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ORIGINAL ARTICLE

Heel quantitative ultrasound (QUS) predicts incident fractures independently of trabecular bone score (TBS), bone mineral density (BMD), and FRAX: the OsteoLaus Study

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Abstract

Summary This study aimed to better define the roleof heel-QUS in fracture prediction. Our results showed that heel-QUS predicts fracture independently of FRAX, BMD, and TBS. This corroborates its use as a case finding/pre-screening tool in osteoporosis management.

Introduction Quantitative ultrasound (QUS) characterizes bone tissue based on the speed of sound (SOS) and broadband ultrasound attenuation (BUA). Heel-QUS predicts osteoporotic fractures independently of clinical risk factors (CRFs) and bone mineral density (BMD). We aimed to investigate whether (1) heel-QUS parameters predict major osteoporotic fractures (MOF) independently of the trabecular bone score (TBS) and (2) the change of heel-QUS parameters over 2.5 years is associated with fracture risk.

Methods One thousand three hundred forty-five postmenopausal women from the OsteoLaus cohort were followed up for 7 years. Heel-QUS (SOS, BUA, and stiffness index (SI)), DXA (BMD and TBS), and MOF were assessed every 2.5 years. Pearson's correlation and multivariable regression analyses were used to determine associations between QUS and DXA parameters and fracture incidence.

Results During a mean follow-up of 6.7 years, 200 MOF were recorded. Fractured women were older, more treated with anti-osteoporosis medication; had lower QUS, BMD, and TBS; higher FRAX-CRF risk; and more prevalent fractures. TBS was significantly correlated with SOS (0.409) and SI (0.472). A decrease of one SD in SI, BUA or SOS increased the MOF risk by (OR(95%CI)) 1.43 (1.18–1.75), 1.19 (0.99–1.43), and 1.52 (1.26–1.84), respectively, after adjustment for FRAX-CRF, treatment, BMD, and TBS. We found no association between the change of QUS parameters in 2.5 years and incident MOF.

Conclusion Heel-QUS predicts fracture independently of FRAX, BMD, and TBS. Thus, QUS represents an important case finding/pre-screening tool in osteoporosis management. The change in QUS over time was not associated with future fractures, making it inappropriate for patient monitoring.

Keywords Bone mineral density · Fracture · Heel quantitative ultrasound · Osteoporosis · Trabecular bone score

Introduction

Osteoporosis is a bone disorder affecting bone quantity and quality, which increases the risk of fracture. Dual-energy X-ray absorptiometry (DXA) scanning in the hip and lumbar spine (LS) is the gold standard for osteoporosis diagnosis. DXA provides the assessment of bone mineral density (BMD)—a bone quantity assessor—in the total hip (TH), femoral neck (FN), and LS, and of trabecular bone score (TBS)—a bone microarchitecture proxy—in the LS [1]. The operational diagnosis of osteoporosis is based on the presence of a fragility fracture and/or low BMD values at any of the three regions (T-score ≤ -2.5 SD) [2]. About 50% of women who have an osteoporotic fracture do not have osteoporotic BMD values [3, 4], suggesting that BMD is insufficient to predict fracture, and confirming its multifactorial nature. Assessment can be completed by using the Fracture Risk Assessment Tool (FRAX), which calculates the 10-year probability

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of having an osteoporotic fracture based on clinical risk factors for fracture (CRF), and/or the DXA-derived parameters: BMD and TBS [5–7]. Unfortunately, despite these diagnosis tools and the fact that fractures are preventable [8], the lack of osteoporosis diagnosis has contributed to an important osteoporosis treatment gap [9–11]. This is partly because DXA exams are performed at a specialized radiology or nuclear medicine facilities. Improving the distribution of a screening strategy for osteoporosis could increase its awareness and eventually diagnosis and treatment. Further, the significant decrease in reimbursement for DXA in the USA and the disappearance of DXA centers because of this is an additional contributor.

