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Quantitative ultrasound assessment of cortical bone properties beyond bone mineral density

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Abstract

The development of quantitative ultrasound (QUS) technologies to measure bone is motivated by the need to overcome the limitations of X-ray based methods, measuring bone mineral density (BMD) which is the gold standard to date for the diagnosis of osteoporosis. Because it uses mechanical waves, the ultrasound modality is a particularly relevant means to probe bone mechanical resistance. The vast majority of QUS technologies commercialized to date merely aim to provide surrogate markers for BMD. During the past decade, innovative QUS approaches have emerged to assess bone beyond BMD. This may be achieved by (1) specifically assessing the cortical bone compartment, independently of trabecular bone, and (2) providing intrinsic bone properties such as cortical bone thickness and material properties. One specific motivation is to estimate intracortical porosity, a quantity reflected in material properties. This article aims at an overview of recent QUS developments to measure cortical bone properties. We also draw a picture of the current knowledge on bone material properties of interest for bone QUS. We discuss the potential of ultrasound to provide novel biomarkers of bone health through the assessment of material properties.

Keywords: ultrasound; cortical bone; elasticity; porosity; thickness; imaging; velocity

Graphical abstract

Highlights

- Bone fragility assessment would benefit from an accurate evaluation of cortical bone

Figure 1: *

[Graphical abstract] Bone anatomy and QUS measurement configurations. (a) Measurement in bone radial direction with a through transmission approach (courtesy of OYO Electric CO., LTD., Japan); (b) Measurement in bone axial direction with bidirectional axial transmission to measure guided waves (courtesy of AZALEE, France) ; (c) Measurement in bone radial direction with a pulse-echo approach (courtesy of Bindex, Finland) ; (d) image of cortical bone microanatomy obtained with synchrotron radiation microtomography showing the vascular porosity mainly oriented along the bone axis ; (e) X-ray image of a cross-section of the distal radius with a depicted region of interest for a typical QUS measurement with axial transmission.

- 30 • Innovative QUS technologies aim to measure intrinsic properties of
- 31 cortical bone
- 32 • Available technologies measure bone thickness and bulk wave velocities
- 33 • Intracortical porosity, a fingerprint of remodeling, can be deduced from
- 34 material properties
- 35 • Ex vivo documentation of material properties of pathological bone
- 36 tissues is lacking

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41 1. Introduction

42 Bone fragility associated to primary or secondary osteoporosis and the
43 consequent risk of fracture is an important medical threat. Among the pop-
44 ulation aged over 50 years old, one in three women and one in five men will
45 suffer a fracture associated to osteoporosis. Nine million fragility fractures
46 occurred annually worldwide at the beginning of the 21th century [1]. Frac-
47 ture risk prediction is assessed based on clinical factors and, in the standard
48 approach, dual energy X-ray absorptiometry (DXA) in order to assess bone
49 mineral density (BMD). However, it is well accepted that BMD assessed with
50 DXA has strong limitations, in particular it has a lack of sensitivity [2, 3],
51 and DXA is a ionizing method.

52 Our bones are comprised of two types of porous tissues: cortical bone
53 is the dense tissue that forms the outer shell of the bones; trabecular, or
54 spongiuous, bone is the more porous tissue partly filling the bones. While
55 for several decades, bone alteration in osteoporosis has essentially been de-
56 scribed to be trabecular bone loss [4], a focus has been placed in recent years
57 on cortical bone which has been recognized to also play a key role in bone
58 resistance in particular at fracture sites such as the proximal femur [5, 6] and
59 the distal radius [7]. Aging is associated with an increased cortical porosity
60 and thinning of the cortical shell. In old age, 70% of all appendicular bone
61 loss may arise from the cortical compartment [8]. It follows that including
62 an accurate evaluation of cortical bone in skeletal status assessment could
63 improve diagnosis and treatment monitoring.

64 Cortical bone mechanical properties depend on the properties of the pore
65 network (volume fraction of pores or, shortly, the porosity, and microarchi-
66 tecture) and the properties of the extracellular mineralized matrix (shortly,
67 matrix) surrounding pores. Pathologies, aging, and treatments may alter
68 matrix material properties through modifications of collagen and mineral
69 [9, 10, 11, 12] and the pore network [13, 8, 11]. In the last years, corti-
70 cal bone porosity has been increasingly recognized as a fracture risk factor
71 [14, 15, 16].

