickness was too great to obtain a good quality measurement

(failure to determine V_{LF} in 10 participants and assessment of low quality in 9 participants). Three participants were excluded as they had sustained previous bilateral wrist fractures. A total of 271 participants with ultrasound assessments (219 women and 52 men) were included in the analyses (Supplemental Fig. 1). Mean age was 71.5 ± 1.4 years, BMI 25.1 ± 3.9 kg/m^2, and 24% of participants (57 women and 9 men) had a history of prior low-trauma fractures (Table 1). Based on central DXA (spine and hip) with female references, 25% had osteoporosis and 53% had osteopenia. Based on central and peripheral DXA (distal 1/3 radius), 29% had osteoporosis. The root mean square coefficient of variation across all the subjects was 0.56%. The relative intraobserver variabilities of V_{LF} measurements were 0.82 ± 0.51%, 0.70 ± 0.68%, and 0.99 ± 0.62% for the three investigators, respectively, with coefficients of variation of the first measurement of V_{LF} of 2.96%, 3.13%, and 2.96%, respectively. The interobserver variabilities were 0.15 ± 1.37% (EB vs JP) and -0.27 ± 1.30% (EB vs AdS) (Supplemental Table 1).

Correlations with central and peripheral aBMD

The magnitude of the associations between V_{LF} and aBMD was dependent of the site of aBMD measurement (Table 2). The highest correlation was between variables measured at the same bone site (distal 1/3 radius, $r = 0.72$, $p < 0.001$), while V_{LF} was moderately correlated with central aBMD ($r = 0.38$, $p < 0.001$ for femoral neck BMD; $r = 0.51$, $p < 0.001$ for lumbar spine BMD) (Fig. 1a, b). Distal 1/3 radius aBMD explained 59% of V_{LF} variance, while ultra-distal radius aBMD explained 44% of its variance (Fig. 1b–d). A threshold of V_{LF} T-score ≥ 1SD, observed in 27% of the study population, had the best performance to exclude osteoporosis on central DXA (negative predictive value 97%, positive predictive value 33%, sensitivity 97%, specificity 35%, AUC 0.659 (0.620, 0.698)) (Supplemental Table 2 and Fig. 1). A threshold of V_{LF} T-score ≥ 1.5SD, observed in 44% of the study population, had the best performance to exclude osteoporosis defined on central and peripheral (distal 1/3 radius) DXA (negative predictive value of 88%, positive predictive value 42%, sensitivity 81%, specificity 54%, AUC 0.676 (0.619, 0.732)) (Supplemental Table 2).

Correlations with peripheral bone geometry, density, and microstructure assessed by HR-pQCT

The correlations of V_{LF} with HR-pQCT parameters were of similar magnitude whether using variables measured during the same visit or HR-pQCT parameters measured 6.8 ± 0.3 years earlier, i.e., at the baseline visit of the GERICO study (Table 2 and Supplemental Table 3). V_{LF} was correlated with Tt area, vBMD, and microstructure parameters at the radius, including Ct porosity quantified with the density assessment method, but not with the morphological one. The highest correlation was observed with cortical area ($r = 0.59$). The magnitude of the correlations were however lower than those observed with aBMD, even at the same bone site than HR-pQCT (ultra-distal radius) (Fig. 1c, d). In a multivariate regression analysis including non-collinear HR-pQCT parameters, Tt area, Ct TMD, and Tb number predicted together 51% of the variance of V_{LF} (Table 3, model 1). Meanwhile, the same HR-pQCT parameters predicted 87% of the variance of UD radius aBMD (same bone site than HR-pQCT) and 73% of the variance of distal 1/3 radius aBMD (same bone site than ultrasounds) (Supplemental Fig. 2). When distal 1/3 radius aBMD was added to radius HR-pQCT parameters in model 2 (predicting 61% of the variance of V_{LF}), Tt area and Ct TMD entered the model together with distal 1/3 radius aBMD (Table 3). The same predictors entered in the model when UD radius aBMD was added instead of distal 1/3 radius aBMD in model 3 (predicting 54% of the variance of V_{LF}). Analyses separated by gender are also reported in Table 3. When age and BMI were added in the model, the proportion of the variance of V_{LF} explained by the model was not improved (model 4, 52% vs model 1, 51%). The association between V_{LF} and BMI was of higher magnitude in men than in women (model 4), but BMI did not enter anymore in models separated by gender and including aBMD (model 5). Taken together, these data indicate that V_{LF} captures, in addition to aBMD, some microstructure bone traits, Tt area, and Ct TMD, which are at least partially independent of aBMD.

