Bi-directional Axial Transmission measurements is an easy to apply methodology allowing risk assessment of fracture in elderly

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BI-DIRECTIONAL AXIAL TRANSMISSION MEASUREMENTS IS AN EASY TO APPLY METHODOLOGY ALLOWING RISK ASSESSMENT OF FRACTURE IN ELDERLY

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ABSTRACT

Accurate measurement of cortical bone parameters may improve fracture risk assessment and help clinicians on the best treatment strategy. The objective of this cross-sectional study was to evaluate the performance of a Bi-Directional Axial Transmission (BDAT) device used by trained operators in a clinical environment with elderly subjects. The device, positioned at one-third distal radius, provides two velocities: VFAS (first arriving signal) and VA0 (first anti-symmetrical guided mode). Moreover, two parameters are obtained from an inverse approach: Ct.Th (cortical thickness) and Ct.Po (cortical porosity). The areal bone mineral density (aBMD) was obtained using DXA at the femur and spine. Eighty seven (65 women, 22 men) from Marien Hospital and St. Anna Hospital (Herne, Germany) were included in this study. Age ranged from 41 to 95 years, while body mass index (BMI) ranged from 17 to 47 kg.m-2. We found the ratio CtPo/Ct.Th to be predictive for non vertebral after sex, BMI and age adjustment (OR=2.62, AUC=0.83), comparable to femoral aBMD (OR=3.48, AUC=0.82). The fracture risk assessment by BDAT method in elderly, in a clinical setting, suggests the benefit of the affordable and transportable device for the routine use.

1. INTRODUCTION

Osteoporosis is a skeletal disease leading to bone fragility and increasing the risk of fractures. [1] Osteoporosis still remains a major public health problem worldwide and it is therefore crucial to prevent severe fractures responsible for excess of mortality and considerable morbidity [2]. Patient at risk of fractures are currently identified as having osteoporosis using Dual-energy X-ray Absorptiometry (DXA), assessing the areal or projected Bone Mineral Density (BMD g.cm^{-2}), directly measured at the main fracture sites, i.e., hip and spine [3]. However, even if DXA remains the current gold standard, it is limited by the difficulty to set a threshold in the BMD distribution for osteoporosis diagnosis. [4] Indeed, the majority of individuals who have low-trauma fractures have a T-score higher than the threshold defined by the World Health Organization (WHO), i.e., T-score = 2.5. [5] Moreover, some diseases (diabetes, obesity) and treatments (glucocorticoids) are associated with an increase of fracture risk without a BMD decrease.

One of the reasons for the DXA limitation is that it does not capture alterations of bone quality factors, namely the material and structural properties, and particularly those of cortical bone. Indeed, because of its projection technique and low spatial resolution, DXA is not able to separate trabecular and cortical compartments. In the past two decades, multiple technologies have emerged to assess bone quality, providing in particular cortical bone parameters. Among these, Quantitative Computed Tomography (QCT) has the ability to provide 3D bone volume, from which image processing techniques propose to extract material and geometrical properties such as cortical thickness (Ct.Th), cortical porosity (Ct.Po) and volumetric bone mineral density (vBMD g.cm-3). On the one hand, QCT has the advantage to be directly performed at the hip and spine. [6] On the other hand, High resolution-peripheral QCT (HR-pQCT) has a better resolution, but it can be performed only at peripheral sites such as tibia and radius. [7]

Quantitative ultrasound (QUS) have the advantages of portability, low cost, absence of radiation and need for a radiographic technologist or designated room, and are sensitive to both elasticity and geometry of the medium explored by the waves. There are currently different approaches for QUS: transverse transmission targeting cancellous bone at the heel, the earliest and best-validated clinical bone ultrasound device, transverse transmission, back scattering, [8] pulse-echo techniques, [9, 10] and axial transmission (AT), with transducers aligned along the bone axis, specifically designed to measure cortical bone.

The typically measured clinical parameter is the velocity of the First Arriving Signal (VFAS also sometimes designated as speed of sound SOS). Its fracture discrimination ability has been shown similar or equivalent to DXA in numerous clinical studies since the 1990's. [11, 12]

To provide QUS parameters beyond FAS and BMD, the complete recorded signals, and not only the first arrival part, could be studied. Indeed, the signal richness is due to the waves guided by the cortical shell, originated in the reflections and interference along the propagation path. Therefore, measured ultrasonic Guided Waves (GW) associated with an appropriate waveguide model have the potential to yield estimates of cortical thickness using the the fundamental flexural guided waves (FFGW), [13] or combined material and geometrical cortical properties using all measured guided modes. [14] Recently, the bidirectional axial transmission (BDAT) allowed the concurrent identification of cortical thickness (Ct.Th) and porosity (Ct.Po) of *ex vivo* human specimens. [15] In a recent clinical study, assessment of CT.Th and Ct.Po by BDAT were used to discriminate between (non traumatic) fractured and non-fractured patients. [16] In this pilot study, BDAT measurements were carried out by physicists. The aim of this study is to test if the device could be easily used in a clinical environment, by hospital operators, in a similar cross-sectional study. Assessment of cortical thickness (Ct.Th) and porosity (Ct.Po) by BDAT may improve the identification of patients at high risk of fracture.

