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In vivo pulse-echo measurement of apparent broadband attenuation and Q factor in cortical bone: A preliminary study

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Abstract

Quantitative UltraSound (QUS) methods have been introduced to assess cortical bone health at the radius and tibia through the assessment of Cortical Thickness (Ct.Th), Cortical Porosity (Ct.Po) and bulk wave velocities. Ultrasonic attenuation is another QUS parameter which is not currently used. We assess the feasibility of *in vivo* measurement of ultrasonic attenuation in cortical bone with a broadband transducer with 3.5 MHz-center frequency. Echoes from the periosteal and endosteal interfaces were fitted with Gaussian pulses using sparse signal processing. Then, the slope of the Broadband Ultrasonic Attenuation (Ct.nBUA) in cortical bone and quality factor Q_{11}^{-1} were calculated with a parametric approach based on the center-frequency shift. Five human subjects were measured at the one-third distal radius with pulse-echo ultrasound, and reference data was obtained with high-resolution X-ray peripheral computed tomography (Ct.Th and Cortical volumetric Bone Mineral Density, Ct.vBMD). Ct.Th was used in the calculation of Ct.nBUA while Q_{11}^{-1} is obtained solely from ultrasound data. The values of Ct.nBUA

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(6.7 ± 2.2 dB.MHz. $^{-1}$.cm $^{-1}$) and Q_{11}^{-1} (8.6 ± 3.1 %) were consistent with the literature data and were correlated to Ct.vBMD ($R^2 = 0.92$, $p < 0.01$, $RMSE = 0.56$ dB.MHz $^{-1}$.cm $^{-1}$, and $R^2 = 0.93$, $p < 0.01$, $RMSE = 0.76\%$). This preliminary study suggests that the attenuation of an ultrasound signal propagating in cortical bone can be measured *in vivo* at the one-third distal radius and that it provides an information on bone quality as attenuation values. It remains to ascertain that Ct.nBUA and Q_{11}^{-1} measured here exactly reflect the true (intrinsic) ultrasonic attenuation in cortical bone. Measurement of attenuation may be considered useful for assessing bone health combined with the measurement of cortical thickness, porosity and bulk wave velocities in multimodal cortical bone QUS methods.

Keywords: cortical bone, broadband ultrasonic attenuation, Quantitative Ultrasound, *in vivo* measurement, Orthogonal Matching Pursuit, sparse reconstruction, Q factor

1 Introduction

2 Osteoporosis fracture risk is currently assessed using Dual energy X-
3 ray Absorptiometry (DXA) in order to assess areal Bone Mineral Density
4 (aBMD). However, DXA has strong limitations, in particular it lacks sen-
5 sitivity (Briot et al., 2013; Siris, 2004) and is not appropriate to monitor
6 cortical bone (Choksi et al., 2018). Cortical bone, the dense tissue that
7 forms the outer shells of the bones, represents about 80% of the human
8 skeleton mass and plays an important role in the skeletal mechanical sta-
9 bility (Holzer et al., 2009; Zebaze et al., 2010; Bala et al., 2014). Aging
10 and bone pathologies are associated with cortical thinning (Nishiyama et al.,
11 2010) and weakening of the bone material mechanical quality reflected in
12 an increase of Cortical Porosity (Ct.Po) (Kral et al., 2017) or a decrease of
13 Cortical volumetric Bone Mineral Density (Ct.vBMD (CT.vBMD) (Ostertag
14 et al., 2016; Paranhos Neto et al., 2019).

15 Several quantitative ultrasound (QUS) approaches have been introduced
16 to assess cortical bone health at the radius and tibia. Some aim at assessing
17 Cortical Thickness (Ct.Th) assuming a nominal value of ultrasound veloc-
18 ity using pulse-echo (Karjalainen et al., 2008), axial transmission (Moilanen,
19 2008), or through transmission measurements (Sai et al., 2010). Other ap-
20 proaches are designed for a combined estimation of Ct.Th and Ct.Po or bulk
21 wave velocities using axial transmission measurements of several guided wave
22 modes (Foiret et al., 2014; Minonzio et al., 2019) or adaptative pulse-echo
23 imaging with a transducer array (Renaud et al., 2018, 2020). Ultrasonic at-
24 tenuation is another QUS parameter which has been exploited for several
25 decades in soft tissues (Mamou and Oelze, 2013) and trabecular bone (Lang-
26 ton and Njeh, 2008); however, until now, it has received little consideration
27 in cortical bone QUS.

28 *Ex vivo* studies on cuboid specimens have established that ultrasonic at-
29 tenuation of bulk waves in cortical bone is related to mass density (Bernard
30 et al., 2015) and to Ct.vBMD (Sasso et al., 2008). Also, simulations have sug-
31 gested that the scattering of ultrasound by the cavities of the pore network
32 is one important mechanism of attenuation (Yousefian et al., 2018, 2021; Iori
33 et al., 2020). It follows that, in addition to ultrasonic velocities measured
34 with QUS approaches (Grimal and Laugier, 2019), attenuation could be in-
35 dicative of the mechanical quality of cortical bone as it is related to Ct.Po
36 and Ct.vBMD.

37 There has been a few attempts to measure attenuation in *ex vivo* bone

38 specimens. Zheng et al. (2007) measured in pulse echo mode a bovine femur
39 specimen and estimated the slope of the frequency-dependent attenuation co-
40 efficient (also referred to as "spectral ratio method") to estimate the so-called
41 Cortical normalized Broadband Ultrasonic Attenuation (Ct.nBUA). They
42 later used a parametric approach introduced by Kuc et al. (1976) which re-
43 lated attenuation to the shift of the center frequency (also referred to as "peak
44 frequency method") (Zheng et al., 2009). Dencks et al. (2008) also used this
45 parametric approach and measured nBUA in proximal femurs in through-
46 transmission. However, these values of nBUA can hardly be interpreted in
47 terms of bulk cortical bone material properties because ultrasound propa-
48 gated along a complex path through both cortical and trabecular bone. As
49 far as we know, *in vivo* measurements of attenuation in cortical bone have
50 not yet been reported.