Associations with prevalent low-trauma fractures

Sixty-six subjects (24%) had a prior low-trauma fracture, at the following fractures sites: forearm ($n = 16$), ankle ($n = 8$), proximal humerus ($n = 6$), tibia/fibula ($n = 6$), elbow ($n = 6$), rib ($n = 5$), metatarsal bone ($n = 5$), sacrum/coccyx ($n = 3$), vertebrae ($n = 2$), carpal bone ($n = 2$), tarsal/calcaneum ($n = 2$), metacarpal bone ($n = 2$), proximal femur ($n = 1$), tibia plateau ($n = 1$), and collar bone ($n = 1$). The associations with prevalent low-trauma fractures were assessed in models adjusted for age and sex. V_{LF} was significantly associated with prevalent clinical low-trauma fractures [OR 95%CI for one SD decrease of V_{LF} 1.50 (1.05, 2.14), $p = 0.024$]. The association was of similar magnitude than the one obtained with femoral neck aBMD [OR 1.53 (1.10, 2.13), $p = 0.011$]. In a multivariate model including V_{LF} and femoral neck aBMD in addition to age and sex, the adjusted OR for prevalent clinical low-trauma fractures was decreased to 1.36 (0.94, 1.97), $p = 0.105$ for one SD decrease of V_{LF} and 1.43 (1.01, 2.01), $p = 0.041$ for one SD decrease of femoral neck aBMD. The association of V_{LF} with fracture was no more significant after adjustment for distal 1/3 radius aBMD. Among the determinants of V_{LF} identified in the multivariate analyses, radius aBMD (1/3 distal and ultra-distal) and cortical TMD, not total

Table 1 Characteristics of participants

	Total ($n = 271$)	Women ($n = 219$)	Men ($n = 52$)
Age (years)	71.5 ± 1.4	71.5 ± 1.4	71.4 ± 1.59
Weight (kg)	68 ± 13	65 ± 11	79 ± 12
Height (cm)	164 ± 8	161 ± 6	176 ± 7
BMI (kg/m^2)	25.1 ± 3.9	24.9 ± 4.1	25.6 ± 3.3
Prior low-trauma fractures	66 (24%)	57 (26%)	9 (17%)
Prior major osteoporotic fractures	26 (10%)	24 (11%)	2 (4%)
DXA			
Lumbar spine T-score (SD)	− 1.02 ± 1.57	− 1.25 ± 1.45	− 0.04 ± 1.72
Total hip T-score (SD)	− 0.89 ± 1.03	− 1.12 ± 0.89	0.10 ± 1.00
Femoral neck T-score (SD)	− 1.45 ± 1.00	− 1.58 ± 0.95	− 0.90 ± 1.03
Radius 1/3 distal T-score (SD)	− 1.01 ± 1.56	− 1.51 ± 1.20	1.10 ± 1.19
Osteoporotic status on DXA			
Osteoporosis on central DXA[a]	67 (25%)	65 (30%)	2 (4%)
Osteoporosis on central and peripheral DXA[b]	78 (29%)	76 (35%)	2 (4%)
Osteopenia[a]	144 (53%)	115 (52%)	29 (56%)
Normal BMD[a]	60 (22%)	39 (18%)	21 (40%)
Low-frequency velocity			
V_{LF} radius (m/s)	3744 ± 112	3714 ± 92	3869 ± 107
V_{LF} radius T-score[c]	− 1.45 ± 0.94	− 1.70 ± 0.77	− 0.41 ± 0.88
HR-pQCT radius			
Tt.area (mm^2)	281 ± 65	259 ± 44	373 ± 56
Tt.vBMD (mg HA/cm^3)	278 ± 61	270 ± 60	312 ± 53
Ct.vBMD (mg HA/cm^3)	823 ± 70	818 ± 72	841 ± 62
Ct.Th (mm)	0.65 ± 0.19	0.62 ± 0.17	0.79 ± 0.21
Ct.area (mm^2)	46.6 ± 15.1	42.0 ± 10.7	65.9 ± 15.7
Ct.TMD (mg HA/cm^3)	993 ± 45	993 ± 47	994 ± 39
Ct.Po (%)	2.8 ± 1.2	2.8 ± 1.2	3.1 ± 1.2
Tb.vBMD (mg HA/cm^3)	141 ± 39	133 ± 35	174 ± 34
Tb.N (mm^{-1})	1.82 ± 0.34	1.77 ± 0.33	2.05 ± 0.28
Tb.Th (mm)	0.064 ± 0.011	0.062 ± 0.010	0.071 ± 0.010