Quantitative ultrasound (QUS) is a technology that sends and receives subaudible soundwaves through the bone. It characterizes bone tissue based on the ultrasound velocity (the speed of sound (SOS, in m/s)), attenuation (broadband ultrasound attenuation (BUA, in dB/MHz), and stiffness index (SI) [12]. Heel (or calcaneus) is the most-established QUS skeletal site for fracture prediction. Heel QUS parameters can predict fractures independently of clinical risk factors and BMD. Its fracture prediction ability is numerically similar to the one of DXA [12]. SOS and BUA reflect the mechanical and physical properties of the bone, such as elasticity, microarchitecture, and strength [13], and thus, their predictive value could be somewhat similar to that of TBS. On the other hand, it has been suggested that QUS might give different information from TBS in vivo; however, these preliminary data need confirmation [14, 15]. Advantages of the heel QUS over DXA are the lack of ionizing radiation, lower cost, and ease at transportation. Despite these clear advantages, currently this technology is not widely used in practice due to the lack of devices (it is no longer serviced in the USA), lack of specific validated thresholds for the QUS parameters, its very low sensitivity to change, and the lack of a clear effect of anti-osteoporotic treatment on QUS [12]. The International Society for Clinical Densitometry (ISCD) suggests using QUS as a prescreening tool for osteoporosis, which would identify people at low risk of fracture based on CRF and QUS parameters and for whom no further diagnostic assessment would be required. The use of QUS for follow-up objectives is not sufficiently studied [16]. Moreover, peripheral sites tend to be less responsive to treatment than axial skeletal sites. Using easily accessible tools, such as QUS, in prescreening strategies for osteoporosis might contribute at improving the existing gap in its diagnosis and treatment.

The overall aim of this study was to better define the role of heel QUS in predicting fracture risk in postmenopausal women in the OsteoLaus cohort. The first aim was to investigate whether heel QUS parameters can predict fractures independently of TBS, in addition to BMD and CRF. The secondary aim was to investigate if the change in percent of heel QUS parameters over 2.5 years is associated with incident fractures risk.

Methods

Study population

OsteoLaus, a sub-study of the CoLaus cohort, is an ongoing populational cohort of postmenopausal women aged ≥ 50 years at baseline, living in Lausanne. The cohort has been previously described in detail [17, 18]. A total of 1475 OsteoLaus participants underwent a baseline visit (March 2010–December 2012) and a follow-up visit every 2.5 years with almost 70% retention at the 4th visit. In this analysis, we use the data collected during the baseline, second, third, and fourth visits, comprising a mean total follow-up period of 6.7 years.

The Ethics Committee for Human Research of Canton Vaud approved the CoLaus Study and subsequently the OsteoLaus Study. All participants signed a written informed consent after having received a detailed description of the funding and aim of the study.

QUS assessments

QUS was measured at the heel at each OsteoLaus visit using the Achilles Express apparatus (GE-Lunar Co., Madison, USA), calibrated daily according to the manufacturer's recommendation. The measurements were performed on the right heel; in case of a prevalent fracture on the right heel, they were performed on the left. All measurements were done by the same operator. The device directly measured SOS and BUA, and its software automatically calculated the SI, a manufacturer composite parameter: $SI = 0.67 \times BUA + 0.28 \times SOS\text{-}420$. The measurement precision, as expressed in coefficient of variation (CV%) in previous articles ranges between 1.85–3.40% for BUA, 0.26–0.30% for SOS, and 1.84–2.35% for SI [19–22]. We calculated the relative change (%) of the QUS parameters (ΔSI, ΔBUA, ΔSOS) between baseline and 2.5y using the next formula: $\Delta parameter = (parameter_{2.5y} — parameter_{baseline})/parameter_{baseline.}$

DXA assessments

DXA was performed on LS and hip using Discovery A System (Hologic Inc., Waltham, MA, USA), at baseline and at first follow-up visit. The machine quality control was performed daily with the spine phantom supplied by the manufacturers. Hip DXA was performed on the left hip. In case of hip replacement, the DXA scan was done on the right side. BMD and BMD T-scores were assessed for the

TH, FN, and LS using NHANES reference database. TBS_{TT} was calculated on the antero-posterior LS DXA scans using a research version of the TBS software, which is corrected for the regional soft tissue thickness (TBS iNsight BetaTT, Medimaps group, Geneva, Switzerland). Both LS BMD and TBS_{TT} were calculated from the L1-L4 region, respecting the ISCD vertebrae exclusion criteria [16]. We calculated the relative change (in %) of DXA parameters (ΔFN BMD and ΔTBS) between baseline and 2.5y visit using the same formula as for the QUS parameters.