72 Cortical bone thickness (CTh) is also a critical quantity for the stability
73 of a bone during daily activities and in falls [5, 17]. A reduction of CTh is
74 usually associated to an increase of porosity [16].

75 Techniques to assess specifically the cortical compartment of the skele-
76 ton have been developed recently. These include X-ray computed tomog-
77 raphy (CT) [18], indentation to specifically probe bone matrix [19], and
78 quantitative ultrasound (QUS) methods. X-ray CT is extensively used for
79 bone quantitative imaging, but essentially in clinical research. The most

80 advanced X-ray CT technique is high-resolution peripheral computed to-
81 mography (HR-pQCT), a method available since 2004. It is a 3-D imaging
82 technique, that allows a quantitative analysis of the cortical and trabecular
83 bone compartments with a physical resolution of the order of 100 μm . It
84 yields estimates of bone density, microarchitecture, and geometry. It can be
85 used to measure CTh and, to some extent, porosity, at the distal radius and
86 tibia. This modality, however, like conventional CT, will unlikely be used as
87 a widespread diagnostic tool for osteoporosis due to cost issues and ionizing
88 radiations. The focus of the present review is on bone QUS methods to
89 measure cortical bone.

90 In the past three decades, researchers have developed QUS methods to
91 measure trabecular and cortical bone [20, 21] motivated by the need to over-
92 come the limitations of DXA and provide a non ionizing, portable, easily
93 accessible, and affordable diagnostic tool for osteoporosis. The ultrasound
94 modality is thought to be a particularly relevant means to probe bone health
95 because it uses mechanical waves which are inherently sensitive to mechan-
96 ical properties contributing to bone overall resistance.

97 One strategy in bone QUS research has long been to provide ultrasound
98 variables, based on attenuation, velocity or backscatter measurements, as
99 surrogate markers for BMD, the gold standard to date for the diagnosis of
100 osteoporosis. The vast majority of bone QUS technologies commercialized
101 and used in clinical studies since the 1990's fall into this category. This
102 includes the earliest and best-validated clinical bone ultrasound devices [22]
103 measuring in transmission the heel bone (mainly composed of trabecular
104 bone), as well as recently developed pulse-echo techniques targeting different
105 skeletal sites such as the spine and hip [23, 24]. The ultrasound surrogate for
106 BMD predicts fracture risk, although, compared to DXA, it has not shown
107 its superiority [25, 20] to date.

108 Another strategy in bone QUS research has been to measure *intrinsic*
109 bone properties that convey information beyond BMD, such as CTh and
110 material properties, such as bulk wave velocities. In that vein, approaches
111 have been proposed during the past decade such as pulse-echo [26] and axial
112 transmission [27] techniques which we cover in this review. The development
113 of such QUS approaches requires a priori knowledge of physiological values of
114 bone material properties and of their expected ranges variation in different
115 pathologies.

116 This paper reviews the recent progress in QUS approaches aiming at the
117 evaluation of bone fragility through the measurement of the thickness and
118 material properties of cortical bone. We also draw a picture of the current
119 knowledge on bone material properties of interest for in vivo ultrasound eval-

uation. After this introduction as background, we review in section 2 cortical bone microanatomy and material properties. Section 3 presents QUS approaches to measure cortical bone. In Section 3.2, we account for the recent research aiming at a concurrent assessment of cortical bone anatomy and material properties. In Section 4, we discuss the potential of ultrasound to provide novel biomarkers of bone health through the assessment of material properties.

2. Cortical bone tissue

2.1. Anatomy

At its highest level of hierarchical organization, i.e., the millimeter (mm)-scale, or mesoscale [28], cortical bone can be considered as a two-phase composite material: a mineralized collagen matrix pervaded by a porous network [29] (Fig. 2(d)). Bone mechanical properties are determined by the properties of the two phases: (1) pore structure and relative volume, and (2) matrix composition and microstructure.