Values are means ± standard deviation (SD) or number (%)

[a] Osteoporosis defined as at least one T-score ≤ 2.5SD, and osteopenia as at least one T-score between − 1 and − 2.5SD with none ≤ 2.5SD at the lumbar spine, total hip, or femoral neck (based on female references)

[b] Osteoporosis defined as at least one T-score ≤ 2.5SD at the lumbar spine, total hip, femoral neck, or distal 1/3 radius (based on female references)

[c] Based on female references from a cohort of 173 healthy Caucasian women 20–40 years of age

area, were associated with prevalent fractures (Table 4). In subgroups analyses by gender adjusted for age, the association of V_{LF} with fracture was only significant in men [OR 3.26 (1.13, 9.34), $p = 0.028$ in men; OR 1.35 (0.92, 1.99), $p = 0.127$ in women]. The higher magnitude of OR for fracture in men was also observed for aBMD and microstructural parameters. The associations of V_{LF} with fracture was of higher magnitude when the fracture group was restricted to fractures of the upper limbs, including distal radius and proximal humerus fractures [OR 1.70 (1.01, 2.89), $p = 0.047$]. The performances of V_{LF} to predict prevalent low-trauma major osteoporotic fractures, assessed by area under the curves, were comparable from those of aBMD at any bone site or of radius Ct area (Fig. 2). The discrimination of subjects with and without MOF was slightly improved when V_{LF} was added to age + sex + FN aBMD (AUC 0.679 vs 0.666).

Discussion

In this population of elderly community-dwelling postmenopausal women and men, measurement of low-frequency velocity at the distal radius using the portable axial transmission ultrasonometer (OsCare Sono®) was highly correlated with

Table 2 Correlations (spearman) between low-frequency axial ultrasound velocity and areal BMD or HR-pQCT parameters at the radius. *P* values in italics are statistically significant at $p < 0.05$

	Total ($n = 271$)		Women ($n = 219$)		Men ($n = 52$)	
	r	*p* value	*r*	*p* value	*r*	*p* value
Age	− 0.06	0.330	− 0.04	0.587	− 0.16	0.265
BMI	0.22	*< 0.001*	0.15	*0.030*	0.37	*0.006*
DXA						
Lumbar spine aBMD	0.51	*< 0.001*	0.44	*< 0.001*	0.43	*0.002*
Femoral neck aBMD	0.38	*< 0.001*	0.31	*< 0.001*	0.15	0.306
Total hip aBMD	0.50	*< 0.001*	0.34	*< 0.001*	0.39	*0.005*
Radius 1/3 distal aBMD	0.72	*< 0.001*	0.59	*< 0.001*	0.66	*< 0.001*
Radius ultra-distal aBMD	0.63	*< 0.001*	0.50	*< 0.001*	0.51	*< 0.001*
Radius total aBMD	0.72	*< 0.001*	0.61	*< 0.001*	0.62	*< 0.001*
HR-pQCT distal radius						
Total (Tt) bone						
Tt area	0.41	*< 0.001*	0.10	0.147	0.14	0.346
Tt vBMD	0.40	*< 0.001*	0.33	*< 0.001*	0.28	0.056
Cortical (Ct) bone						
Ct area	0.59	*< 0.001*	0.44	*< 0.001*	0.46	*0.001*
Ct thickness	0.46	*< 0.001*	0.37	*< 0.001*	0.36	*0.012*
Ct vBMD	0.41	*< 0.001*	0.42	*< 0.001*	0.35	*0.014*
Cortical porosity	− 0.03	0.683	− 0.12	0.084	− 0.04	0.768
Ct TMD	0.38	*< 0.001*	0.48	*< 0.001*	0.42	*0.003*
Trabecular (Tb) bone						
Tb vBMD	0.39	*< 0.001*	0.24	*< 0.001*	0.24	0.103
Tb area	0.34	*< 0.001*	0.03	0.656	0.04	0.782
Tb number	0.39	*< 0.001*	0.29	*< 0.001*	0.09	0.531
Tb thickness	0.24	*< 0.001*	0.11	0.104	0.22	0.134