Fracture's assessments

Major osteoporotic fractures (MOFs) comprised radiological VF, and clinical hip, forearm, or humerus fractures. Hip, forearm, and humerus fractures data were collected from questionnaires. In the questionnaire, for each fracture, the date of occurrence, type (traumatic, non-traumatic, pathological), and site were specified. Vertebral fractures (VF) were assessed from the vertebral fracture assessment (VFA). Each study participant had a VFA image at each study visit, baseline, and follow-up visits. The presence of VF was assessed at each visit by two independent readers using the Genant's semi-quantitative method [23]; discrepancies were adjudicated with the presence of a third reader. This method grades vertebral fractures from grade 1 to 3, where 3 is the most severe with a vertebra height loss of > 40% and 1 the mildest with a vertebra height loss of 20–25%. In this analysis, moderate (grade 2) and severe (grade 3) VF were included; two grade 1 VF were considered as one grade 2. To note, the percentage height loss is calculated as compared to the adjacent vertebra or its own anterior/posterior/middle height.

CRF and FRAX assessments

General characteristics, history of fractures, bone active medication intake (bisphosphonate, raloxifene, strontium ranelate, denosumab, teriparatide), and CRF data were collected from the questionnaires. The Swiss $FRAX^R$ assessment tool [www.shef.ac.uk/FRAX] was used to estimate the 10-year probability of having a major osteoporotic fracture based only on the CRF.

Statistical analysis

Baseline characteristics of participants were expressed as means and standard deviations (SDs) for continuous variables and as count (%) for categorical variables. Shapiro–Wilk test was used to assess whether variables were normally distributed. Differences between the women who had an incident MOF over 7 years and those who did not were assessed with independent-sample two-tailed *t*-tests or chi-square tests, as appropriate.

Pearson correlation coefficients were used to assess bivariate associations between DXA (LS BMD, FN BMD, LS TBS) and QUS parameters (SI, BUA, SOS, ΔSI, ΔBUA, and ΔSOS). Multivariate binary logistic regressions were used to assess the risk estimates of having an incident MOF per one standard deviation lower value for each three QUS parameters SOS, BUA, and SI (analysis 1) or their relative changes from baseline to the first follow-up visit after 2.5 years (ΔSOS, ΔBUA, ΔSI; analysis 2). For the analysis 1, models were adjusted for (i) FRAX and osteoporosis treatment intake (bisphosphonate, raloxifene, strontium ranelate, denosumab, teriparatide), (ii) additionally for FN BMD, and (iii) additionally for TBS. For analysis 2, models were adjusted for (i) the corresponding baseline QUS value, FRAX and osteoporosis treatment intake (bisphosphonate, raloxifene, strontium ranelate, denosumab, teriparatide), (ii) additionally for ΔFN BMD, and (iii) additionally for ΔTBS.

Incident MOF that had occurred during the 7.5-year period between baseline and visit 4 were considered in the models with baseline QUS parameters (analysis 1). Incident MOF that had occurred during the 5-year period between visit 2 and visit 4 were considered for the models of ΔQUS parameters (analysis 2). The results were expressed as beta standardized coefficients with their respective 95% confidence intervals (95% CI).

$P < 0.05$ was considered statistically significant. All statical analysis were conducted using SPSS Statistics for Macintosh, Version 27.0. Armonk, NY: IBM Corp.

Results

Baseline characteristics

Out of the 1475 post-menopausal women who participated at the baseline visit, 1345 were included in the analysis using the baseline values of the QUS parameters, and 1185 were included in the analysis using the relative changes of the QUS parameters. A flowchart of the study population is shown in Fig. 1.

The baseline characteristics of all study participants and the differences in baseline characteristics between the fractured and non-fractured participants are shown in Table 1. The clinical characteristics of excluded and included participants are provided in supplementary material.

During the mean follow-up period of 6.7 (SD 1.5) years, 200 women experienced a MOF, of which 64% were a VF, 8% hip, 16% humerus, and 12% forearm (7% had two or more MOF). Women who fractured were older; had lower QUS, BMD, and TBS values; higher FRAX-CRF risk; and were more likely to have received osteoporosis treatment.