51 The aim of this paper was to assess the feasibility of *in vivo* measurement
52 of attenuation in cortical bone. We have conducted a preliminary study on
53 the radius of five human subjects. Ultrasound echoes stemming from the
54 normal-incidence reflection on the outer (periosteal) and inner (endosteal)
55 cortical bone interfaces were recorded and processed with Orthogonal Match-
56 ing Pursuit (OMP) to retrieve the time delay, the temporal echo width and
57 the frequency shift of the center frequency from which Ct.nBUA and the
58 quality factor Q were calculated with a parametric approach (Kuc et al.,
59 1976). The quality factor is introduced as a quantity related to the dissipa-
60 tion of energy which can be measured without the need of the knowledge of
61 the bulk wave velocity. Ultrasound parameters Ct.nBUA and Q were com-
62 pared to reference values of Ct.vBMD of each subject which were obtained
63 with High-Resolution X-ray peripheral Quantitative Computed Tomography
64 (HR-pQCT). The results are of interest for the development of future multi-
65 modal cortical bone QUS approaches estimating bone structural (thickness)
66 and material (porosity, velocities, attenuation) properties for the evaluation
67 of bone health.

68 1. Method

69 1.1. Extraction of echoes

70 The signal received in the pulse-echo ultrasound measurement is modeled
71 as a sum of two Gaussian pulses $s_i(t)$, or Gabor functions, i.e., the product
72 of a Gaussian function with a complex sinusoid (Demirli and Saniie, 2001)

$$y(t) = \sum_{i=1}^2 s_i(t) + n(t) = \sum_{i=1}^2 A_i \exp\left[-\frac{(t-t_i)^2}{2\sigma_{t_i}^2}\right] \cos[2\pi f_i(t-t_i)] + n(t), \quad (1)$$

73 where σ_{t_i} is the standard deviation of the temporal Gaussian function, f_i is
 74 the central frequency, t_i is the group delay and A_i is the amplitude of i -th
 75 echo. The error between the model and the measured signal, including noise,
 76 is $n(t)$. The first and second echoes correspond to the reflections on the outer
 77 (periosteal) and inner (endosteal) bone surfaces, respectively.

78 For further use, we write the temporal Fourier transform of one echo as

$$S_i(f) = \frac{A_i}{\sqrt{2\pi}\sigma_{f_i}} \exp\left[-\frac{(f-f_i)^2}{2\sigma_{f_i}^2}\right] \exp[-j2\pi f t_i], \quad (2)$$

79 where the standard deviation of the Gaussian function σ_{f_i} satisfies $2\pi\sigma_{f_i} =$
 80 $1/\sigma_{t_i}$. The -6dB frequency bandwidth, or full width at half maximum, is
 81 related to σ_{f_i} , and is equal to $2\sqrt{2\ln(2)}\sigma_{f_i} \approx 2.35\sigma_{f_i}$.

82 The echoes are isolated using a sparse signal processing method in the
 83 time domain which provides the quantities σ_{t_i} , f_i , t_i , and A_i ($i = 1, 2$). The
 84 method is detailed in Appendix ; shortly, the signal model, given by (1),
 85 discretized in time can be represented as

$$\mathbf{y} = \mathbf{D}\mathbf{x} + \mathbf{n}, \quad (3)$$

86 where \mathbf{y} and \mathbf{n} are $N_t \times 1$ vectors corresponding to the sampling of $y(t)$ and
 87 $n(t)$ at N_t discrete time points, respectively. Likewise, \mathbf{x} is a $N_m \times 1$ vector
 88 collecting the N_m relative amplitudes of the echoes. In a sparse point of view,
 89 only a few elements of this vector are non zero. Finally, \mathbf{D} is a $N_t \times N_m$ ma-
 90 trix corresponding the so-called dictionary. Each column $\mathbf{d}(t; \sigma_{t_m}, f_m, t_m)$,
 91 with $m = 1 \cdots M$, of \mathbf{D} is one of the M Gabor functions discretized at
 92 N_t time points, defined by the set of parameters (σ_{t_m}, f_m, t_m) . For a given
 93 measurement $y(t)$, the problem amounts to determine the two non-zero com-
 94 ponents of \mathbf{x} , which indices yield the set of parameters corresponding to the
 95 two echoes. This is done by sparse reconstruction with Orthogonal Matching
 96 Pursuit (OMP) (Tropp and Gilbert, 2007). The details of the construction of
 97 the dictionary and of the implementation of OMP can be found in Appendix.

98 *1.2. Measurement of attenuation: Theory*

99 The cortical bone layer is modeled locally as a plate of thickness Ct.Th.
 100 We assume that the temporal signals can be decomposed into monochromatic
 101 plane waves propagating in bone at normal incidence on the plate surfaces.
 102 The complex wavenumber is denoted $(k + i\alpha)$, where α is the imaginary part
 103 and is assumed to present a linear attenuation with frequency in cortical
 104 bone, i.e., $\alpha = \beta f$ (Minonzio et al., 2011). This linear approximation, or
 105 first order Taylor expansion, is valid around a central frequency f_0 as long as
 106 the frequency deviation Δf is narrow, i.e., $\Delta f/f_0 \ll 1$, even if the attenua-
 107 tion variation for larger frequency is not linear (Szabo, 1995; Yousefian et al.,
 108 2021). Note that the real part k of the wavenumber is assumed to be fre-
 109 quency independent within the considered bandwidth. With this plane wave
 110 model, the modulus of the ratio of the spectra of the two echoes (from the pe-
 111 riosteal and endosteal surfaces) is proportional to $\exp(-\beta f 2Ct.Th)$ (Zheng
 112 et al., 2009). Note that the ultrasound signal does not need to be corrected
 113 for the overlying soft tissues, as we are studying the ratio between endosteal
 114 and periosteal echoes. Both echoes are indeed equally affected by the prop-
 115 agation within the soft tissue layer. Thus, the ratio only depends on the
 116 propagation inside the cortical bone layer.

117 Following Kuc (Kuc et al., 1976), the attenuation coefficient β can be
 118 estimated from pulse-echo measurements with a parametric approach from
 119 the shift of the center frequency of the Gaussian pulse. Assuming that the
 120 central frequency variation $\Delta f = f_1 - f_2$ is small compared to the central
 121 frequency (i.e., σ_f remains unchanged), the coefficient β writes (Kuc et al.,
 122 1976; Narayana and Ophir, 1983)

$$\beta = \frac{1}{2Ct.Th} \frac{\Delta f}{\sigma_f^2}, \quad (4)$$

123 with the frequency in MHz and distance in mm, β is in $\text{Np.mm}^{-1}.\text{MHz}^{-1}$.
 124 This parametric estimation is well adapted in both transmission (Kuc et al.,
 125 1976) and reflection (Kuc, 1984) and has been successfully applied to bone
 126 on *ex vivo* specimens in both configurations (Dencks et al., 2008; Zheng
 127 et al., 2007, 2009). Finally, the cortical broadband ultrasound attenuation
 128 in $\text{dB.cm}^{-1}.\text{MHz}^{-1}$, is obtained as

