Relationship between the apparent Young’s modulus and the ultrasonic parameters in human trabecular bone

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Abstract:

The physical principles underlying quantitative ultrasound (QUS) measurements are not fully understood yet. Therefore, the translation of QUS results into bone strength remains elusive. However, ultrasound being mechanical waves, it is likely to assess apparent bone mechanical properties such as apparent bone elasticity. The aim of this study is to derive the sensitivity of normalized Broadband Ultrasonic Attenuation (nBUA) and Speed of Sound (SOS) to variations of apparent bone elasticity which is considered as a good surrogate for strength. For this purpose, 34 human trabecular bone samples were cut from human proximal femurs and their geometry reconstructed using 3-D synchrotron micro computed tomography. Finite-difference time domain simulations coupled to 3-D micro-structural models were performed in the antero-posterior direction, leading to the computation of nBUA and SOS for each sample. In parallel, a voxel-based micro finite element linear analysis was employed to compute the apparent Young’s modulus (E) of each sample for each direction. For the direction of testing corresponding to the antero-posterior direction (clinical situation at the femur), the coefficient of determination of SOS and nBUA to assess E was equal to 0.90 and 0.87, respectively, which is better than what is obtained using bone density alone. Our results, which were obtained using two distinct numerical simulation tools applied on the same set of samples,
highlight the potential of QUS techniques to assess bone mechanical strength.

Mots clefs : Trabecular bone, Quantitative Ultrasonic (QUS) parameters, bone strength

1 Introduction

The prevention of osteoporosis requires non-invasive methods to assess bone fragility and predict fracture risk. Direct bone strength estimation is difficult to achieve in vivo and surrogate measurements aiming at predicting fracture risk are performed clinically. Quantitative ultrasonic (QUS) techniques have the advantage over x-ray and MRI based techniques to be less expensive, free of ionizing radiation and to be based on the analysis of the propagation of mechanical waves. Therefore, the results obtained with QUS techniques are intrinsically related to bone mechanical and structural properties that pertain to bone strength. Recent technological developments [1, 2] suggest that the in vivo QUS evaluation of the proximal femur (the most important site of fracture) may be feasible. Much interest should be placed in relating the QUS parameters with bone strength of the investigated region of interest. Finite-difference time-domain (FDTD) computations have been used to simulate ultrasound propagation through realistic trabecular microstructures. Newly developed 2-D or 3-D FDTD codes [3-5] coupled with high-resolution imaging techniques such as synchrotron radiation micro-computed tomography (SR-µCT) allow modelling the interaction between the ultrasonic wave and bone microstructure. These computation methods have been shown to provide valuable insight into the interaction of the ultrasonic waves propagating through trabecular structures [3, 6-8].

QUS variables are affected by the microstructural and tissue material properties of trabecular bone and FDTD numerical computations may be used to assess the sensitivity of QUS variables to these properties [9, 10]. However, the ultimate goal of QUS techniques being bone strength assessment, it would be enlightening to relate QUS variables directly to bone strength rather than the microstructure or tissue properties. An interesting solution would consist in considering the use of more realistic computational models based on micro-finite element analysis (µFEA) [11-13]. µFEA can be used to compute trabecular bone elastic properties from the knowledge of bone tissue properties and realistic 3-D microstructure, leading to the apparent Young’s modulus (E), which is a good predictor of bone strength ($R^2 \geq 0.95$; [14-16]).

The aim of this simulation study is to assess the ability of QUS techniques to predict the elastic Young’s modulus derived from µFEA computations using 3-D numerical trabecular samples. FDTD simulations are performed to assess QUS variables of SR-µCT-reconstructed 3-D numerical femoral trabecular bone models tested in the anteroposterior direction. Then, a µFEA is applied along the same direction to each sample. The predictive power of the QUS parameters to assess the Young’s modulus is compared with that of BV/TV, BV/TV being related to bone mineral density obtained from DXA measurements.

2 Material and methods

2.1 3-D numerical models of trabecular bone structure

The 3-D FDTD numerical computations of wave propagation and the µFEA are coupled to 3-D binary numerical models of trabecular structures. Cylindrical cores are machined in 34 human proximal femur specimens. The 3-D microarchitecture of these samples is obtained using SR-µCT performed at ESRF (European Synchrotron Radiation Facility, France), with an isotropic voxel size of 10 µm. Down sampling was applied to obtain a voxel size of 30 µm used in the simulation [17]. Parallelepiped domains with dimensions 5.6x5.6 mm² in the transverse dimensions ($X$, $Y$) and 10 mm along the $Z$ axis are extracted from each synchrotron acquisition. The $Z$ direction corresponds to the anteroposterior direction.