aBMD at the same site. In particular, a V_{LF} T-score threshold above − 1SD of young female references, as found in 27% of the study population, had an excellent negative predictive value (97%) to exclude osteoporosis as evaluated by central DXA. In a screening perspective, V_{LF} measurement could therefore avoid performing DXA examinations in about a quarter of the elderly, community-dwelling population. However, this very high negative predictive value was associated with a low positive predictive value, as shown with other peripheral QUS devices [28].

V_{LF}also captured bone traits relative to bone geometry (total and particularly cortical area) and matrix mineralization (Ct TMD). This result is of potential interest in the context of the high association between cortical area and fracture risk, which was recently demonstrated in prospective cohorts [6, 8]. Using transducers operating at low-frequency ultrasound (around 200 kHz), the OsCare Sono® signal penetrates through the radial cortex, where the speed of sound has been shown to depend on the cortical thickness, BMD, and elasticity, which are all important determinants of bone strength [18]. The higher associations of V_{LF} with Ct parameters compared to trabecular ones were therefore expected. However, we found that trabecular number is an independent predictor of V_{LF} in women, not in men. There are two potential explanations for this finding: first, since Ct compartment is thinner in women than men, the ultrasound waves may reach the trabecular compartment in women and not in men; second, there is a certain degree of correlation between trabecular and cortical parameters assessed by HR-pQCT, so that even if the Tb compartment is not directly reached by the ultrasound wave, some associations may be found. Looking at the proportion of variance accounted for by each variable in models including aBMD, the data of this exploratory study indicate that V_{LF} assessed by OsCare Sono® mainly captures aBMD and matrix mineralization (Ct TMD) rather than cortical microstructural bone traits. Although most of the variations of bone elasticity with aging is due to change in the intracortical porosity (mineralized matrix does not undergo large variations), the influence of Ct porosity, evaluated by the morphologic method, was not found in our study probably because Ct porosity was very low at the distal radius (2.8 ± 1.2%), contrary to other bone sites (tibia), and underestimated by this method [29].

We previously reported the associations of distal radius aBMD and Ct parameters with both prevalent and incident