$$\text{Ct.nBUA} = 10 \frac{20}{\ln(10)} \beta \approx 86.9\beta. \quad (5)$$

129 The above equations indicate that the experimental determination of
 130 nBUA or β requires the knowledge of Ct.Th. This can be obtained from
 131 the X-ray computed tomography scan of the bone, or, alternatively, from
 132 ultrasound signals as

$$\text{Ct.Th} = v_{11} \frac{\Delta t}{2}, \quad (6)$$

133 where $\Delta t = t_2 - t_1$, providing the longitudinal bulk wave velocity v_{11} (in
 134 $\text{mm} \cdot \mu\text{s}^{-1}$) is known. The index "11" refers to the radial bone direction com-
 135 monly denoted direction 1 in previous studies (Foiret et al., 2014; Bernard
 136 et al., 2015). In a first approach, a nominal value of v_{11} may be assumed,
 137 i.e., the velocity is supposed to be known and identical for all subjects (Kar-
 138 jalainen et al., 2008; Grimal and Laugier, 2019). Thus, the β coefficient may
 139 be rewritten without reference to Ct.Th, using equations (4) and (6), as

$$\beta = 2 \frac{\pi}{v_{11}} \frac{\sigma_t}{\Delta t} \frac{\Delta f}{\sigma_f}. \quad (7)$$

140 The quality factor Q is a dimensionless parameter, classically used to
 141 describe the resonance of a resonator, usually defined by the ratio between the
 142 central frequency and the frequency bandwidth. High Q values correspond
 143 to low attenuation. It is possible to define a quality factor related bulk
 144 wave velocity v_{11} as $Q_{11}^{-1} = \frac{\Im(C_{11})}{\Re(C_{11})}$ (Bernard et al., 2015), where C_{11} is the
 145 complex elastic coefficient related to v_{11} . Interestingly, as we show below,
 146 Q_{11}^{-1} does not require the knowledge of the bulk wave velocity. In case of
 147 weak attenuation, i.e., $Q_{11}^{-1} \ll 1$ or $\alpha \ll k$, which is usually satisfied in
 148 cortical bone at low frequency, i.e., less than a few MHz, (Bernard et al.,
 149 2015), the quality factors writes

$$Q_{11}^{-1} \approx \frac{2\alpha}{k} \approx \frac{\beta v_{11}}{\pi}. \quad (8)$$

150 Which can advantageously be rewritten

$$Q_{11}^{-1} \approx \frac{1}{\pi \sigma_f^2} \frac{\Delta f}{\Delta t}, \quad (9)$$

151 which expression does not depend on the bulk wave velocity v_{11} but only on
 152 the parameters Δt , Δf and σ_f which can be extracted from the measured

153 signals. Thus, evaluating Q_{11}^{-1} to measure attenuation could be an advantage
154 as this does not require the knowledge of the bulk wave velocity.

155 1.3. *In vivo ultrasound measurements*

156 This study has been approved by the ethical committee of the Committees
157 for the protection of persons Sud-Méditerranée. A written informed consent
158 was provided by the five healthy subjects (24-38 years old) recruited in this
159 study. The ultrasound measurements were approximately performed in the
160 one-third distal extremity of the left radius. Precisely, a mark with a pen was
161 done on the upper medial part of the forearm at 7 cm from the radial styloid
162 and the transducer was positioned on this mark. This position exactly cor-
163 responded to the center of the region of interest scanned with HR-pQCT. A
164 3.5 MHz-center frequency mono element transducer (Olympus V384, 25-mm
165 diameter, - 6dB bandwidth of 2.03MHz, Webster, TX 77598, USA) was used.
166 The transducer was connected to a wave pulse/receiver (Olympus 5077PR
167 SQUARE, Waltham, MA 02453, USA) and an oscilloscope (PicoScope 5000
168 Series, Picotechnology, Cambridgeshire, United Kingdom) for data acquisi-
169 tion. The sampling frequency was equal to 125 MHz. Ultrasound echoes
170 stemming from the reflection on the outer (periosteal) and inner (endosteal)
171 cortical bone interfaces were recorded. The waveform of the received signal
172 was displayed on the computer screen in real time. The operator ensured
173 a correct positioning of the probe (perpendicular to interfaces) by slightly
174 moving the probe so as to minimize the time delay between echoes. When
175 a satisfactory position was achieved, the operator started the acquisition of
176 30 consecutive signals. Note that the ultrasound signal does not need to be
177 corrected for the overlying soft tissues, as we are studying the ratio between
178 endosteal and periosteal echoes.

179 In order to illustrate the validity of the linear frequency dependence of
180 the attenuation coefficient, a typical example of *in vivo* pulse echo measure-
181 ment is shown in Figure 1. The two separated echoes can be observed on
182 Figure 1(a), while the two associated spectra $S_1(f)$ and $S_2(f)$ are shown in
183 Figure 1(b). Those spectra were obtained by the temporal Fourier trans-
184 forms of segments $s_1(t)$ and $s_2(t)$, indicated with thick lines, corresponding
185 to 1.2 μ s from each side of the envelop maxima (Karjalainen et al., 2008).
186 Finally, on Figure 1(c), one can observe that the variation of the spectrum
187 ratio $\ln(|S_2(f)/S_1(f)|)$ is in agreement with the slope $\Delta f/\sigma_f^2$ of the linear
188 approximation (Kuc et al., 1976). Note that the spectral ratio method is

189 based on the slope evaluation, while the peak frequency method is based on
 190 Kuc's formula.

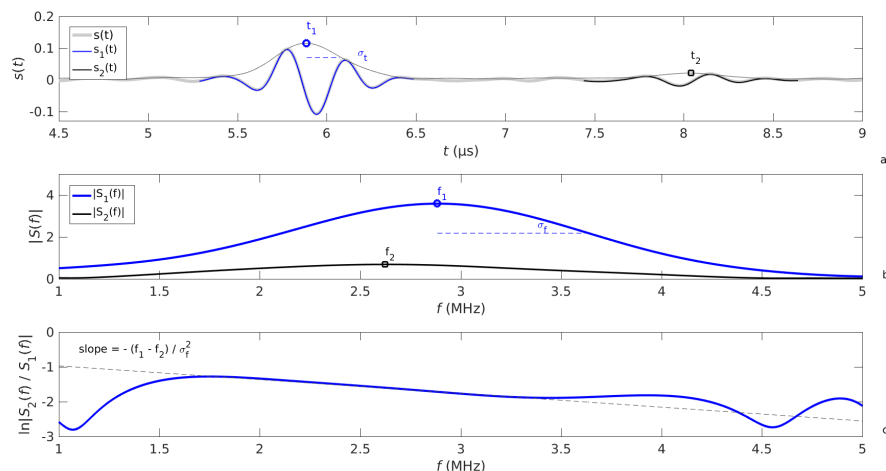


Figure 1: An example of received echoes (for subject number 3) and illustration of the linear frequency dependence of the attenuation coefficient : (a) complete temporal ultrasound signal and retained segments $s_1(t)$ and $s_2(t)$; (b) frequency spectrum of the two echoes and (c) spectrum ratio $\ln(|S_2(f)|/|S_1(f)|)$ compared with the slope $\Delta f/\sigma_f^2$ obtained with Kuc's formula . The parameters $t_{1,2}$, $f_{1,2}$ and σ_t obtained with OMP in this study are indicated on the figures.