2. MATERIALS AND METHODS

2.1 Subjects

One hundred and nineteen patients (93 women, 26 men), aged from 41 to 95 years old, BMI from 16 to 47 $kg.m^{-2}$, were recruited from Marien Hospital and St. Anna Hospital (Herne, Germany) between August 2018 and February 2019. Exclusion criteria were: traumatic fracture (n = 1), femoral DXA failure (n = 10), vertebral DXA failure (n = 10) and ultrasonic measurement failure (n = 11). Thus, 87 patients are the basis of this study. A written informed consent was provided by the subjects. The procedure of the study was in accordance with the Declaration of Helsinki. The information about non-traumatic fracture, including site and time, was collected in medical records. Three groups were created: a control group with patients without non-traumatic fracture (NF); patients with any non-traumatic fracture (F); patients without vertebral fracture (NVF). Each patient of the fractured group presented only one non-traumatic fracture, i.e., there is no patient with multiple fracture.

2.2 Measurements

Ultrasonic measurement were performed using the QUS device (Azalée, Paris, France) consisting in three custom-made parts. First, a 1-MHz bi-directional axial transmission (BDAT) probe adapted to forearm measurements (Vermon, Tours, France), is composed of a linear array of piezocomposite elements divided in three parts: one array of 24 receivers surrounded by two arrays of 5 transmitters each. Second, an electronic device used to transmit, receive and digitize signals (Althaïs, Tours, France). The electronic device allows exciting each transmitter successively with a wideband pulse (170 V, 1-MHz central frequency). Third, a human machine interface (HMI), developed to display the spectrum of guided waves and provide the cortical parameters in quasi real-time (at a frame rate up to 4 Hz) and to guide the operator in finding during measurement the optimal position of the probe with respect to the main bone axis (Bleu Solid, Paris, France).

Estimation of cortical thickness and porosity is an extension of the signal processing applied to extract the experimental guided mode wave numbers from the maxima of the so-called *Norm* function. [17] Details can be found in Refs. [15] and [16]. In addition, two ultrasonic velocities VFAS and VA0 are also measured. [18] Finally, four cortical parameters is achieved through an approach described in previous works. A specific scanning methodology was carefully followed for measuring the patients. Measurements were done on the non-dominant forearm. When the non-dominant forearm undergoes a recent fracture for example, measurements were done on the contralateral arm. BDAT measurements were performed on a standardized region of interest (ROI), i.e., the center of the probe is placed at the lateral side of the one-third distal radius. The probe was placed in contact with the skin using ultrasonic gel for coupling (Aquasonic, Parker Labs Inc., Fairfield NJ, USA). The measurement protocol consists of four series of ten acquisitions. By means of the parameter values displayed in real-time by the HMI, once a correct position is found, a series of ten successive acquisitions are recorded without moving the probe. Each series corresponds to an intermediate repositioning of the probe. The final values of the identified waveguide parameters are set to the mean of the values of each successful series. The BDAT measurement on a patient typically lasts 10 to 15 minutes. Measurement were performed by clinical operators after a 2 day training session.

DXA measurements of the L1–L4 lumbar spine (BMD spine), femoral neck (BMD neck) and total femur (BMD femur) were performed on patients. The femoral BMD values corresponded to the mean of both femurs. If only one side was available, the retained BMD corresponded to the existing value.

2.3 Statistical analysis

Statistical analyses have been performed using the Statistics and Machine Learning Toolbox provided by Matlab (MathWorks, Natick, MA USA). Non parametric tests were used. For each variable, a Wilcoxon–Mann–Whitney test was performed to determine whether the values were significantly different between the non-fractured group and any non-traumatic fractured group. Spearman's rank correlation analysis was used to compare estimates of ultrasonic parameters with age, BMI and BMD values. The level of statistical significance in both tests was determined at a p-value below 0.05.

