# PEER-REVIEWED SCIENTIFIC ARTICLES ON OSCARE SONO AXIAL TRANSMISSION ULTRASOUND TECHNOLOGY

The newest articles from 2011-2014 are in vivo studies demonstrating the correlation of Oscare measurement results with radius cortical thickness and mineral density within the cortex as well as subcortically, and the ability of the Oscare measurement to discriminate fractures. The articles from between 2004-2008 are ex vivo and phantom studies related to the development of the measurement methodology and technology. The articles from 2002-2003 are the first studies on the new method including both in vivo and phantom measurements. The in vivo –studies include data on altogether 945 patients.

*M. Määttä, P. Moilanen, J. Timonen, P. Pulkkinen, R. Korpelainen, T. Jämsä, ”Association between low-frequency ultrasound and hip fractures – comparison with DXA-based BMD”, BMC Musculoskelet Disord, 15:208, 2014*

This study investigates the association between speed of low-frequency ultrasound measured from tibia and the occurrence of fractures. The measurement from the tibia has a wider standard deviation than the measurement from the radius which is the method used in the commercial Oscare product, however despite this the study is able to show an association between ultrasound velocity and hip fractures with an odds ratio of 3.3.

Background: New methods for diagnosing osteoporosis and evaluating fracture risk are being developed. We aim to study the association between low-frequency (LF) axial transmission ultrasound and hip fracture risk in a population-based sample of older women.

Methods: The study population consisted of 490 community-dwelling women (78-82 years). Ultrasound velocity (V(LF)) at mid-tibia was measured in 2006 using a low-frequency scanning axial transmission device. Bone mineral density (BMD) at proximal femur measured using dual-energy x-ray absorptiometry (DXA) was used as the reference method. The fracture history of the participants was collected from December 1997 until the end of 2010. Lifestyle-related risk factors and mobility were assessed at 1997.

Results: During the total follow-up period (1997-2010), 130 women had one or more fractures, and 20 of them had a hip fracture. Low V(LF) (the lowest quartile) was associated with increased hip fracture risk when compared with V(LF) in the normal range (Odds ratio, OR = 3.3, 95% confidence interval (CI) 1.3-8.4). However, V(LF) was not related to fracture risk when all bone sites were considered. Osteoporotic femoral neck BMD was associated with higher risk of a hip fracture (OR = 4.1, 95% CI 1.6-10.5) and higher risk of any fracture (OR = 2.4, 95% CI 1.6-3.8) compared to the non-osteoporotic femoral neck BMD. Decreased VLF remained a significant risk factor for hip fracture when combined with lifestyle-related risk factors (OR = 3.3, 95% CI 1.2-9.0).

Conclusion: Low V(LF) at mid-tibia was associated with hip fracture risk in older women even when combined with lifestyle-related risk factors.

*P. Moilanen, M. Määttä, V. Kilappa, L. Xu, P.H. Nicholson, M. Alén, J. Timonen, T. Jämsä, S. Cheng, " Discrimination of fractures by low-frequency axial transmission ultrasound in postmenopausal females", Osteoporos Int, 24(2):723-730, 2013.*

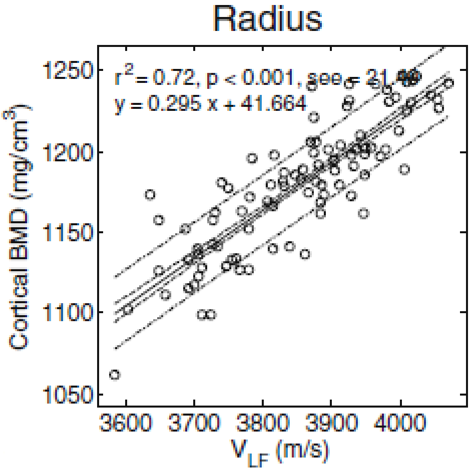
The aim of the study was to evaluate the ability of low-frequency axial transmission ultrasound to discriminate fractures retrospectively in postmenopausal women. The study involved 95 female subjects aged 45-88 years, whose fracture information was gathered retrospectively. The fracture group was defined as subjects with one or more low or moderate energy fractures. The radius and tibial shaft were measured with a low-frequency ultrasonometer to assess the velocity of the first arriving signal. Site-matched pQCT was used to measure volumetric cortical and subcortical bone mineral density and cortical thickness. DXA was used to measure areal BMD for the whole body, lumbar, spine and hip.

The majority of the fractures were in the upper limb. V(LF) in the radius (but not in the tibia) discriminated fractures with an age and BMI adjusted odds ratio of 2.06 (95% CI 1.21-3.50, p<0.01), better than pQCT or DXA.