191 Processing of the signal with OMP yields the parameters (σ_{f_1}, f_1, t_1) and
 192 (σ_{f_2}, f_2, t_2) of the echoes which were used to calculate Ct.nBUA (eq. 5) us-
 193 ing the cortical thickness value obtained from HR-pQCT (see section 1.4)
 194 (eq. 4) and Q_{11}^{-1} (eq. 9). The extraction of the parameters (σ_{t_1}, f_1, t_1) and
 195 (σ_{t_2}, f_2, t_2) is illustrated on Figure 1 using the same signal as for figure 1.
 196 It can be observed in Figure 2(b) that the retained parameters (best model
 197 number m) are associated with the two maxima, for all m , of the scalar prod-
 198 uct $\langle s(t)|\mathbf{d}(t; \sigma_{t_m}, f_m, t_m) \rangle$ between the dictionary and the signal. The
 199 maximum of this scalar product can be interpreted as the maximum quality
 200 of the signal fit, as the dictionary vectors \mathbf{d} are normalized. Accordingly, for
 201 each subject, we retained the 10 (out of 30) measurements with the highest
 202 values in order to remove the poorest measurements corresponding e.g., to a
 203 poor alignment of the probe with the bone surface. The final values of nBUA
 204 and Q_{11}^{-1} , and their errors, were obtained using the mean and the standard
 205 deviation calculated on the 10 retained measurements.

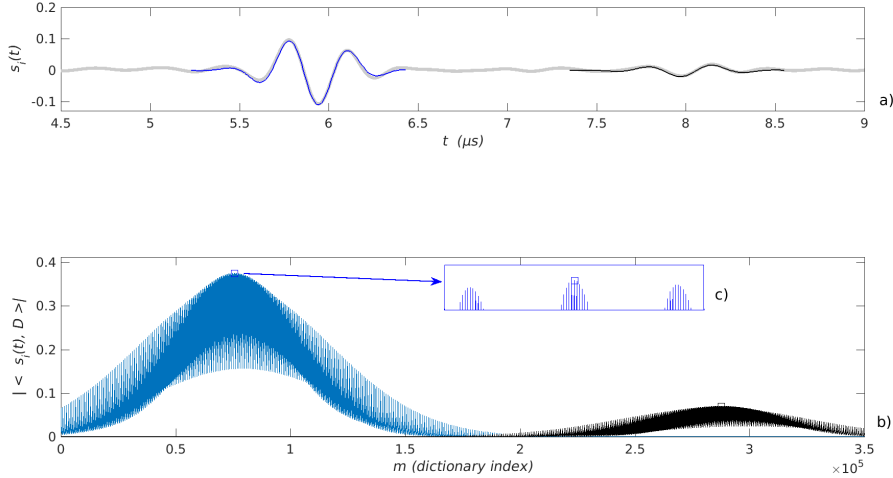


Figure 2: Principle of the evaluation of the parameters (σ_{t_m}, f_m, t_m) of the Gabor functions matching the two echoes using OMP. Original signal $y(t)$ compared with the two reconstructed echoes $s_1(t)$ (blue) and $s_2(t)$ (black) (a) associated with dictionary indices m corresponding to the two largest values of the scalar product between the signal and the dictionary (b). (c): zoom around the first maximum.

206 1.4. HR-pQCT

207 The left radius of each subject was scanned with high-resolution X-ray
 208 peripheral computed tomography (HR-pQCT, XtremeCT, Scanco Medical,
 209 Brüttisellen, Switzerland) using the standard manufacturer *in vivo* acqui-
 210 sition parameters (60 kVp, 1000 mA, 100 ms integration time, voxel size
 211 $82 \mu\text{m}$). The measurements were approximately performed at the one-third
 212 distal radius site. To ensure that HR-pQCT imaging is site-matched with
 213 ultrasound measurement, we used an initial large view image allowing to
 214 center the scanning windows at 7 cm from the radial styloid corresponding
 215 to the ultrasound measurement point. The acquired volume corresponded to
 216 9.02 mm along the bone axis (110 cross-sectional slices). The central slice
 217 is illustrated in Figure 3 for each subject. The region of interest (ROI),
 218 site-matched with the ultrasound measurement site, is highlighted. Meth-
 219 ods used to process the CT data have been previously described in detail
 220 (Laib et al., 1998; Boutroy et al., 2005; MacNeil and Boyd, 2007; Ostertag
 221 et al., 2016). Briefly, cortical limits were determined using a threshold-based
 222 algorithm. The threshold used to discriminate cortical bone was set to one

223 third of the apparent cortical bone density value (D_{cort}). Cortical thickness
224 was calculated for each slice as the mean distance between the periosteal
225 and endosteal contours. Finally, the mean and standard deviation of all slice
226 cortical thickness was retained for each subject. Volumetric bone mineral
227 density of the cortical bone in the ROI (Ct.vBMD) was obtained directly
228 from D_{cort} . The mean and standard deviation of all slice D_{cort} was retained
229 for each subject.