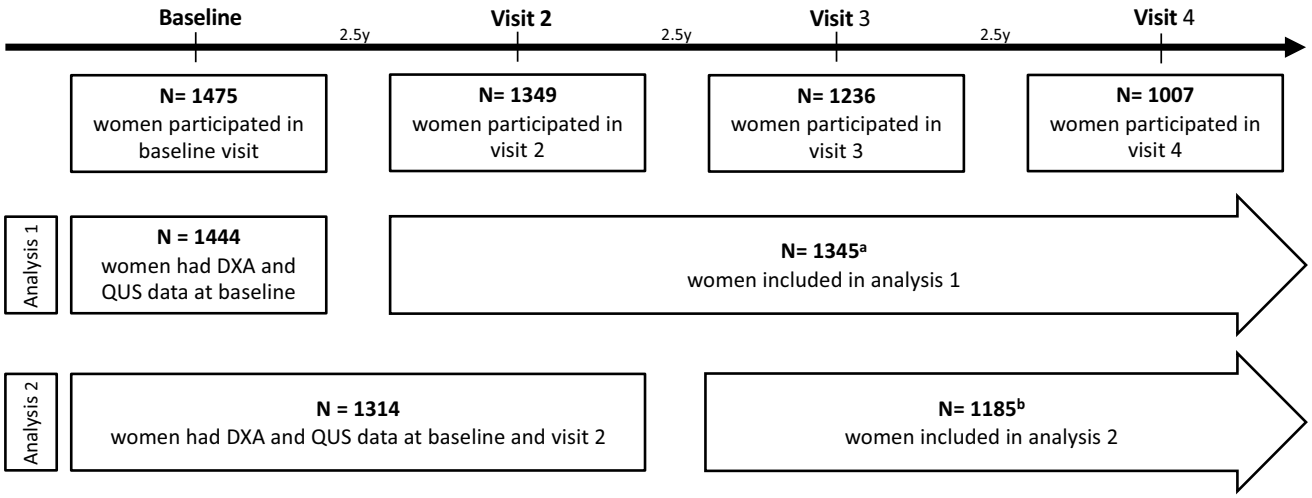

Fig. 1 Flowchart of the study population. Analysis 1: fracture prediction at 7.5 years by baseline QUS; analysis 2: fracture prediction at 5 years by ΔQUS. DXA, dual-energy X-ray absorptiometry; QUS, quantitative ultrasound. [a]Were included those who had DXA and QUS data at baseline and participated at least at visit 2 or 3 or 4; [b]were included those who had ΔDXA and ΔQUS data and participated at least at visit 3 or 4

However, there was no difference between the two groups for ΔBUA and ΔSOS.

Correlation among and between QUS and DXA parameters

We first calculated Pearson's correlation coefficients between LS BMD, FN BMD, LS TBS, SI, BUA, SOS, ΔSI, ΔBUA, and ΔSOS (Table 2). All QUS parameters were moderately positively correlated with FN BMD, LS BMD, and TBS, with SI coefficients higher than for BUA or SOS ($r = 0.449$ to 0.472; vs. 0.376 to 0.422); correlation between BUA and SOS was only slightly stronger ($r = 0.532$; all $p < 0.01$). TBS was significantly correlated with SOS (0.409) and SI (0.472). SI, BUA, and SOS were weakly negatively correlated with their relative change in 2.5 years. There was no significant correlation between QUS relative changes and BMD or TBS values. Partial correlation coefficients adjusted for age and anti-osteoporotic treatment intake showed similar results (not shown).

Performance of QUS parameters in fracture prediction

The odds ratios (95% CI) of having a MOF in the following 6.7 years were, for each SD decrease in SI, BUA, and SOS, 1.59 (1.33–1.90), 1.33 (1.13–1.57), and 1.69 (1.41–2.02), respectively, in a model adjusted for FRAX and anti-osteoporotic treatment intake (Table 3, model 1). These results remained significant after additional adjustment for FN BMD (model 2) and FN BMD and TBS (model 3), except for BUA in model 3 although showing a trend at the limit of significance. For every one SD in SI, BUA, or SOS, there was an inverse increase in the risk of MOF by 1.43 (1.18–1.75), 1.19 (0.99–1.43), and 1.52 (1.26–1.84), respectively, after adjustment for FRAX-CRF, osteoporosis treatment, BMD, and TBS. Similar trends were seen in the analysis for VF only (Supplementary Material). The relative percentage change of SI, BUA, or SOS over 2.5 years was not associated with the odds of having a fracture in the next 5 years in any of the three models (Table 4), which is consistent with QUS ability to provide a screening one-time assessment of fracture risk, in contrast to BMD and TBS which can provide accurate longitudinal measurements.