At the nanometer scale, collagen molecules form fibrils which are progressively mineralized forming the elementary blocks of the matrix. Arrays of mineralized collagen fibrils assemble into lamellae to form cylindrical structures called osteons, which are the most prominent motifs at the highest microstructural level in cortical bone. In long bones, osteons align roughly parallel to the axis of the diaphysis (central tube-like part of long bones) and to the bone outer surface [30]. The vascular pore network is comprised of the roughly cylindrical Haversian canals (median size $\sim 50 \mu\text{m}$) occupying the center of osteons, connected transversely by the Volkmann's canals. Unbalanced bone remodeling occurring, e.g., in aging tend to change the porosity and the morphology of the pores. While pores occupy more or less 5% of the bone material volume before 40 years old, after 40, differences are reported between women and men, the inter-individual variations increase, and, in women, the average porosity may reach about 15% [13, 31]. Also, porosity is known to be spatially heterogeneous within a bone, e.g., around the circumference and in the radial direction [13, 32, 33].

2.2. Notations

Anatomical directions in a bone diaphysis are conveniently associated to a Cartesian reference frame where directions 1, 2, and 3 stand for radial, circumferential, and axial (along the diaphysis) directions (Fig. 2).

Ultrasound propagation in bone comprises the propagation of dilatational and shear waves and is affected by material anisotropy leading to a

Figure 2: Bone anatomy and QUS measurement configurations. (a) Measurement in bone radial direction with a through transmission approach (courtesy of OYO Electric CO., LTD., Japan); (b) Measurement in bone axial direction with bidirectional axial transmission to measure guided waves (courtesy of AZALEE, France) ; (c) Measurement in bone radial direction with a pulse-echo approach (courtesy of Bindex, Finland) ; (d) image of cortical bone microanatomy obtained with synchrotron radiation microtomography showing the vascular porosity mainly oriented along the bone axis ; (e) X-ray image of a cross-section of the distal radius with a depicted region of interest for a typical QUS measurement with axial transmission.

direction-dependent speed of sound. Speed of sound is the square root of an elasticity-to-mass density ratio. We recall that the elasticity law may be written using Voigt notation as $\sigma_i = C_{ij}\epsilon_j$, where σ_i and ϵ_j are components of the stress and strain vectors respectively, and C_{ij} is the stiffness matrix. Stiffness constants C_{ii} ($i = 1 \dots 3$) correspond to longitudinal loadings (of traction-compression type) along the different anatomical directions, C_{ii} ($i = 4 \dots 6$) are the shear moduli, and $C_{ij} = C_{ji}$ ($i \neq j$) correspond to mixed mode loadings. Engineering moduli, i.e., Young's moduli and Poisson ratios are defined as combinations of stiffness constants [34]. In the following, the bulk wave velocity (BWV) of dilatational waves, $\sqrt{C_{11}/\rho}$, and $\sqrt{C_{33}/\rho}$, where ρ is the mass density, are denoted respectively radial BWV and axial BWV.

2.3. Elastic anisotropy

Cortical bone is most often described as an orthotropic material, that is, the material has a plane of symmetry associated to each anatomical direction. Such a material is characterized by nine distinct elastic moduli. Where orthotropy is weak as in the central portion of the diaphysis, a transversely isotropic material model, characterized by five moduli only [35, 36],

is usually assumed. In long bones, the typical anisotropy ratio between longitudinal coefficients in the axial and radial (or circumferential) directions is between 1.3 and 2.5 [35, 37]. Anisotropy of cortical bone is due to both the preferential orientation of the vascular pores and the elastic anisotropy of the mineralized matrix due to the orientation of the mineralized collagen fibers. Theoretical studies have shown that bone mesoscale anisotropy mostly stems from the anisotropy of the matrix, the preferential orientation of the pores leading to moderate values of anisotropy ($C_{33}/C_{11} \sim 1.1-1.3$ depending on the pore volume fraction) when the mineralized matrix is assumed to be isotropic [38, 39, 40].

2.4. Bone material properties

A large number of ex vivo studies have reported elasticity values in cortical bone. The average Young's modulus along the diaphysis is typically around 14-20 GPa [41, 42, 37]. The average Young's modulus perpendicular to the diaphysis is around 11 GPa [37] but is much less documented. The average shear modulus corresponding to a torsion experiment around an axis parallel to the diaphysis is about 4-6 GPa [42, 37].

