Correlations of ultrasound attenuation of cortical bone with elastic modulus, mineral density, and UTE-MRI-based measures of water content and macromolecules

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INTRODUCTION: Properties of cortical bone are critical in regulating bone resistance to fracture [1]. Several quantitative ultrasound (QUS) techniques have been developed to assess cortical bone, motivated by ultrasound (US) accessibility and affordability, for osteoporosis assessment without exposing patients to ionizing radiation. QUS-based parameters for bone assessment have been mainly focused on estimating the ultrasound US wave velocity (or speed of sound (SoS)), US attenuation, normalized US attenuation over frequency changes, and US backscatter. The main perspective of previous QUS studies on the bone was the search for a QUS measure with a significant correlation with bone mineral density (BMD). However, most reports lack investigation of the QUS relationship with other major components of the cortical bone, such as water and macromolecules, the latter comprising up to 60% of the bone volume. This study aimed to investigate the relationship of SoS and attenuation coefficient (α), with water and macromolecular contents of bovine cortical bone strips as measured with ultrashort echo time (UTE) MRI. We also explored correlations of SoS and α with microstructural and mechanical properties of bone.

METHODS: 36 rectangular bone strips (6mm×3mm×40mm) were excised from 4 bovine femoral shafts. A single-element US transducer with 5 MHz center frequency was used to measure SoS and α along the thickness of the bone strips (~3 mm, corresponds to the radial direction in femoral bone shaft). Figures 1A-B show the experimental setup and schematics for the QUS measurement. SoS and α measurements were performed based on the time of flight (TOF) principles described earlier by Lees, et al.[2] that accommodate reflection losses. Specimens later were scanned together using UTE MRI in a birdcage wrist coil at 3T (GE MR750, USA) to measure total, bound, and pore water proton density (TWPD, BWPD, and PWPD) as well as macromolecular proton fraction (MMF) and macromolecular transverse relaxation time (T2-MM). Bone strips were also scanned using a Skyscan 1076 (Kontich, Belgium) µCT scanner at 9 µm isotropic voxel size to measure BMD, porosity, and pore size. The dynamic elastic modulus (E) of each bone strip was measured using a four-point bending setup, with an applied load well below the yielding point. Spearman's rank correlations were calculated between the QUS, UTE-MRI, microstructural, and mechanical parameters.

RESULTS SECTION: The average results for the 36 samples are presented in Table 1. Spearman's correlations are presented in Table 2. SoS did not show significant correlations with mechanical, µCT- and MRI-based results. α demonstrated significant positive correlations with E (R=0.69) and BMD (R=0.44) while showing significant negative correlations with porosity (R=-0.41), T2-MM (R=-0.47), TWPD (R=-0.68), BWPD (R=-0.67), and PWPD (R=-0.45).

DISCUSSION: The positive significant α/BWPD correlation, even higher than α/BWPD, likely defines the QUS relationship with the density of the collagenous matrix. The negative significant α/T2-MM correlation likely indicates the relationship between QUS and the organization of the collagen matrix. However, such conclusions require comprehensive investigations using ground truth histological and biochemical evaluations of the bone. This study highlights the importance of future investigations exploring the relationship between QUS measures and all major components of the bone, particularly the collagenous matrix and water distributed as BW and PW.

SIGNIFICANCE/CLINICAL RELEVANCE: A set of validated QUS measures with high correlations with bone mineral, organic, and water contents can help monitor more patients suffering from osteoporosis, due to the accessibility and affordability of US.

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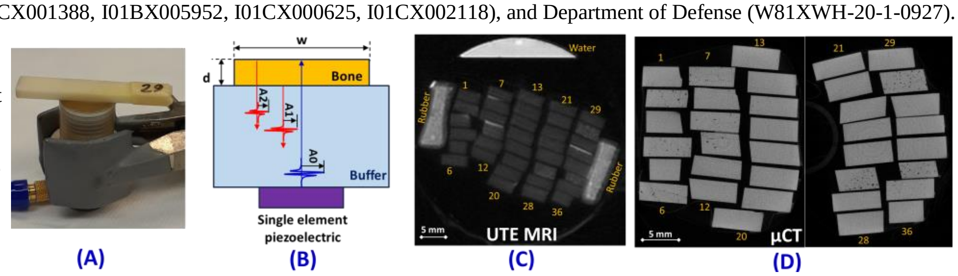

Figure 1: (A) Experimental setup for QUS measurement using a single-element transducer with 5 MHz center frequency. (B) Schematics of the generated trigger pulse by the piezoelectric element and the reflected echoes to measure SoS and α. (C) UTE-MRI and (D) µ-CT images of the 36 bovine cortical bone specimens.

Table 1: The average, standard deviation (SD), and ranges of QUS, mechanics, µCT, and UTE-MRI measures of the bone strips.

QUS		Mechanics	µCT			UTE-MRI								
SoS (km/s)	α (db/mm)	E (Gpa)	BMD (gr/cm3)	Porosity (%)	Pore Size (µm)	T1 (ms)	MMF (%)	T2-MM (µs)	TWPD (mol/L)	BWPD (mol/L)	PWPD (mol/L)	MTR−800 (%)	MTR−600 (%)	MTR−400 (%)
3.13±0.27	7.07±2.82	18.8±2.1	1.30±0.09	4.4±3.5	80±31	258±8	34.7±2.7	11.3±0.2	11.5±1.1	6.3±0.5	5.1±0.9	42.3±1.7	30.8±1.3	16.9±0.8
[2.70−3.40]	[0.70−12.40]	[15.1−23.7]	[1.10−1.46]	[0.5−13.2]	[43−147]	[242−276]	[29.2−38.5]	[10.9−11.8]	[10.0−14.6]	[5.4−7.4]	[4.2−8.0]	[38.2−44.4]	[27.6−32.5]	[14.8−18.1]

Table 2: Spearman's correlation coefficients of QUS measures with mechanical, microstructural, and UTE-MRI-based properties of the cortical bone strips.

	E	BMD	Porosity	Pore Size	T1	MMF	T2-MM	TWPD	BWPD	PWPD	MTR−800	MTR−600	MTR−400
SoS	-0.01 (p=0.99)	0.23 (p=0.18)	-0.18 (p=0.29)	0.23 (p=0.19)	0.07 (p=0.67)	-0.19 (p=0.28)	-0.23 (p=0.19)	-0.14 (p=0.42)	-0.34 (p=0.06)	-0.03 (p=0.86)	0.02 (p=0.93)	0.09 (p=0.60)	0.01 (p=0.96)
α	**0.69 (p<0.01)**	**0.44 (p<0.01)**	**-0.41 (p<0.01)**	-0.24 (p=0.16)	-0.03 (p=0.87)	0.20 (p=0.26)	**-0.47 (p<0.01)**	**-0.68 (p<0.01)**	**-0.67 (p<0.01)**	**-0.45 (p<0.01)**	0.31 (p=0.07)	0.28 (p=0.11)	0.30 (p=0.08)