In order to assess the ability of the different measurements to discriminate the any fractured group from the non-fractured group, odds ratios (ORs) were calculated using binomial logistic regression analysis. ORs are expressed as increases in the estimated fracture risk per one standard deviation decrease. To estimate the sensitivity and specificity of the different parameters for the fracture discrimination, the receiver operator characteristic (ROC) curves were calculated. In addition, the area under the curve (AUC) was determined. Adjusted ORs and AUCs were computed with age, sex and BMI as covariates. Combinations of QUS parameters were also investigated.

3. RESULTS

3.1 BDAT measurement failure

The ultrasonic measurement failed for 9.2 % of the total cohort (11 out of 119). Figure 1 displays the failure rate as a function of BMI or age together with the BMI and age distributions. It can be observed that failure rate tends to increase with age and BMI. No association were observed between measurement failure and fractures.

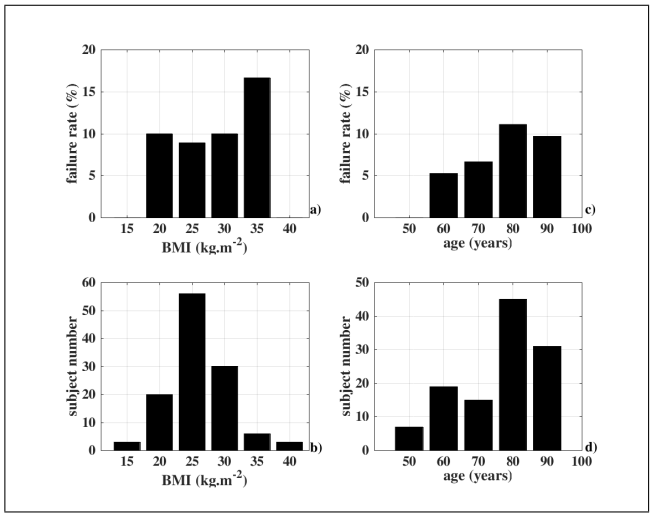

Figure 1. Failure rate and distribution for BMI and age.

3.2 Patient characteristics

Among the 87 patients for for whom the measurements were successful, 64 belongs to the control group without fracture (NF), 23 with non-traumatic fractures (F), 10 with vertebral fractures and 13 with non vertebral fractures (NVF) corresponding to the following sites: femur (n = 10), humerus (n = 2) and elbow (n = 1). The patient characteristics are shown in Table 1. As expected, age was significantly higher for fractured population (79.9 years) than for controls (72.9 years). The age difference is larger between non-vertebral fractures (84.5 years) and controls. No significant difference were observed in BMI, height and weight between groups. Femoral BMD (total and neck) were lower in fractured groups ($p < 0.01$) while BMD spine was not different between fractured and non-fractured groups. Ct.Th was marginally lower in fractured groups (2.3 - 2.4 mm; p = 0.10) in comparison with the non-fractured group (2.6 mm). Ct.Po was higher in the fractured groups (11.1-12.9 %) compared to the non-fractured group (9.7 %), however the difference was only significant for the NVF group (p = 0.03). The ratio Ct.Po / Ct.Th was significantly higher in both fractured groups (4.8 – 5.9) compared to the non-fractured group (3.8). The two ultrasonic velocities VFAS and VA0 are lower in the fractured groups. The VFAS difference is significant for both groups while VA0 difference is significant only for NVF fractures.

Table 1. Descriptive characteristics as mean and standard deviation

	NF (N = 64)	F (N = 23)	NVF (N = 13)
age (years)	72.9 (13.4)	79.9 (9.7) *	84.5 (6.7) **
Height (cm)	165.4 (8.6)	164.3 (8.5)	163.1 (8.3)
Weight (kg)	72.9 (18.9)	69.9 (11.3)	66.6 (10.6)
BMI (kg.m^{-2})	26.4 (5.6)	25.9 (3.6)	25.0 (3.0)
sex ratio (men/total %)	23.4	30.4	23.1
US Ct.Th (mm)	2.64 (0.62)	2.38 (0.67)	2.29 (0.67)
US Ct.Po (%)	9.7 (4.7)	11.1 (4.6)	12.9 (4.4) *
US Ct.Po / Ct.Th	3.81 (1.84)	4.83 (1.79) *	5.69 (1.48) **
US VFAS (m.s-1)	4003 (96)	3948 (86) *	3937 (78) *
US VA0 (m.s-1)	1686 (71)	1658 (70)	1635 (63) *
BMD tot (g.cm-2)	881.5 (166.4)	773.8 (134.2) **	748.4 (136.8) **
BMD fn (g.cm-2)	834.5 (148.9)	729.2 (115.4) **	692.2 (109.3) **
BMD spine (g.cm-2)	1073.5 (247.0)	988.3 (197.9)	961.3 (178.9)

BMI, body mass index; US ultrasound; Ct.Th, cortical thickness;
Ct.Po cortical porosity;
BMD, bone mineral density; NF non fractured, F all non traumatic fractures
NVF non vertebral fractures
*p<0.05 vs non-fractured group, **p<0.01 vs non-fractured group,
***p<0.001 vs non-fractured group.