The mass density of cortical bone ranges typically between 1.6 and 2 g.cm⁻³. The variations of mass density are due to a combination of variations of the bone volume fraction in a volume of interest (i.e., the bone is more or less porous) and the variations of the mass density of the extracellular mineralized matrix. The latter are usually small because the volume fraction of mineral in mature bone remains relatively constant[43]. It follows that in practice mass density and porosity are highly correlated. The above interval ([1.6-2] g.cm⁻³) approximately corresponds to a range of porosity between 30% (extremely high porosity for cortical bone) and a few percents. In this range of density values, the elastic constants vary of $\pm 30-50\%$ around their nominal values [37] (Fig. 3).

In a large number of ex vivo studies, BWVs in cortical bone specimens have been measured together with mass density in order to derive elasticity [44]. However, the BWVs values were not reported as such. Overall, compared to elasticity, BWV is much less documented. Eneh et al. [45] measured radial BWV ex vivo on parallelepiped samples of femoral bone from 18 donors and found 3202 m/s (± 77)(Fig. 4). Lefevre et al. [46] measured radial and axial BWVs ex vivo in samples of fibula from 16 donors and found, respectively, 3137 m/s (± 486) and 3994 m/s (± 178). Grondin et al. [47], combining measurements in several quadrants of the femur of 4 donors found 3976 m/s (± 72) for axial BWV. Mathieu et al. [48] investigated the radial variation of axial BWV in 11 femurs and found 3586 m/s (± 255). In

Figure 3: This figure, reproduced from [37], illustrates the ranges of variations of elastic coefficients (ex vivo measurements). Stiffness and engineering coefficients of 55 cortical bone specimens from the tibia, are plotted as a function of C_{66} to illustrate the interdependency of the different elastic coefficients. The range of mass density values is $[1.6-2.0] \text{ g.cm}^{-3}$ for the different specimens.

214 vivo, Greenfield et al. [49] combined radiographic measurement of radius
 215 thickness and pulse echo data to determine BWV in the radial direction,
 216 they found (mean ± 1.5 standard deviation) 3311 m/s (± 307) in men and
 217 3359 m/s (± 297) in women.

Figure 4: Reproduced from [45]. Histogram (numbers represent the center of bins that are 60 m/s in width) of the average values of radial bulk wave velocity (denoted SOS for 'speed of sound' in the figure) in 44 cortical bone samples from the femur diaphysis. The black and white bars represent radial BWV measured at 2.25 and 5.00 MHz, respectively.

218 As explained in sec 3, the design of future bone QUS methods to measure
 219 material properties rely on reference data at the typical measurement sites
 220 (radius, tibia). Some ex vivo studies have provided values for cortical bone
 221 material properties such as elasticity, density and BWVs. However, the large
 222 majority of this data was obtained from the diaphysis of the femur, which is
 223 not a site measured with QUS, and, to a lesser extent, from the tibia. Little
 224 data exists on radius bone due to the difficulty to measure small samples.

225 The available data was obtained on cadaveric bones, usually from el-
 226 derly donors without documentation on the existence of bone pathologies.
 227 During childhood, there is a well documented effect of age on bone mineral
 228 density [50]. The changes over age of material properties are not covered
 229 in the present review, although a bone QUS method can be dedicated to
 230 measure children's bones.

231 To conclude, elastic properties and BWVs at radius and tibia need to
 232 be better documented. In particular, it is not clear whether or not bone
 233 material has distinct characteristics at these two sites (tibia, as opposed to
 234 radius, is a weight-bearing bone) and if these sites are comparable to the
 235 femur for which much more data is available. A better documentation of
 236 the tibia and radius bones may be obtained with resonant ultrasound spec-
 237 troscopy (RUS) [51, 52] a technique that allows retrieving the full stiffness
 238 tensor from small-sized rectangular parallelepiped specimens.

239 3. Cortical bone quantitative ultrasound

240 We review below cortical bone QUS approaches aiming at the measure-
241 ment of cortical bone thickness (CTh) and material properties. These QUS
242 approaches are essentially developed for the radius and tibia [53] because
243 these sites are easily accessible to ultrasound. The radius, but not the tibia,
244 is an osteoporotic fracture site. Osteoporosis is a systemic disease, accord-
245 ingly, measuring bone at any site is expected to have a clinical value, which
246 has been proven with several approaches implemented at the heel, phalanx,
247 tibia and radius.