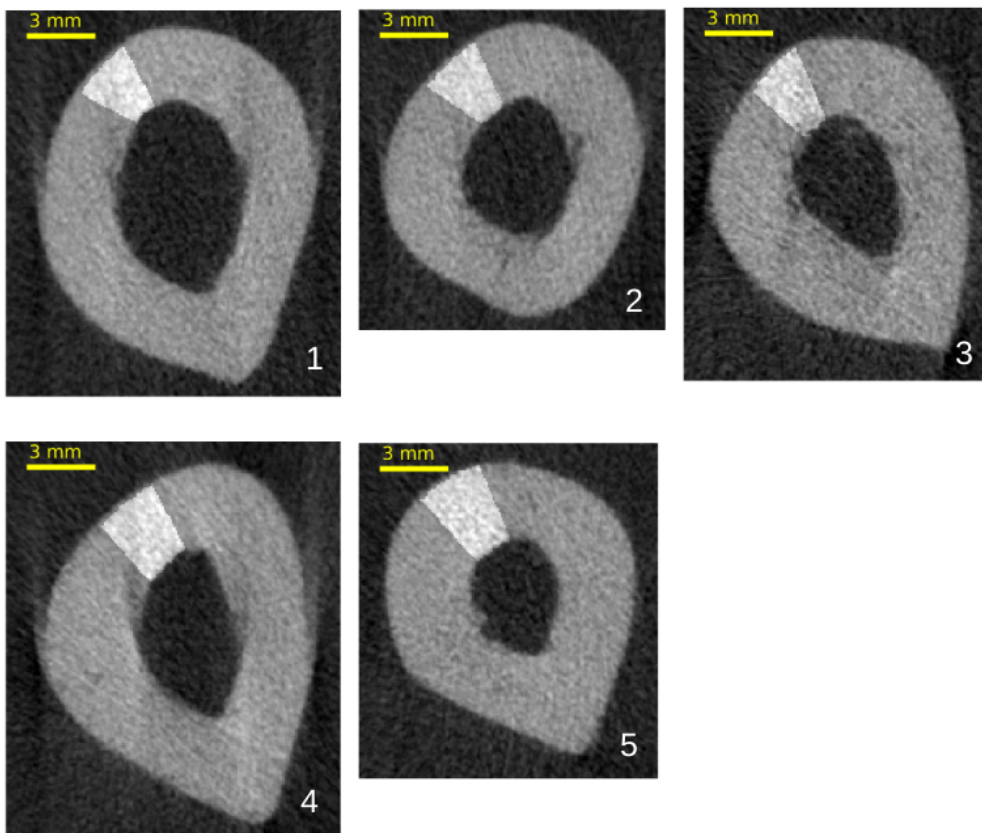


Figure 3: A representative cross-sectional HR-pQCT slice of the radius for each subject. The region of interest corresponding the ultrasound measurement site is highlighted

230 1.5. Data analysis

231 The relationships between ultrasound parameters and reference param-
232 eters obtained with HR-pQCT were assessed using linear correlations. We

233 report Pearson's correlation coefficient and linear regression equations.

234 Results

235 The mean and standard deviation, calculated over the ten retained mea-
 236 surements, of the estimated parameters Δt , Δf , σ_f for each subject are
 237 reported in Table 1. The next last column corresponds to Q_{11}^{-1} obtained
 238 combining previous parameters using equation (9). Finally, values of Ct.Th,
 239 Δf and σ_f were used to compute Ct.nBUA according to equations (4) and
 240 (5) (last column of Table 1). HR-pQCT parameters Ct.Th and Ct.vBMD
 241 are reported in Table 2.

242 High correlations were observed between Q_{11}^{-1} and Ct.vBMD, obtained
 243 by HR-pQCT ($R^2 = 0.93$, $p < 0.01$, RMSE= 0.76%, Fig. 4) and between
 244 Ct.nBUA and Ct.vBMD ($R^2 = 0.92$, $p < 0.01$, RMSE = 0.56 dB.MHz⁻¹.cm⁻¹,
 245 Fig. 5). The linear regression equation was Ct.nBUA = $-34.1 \times$ Ct.vBMD +
 246 45.6, where Ct.nBUA is expressed in dB.MHz⁻¹.cm⁻¹ and Ct.vBMD in
 247 g.cm⁻³. Likewise, the second linear regression equation was $Q_{11}^{-1} = -49.2 \times$
 248 Ct.vBMD + 64.9, where Q_{11}^{-1} is expressed in % and Ct.vBMD in g.cm⁻³. The
 249 corresponding longitudinal bulk wave velocities v_{11} , ranging from 3.2 to 3.9
 250 mm. μ s⁻¹, are given in Table 3 for comparison with other studies.

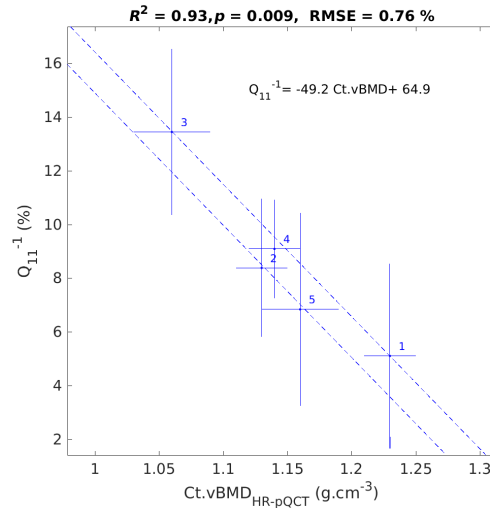


Figure 4: Correlation between quality factor Q_{11}^{-1} obtained by pulse echo and Ct.vBMD obtained by HR-pQCT.

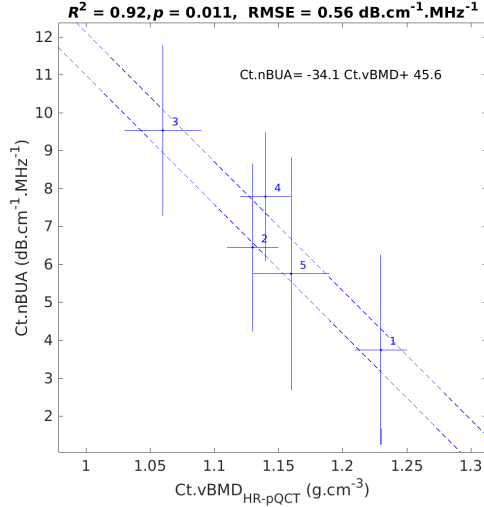


Figure 5: Correlation between Ct.nBUA and Ct.vBMD.

251 Discussion

252 This work considered pulse-echo measurements to measure the attenu-
 253 ation of signals from ultrasonic waves propagating in cortical bone at the
 254 radius *in vivo*. The two echoes stemming from normal-incidence reflections
 255 on the periosteal and endosteal bone surfaces were modeled as the sum of
 256 two elementary waveforms (Gabor functions), and the parameters of these
 257 waveforms (time delay, central frequency and frequency bandwidth) were re-
 258 covered using sparse signal processing (OMP). Attenuation was assessed in
 259 two ways: (1) as Ct.nBUA with a parametric method using OMP param-
 260 eters combined with Ct.Th from HR-pQCT ; and (2) as a quality factor Q_{11}^{-1}
 261 calculated from OMP parameters only.