3.3 Fracture discrimination

Weak to moderate significant Spearman's correlations (R ranging from 0.26 to 0.62, $p < 0.05$) were found between ultrasound parameters and age, BMI and aBMD. Due to these correlations, systematic adjustment for cofounder variables age, BMI and sex was made for all the analyses. The results of the logistic analysis and AUC are shown in Table 2 for the NVF group. The p values of significant results ($p < 0.05$) are indicated in bold letters. Unadjusted and adjusted femoral BMDs were discriminant for all non-traumatic [AUC : 0.74; OR: 2.6-2.9] and non-vertebral fractured [AUC: 0.84; OR: 3.3-3.5] groups. Lumbar spine BMD was not discriminant for any fractured group. Unadjusted VFAS and Ct.Po/Ct.Th were discriminant for all non-traumatic [AUCs: 0.65-0.67; ORs: 1.7-1.8] and non-vertebral fractured [AUCs: 0.71-0.78; ORs: 2.1-3.1] groups. In addition, unadjusted VA0 and CT.Po were discriminant only for non-vertebral fractured [AUCs: 0.7; ORs: 2.0-2.2]. Considering the unadjusted combination of Ct.Th and CT.Po, Ct.Th could discriminate all fractured group from the non-fractured group [AUC: 0.66; OR: 1.7] while both parameters could discriminate non-vertebral fractures [AUC: 0.79; ORs: 2.8-3.2].

No adjusted BDAT parameters could discriminated non-traumatic fractures, however VFAS was found marginally discriminant (p = 0.10). In case of non-vertebral fractures, both Ct.Po/Ct.Th and Ct.Po combined with Ct.Th were found significantly discriminant [AUC: 0.83; ORs: 2.6-3.0].

For all non-traumatic, BMD femur performed better than BDAT parameters in terms of AUCs and ORs. On the contrary for non-vertebral fractures, femoral BMD and combined BDAT Ct.Th and CT.Po discrimination performance were comparable. It can be noted the discrimination was improved by combining Ct.Th and CT.Po parameters in comparison with sole parameters. Combinations with VFAS and VA0 or between BDAT and BMD parameters were not found increasing discrimination. No parameter (BDAT nor DXA) was found discriminant of the 10 patients with vertebral fractures.

Table 2. Odds ratios (OR) and areas under the ROC curve (AUC)

	Non vertebral fractures NVF (N = 13)		
	AUC [95% CI]	OR [95% CI]	*p*
unadjusted parameters			
Ct.Th	0.65 [0.45 - 0.79]	1.71 [0.92 - 3.16]	0.082
Ct.Po	0.69 [0.46 - 0.82]	1.99 [1.05 - 3.77]*	**0.031**
VFAS	0.71 [0.55 - 0.83]	2.06 [1.07 - 3.99]*	**0.028**
VA0	0.71 [0.55 - 0.85]	2.25 [1.08 - 4.65]*	**0.026**
BMD tot	0.74 [0.60 - 0.86]	2.53 [1.19 - 5.40]*	**0.014**
BMD fn	0.77 [0.62 - 0.89]	3.48 [1.43 - 8.50]**	**0.005**
BMD spine	0.63 [0.49 - 0.77]	1.69 [0.85 - 3.37]	0.128
Combination of ultrasonic parameters			
Ct.Po / Ct.Th	0.78 [0.60 - 0.88]	3.05 [1.44 - 6.46]**	**0.003**
Ct.Th	0.79 [0.67 - 0.91]	2.76 [1.20 - 6.34]*	**0.015**
Ct.Po		3.21 [1.33 - 7.72]**	**0.008**
ajusted parameters			
Ct.Th	0.77 [0.60 - 0.86]	1.13 [0.56 - 2.30]	0.731
Ct.Po	0.81 [0.72 - 0.92]	1.75 [0.84 - 3.65]	0.125
VFAS	0.77 [0.62 - 0.88]	1.39 [0.61 - 3.14]	0.421
VA0	0.77 [0.60 - 0.85]	1.69 [0.64 - 4.50]	0.282
BMD tot	0.81 [0.64 - 0.92]	3.33 [1.10 - 10.04]*	**0.029**
BMD fn	0.82 [0.71 - 0.91]	3.48 [1.11 - 10.91]*	**0.029**
BMD spine	0.78 [0.65 - 0.87]	1.62 [0.64 - 4.07]	0.296
adjusted combination of ultrasonic parameters			
Ct.Po / Ct.Th	0.83 [0.71 - 0.91]	2.62 [1.02 - 6.75]*	**0.042**
Ct.Th	0.83 [0.73 - 0.92]	2.33 [0.81 - 6.72]	0.112
Ct.Po		3.04 [1.04 - 8.92]*	**0.038**