248 In general, the measurement of CTh with ultrasound in vivo relies on
249 an a priori knowledge, or a joined measurement, of one or several material
250 properties. When measuring bone in the radial direction with a pulse-echo
251 method (Fig. 2(c)), the ultrasound raw data, in terms of time-of-flight, cou-
252 ple information on material properties (BWVs) and anatomy (CTh). With
253 the axial transmission method, measuring the propagation of guided waves
254 in the cortical envelope of the diaphysis (Fig. 2(b)), information on bulk
255 wave velocities and CTh are also coupled (except in the limit case of a suf-
256 ficiently large CTh and high frequency, in which case a lateral wave can be
257 measured [54], giving access directly to the axial BWV without requiring
258 the knowledge of thickness).

259 At QUS measurement sites, CTh shows a large range of values across
260 individuals: typically 1 to 4 mm in radius and 1.5 to 5 mm in tibia [26, 55].
261 In contrast, the range of variations of material properties is smaller, e.g.,
262 typically, the mass density varies between 1.8 and 2 g.cm⁻³, and the BWVs
263 and elastic coefficients may respectively vary of $\pm 10\%$ and $\pm 50\%$ around
264 an average value. Because it is intrinsically difficult to retrieve concurrently
265 several bone characteristics (namely CTh and material properties), to date,
266 clinical implementations of QUS approaches only provide CTh assuming
267 fixed values of material properties. Several approaches are under develop-
268 ment to overcome this limitation.

269 3.1. Current approaches

270 Karjalainen et al. [26], following Greenfield et al. [49] and Wear [56]
271 implemented a pulse-echo method (Fig. 2(c)) to measure CTh at the tibia
272 and radius using a fixed value of the radial BWV (3565 m/s). This value
273 was chosen such that CTh determined from the QUS measurement matches
274 the reference CTh obtained from HR-pQCT in healthy volunteers.

275 Otani et al. developed a method to measure the distal radius in through-
276 transmission, i.e., the wrist is placed between a pair of confocally aligned

transducers, [57] (Fig. 2(a)). Ultrasound passes through both the lateral and medial cortical layers and through the trabecular bone in the metaphysis. Assuming a layered model of bone and some fixed material properties (radial BWV in cortical bone is set to 3300 m/s), the method yields, among other parameters, the sum of the cortical thicknesses at the inlet and outlet sides of the the US beam.

So-called axial transmission measurements involve guided waves propagating in the cortical layer in the direction of the bone axis (Fig. 2(b)). Guided waves propagation is highly sensitive to variations of CTh [27, 58]. The waveguide thickness is retrieved by resorting to an optimization algorithm to solve an inverse problem. Precisely, the cortical bone layer is modeled as a plate of given (fixed) material properties and unknown thickness (CTh), to be determined by fitting the simulated ultrasonic behavior of the plate to experimental data. Moilanen et al. [59] demonstrated on ex vivo radii that CTh can be retrieved from the signal of a 200 kHz guided wave; in this work, bone material was assumed isotropic with fixed properties (BWV=4000 m/s). In a subsequent study, Vallet et al. [55] exploited several guided modes [60] to retrieve CTh using US signals centered at 1MHz and transverse isotropic fixed properties (radial BWV=3024 m/s; axial BWV=3753 m/s).

During the last few years, the first clinical studies with the above approaches have been conducted. CTh was found to be different in fractured versus non fractured patients, all with impaired kidney function [61]. Sai et al. [57] observed the expected decrease of CTh with age in an healthy population and the higher thickness of males compared to females. The pulse echo method of Karjalainen et al. [26], combining measurement of CTh and patient's characteristics, was shown to predict femoral neck BMD with good accuracy [62] and to discriminate patients with hip osteoporosis from controls [63, 24].

3.2. Future of cortical bone QUS

In all the above-mentioned approaches, cortical bone material properties are assumed to be identical for all subjects. This a limitation as tissue properties may vary between individuals and between sites (section 2). Not only this likely impairs the accuracy of the determination of CTh but also material properties themselves may give a valuable additional information on bone quality. In particular, material properties are strongly related to porosity, which is a recognized fracture risk factor [64, 15] (see sec. 4).