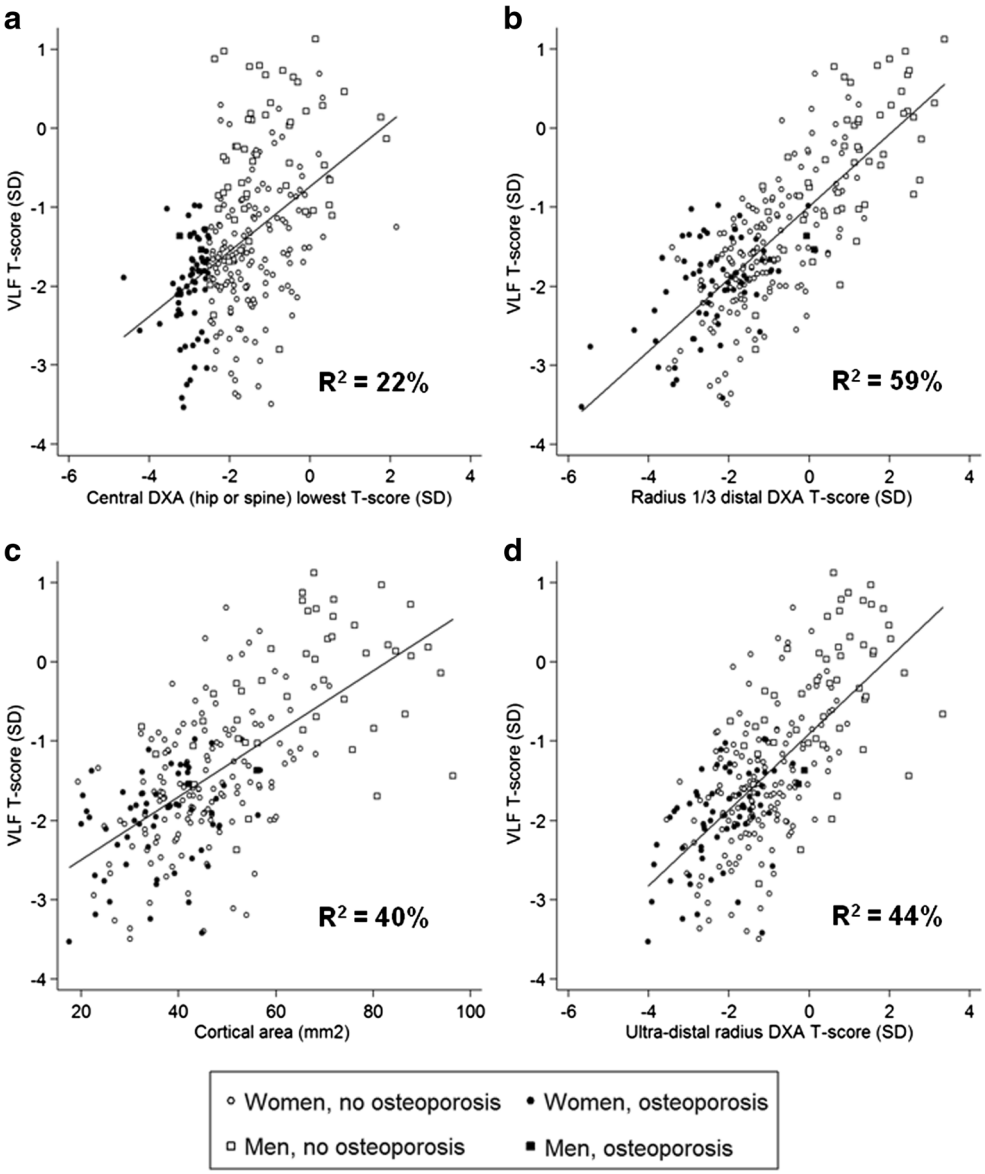

Fig. 1 Associations between low-frequency velocity (V_{LF}), T-scores, and **a** central DXA T-scores (lowest T-score at total hip, femoral neck, or lumbar spine, used for the operational definition of osteoporosis); **b** distal third radius aBMD T-scores (same bone site); **c** cortical area at the ultra-distal radius and **d** ultra-distal radius aBMD T-scores. Subjects with osteoporosis on central DXA are indicated with black markers, illustrating the negative predictive value of osteoporosis for a V_{LF} T-score higher than − 1 SD. All T-scores were calculated based on female references. The proportion of the variance of V_{LF} explained by each parameter is indicated (R-squared)

fractures in whole women of the GERICO cohort [6, 25]. In this study on a subset of the whole cohort, the performance of V_{LF} to discriminate subjects with and without prevalent fractures were not different than those observed with central DXA or BMD/cortical microstructure parameters at the distal radius. In subgroups analyses, the association with prevalent low-trauma fractures was significant in men only. By capturing bone areas in addition to BMD, V_{LF} might better reflect the sex-specific differences in the structural and material properties of bone and thereby the determinants of fracture, especially in men [30]. The association of V_{LF} with fracture was no more significant after adjustment for distal 1/3 radius aBMD. This is fully expected since V_{LF} and radius 1/3 distal aBMD are measured at the same bone site and are highly correlated, similarly to what we previously reported for failure load assessed by HR-pQCT and aBMD assessed by DXA at the ultra-distal radius for the prediction of incident fractures [6]. The association of V_{LF} with fracture was also no more significant after adjustment for femoral neck aBMD. This result reinforces the point that V_{LF} might be a surrogate to DXA to predict fractures in patients in which DXA is not accessible.