262 The values of Ct.nBUA (6.7 ± 2.2 dB.MHz.⁻¹.cm⁻¹) are in the range of
 263 the attenuation values reported in the literature on bovine and human femur
 264 (Table 4). To which extent Ct.nBUA and Q_{11}^{-1} reflect the true (intrinsic)
 265 ultrasonic attenuation in cortical bone remains to be investigated. Such
 266 quantity can only be evaluated *ex vivo* using dedicated experimental condi-
 267 tions in order to minimize the effect of diffraction and other losses unrelat-
 268 ed to attenuation within the tissue.

269 We found that Ct.nBUA was strongly correlated to volumetric bone min-
 270 eral density (Ct.vBMD) measured from X-ray attenuation ($R^2 = 0.92$, Fig.5).

271 This finding is in line with the *ex vivo* results of Sasso et al. (Sasso et al.,
 272 2008) who reported a correlation between Ct.nBUA and Ct.vBMD in bovine
 273 bone measured *ex vivo* ($R^2 = 0.57$, $p < 10^{-5}$, RMSE=1.6). These au-
 274 thors also reported the linear fit equation between Ct.nBUA and Ct.vBMD
 275 (Ct.nBUA = $-25.2 \times \text{Ct.vBMD} + 40.6$) which can be compared to our re-
 276 sult (Ct.nBUA = $-34.1 \times \text{Ct.vBMD} + 45.6$). The differences between these
 277 equations may in part be due to the Ct.vBMD range which was different in
 278 the two studies: [1.15-1.65] g.cm⁻³ in (Sasso et al., 2008) compared [1.05-
 279 1.22] g.cm⁻³ in the present study.

280 Quality factor Q_{11}^{-1} (Table 1) values associated to the propagation of a
 281 longitudinal wave can be compared to shear mode quality factor Q_{44}^{-1} mea-
 282 sured from the first resonance peak (falling in the range [100–300 kHz]) of a
 283 cuboid bone specimen (Bernard et al., 2015). In the latter study, the aver-
 284 age Q_{44}^{-1} was 3.5% to be compared to a mean value of 8.6% in the present
 285 study. These values compare well although the comparison should be made
 286 with caution because (i) Q_{44}^{-1} was obtained at a much lower frequency (one
 287 order of magnitude); (ii) the polarization is different and a larger attenuation
 288 is expected for shear waves; (iii) the collection of samples used in (Bernard
 289 et al., 2015) includes low density (high porosity) samples which may not be
 290 representative of the bone of healthy volunteers in the present study.

291 Ct.nBUA was calculated from measured ultrasound parameters and a
 292 value of Ct.Th obtained from the HR-pQCT image of each subject. If only
 293 ultrasound data is available, the quality factor Q_{11}^{-1} can be calculated as it
 294 does not depend on the bulk wave velocity (Eq. 9). Our results suggest that
 295 Q_{11}^{-1} could be of clinical interest as it is correlated with Ct.vBMD ($R^2 = 0.92$,
 296 Fig.4). Furthermore, Fan et al. (2021) have shown that the shear wave quality
 297 factor is correlated to porosity ($R^2=0.53$), and it is reasonable to infer that
 298 Q_{11}^{-1} measured in this study is also related to porosity.

299 Signal parameters were estimated in the ultrasound signal with OMP,
 300 which has several advantages. The segmentation of the two echoes in the
 301 time domain was performed automatically in a robust manner, which can
 302 be an advantage in case of overlapping of echoes (which can occur for thin
 303 cortices). Also, because the Gabor function offers a reliable parametrization
 304 of the echoes, the calculation of Fourier domain parameters is done avoiding
 305 a Fourier transform of the signal which can be polluted by the choice of the
 306 time window for time segmentation.

307 The parametric method used to estimate attenuation relies on the mea-
 308 surement of Δf . In equation (7), β is written in terms of temporal and

309 frequency shifts divided by their associated standard deviations, leading to
310 normalized shifts or Z-scores. Using equations (8), Q_{11}^{-1} can also be written
311 in term of these ratios as $\frac{\Delta f}{\sigma_f} = \frac{1}{2}Q_{11}^{-1}\frac{\Delta t}{\sigma_t}$. As the ratio $\Delta t/\sigma_t$ is of the order of
312 1 and Q_{11}^{-1} is small compared to 1, one can expect the ratio $\Delta f/\sigma_f$ to be also
313 small compared to 1 in accordance with the weak attenuation hypothesis.
314 Thus, special attention should be paid to the evaluation of Δf . Indeed, it
315 can be observed in Table 1 that the largest relative uncertainties, up to 70%,
316 are obtained for the frequency Δf parameter, while the uncertainties on the
317 temporal Δt parameter are about a few percents. This observation should
318 be taken into account in order to propose a robust clinical measurement.

319 The calculation of Ct.nBUA requires the knowledge of cortical thickness
320 Ct.Th, which was obtained from HR-pQCT in the present proof-of-concept
321 study. Our method to measure attenuation could however be implemented
322 together with other ultrasound sequences and signal processing providing
323 speed of sound and cortical thickness as described in Renaud et al. (2018) or
324 Nguyen Minh et al. (2020).

325 This study has a number of limitations. (1) Only 5 healthy subjects
326 were considered. The range of cortical bone properties (thickness, material
327 properties) may not be representative of the general population or subjects
328 with bone pathologies. (2) The endosteal interface of cortical bone of young
329 healthy subjects is known to be quasi-plane and regular, whereas it is likely
330 to be irregular and discontinuous for elderly subjects or patients with bone
331 diseases as a result of age- or disease-related bone deterioration and trabec-
332 ularization (Zebaze et al., 2010). Such irregular interface may give rise to a
333 wave pattern more complex than the specular echo observed in the young sub-
334 jects in the present study. Also, as the attenuation is expected to increase
335 with porosity, the signal from the endosteal interface in osteoporotic or old
336 patients should be weaker compared to the signals processed in this study.
337 The applicability of our method to assess aged or diseased bone remains to
338 be assessed. (3) Because the probe was handheld, some pulse echo acqui-
339 sitions had to be discarded. We used a quality criterion provided by OMP
340 processing based on the value of the scalar product between the recorded
341 signal and the dictionary. This criterion is believed to be robust as it relies
342 on the expected shape of the echo waveform. Nevertheless, reproducibility of
343 the method should be assessed in future studies on a larger number of sub-
344 jects. Moreover, all measurements have been carried out at the same central
345 frequency of 3.5 MHz. This frequency may need to be adapted for smaller or

346 larger thicknesses in order to remain with an endosteal echo clearly separated
347 and not too much attenuated. As attenuation in cortical bone may have a
348 nonlinear dependence on frequency (Yousefian et al., 2021), attenuation val-
349 ues obtained at different frequencies may not be directly compared with the
350 values obtained in the present study.