3.2.1. Innovative methods

One perspective for cortical bone QUS, based on existing approaches, is to couple the determination of CTh and that of material properties. This can be achieved with several approaches. In pulse-echo mode, methods using a transfer function approach [65, 66, 67] could in principle be designed to retrieve BWVs, density, attenuation, and CTh exploiting the times-of-flight and amplitudes in the reflected signals. The multimode axial transmission technique allows retrieving CTh and material properties or porosity, which has been demonstrated *ex vivo* [68, 69, 70].

Obtaining ultrasound images of the internal structure of cortical bone is another exciting perspective. Conventional ultrasound scanners are used in clinical practice to image the outer surface of bones allowing for the diagnosis of bone fractures [71]. However, these ultrasound systems fail to reveal the internal structure of bones because (1) the algorithm used to construct the image assumes that ultrasound follow a straight path and that BWVs do not vary along the path; (2) attenuation in cortical bone is relatively large; and (3) important energy loss occur at the soft tissue-bone interface caused by the large acoustic impedance mismatch. Using wave scattering theory to model the wave path, Zheng et al. [72] obtained *ex vivo* an image of the cortical layer of a bovine femur. Taking advantage of the tremendous performance improvement of hardware electronics in ultrasound scanners in the last years and developing a dedicated image reconstruction technique, Renaud et al. [73] have recently obtained *in vivo* quantitative images of the cortical layer of human radius and tibia (Fig. 5). The velocity of bulk dilatational waves in the different anatomical directions is recovered by combining a measurement of the lateral wave and optimizing image quality.

Figure 5: Reproduced from [73]. Ultrasound image of the cortical layer of a radius *in vivo*. Red and blue lines correspond to the periosteum and endosteum. Straight lines (dotted black line) approximate the interfaces. The cortical thickness, defined as the mean distance between these lines is found to be 3.5 mm for this acquisition and is in agreement with the thickness measured with HR-pQCT.

340 Lasaygues et al. have proposed to reconstruct a quantitative image of
 341 an entire transverse cross-section of a long bone with a tomography setup,
 342 using scattering theory and Born approximation [74] or using a full waveform
 343 approach [75].

344 3.2.2. *Models of material properties for cortical QUS*

345 Depending on the QUS measurement approach and the type of waves
 346 involved (shear and dilatational waves in different anatomical directions),
 347 more or less material parameters are involved in the processing of ultrasound
 348 signals. While only the radial dilatational BWV is involved in pulse-echo
 349 methods, no less than four material parameters may be involved in axial
 350 transmission configuration (e.g., one BWV and three elastic anisotropy ra-
 351 tios [68]). The latter parameters are the quantities directly accessible from
 352 a measurement. In the methods implemented for clinical applications, nor
 353 mass density nor elastic coefficients can be inferred without resorting to a
 354 model of bone material properties (e.g., [40]) relating these quantities and
 355 those directly accessible from a measurement.

356 A priori knowledge of bone material properties is mandatory to solve
 357 the coupled problem of the determination of CTh and material properties.
 358 Such information is all the more important that the number of parameters to
 359 retrieve is large. It has been pointed out that the different elastic coefficients
 360 are correlated (Fig. 3) and strongly depend on density [76, 41, 77, 37, 52],
 361 and porosity [36] (see also sec. 4). As a consequence, a simplified model of
 362 cortical bone elastic properties with a limited number of parameters [78, 79]
 363 could be used in order to reduce the number of unknowns when solving
 364 the QUS inverse problem. Such an approach was implemented by Bochud
 365 et al. [69] where cortical bone was modeled as a pore network of variable
 366 porosity embedded in a matrix with fixed elastic properties [40, 80] (an
 367 implementation of the model is available online [81]; the model predictions
 368 are plotted against ex vivo elasticity measurements in Fig. 6).

369 4. Measuring material properties as potential biomarkers of bone 370 health

371 Managing bone health often starts by assessing the risk of fracture of
 372 an individual. This depends on many factors related to the risk of an in-
 373 dividual to fall, and to the ability of a bone to resist a low trauma. The
 374 latter depends both on bone size and geometry, and material properties. In
 375 this section, we briefly review the relationships between, on the one hand,
 376 material properties that may be derived in vivo from QUS measurements

377 and, on the other hand, strength, fracture risk factors, and quality of the
378 extracellular matrix.