For each of the 34 original bone samples, 3-D datasets are deduced from the projection of the microstructure using microtomographic reconstruction techniques. Then a threshold is applied to separate bone from the background, leading to 3-D binary datasets [10]. Figure 1 shows an image of the 3-D structure obtained with this method. The samples are studied using FDTD simulation and µFEA in the direction $Z$. The bone models directly obtained from SR-µCT are used to simulate ultrasonic propagation in the $Z$
direction. The simulation of wave propagation, described in the next subsection and the µFEA analysis described in section 2.3 are performed for each numerical bone model.

![Image of a given 3-D trabecular structure obtained from the imaging technique and used in the µFEA analysis and in the FDTD simulation tool.](image)

**Figure 1:** Image of a given 3-D trabecular structure obtained from the imaging technique and used in the µFEA analysis and in the FDTD simulation tool.

### 2.2 Modeling ultrasonic propagation

The approach adopted to compute the QUS parameters as a function of bone properties has been described in detail in [7-10] and is recalled briefly in what follows. It consists in combining 3-D FDTD numerical simulation tools with 3-D binary numerical models of trabecular structures. Simulations of ultrasonic propagation are performed using the finite-difference time-domain (FDTD) simulation software SimSonic developed by the Laboratoire d’Imagerie Paramétrique and described elsewhere [3, 18]. The rectangular ultrasonic pressure source and receiver are displayed respectively at $Z=0$ mm and $Z=10$ mm.

For all simulations, bone tissue is assumed to be isotropic, non absorbing and homogeneous (i.e., same material properties are assigned to all the bone voxels of a given structure). The elastic properties of the bone matrix are selected to give a longitudinal velocity of 4000 m/s and a transverse wave velocity of 1800 m/s for a density of 1.85 g/cm$^3$, which are typical acoustical characteristics and density of cortical bone found in the literature [19]. The marrow is considered to be non viscous and is replaced by water, with a density of 1 g/cm$^3$ and acoustic wave velocity of 1500 m/s. Our model does not account neither for absorption phenomena such as viscous effects occurring within the solid tissue and filling fluid, nor for dissipation that would occur at the interface between bone and fluid.

The planar source emits a broadband pressure pulse whose frequency bandwidth is centered at 1 MHz. The frequency dependent attenuation coefficient (also referred to as normalized broadband ultrasonic attenuation, nBUA, dB/cm.MHz) and the speed of sound are computed by comparing the signals transmitted through water and through bone. The frequency-dependent attenuation coefficient is derived from the ratio of the amplitude spectra of the received waveform that has propagated through water and through the bone specimen [20]. Normalized BUA is then computed from the slope of the attenuation coefficient as a function of frequency [20] in the 400 kHz-1.4 MHz bandwidth. Speed of sound (SOS) is computed using an early threshold-based time marker on the signal as this method has been shown to be optimal in the context of bone characterization [21]. The threshold chosen to compute SOS is low (0.5% of the maximum amplitude of the signal) in order to detect early arrival wave. Note that our approach has been validated by comparing the results of the numerical simulations to experiments performed with the same bone specimens [6].

### 2.3 The micro finite element analysis

The micro finite element analysis was carried out following the method used in [13] and briefly described in what follows. The direction of testing (Z axis) and the material properties chosen for the bone matrix used for
µFEA are the same as the one used in the FDTD simulation. The displacement applied at one of the extremities of the simulation domain in the Z direction was set equal to zero so that we work under fixed grip conditions. At the other extremity, a homogeneous displacement is applied over the entire surface of the virtual sample, and the force necessary to impose this displacement is computed. This procedure is applied in the linear regime only, so that the result of the µFEA is the determination of an apparent Young’s modulus for the total homogenized bone structure for the direction Z.

2.4 Statistical data analysis

Median, interquantile range, maximum and minimum values were used in order to characterize the distribution of the bone parameters. The relationships between QUS parameters, the Young’s modulus and microarchitectural parameters were investigated using simple linear regressions and Spearman's correlation coefficients. Optimal combination of bone properties and QUS variables for predicting the Young’s modulus was evaluated using multiple linear regression analyses. All statistical computations were processed with Matlab Statistics Toolbox (Mathworks, Natick, MA).

3 Results and discussion

Table 1 shows the distribution of the values of the apparent Young’s modulus (E), of the QUS parameters and of the microstructural parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median ± interquartile</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>E (MPa)</td>
<td>96.3±98.4</td>
<td>2.03</td>
<td>429.8</td>
</tr>
<tr>
<td>nBUA (dB/cm/MHz)</td>
<td>15.3±9</td>
<td>3.32</td>
<td>46.6</td>
</tr>
<tr>
<td>SOS (m/s)</td>
<td>1576±52.7</td>
<td>1517</td>
<td>1755</td>
</tr>
<tr>
<td>BV/TV (%)</td>
<td>10.4±5.2</td>
<td>4.1</td>
<td>22.7</td>
</tr>
</tbody>
</table>

Table 1: Median value, interquartile range, minimal and maximal values of the apparent Young’s Modulus, of the QUS parameters, of BV/TV and of the microstructural parameters.