*V. Kilappa, P. Moilanen, L. Xu, P.H. Nicholson, J. Timonen, S. Cheng, "Low-frequency axial ultrasound velocity correlates with bone mineral density and cortical thickness in the radius and tibia in pre- and postmenopausal women", Osteoporos Int 22(4):1103-13, 2011.*

LF US provides enhanced sensitivity to thickness and endosteal properties of the cortical wall of radius and tibia compared to using higher frequencies (e.g. 1 MHz). The aim of this study was to evaluate the extent to which LF measurement reflects cortical thickness and bone mineral density. LF US velocity was compared to site matched pQCT measurements. The study included 159 premenopausal and 95 postmenopausal females.

V(LF) correlated best with cortical bone mineral density in postmenopausal females in the radius (R=0,85, p<0.001), but significantly also with subcortical bone mineral density (R=0.759) and with cortical thickness (R=0.761), p<0.001. Similar trends but weaker correlations were found for tibia and for premenopausal women.



*M. Muller, D. Mitton, P. Moilanen, V. Bousson, M. Talmant, and P. Laugier, "Prediction of bone mechanical properties using QUS and pQCT: Study of the human distal radius", Med Eng Phys, 30(6): 761-767, 2008.*

The objective was to compare the prediction of bone mechanical properties provided by axial transmission to that provided by peripheral quantitative computed tomography (pQCT) at the distal radius. Measurements of the radial speed of sound were performed using three axial transmission devices: a commercial device (1.25 MHz), a bi-directional axial transmission prototype (1 MHz), both measuring the velocity of the first arriving signal (FAS), and a low frequency (200 kHz) device, measuring the velocity of a slower wave. Co-localized pQCT measurements of bone mineral density and cortical thickness were performed. Ultrasound and pQCT parameters were compared to mechanical parameters such as failure load and Young's modulus. Correlations of the ultrasound and pQCT parameters to mechanical parameters were comparable. The best predictor of failure load was the pQCT measured cortical thickness. The best predictor of Young's modulus was the bi-directional SOS. The low frequency device significantly correlated to cortical thickness and failure load. The association of different axial transmission techniques should be able to provide a good prediction of bone mechanical parameters, and should therefore be helpful for fracture risk prediction.

*P. Moilanen, "Ultrasonic guided waves in bone", IEEE Trans. Ultrason. Ferroelect. Freq. Contr., 55(6): 1277-1286, 2008.*

Recent progress in quantitative ultrasound (QUS) has shown increasing interest toward measuring long bones by ultrasonic guided waves. This technology is widely used in the field of nondestructive testing and evaluation of different waveguide structures. Cortical bone provides such an elastic waveguide and its ability to sustain loading and resist fractures is known to be related to its mechanical properties at different length scales. Because guided waves could yield diverse characterizations of the bone's mechanical properties at the macroscopic level, the method of guided waves has a strong potential over the standardized bone densitometry as a tool for bone assessment. This paper discusses the promises and challenges related to bone characterization by ultrasonic guided waves.

*P. Moilanen, M. Talmant, V. Kilappa, P.H.F. Nicholson, S. Cheng, J. Timonen, P. Laugier, "Modeling the impact of soft tissue on axial transmission measurements of ultrasonic guided waves in human radius", J. Acoust. Soc. Am., 124(4): 2364-2373, 2008.*

Recent in vitro and simulation studies have shown that guided waves measured at low ultrasound frequencies (f=200 kHz) can characterize both material properties and geometry of the cortical bone wall. In particular, a method for an accurate cortical thickness estimation from ultrasound velocity data has been presented. The clinical application remains, however, a challenge as the impact of a layer of soft tissue on top of the bone is not yet well established, and this layer is expected to affect the dispersion and relative intensities of guided modes. The present study is focused on the theoretical modeling of the impact of an overlying soft tissue. A semianalytical method and finite-difference time domain simulations were used. The models developed were shown to predict consistently real in vivo data on human radii. As a conclusion, clinical guided wave data are not consistent with in vitro data or related in vitro models, but use of an adequate in vivo model, such as the one introduced here, is necessary. A theoretical model that accounts for the impact of an overlying soft tissue could thus be used in clinical applications.