379 4.1. Bone resistance

380 As mentioned in the introduction, one potential advantage of ultrasound
381 over X-ray approaches is to assess material properties beyond the mere quan-
382 tity of bone reflected in BMD measured with an X-ray based technique.

383 Bone resistance to fracture is typically characterized by strength (i.e.,
384 ultimate stress before rupture) and toughness (i.e., resistance to crack prop-
385 agation) [82]. It is yet unclear to which extent ultrasound, probing bone
386 at very small strains in a linear regime, may yield information on bone
387 resistance.

388 Correlations have been reported between bone resistance and elastic
389 properties as for engineering and natural materials in general [83]. Indeed,
390 post-yield and elastic properties are all determined by the biochemical com-
391 position and the microstructure of bone. It is thus expected that elasticity
392 and BWVs reflect material resistance to some extent. Pooling results of com-
393 pression testing of children and adult bone, Öhman et al. [84] found a high
394 correlation between yield stress and Young's modulus ($R^2=0.88$). Weaker
395 correlations have been found in studies considering only specimens from
396 adult donors ($R^2=0.25$ in three-point bending tests [85] ; $R^2=0.53$ and 0.56
397 in tension and compression tests, respectively [41]). Further studies should
398 elucidate more precisely how much of bone material resistance (strength or
399 toughness) can be learned from the measurement of elastic properties and
400 BWVs.

401 4.2. Elasticity and bulk wave velocities reflect porosity and matrix properties

402 Porosity, a fracture risk factor [15], is an important determinant of stiff-
403 ness variations [86, 87]. Several authors have reported correlations between
404 porosity and elastic moduli, although the range of correlation coefficients
405 is quite large. For example, Mirzaali et al. [42] found $R^2=0.08$ (Young's
406 modulus) and $R^2=0.47$ (shear modulus), Granke et al. [36] and Cai et al.
407 [88] found R^2 in the range 0.70-0.84 for all shear and longitudinal stiffness
408 coefficients. Relatively large relative variations of stiffness in the porosity
409 range [2.9-26.9%] were reported [36]: 58%, 34%, 48%, and 59% for C_{11} , C_{33} ,
410 C_{44} , and C_{66} , respectively (Fig. 6). Overall, as porosity increases, C_{11} (lon-
411 gitudinal elasticity transverse to Haversian canals) decreases more compared
412 to C_{33} (longitudinal elasticity in the direction of Haversian canals). This is
413 consistent with results of theoretical studies [89, 79, 40].

414 Data suggest that porosity is also a strong determinant of BWVs. In
 415 axial direction, porosity was found to explain about 30% of BWV variation
 416 [47, 48]. In radial direction it was found to explains about 50% of BWV
 417 variations [45].

Figure 6: Reproduced from [36]. (a) Longitudinal and (b) shear mesoscopic elastic coefficients versus porosity in 21 cortical bone samples from the femur. The model based on continuum mechanics laws (solid and dotted lines), assuming fixed matrix properties and variable porosity, predicts the trend of variation of elasticity.

418 There is few data suggesting that variations of material properties of
 419 the matrix may be reflected in QUS signals in human bones [90]. There is,
 420 however, ex vivo data on prepared specimens pointing at an effect of matrix
 421 properties variations on mesoscale elasticity. For instance, Rho et al. [91]
 422 found that variations of the mesoscale axial Young's modulus ($R^2=0.49$)
 423 correlated to the variations of the matrix elasticity (probed with nanoinden-
 424 tation). Granke et al.[36] found that mesoscale elasticity was correlated with
 425 matrix acoustical impedance (a proxy for stiffness) probed with acoustic mi-
 426 croscopy ($R^2 < 0.25$). In another study, variations of matrix impedance has
 427 been found to explain as much as 52% of axial BWV [47]. Eneh et al. [92]
 428 showed, with simulations performed on a limited number of samples, that
 429 the correlation of BWV in the radial direction with porosity may be lost
 430 due to inter-individual variations of matrix properties.