Discussion

This study investigated the fracture's prediction ability of QUS-derived parameters, and of their relative change in 2.5 years. Our findings showed that the QUS-derived parameters are associated with the odds of having a MOF over a period of 7 years independently not only of the clinical risk factors and BMD, but of TBS also. This implicates that QUS-derived parameters give information on bone health, additionally to BMD and TBS. The relative change of SI, BUA and SOS over 2.5 years was not associated with the odds of having a MOF in the next 5 years.

Correlation between the QUS- and DXA-derived bone parameters

The correlations found between the QUS parameters and BMD values were within the range reported by previous studies,

Table 1 Baseline characteristics of the study population

Characteristic	All, $N=1345$	Incident MOF	
		Yes, $n=200$	No, $n=1145$
Age (years)	64.3 (7.4)	67.1 (7.0)**	63.8 (7.4)**
Weight (kg)	67.4 (12.1)	68.6 (12.4)	67.1 (12.0)
Height (cm)	161.5 (6.7)	162.0 (6.9)	161.4 (6.6)
BMI (kg/m^2)	25.9 (4.5)	26.2 (4.5)	25.8 (4.5)
QUS parameters			
SI	85.43 (15.29)	78.83 (15.19)**	86.59 (15.02)**
BUA (dB/MHz)	108.12 (13.28)	103.95 (12.95)**	108.85 (13.21)**
SOS (m/s)	1548.29 (30.94)	1534.41 (31.41)**	1550.72 (30.22)**
ΔSI %	1.95 (8.64)	3.07 (8.48)*	1.75 (8.66)*
ΔBUA %	1.77 (8.56)	2.29(8.44)	1.68 (8.58)
ΔSOS %	0.06 (1.14)	0.20 (1.13)	0.04 (1.14)
DXA parameters			
FN BMD (g/cm^2)	0.730 (0.114)	0.699 (0.108)**	0.736 (0.115)**
TH BMD (g/cm^2)	0.856 (0.118)	0.816 (0.116)**	0.863 (0.117)**
LS BMD (g/cm^2)	0.926 (0.160)	0.878 (0.155)**	0.936 (0.160)**
FN BMD T-score (SD)	−1.07 (1.03)	−1.35 (0.97)**	−1.01 (1.03)**
TH BMD T-score (SD)	−0.71 (0.96)	−1.03 (0.95)**	−0.65 (0.96)**
LS BMD T-score (SD)	−1.05 (1.47)	−1.50 (1.43)**	−0.96 (1.47)**
LS TBS_{TT}	1.322 (0.100)	1.282 (0.098)**	1.329 (0.099)**
Prevalent MOF at baseline	143 (10.6%)	41 (20.5%)**	102 (8.9%)**
FRAX-CRF (%)	15.43 (9.98)	19.80 (11.28)**	14.86 (9.81)**
Ever had treatment at baseline	131 (9.7%)	28 (14.0%)*	103 (9.0%)*

All values are expressed as mean (SD) or count (%). The differences between the two groups were assessed using a two-tailed independent *t*-test, except for "Ever had a treatment at baseline" and "Prevalent MOF at baseline," for which we used chi-square

MOF = major osteoporotic fracture; BMI = body mass index; QUS = quantitative ultrasound; SI = stiffness index; BUA = broadband ultrasound attenuation; SOS = speed of sound; ΔSI%, ΔBUA%, ΔSOS% = percentage relative change of SI, BUA, SOS over 2.5 years between baseline and visit 2; DXA = dual-energy X-ray absorptiometry FN = femoral neck; BMD = bone mineral density; TH = total hip; LS = lumbar spine; TBS_{TT} = trabecular bone score adjusted to tissue thickness; FRAX-CRF = 10 year probability of having a major osteoporotic fracture based on clinical risk factors

*Statistically significant at $p<0.05$; **statistically significant at $p<0.01$

Table 2 Pearson's correlation coefficient between QUS and DXA parameters

Variable	SI	BUA	SOS	ΔSI	ΔBUA	ΔSOS	LS BMD	FN BMD
BUA	0.877**							
SOS	0.867**	0.532**						
ΔSI	−0.247**	−0.250**	−0.136**					
ΔBUA	−0.174**	−0.385**	0.098**	0.658**				
ΔSOS	−0.095**	0.122**	−0.308**	0.456**	−0.256**			
LS BMD	0.449**	0.409**	0.383**	−0.044	−0.021	−0.025		
FN BMD	0.453**	0.418**	0.376**	−0.065*	0.000	−0.055*	0.616**	
LS TBS	0.472**	0.422**	0.409**	−0.055*	0.006	−0.073**	0.661**	0.577**