Reference category is non fractured (NF) *N* = 64. CI confidence interval.
ROC receiver operating characteristic
AUC and OR are adjusted for age, BMI and sex. *p < 0.05. **p < 0.01
***p < 0.001

4. DISCUSSION

This study investigated the ability of the four QUS parameters Ct.Th, Ct.Po, vFAS, and VA0 estimated from measurements at the one-third distal radius. The measurements were performed using a guided wave technology to retrospectively discriminate patients with non-traumatic fractures from the control group in a clinical environment. The discriminator values of QUS parameters were assessed using a binomial logistic regression analysis. The main findings from this study were that combination of Ct.Po and Ct.th was discriminant for all non-traumatic fractures (F) and in particular, for non-vertebral fractures (NVF) comparable to femoral BMD.

A second observation was that the failure rate decreased to 9 % (11 out of 119) lower than 20 % observed in the pilot clinical study. [16]) This is likely due to the improvement of the guiding interface and protocol adapted for trained operators. The current version provides a real time numerical feedback about the probe alignment while previously the feedback was visual and more operator dependant.It can be noticed that this failure rate is comparable with DXA failure rate (10 – 11%) [19] and previous ultrasonic devices. [12, 13] It can be noticied that four patients corresponded to failure for both BDAT and vertebral DXA.

Our study demonstrate the clinical utility of bi-directional axial transmission measurements, corroborating previous BDAT study showing Ct.Po adjusted with age, BMI and cortisone, as discriminant parameter. [16] However, in the pilot clinical study, the reference population was younger (NF 62 $\pm$ 7 years *vs* 73 $\pm$ 13 in this study) and no men were included. The lack of sensitivity to vertebral fractures in this study may be partly explained by the fact that vertebral fractures are associated with trabecular bone [20] whereas the measurement site (one-third distal radius) is mainly cortical.

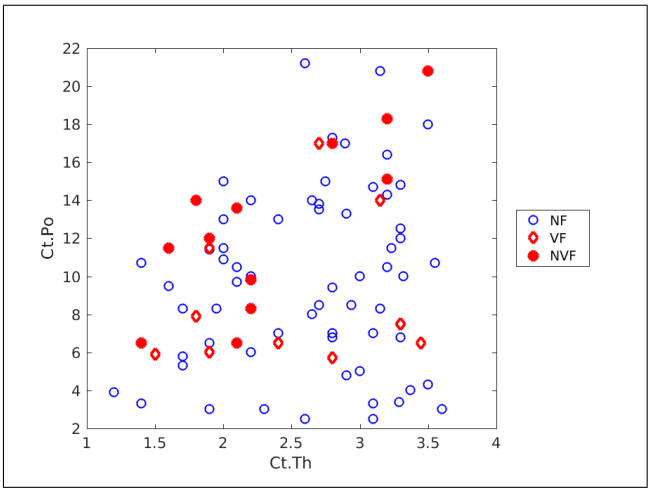

Figure 2. values of Ct.Th and Ct.Po for the non fractured patients (NF, blue circle) and patients with vertebral (VF, red diamond) and non-vertebral (NVF, full red circles) fractures.

Figure 2 illustrates how the discrimination occurred in the 2D Ct.Th – Ct.Po plane in agreement with Table 2 indicating that discrimination was better for combination of parameters Ct.Po and Ct.Th than sole parameter. One can also observe that the discrimination was better for non-vertebral fractures (NVF) than vertebral fractures (VF). This latter finding is in agreement with the conclusion provided by Choksi *et al* in their recent review paper: [5] "*New*

techniques that not only measure aBMD but also measure critical indices directly related to fracture risk such as bone size, porosity, cortical thickness [...] are needed. Even better, having such a device that is affordable and appropriately sized allowing clinicians to assess fracture risk in the clinic is the future of osteoporosis care."

5. CONCLUSION

In summary, this study shows the potential of BDAT measurements to provide *in vivo* cortical thickness and porosity estimates using a portable and non-ionizing device.The fracture risk assessment by BDAT method in elderly, in a clinical setting, suggests the benefit of the affordable and transportable device for the routine use.

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