431 The main determinant of matrix stiffness variations is commonly thought
 432 to be the mineral content. This is well evidenced considering a large variety
 433 of bone samples taken from different species [86], and theoretical calcula-
 434 tions predict that a change of 10% of mineral volume fraction leads to a
 435 change of typically more than 20% of matrix elastic coefficients [93, 94, 78].
 436 In a recent study on femoral bone specimens from 19 elderly donors, Cai
 437 [88] found that more than 50% of mesoscale elasticity variations were asso-
 438 ciated to variations of mineral content. Collagen fibers mechanical quality

439 and organizational patterns have also been proposed as possible determi-
 440 nants of mesoscopic properties. As far as we are aware, there is no data
 441 for human bone showing an effect of a pathological alteration of collagen on
 442 mesoscale elastic properties. However, artificial degradation of the collagen
 443 with chemical treatments is known to alter elastic properties [95].

444 From a mechanical standpoint, mesoscale cortical bone material proper-
 445 ties such as density, elasticity, or BWVs are fully determined by the proper-
 446 ties of the pore network and of the matrix. Whether or not a change of these
 447 properties is reflected at the mesoscale in a given dataset critically depends
 448 on the range of variations of the properties at the different scales. The data
 449 reported above was obtained from the tissues of donors with no documented
 450 medical history, hence the conclusions drawn from these studies only per-
 451 tain to this type of population and cannot be extrapolated to groups of
 452 subjects carrying specific bone diseases. To conclude, for these bones from
 453 non-targeted populations, the available data suggest that a large part of
 454 the elasticity and BWVs variations is explained by the variation of porosity.
 455 This is consistent with the prediction of theoretical models which assume
 456 that the matrix properties have limited inter-individual variations and that
 457 porosity varies in a relatively large interval [78, 80] (sec. 3.2.2). Variations
 458 of the properties of the matrix (mineral content, impedance, elasticity) also
 459 impact mesoscale elastic properties and BWVs, however, only limited data is
 460 available. Some pathologies involving a low mineral content or a weak align-
 461 ment of collagen fibers are expected to strongly affect mesoscale properties
 462 through modifications of both the porosity and the matrix. This calls for
 463 more studies designed to investigate the variations of BWVs and elasticity
 464 in different targeted populations.

465 4.3. *Biomarkers of material heterogeneity*

466 Aging may be associated to an increase of the heterogeneity of the distri-
 467 bution and size of the pores in the cortical bone layer, resulting in a gradient
 468 of porosity: high porosity close to the marrow and relatively low porosity
 469 close to the external surface of the bone [8] . In terms of mechanics of
 470 materials, this raises the question of the existence of a representative vol-
 471 ume element of cortical bone material[28]. If the local variations of porosity
 472 are too strong, the cortical bone material can not be evaluated per se and
 473 the cortex needs to be considered as a structure. In case of a mild hetero-
 474 geneity of porosity, it may be relevant to model the cortex material as a
 475 heterogeneous field of material properties. This issue has in part been theo-
 476 retically addressed in an axial transmission QUS configuration [96, 97] but
 477 has not been implemented in clinical practice as far as we know. Since the

478 heterogeneity of material properties within the cortex is expectedly associ-
479 ated to a reduced mechanical competence, it could be interesting to develop
480 ultrasound biomarkers reflecting heterogeneity.

481 5. Conclusion

482 QUS technologies to measure cortical bone thickness, a proven biomarker
483 of bone health, are available and used in vivo. Improvements of these tech-
484 nologies and disruptive technologies are expected to be available in a near
485 future, which will achieve a coupled assessment of cortical thickness and
486 material properties. One motivation is to estimate intracortical porosity,
487 a quantity hardly directly measurable in vivo. Assessing porosity with ul-
488 trasound would be a significant progress because porosity is a recognized
489 fracture risk factor and because it is a fingerprint of the remodeling activ-
490 ity. One route to infer porosity is to use empirical relationships, or material
491 models, relating quantities measured with QUS and porosity. Other routes
492 are currently being explored such as imaging blood perfusion using ultra-
493 sound contrast agent [98] and measuring ultrasonic attenuation assuming
494 it has a strong relationship with pore properties [99].

495 Probing the quality of the mineralized collagen matrix in vivo with ul-
496 trasound is a far-reaching goal. It may be a reasonable objective in targeted
497 pathologies providing that alterations of porosity and matrix properties are
498 well documented ex vivo. Such documentation of acoustical properties in
499 bone tissue with different pathologies is a keystone of the future development
500 of bone QUS methods.

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