351 The results of this study suggest that ultrasonic quantities (Ct.nBUA and
352 Q_{11}^{-1}) related to attenuation in cortical bone can be measured *in vivo* at the
353 radius, which provide an information on bone quality as they were found to
354 be highly correlated to Ct.vBMD values. Indeed, Ct.vBMD is an established
355 biomarker of bone health related to bone porosity and mineralization (En-
356 gelke, 2017). If these results are confirmed in studies with a larger number
357 and diversity of subjects, measurement of attenuation may be considered
358 useful for assessing bone health. This can be combined with the measure-
359 ment of cortical thickness, porosity and bulk wave velocities in multimodal
360 cortical bone QUS evaluation methods. Future studies should investigate to
361 which extent Ct.nBUA and Q_{11}^{-1} measured with the method of this study
362 reflect the true (intrinsic) ultrasonic attenuation in cortical bone. Advanced
363 signal processing techniques such as neural network (Mohanty et al., 2019),
364 machine learning (Minonzio et al., 2020) or deep learning (Li et al., 2021)
365 will be investigated in order to improve the robustness of the approach.

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374 APPENDIX: Orthogonal Matching Pursuit

375 *Dictionary*

376 To implement the sparse signal processing method, the first issue is to
377 discretize the Gabor functions into an over-complete dictionary \mathbf{D} , where the
378 columns of \mathbf{D} are built resorting to the Gabor functions basis

$$\mathbf{d}(t, \Theta) = \zeta_{\Theta} \exp[-s(t - \tau)^2] \exp[j2\pi f(t - \tau)] \quad (.1)$$

$$\Theta = [s, \tau, f] \quad (.2)$$

379 where ζ_{Θ} is a normalization parameter that ensures $\|\mathbf{d}(\Theta, t)\|_2 = 1$ (l_2 -
380 norm). To build a suitable elementary atom of \mathbf{D} , the columns use a dis-
381 cretization of the different parameters that characterize each Gabor func-
382 tion. The possible values of the set of parameters Θ are sampled on M
383 discrete points. For this purpose, we define an *a priori* range for s , τ , and
384 f , these ranges being subdivided into L , S and K regular intervals, respec-
385 tively. Furthermore, each Gabor function is sampled at N_t discrete time
386 points $\mathbf{t} = [t_1, t_2, \dots, t_{N_t}]$. The dimension of the over-complete dictionary is
387 $M = L \times S \times K$, with $M \gg N_t$. The dictionary can be represented as

$$\mathbf{D} = \begin{bmatrix} d(t_1, \Theta_1) & d(t_1, \Theta_2) & \cdots & d(t_1, \Theta_M) \\ d(t_2, \Theta_1) & d(t_2, \Theta_2) & \cdots & d(t_2, \Theta_M) \\ \vdots & \vdots & \ddots & \vdots \\ d(t_{N_t}, \Theta_1) & d(t_{N_t}, \Theta_2) & \cdots & d(t_{N_t}, \Theta_M) \end{bmatrix} \quad (.3)$$

388 where

$$\Theta_m = [s_l, \tau_s, f_k], \\ l \in [1, L], s \in [1, S], k \in [1, K], m \in [1, M].$$

389 The ranges of variations of s , τ and k are defined as follows. The range
390 of frequency f can be obtained from the bandwidth of the received signal, as
391 discussed in (Mor et al., 2010). Similarly, the range for the bandwidth factor
392 s can be deduced from the bandwidth of the emitted signal. The time delays
393 τ of the different echoes are searched around the peaks of the envelope of
394 the received signal. Overall, the selection of the parameter intervals is quite
395 flexible due to the robustness and efficiency of the OMP method. Using the
396 dictionary, the signal model (1) can be represented as

$$\mathbf{y} = \mathbf{D}\mathbf{x} + \mathbf{n} \quad (.4)$$

397 where \mathbf{y} and \mathbf{n} are the sampling of $y(t)$ and $n(t)$ at discrete time points
398 respectively, \mathbf{x} is the amplitude vector corresponding to each column in \mathbf{D} .

399 This dictionary can be interpreted as an extension of the classical Fourier
400 transform. In the case of the temporal Fourier transform, Θ is reduced to

401 the frequency f and a element of the dictionary matrix writes as $d(t, \Theta) =$
 402 $d(t, f) = \exp(-j2\pi ft)$ and previous equation, i.e., the signal reconstruction,
 403 corresponds to the inverse Fourier transform. In case of the Gabor basis, the
 404 reconstruction is sparse, i.e., only a finite number of function are necessary
 405 for reconstruction, contrary to the Fourier basis for which the reconstruction
 406 is continuous.

407 We evaluated the numerical cost of the OMP algorithm. For a dictionary
 408 size varying from 1000×50000 ($N_t = 1000; L = 20, K = 10, S = 250$) to
 409 1000×80000 ($N_t = 1000; L = 20, K = 10, S = 400$), the computation time
 410 ranges approximately between 0.2 and 0.7 s on a standard personal computer
 411 (Intel(R) Xeon(R) CPU E5-2620 v2 at 2.10GHz, 32Gbytes memory, Dell,
 412 USA).

413 *Orthogonal Matching Pursuit with complex dictionary*

414 The application considered in this paper is the reconstruction the echoes
 415 from the periosteal and endosteal surfaces of the cortical bone. Accordingly,
 416 we restrain our analysis to the two first echoes, thus we set $P = 2$ in (1).
 417 As a consequence, we expect only 2 non-zero components of \mathbf{x} , which is
 418 much smaller than its dimension (M). The determination of the two main
 419 echoes requires only two iterations using sparsity constrained OMP. Since the
 420 columns of the dictionary defined in (3) are complex-valued, the correspond-
 421 ing steps of the OMP have to be adapted. Each iteration step consists in
 422 searching the best matching column with the residual from the previous iter-
 423 ation. In the case of a complex dictionary, the matching between a particular
 424 complex column and the given signal r is (Lu and Michaels, 2008)

$$425 \quad \langle \mathbf{r}, \mathbf{d}^H \rangle = \mathbf{d}^H \mathbf{r} = C e^{j\phi} \quad (.5)$$

426 where \mathbf{r} is the residual signal from last iteration, H denotes the complex
 427 conjugate transpose operator, C indicates the matching level and ϕ the phase
 of the residual.