The majority of prior data on ultrasounds and fractures were obtained at the calcaneum. In a meta-analysis, the predictive value of heel ultrasound for incident fractures was the same for men and women and for all ages, while a study in men identified associations which were independent of central DXA [31, 32]. Regarding radius and tibia ultrasounds, the quantity of evidence is lower than for heel devices [33]. A previous study in women found that speed of sound (SOS) at the tibial midshaft (pulse transmission at a frequency of 250 kHz) was less effective than central DXA to discriminate women with and without fractures [34]. In a previous study in

Table 3 Independent predictors of radius V_{LF} among BMD and microstructure variables selected from multivariate regression analyses

Variables in regression model	Variables selected in model	Total ($n = 271$)				Women ($n = 219$)				Men ($n = 52$)			
		β (95%CI)*	p	Partial eta squared **	Eta squared	β (95%CI)*	p	Partial eta squared **	Eta squared	β (95%CI)*	p	Partial eta squared **	Eta squared
Model 1: HR-pQCT variables	Tt area	0.53 (0.43, 0.63)	< 0.001	31%	51%	0.34 (0.21, 0.48)	< 0.001	11%	36%	0.66 (0.30, 1.02)	0.001	25%	38%
	Ct TMD	0.47 (0.32, 0.62)	< 0.001	13%		0.51 (0.34, 0.68)	< 0.001	15%		0.55 (0.11, 1.00)	0.016	13%	
	TbN	0.20 (0.09, 0.30)	< 0.001	5%		0.20 (0.09, 0.31)	0.001	6%			NS		
Model 2: HR-pQCT variables + radius 1/3 distal aBMD	1/3D aBMD	0.61 (0.45, 0.76)	< 0.001	20%	61%	0.54 (0.36, 0.71)	< 0.001	16%	46%	0.82 (0.43, 14.21)	< 0.001	31%	57%
	Ct TMD	0.30 (0.16, 0.44)	< 0.001	7%		0.33 (0.16, 0.49)	< 0.001	7%		0.52 (0.15, 0.90)	0.007	17%	
	Tt Area	0.21 (0.09, 0.33)	0.002	4%			NS				NS		
Model 3: HR-pQCT variables + radius ultra-distal aBMD	Tt area	0.36 (0.23, 0.49)	< 0.001	11%	54%		NS		41%	0.60 (0.15, 1.05)	0.010	15%	38%
	UD aBMD	0.47 (0.23, 0.71)	< 0.001	6%		0.51 (0.26, 0.76)	< 0.001	8%			NS		
	Ct TMD	0.40 (0.25, 0.55)	< 0.001	10%		0.44 (0.27, 0.61)	< 0.001	12%		0.54 (0.08, 0.99)	0.022	12%	
	Ct.Th		NS			−0.25 (−0.47, −0.04)	0.022	3%			NS		
	Tb.Th		NS			−0.13 (0.26, 0.00)	0.049	2%			NS		
Model 4: HR-pQCT + age + BMI	Tt area	0.54 (0.44, 0.63)	< 0.001	32%	52%	0.35 (0.21, 0.49)	< 0.001	12%	37%	0.49 (0.10, 0.88)	0.014	14%	45%
	Ct TMD	0.50 (0.35, 0.65)	< 0.001	14%		0.54 (0.37, 0.72)	< 0.001	17%		0.68 (0.23, 1.13)	0.004	19%	
	Tb N	0.06 (0.08, 0.29)	0.001	5%		0.18 (0.07, 0.30)	0.002	5%			NS		
	BMI	0.11 (0.01, 0.21)	0.031	2%		0.11 (0.00, 0.21)	0.045	2%		0.36 (0.03, 0.70)	0.035	11%	
Model 5: HR-pQCT variables + radius 1/3 distal aBMD + BMI	1/3D aBMD	0.60 (0.45, 0.76)	< 0.001	20%	62%	0.53 (0.35, 0.70)	< 0.001	16%	47%	0.76 (0.38, 1.15)	< 0.001	29%	61%
	Ct TMD	0.33 (0.18, 0.47)	< 0.001	8%		0.36 (0.19, 0.53)	< 0.001	8%		0.63 (0.25, 1.01)	0.002	22%	
	Tt area	0.20 (0.08, 0.33)	0.001	4%		NS				NS			
	Ct.Th	NS				0.21 (0.02, 0.40)	0.033	2%		0.42 (0.08, 0.77)	0.016	14%	
	BMI	0.09 (0.00, 0.18)	0.048	2%		NS				NS			