SI = stiffness index; BUA = broadband ultrasound attenuation; SOS = speed of sound; ΔSI/ΔBUA/ΔSOS = relative change of SI/BUA/SOS over 2.5 years between baseline and visit 2; LS BMD = lumbar spine bone mineral density; FN = femoral neck; TBS = trabecular bone score

*Statistically significant at $p<0.05$; **statistically significant at $p<0.01$

Table 3 Association between incident MOF and SI, BUA, or SOS

OR (95% CI) for MOF per 1 SD lower value in:			
	SI	BUA	SOS
Model 1	1.59 (1.33–1.90)*	1.33 (1.13–1.57)*	1.69 (1.41–2.02)*
Model 2	1.53 (1.26–1.85)*	1.26 (1.05–1.50)*	1.61 (1.34–1.94)*
Model 3	1.43 (1.18–1.75)*	1.19 (0.99–1.43)	1.52 (1.26–1.84)*

Model 1: adjusted for FRAX and antiosteoporotic treatment; model 2: model 1 adjusted for femoral neck bone mineral density; model 3: model 2 adjusted for trabecular bone score; FRAX: 10-year probability of having a MOF based on clinical risk factors

OR = odds ratio; CI = confidence interval; MOF = major osteoporotic fracture; SD = standard deviation; SI = stiffness index; BUA = broadband ultrasound attenuation; SOS = speed of sound

*Significant at $p < 0.05$

Table 4 Association between incident MOF and the relative percent change over 2.5 years of SI, BUA, or SOS

OR (95% CI) for MOF per 1 SD lower value in relative change (in 2.5 years) of:			
	ΔSI	ΔBUA	ΔSOS
Model 1	0.96 (0.80–1.15)	1.03 (0.84–1.25)	0.98 (0.76–1.27)
Model 2	0.94 (0.78–1.13)	1.01 (0.83–1.24)	0.96 (0.69–1.33)
Model 3	0.94 (0.78–1.13)	0.99 (0.81–1.21)	0.97 (0.73–1.30)

Model 1: adjusted for FRAX, antiosteoporotic treatment and baseline value of the respective parameter SI, BUA or SOS; model 2: model 1 adjusted for Δ femoral neck bone mineral density; model 3: model 2 adjusted for Δ trabecular bone score

OR = odds ratio; CI = confidence interval; MOF = major osteoporotic fracture; SD standard deviation; ΔSI, ΔBUA, ΔSOS = relative change of SI, BUA, SOS over 2.5 years between baseline and visit 2; FRAX = 10-year probability of having a MOF based on clinical risk factors

with BUA being generally more strongly correlated with all BMD values than SOS [24–27]. The degree of correlation between each of the QUS parameters was very close for both BMD and TBS, while previous studies have reported lower correlations between QUS parameters and TBS [14, 15]. As BUA is known as an estimator of bone structure, Olmos et al. speculated that TBS and QUS might be capturing different aspects of bone microarchitecture [14]. The higher correlation between QUS and TBS seen in our study might be due to the TBS version that we use—TBS_{TT}—which is adjusted for tissue thickness, while previous studies used TBS adjusted for BMI. To note, TBS_{TT} has been reported to better predict incident fractures than previous TBS adjusted for BMI [28]. However, the difference between both TBS software version does not substantially affect the correlation of bone properties that QUS and TBS indicate.

Furthermore, SI, BUA, and SOS were all weakly negatively correlated with their relative change over 2.5 years, suggesting that those with higher values of SI, BUA or SOS loose more of the respective parameter over the next 2.5 years than those with lower values. Also, as previously seen, ΔSOS and ΔBUA were negatively correlated, indicating for changes in different directions over the 2.5 years. Schott et al. [29] followed 113 healthy post-menopausal women for 1.9 years and found no significant correlation between ΔSOS and ΔBUA ($R = +0.13$; $p = 0.2$). Rosenthall et al. [30] studied the change of QUS parameters after 1 to 4 years of treatment with estrogen, bisphosphonate, high-dose vitamin D, and calcium or combination of them in 673 postmenopausal women and reported a negative correlation between SOS and BUA changes only among the treated individuals. They attributed this difference to the different bone properties assessed by the two parameters. In vivo studies [31, 32] have shown that BUA is influenced by bone density and structure, and SOS by bone density and elasticity. In our analysis, this correlation remained negative after adjusting for anti-osteoporotic treatment intake, suggesting that there was no effect of treatment on this correlation.