428 The best correlated column from the dictionary \mathbf{D} corresponds to the
 429 largest value of C . The corresponding position index in vector \mathbf{x} is denoted

$$430 \quad i_{max} = \max_i \{ |\mathbf{D}(:, i)^H \mathbf{r}| \}, \quad (.6)$$

and the phase is given by

$$431 \quad \phi = \text{angle}\{ \mathbf{D}(:, i_{max})^H \mathbf{r} \}. \quad (.7)$$

431 It should be noticed that the residual cannot be iterated directly, since
432 it is defined as the linear combination of two real Gaussian pulses instead
433 of complex-values Gabor functions as introduced in (.1). After computation
434 of (.6) and (.7), The real Gaussian pulses $\mathbf{D}_r(i_{max})$ are obtained using the
435 relationship

$$\mathbf{D}_r(:, i_{max}) = \Re\{\mathbf{D}(:, i_{max})e^{-j\phi}\}. \quad (.8)$$

436 The OMP processing is illustrated in Algorithm 1.

Algorithm 1 Orthogonal Matching Pursuit algorithm

Input: $\mathbf{y} \in \mathbb{R}^N$, $\mathbf{D} \in \mathbb{C}^{N \times M}$, target sparsity=2

Output: sparse solution $\mathbf{x} \in \mathbb{R}^M$

- 1: Set $I = ()$, $\mathbf{r} = \mathbf{y}$, $\mathbf{D}_r = \mathbf{D}(:, I)$
 - 2: **for** target sparsity **do**
 - 3: $i_{max} = \max_i |\mathbf{D}(:, i)^H \mathbf{r}|$
 - 4: $\mathbf{I} = (\mathbf{I}, \mathbf{i}_{max})$
 - 5: $\phi = \text{angle}\{\mathbf{D}(:, i_{max})^H \mathbf{r}\}$
 - 6: $\mathbf{D}_r(:, i_{max}) = \Re\{\mathbf{D}(:, i_{max})e^{-j\phi}\}$
 - 7: $\mathbf{x}(I) = \mathbf{D}_r(:, I)^\dagger \mathbf{y}$ \dagger denotes pseudo inverse
 - 8: $\mathbf{r} = \mathbf{y} - \mathbf{D}_r(:, I)\mathbf{x}(I)$
 - 9: **end for**
-

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610 **Tables**

611 **Table 1:** Ultrasound measurements: Δt is the arrival time difference be-
 612 tween the two echoes, Δf is the shift of central frequency, σ_f is related
 613 to the frequency bandwidth. The quality factor Q_{11}^{-1} is calculated from
 614 these three quantities and Ct.nBUA is calculated using the ultrasound
 615 measurements and Ct.Th measured with Ht-pQCT.
 616

Subject No.	Δt (μs)	Δf (MHz)	σ_f (MHz)	Q_{11}^{-1} (%)	Ct.nBUA (dB.MHz $^{-1}$.cm $^{-1}$)
1	1.67 \pm 0.02	0.21 \pm 0.15	0.94 \pm 0.03	5.1 \pm 3.4	3.7 \pm 2.5
2	1.75 \pm 0.04	0.34 \pm 0.13	1.05 \pm 0.19	8.4 \pm 2.6	6.5 \pm 2.2
3	1.70 \pm 0.02	0.46 \pm 0.07	0.81 \pm 0.02	13.5 \pm 3.1	9.5 \pm 2.3
4	2.14 \pm 0.08	0.51 \pm 0.11	0.93 \pm 0.06	9.1 \pm 1.8	7.8 \pm 1.7
5	2.32 \pm 0.04	0.37 \pm 0.16	0.89 \pm 0.06	6.8 \pm 3.6	5.8 \pm 3.1
mean \pm std	1.92 \pm 0.30	0.38 \pm 0.12	0.92 \pm 0.09	8.6 \pm 3.1	6.7 \pm 2.2

619 **Table 2:** Cortical thickness (Ct.Th) and volumetric bone mineral density
 620 (Ct.vBMD) obtained from HR-pQCT images.
 621

Subject No.	HR-pQCT	
	Ct.Th (mm)	Ct.vBMD ($g.cm^{-3}$)
1	3.11 \pm 0.08	1.23 \pm 0.02
2	3.13 \pm 0.02	1.13 \pm 0.02
3	3.28 \pm 0.06	1.06 \pm 0.03
4	3.43 \pm 0.02	1.14 \pm 0.02
5	3.79 \pm 0.03	1.16 \pm 0.03
mean \pm std	3.35 \pm 0.28	1.14 \pm 0.06

623

624 **Table 3:** Longitudinal bulk wave velocities calculated as $v_{11} = 2Ct.Th/\Delta t$
 625 using values given in Tables 1 and 2

Subject No.	v_{11} ($mm.\mu s^{-1}$)
1	3.72 ± 0.14
2	3.58 ± 0.10
626 3	3.86 ± 0.12
4	3.21 ± 0.14
5	3.27 ± 0.08
627 mean \pm std	3.53 ± 0.28

628 **Table 4:** Normalized broadband ultrasonic attenuation (nBUA) values pub-
629 lished in the scientific literature and in this study. Mean values are
630 given, and standard deviation when available.

631 * In Talmant et al. (2019), the reported attenuation normal to the direction
632 of osteons is, at 4 MHz, $3.9 \text{ dB}\cdot\text{cm}^{-1}$ per percentage of porosity ; the value
633 given in the table is calculated for a very moderate porosity of 5% charac-
634 teristic of the bone of a healthy young adult.

Reference	Species and skeletal sites	Number of samples	Frequency range or center frequency (MHz)	nBUA (dB $\text{MHz}^{-1}\text{cm}^{-1}$)
Lakes et al. (1986)(Lakes et al., 1986)	bovine femur (<i>ex vivo</i>)	1	1-7	~ 3
Lees and Klopholtz (1992)(Lees and Klopholz, 1992)	bovine femur (<i>ex vivo</i>)	4	0-30	~ 4
636 Han et al. (1996)(Han et al., 1996)	bovine femur (<i>ex vivo</i>)	5	0.3-0.7	5 - 12
Zheng et al.(2007)(Zheng et al., 2007)	bovine femur (<i>ex vivo</i>)	8	2.25	4.91 ± 0.65
Sasso et al.(2008)(Sasso et al., 2008)	bovine femur (<i>ex vivo</i>)	40	3.5-4.5	4.2 ± 2.4
Talmant et al. (2019) *	human femur (<i>ex vivo</i>)	35	2-8	4.9
This paper	one-third distal radius (<i>in vivo</i>)	5	3.5	6.7 ± 2.2

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