HR-pQCT variables include non-collinear variables measured at the distal radius, i.e., Ct.Th, Ct.TMD, Ct.Po, Tt.Ar, Tb.N, and Tb.Th. Only variables significantly associated with V_{LF} in the model are reported in the table. *NS* not significant

*β coefficient (95%CI) of the corresponding variable expressed in SD, associated with one SD increase of radius V_{LF} in the regression model

**Percentage of the variance explained by the corresponding variable and unexplained by effects of the other variables of the model

Table 4 Associations between radius low-frequency velocity, areal bone mineral density or cortical microstructure parameters, and prior low-trauma clinical fractures. *P* values in italics are statistically significant at $p < 0.05$

	Total ($n = 271$)		Women ($n = 219$)		Men ($n = 52$)	
Variables	OR (95%CI)[a]	*p*	OR (95%CI)[b]	*p*	OR (95%CI)[b]	*p*
V_{LF}	1.50 (1.05, 2.14)	*0.024*	1.35 (0.92, 1.99)	0.127	3.26 (1.13, 9.34)	*0.028*
Femoral neck aBMD	1.53 (1.10, 2.13)	*0.011*	1.50 (1.06, 2.13)	*0.023*	2.12 (0.75, 5.98)	0.156
Lumbar spine aBMD	1.74 (1.23, 2.47)	*0.002*	1.60 (1.11, 2.31)	*0.012*	4.36 (1.15, 16.57)	*0.030*
Distal third radius aBMD	1.72 (1.16, 2.54)	*0.007*	1.55 (1.02, 2.34)	*0.039*	4.18 (1.19, 14.69)	*0.026*
Ultra-distal radius aBMD	2.15 (1.45, 3.18)	*< 0.001*	2.00 (1.33, 3.03)	*0.001*	3.99 (1.15, 13.85)	*0.029*
Ct area	1.67 (1.13, 2.46)	*0.010*	1.57 (1.04, 2.37)	*0.033*	3.06 (0.86, 10.80)	0.083
Ct TMD	1.40 (1.01, 1.92)	*0.041*	1.32 (0.95, 1.84)	0.101	3.03 (0.73, 12.58)	0.126
Total Ct porosity	1.84 (1.30, 2.61)	*0.001*	1.73 (1.21, 2.47)	*0.003*	4.13 (0.96, 17.84)	0.057
Total area	0.85 (0.56, 1.30)	0.464	0.75 (0.47, 1.19)	0.217	3.10 (0.77, 12.40)	0.111

[a] Adjusted for age and sex

[b] Adjusted for age

Data are odd ratios associated with one standard deviation impairment of V_{LF} or aBMD, obtained from logistic regressions. Only total Ct porosity, quantified with StrAx1.0 software, was not assessed concomitantly of V_{LF}. *OR* odd ratio, *CI* confidence interval, V_{LF} low-frequency velocity, *aBMD* areal bone mineral density, *Ct* cortical

premenopausal and postmenopausal women using the same ultrasound device as in our study, V_{LF} at the radius, not at the tibia, discriminated fractures with an age and BMI adjusted odds ratio of 2.06 (95%CI 1.21–3.50, $p < 0.01$). It should be noted that in this study, the majority of fractures occurred at the distal radius [21]. Similarly, the association of V_{LF} with fracture in our study was of higher magnitude when the fracture group was restricted to fractures of the upper limbs [OR 1.70 (1.01, 2.89)]. Taken together, these data are consistent with the old notion that the associations of bone traits with fracture risk are better when assessed site specifically. The predictive value of V_{LF} tested in this particular population with a high proportion of forearm fractures might be not as good in older or different populations with a larger proportion of hip or other fractures. Whether V_{LF} might improve fracture prediction beyond DXA thanks to the microstructural bone traits it reflects remains to be demonstrated in larger prospective cohorts.