For each group of sample, a simple linear regression analysis was used to assess the relationship between E and the QUS variables. The estimated Young’s modulus $E_{SOS}$ (respectively $E_{BUA}$) is given by:

$$E_{BUA} = \alpha_{BUA} + \beta_{BUA} \cdot nBUA$$
$$E_{SOS} = \alpha_{SOS} + \beta_{SOS} \cdot SOS$$

where $\alpha_{BUA}$, $\beta_{BUA}$, $\alpha_{SOS}$ and $\beta_{SOS}$ are the coefficients of the regression lines. Similarly, BV/TV was used as single independent variables in a linear regression analysis to predict Young’s modulus. Because the distributions of the bone parameters do not follow normal distributions, the data were log-transformed and the logarithm of the absolute value of $E_{SOS}$ (respectively $E_{BUA}$) was plotted as function of the logarithm of the Young’s modulus obtained with µFEA. Finally, a linear regression analysis was carried out in order to estimate the goodness of the prediction. Figure 2 shows the predicted values of E using SOS and nBUA as a function of the µFEA-simulated value. We chose to consider logarithmic values in order to obtain approximately normal distributions, especially for the values of E and SOS. A similar analysis was
conducted for the modulus estimated using BV/TV alone.

![Graph showing the relationship between the logarithm of the apparent Young's modulus simulated with the micro-finite element analysis and the Young's modulus predicted using (a) SOS and (b) nBUA as a dependent variable. The determination coefficient is shown in each Figure.](image)

Figure 2: Relationship between the logarithm of the apparent Young’s modulus simulated with the micro-finite element analysis and the Young’s modulus predicted using (a) SOS and (b) nBUA as a dependent variable. The determination coefficient is shown in each Figure.

Table 2 shows the determination coefficients ($r^2$) and its confidence interval resulting from the regression analyses between the logarithm of the µFEA-computed Young’s modulus and the logarithm of the estimated Young’s modulus. The best predictive power is obtained with SOS ($r^2=0.9$), but all the models appear to be statistically equivalent. QUS parameters can predict the Young’s modulus at least as well as BV/TV alone. The present study shows strong relationships between QUS parameters and apparent elastic modulus and suggests that the ability of QUS to predict apparent Young’s modulus is comparable or even slightly higher than that of bone quantity (BV/TV). SOS appears to be the best predictor of apparent elastic modulus.

<table>
<thead>
<tr>
<th>Prediction of E with:</th>
<th>BVTV</th>
<th>nBUA</th>
<th>SOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$</td>
<td>0.84 (0.72-0.92)</td>
<td>0.87 (0.84-0.9)</td>
<td>0.9 (0.81-0.9)</td>
</tr>
</tbody>
</table>

Table 2: Correlation between the logarithm of the apparent Young’s Modulus (E) estimated using µFEA and obtained through linear regression analyses using BV/TV, nBUA and SOS. The determination ($R^2$) and its 95% confidence interval are indicated.

As direct in vivo measurements of bone strength to assess fracture risk in osteoporotic patients is not feasible, several modalities, such as DXA, QUS, microimaging (MRI, pQCT) and finite element analysis coupled to bone models derived from radiographic images have been developed to provide clinically useful surrogate markers for bone strength. This study examines whether the outcome measures of QUS (nBUA, SOS) can be used to predict cancellous bone strength assessed here through estimates of elastic properties, which are highly correlated to strength. We compare simultaneously the predictive power of QUS parameters with that of BV/TV. The approach adopted herein using well validated numerical simulations allows us to avoid the influence of experimental errors. In addition, a purely in silico approach allows in principle to separate the respective contribution of the structure and of the mechanical properties of bone tissue [10, 22]. Consequently, homogeneous tissue elastic modulus is assumed for the simulations, following a commonly adopted approach in recent FEA and FDTD simulation studies [3, 22].

Several limitations apply to the present study. First, the numerical method employed to determine the QUS parameters does not account for viscous absorption, but fully account for scattering as well as mode conversions in the trabeculae. The absorption in bone marrow has recently [23] been shown to induce an increase of BUA between 4% and 14% according to the value of the volume fraction, but this assumption should not lead to substantial modifications of the conclusion obtained in the present study. Second,
similar and homogeneous isotropic material properties were input into the numerical bone models for the computation of the QUS parameters and of E. However, this assumption leads to accurate predictions of QUS properties using FDTD [6] and to be a relevant approximation when performing μFEA [24].

References