CRF-, BMD-, and TBS-independent association with fracture risk of the QUS parameters

Our study showed the QUS-derived parameters ability to predict MOF independently of FRAX, BMD, TBS, and anti-osteoporotic treatment intake over a mean follow-up period of 6.7 years. As a summary of previous studies, McCloskey et al. [6] concluded, in an individual level meta-analysis regrouping 46,124 participants, that QUS is a predictor of fracture in men and women independently of both age and BMD, particularly at low value, but its prediction ability decreases over the follow-up time since QUS assessment.

Our results showing that QUS predicts MOF independently of FRAX are consistent with the data from other prospective studies. Hans et al. [33] followed 13,000 postmenopausal women and found that combining CRF and SI predicts better the 10-year hip fracture probability than CRF or SI alone. Another similar study concluded that BUA could predict fractures independently of CRF and BMD [34]. Also, in accordance with other studies, the predictive value of QUS parameters dropped when further adjusting for BMD although remaining significant [6, 35]. In our study, this remained true after additional adjustment for TBS, with the OR for BUA at the limit of significance. This independence in fracture prediction could be explained by the fact that QUS is measured at a different site than TBS and BMD; it is known that bone measurements differ from one site to another. Also,

QUS and DXA might capture complementary properties of bone health, which are predictors of fracture.

Among the three QUS parameters assessed, in the current study, SOS has the highest association with the odds of fracture, approximately 10 to 40% higher than SI and BUA, respectively. Other studies have reported that SI or BUA are superior to SOS at fracture prediction [6, 35]. This variability might be due to the type of osteoporotic fractures considered, as 64% of the MOF in our study were VF; a similar trend with SOS being a better predictor than BUA was observed in other studies on VF [6, 35, 36].

The change of QUS parameters over 2.5 years and its fracture predictive ability

This analysis showed that the changes of all three QUS parameters over 2.5 years were not associated with the odds of having a fracture in the following 5 years. The variation of QUS over time in adults has been studied in different contexts, mainly in interventional studies [25, 30, 37–40], in the evolution of QUS with ageing [29], in the comparison of QUS and DXA [20], and in the evaluation of the performance of QUS devices [19, 21]. In overall, QUS has a good precision, yet it remains low compared to the observed rates of change. In fact, the precision error of BUA and SOS is respectively 6–9 and 2–8 times larger than their annual rate loss [41]. This limits the QUS use as a relevant tool for treatment monitoring. However, Sahota et al. [25] suggested that it might be useful for longer-term monitoring. In this line, the lack of association of the QUS parameters changes over 2.5 years with fracture risk in our study, was expected.

Strengths and limitations

To our knowledge, this is the first study assessing the prediction of fracture from QUS parameters independently of TBS in addition to FRAX and BMD. The monocentric nature of the OsteoLaus cohort, where all measurements were done under the same conditions (QUS, DXA, VFA), the homogeneity of the cohort (women over 50 years), and the performance of the QUS assessments by the same technician at each visit for all visits represent a significant strength for the current study.

Some limitations need to be considered. First, the cohort is composed of European post-menopausal women; thus, the results may not be applicable to non-Europeans and to men. Second, the non-VF MOF were self-reported. Efforts to confirm them from medical records were made, but this could not be achieved for each case. However, VF which constitute 63% of the MOF, were assessed from VFAs by two independent experts. Third, the 2.5-year period to calculate a variation of QUS may be too short, as natural variation of QUS parameters is low regarding their precision [41]. Fourth, the precision of the QUS measurements was not calculated in the OsteoLaus Study center.

Conclusion

In conclusion, this study shows that heel QUS predicts fractures over a 6.7-year study duration, independently of FRAX-CRF, femoral neck BMD, and TBS. These results reinforce the rationale for using QUS combined with CRFs as a case finding/pre-screening tool as an alternative to FRAX-CRF or DXA when the latter is unavailable. Variation of QUS over 2.5 years did now show promise for future fracture prediction. Thus, it should not be used to monitor patients given changes in QUS are not associated with fracture risk.

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Declarations

Conflict of interest Didier Hans holds stock in Medimaps Group, the makers of the Trabecular Bone Score software. Antoine Métrailler, Olivier Lamy, Elena Gonzalez Rodriguez, and Enisa Shevroja declare that they have no conflict of interest.

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