This study is the first investigating a QUS device in parallel with a high-resolution QCT. In addition, few data have been reported with last generation of low-frequency ultrasound devices applicable to the radius, an easily analyzable bone site which is also a site of frequent major osteoporotic fractures. We acknowledge however a number of limitations to our study. First, the measurement of V_{LF} with OsCare Sono® and of microstructural bone traits with XtremeCT were not performed at the same radius bone site, according to the manufacturers' recommendations for each device, i.e.,

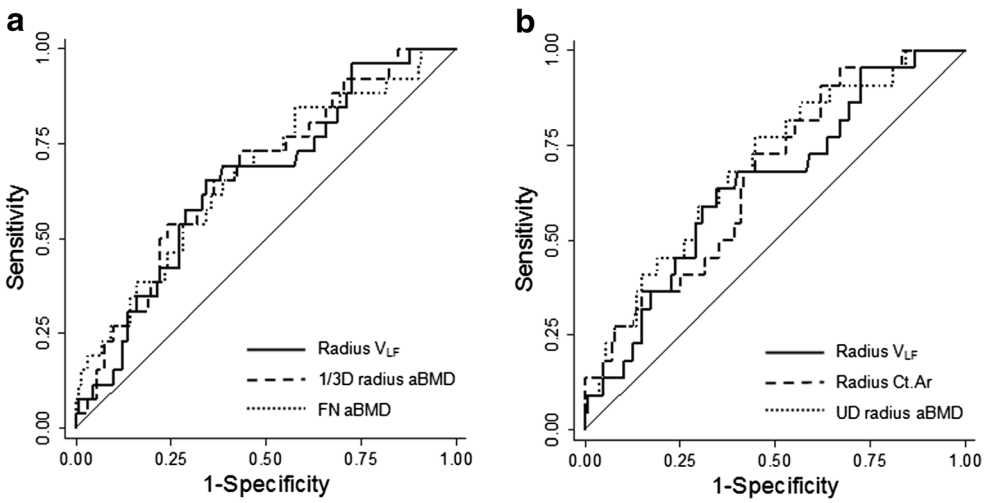

Fig. 2 Receiver operating characteristic curves adjusted for age and sex for the discrimination of subjects with major osteoporotic fracture vs subjects without prior fracture. The area under the curve for V_{LF} was similar to those of FN or distal 1/3 radius aBMD assessed by DXA (**a**), and not statistically different of aBMD assessed by DXA and cortical area assessed by HR-pQCT at the ultra-distal radius (**b**). V_{LF}, low-frequency velocity; FN, femoral neck; BMD, bone mineral density; aBMD, areal BMD; UD, ultra-distal

microstructure was evaluated more distally. This might have affected the magnitude of the correlations compared to those obtained in a previous study with QCT measurement at the same bone site [18]. Secondly, the number of prevalent fractures was relatively small, especially in men. Therefore, the value of V_{LF} for fracture prediction needs to be replicated in additional prospective studies with incident fractures as primary outcome and including a higher proportion of men.

In conclusion, V_{LF} assessed at the radius is highly correlated with aBMD at this site and also captures some microstructural dimensions which are partly independent of aBMD, in particular bone size and cortical tissue mineral density. It has an excellent negative predictive value to exclude osteoporosis on DXA and, conversely, it is associated with prevalent low-trauma fractures in men. If confirmed in additional studies, the data of this exploratory study suggest that V_{LF} could be used for screening purposes prior to DXA to evaluate fracture risk.

Acknowledgments We are indebted to F. Merminod, A. Sigaud, and M. Hars for the management of participants, C. Genet and G. Conicella to for DXA and HR-pQCT measurements. We thank Dr. R. Zebaze and Pr E. Seeman for cortical porosity quantification with StrAx1.0 software. We thank the Swiss Foundation for Research on Ageing AETAS for the kind supply of its mobile osteodensitometer, the Geneva University Hospitals and Faculty of Medicine Clinical Research Center, the HUG Private Foundation, and Oscare Medical for their support. None of the funders had any influence on the study design, implementation, and analysis, and on interpretation of the data.

Compliance with ethical standards

The study protocol received approval from the Geneva University Hospitals' Ethics Committee, and all participants provided written informed consent.

Conflicts of interest Dr. E. Biver and Pr S. Ferrari report a research grant from Oscare Medical for a research project; Dr. Pepe, Dr. de Sire, and Pr Chevalley declare that they have no conflicts of interest.

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