*P. Moilanen, P. H. Nicholson, V. Kilappa, S. Cheng, and J. Timonen, "Assessment of the cortical bone thickness using ultrasonic guided waves: modelling and in vitro study", Ultrasound Med Biol, 33: 254-262, 2007.*

Determination of cortical bone thickness is warranted, e.g., for assessing the level of endosteal resorption in osteoporosis or other bone pathologies. We have shown previously that the velocity of the fundamental antisymmetric (or flexural) guided wave, measured for bone phantoms and bones in vitro, correlates with the cortical thickness significantly better than those by other axial ultrasound methods. In addition, we have introduced an inversion scheme based on guided wave theory, group velocity filtering and 2-D fast Fourier transform, for determination of cortical thickness from the measured velocity of guided waves. In this study, the method was validated for tubular structures by using numerical simulations and experimental measurements on tube samples. In addition, 40 fresh human radius specimens were measured. For tubes with a thin wall, plate theory could be used to determine the wall thickness with a precision of 4%. For tubes with a wall thicker than 1/5 of the outer radius, tube theory provided the wall thickness with similar accuracy. For the radius bone specimens, tube theory was used and the ultrasonically-determined cortical thickness was found to be U-Th = 2.47 mm +/- 0.66 mm. It correlated strongly ($r(2) = 0.73$, $p < 0.001$) with the average cortical thickness, C-Th = 2.68 +/- 0.53 mm, and the local cortical thickness ($r(2) = 0.81$, $p < 0.001$), measured using peripheral quantitative computed tomography. We can conclude that the guided-wave inversion scheme introduced here is a feasible method for assessing cortical bone thickness.

*P. Moilanen, M. Talmant, V. Bousson, P. H. F. Nicholson, S. Cheng, J. Timonen, and P. Laugier, "Ultrasonically determined thickness of long cortical bones: Two-dimensional simulations of in vitro experiments", J Acoust Soc Am, 122: 1818-1826, 2007.*

Previously it has been demonstrated that cortical bone thickness can be estimated from ultrasonic guided-wave measurements, in an axial transmission configuration, together with an appropriate analytical model. This study considers the impact of bone thickness variation within the measurement region on the ultrasonically determined thickness (UTh). To this end, wave velocities and UTh were determined from experiments and from time-domain finite-difference simulations of wave propagation, both performed on a set of ten human radius specimens (29 measurement sites). A two-dimensional numerical bone model was developed with tunable material properties and individualized geometry based on x-ray computed-tomography reconstructions of human radius. Cortical thickness (CTh) was determined from the latter. UTh data for simulations were indeed in a excellent accordance (root-mean-square error was 0.26 mm; $r2=0.94$, $p<0.001$) with average CTh within the measurement region. These results indicate that despite variations in cortical thickness along the propagation path, the measured phase velocity can be satisfactorily modeled by a simple analytical model (the A(0) plate mode in this case). Most of the variability (up to 85% when sites were carefully matched) observed in the in vitro ultrasound data was explained through simulations by variability in the cortical thickness alone.

*P. Moilanen, M. Talmant, P. H. F. Nicholson, S. Cheng, J. Timonen, and P. Laugier, "Ultrasonically determined thickness of long cortical bones: Three-dimensional simulations of in vitro experiments", J Acoust Soc Am, 122, 2439-2445, 2007.*

It was reported in a previous study that simulated guided wave axial transmission velocities on two-dimensional (2D) numerically reproduced geometry of long bones predicted moderately real in vitro ultrasound data on the same bone samples. It was also shown that fitting of ultrasound velocity with simple analytical model yielded a precise estimate (UTh) for true cortical bone thickness. This current study expands the 2D bone model into three dimensions (3D). To this end, wave velocities and UTh were determined from experiments and from time-domain finite-difference simulations of wave propagation, both performed on a collection of 10 human radii (29 measurement sites). A 3D numerical bone model was developed with tuneable fixed material properties and individualized geometry based on X-ray computed tomography reconstructions of real bones. Simulated UTh data were in good accordance (root-mean-square error was 0.40 mm; $r(2)=0.79$, $p<0.001$) with true cortical thickness, and hence the measured phase velocity can be well estimated by using a simple analytical inversion model also in 3D. Prediction of in vitro data was improved significantly (by 10% units) and the upgraded bone model thus explained most of the variability (up to 95% when sites were carefully matched) observed in in vitro ultrasound data.

*P. Moilanen, P.H.F. Nicholson, V. Kilappa, S. Cheng, J. Timonen, "Measuring guided waves in long bones: modeling and experiments in free and immersed plates", Ultrasound Med Biol, 32: 709-719, 2006.*

Guided waves, consistent with the A0 Lamb mode, have previously been observed in bone phantoms and human long bones. Reported velocity measurements relied on line fitting of the observed wave fronts. Such an approach has limited ability to assess dispersion and is affected by interference by other wave modes. For a more robust identification of modes and determination of phase velocities, signal processing techniques using the fast Fourier transform (FFT) were investigated. The limitations of FFT because of spatial resolution were addressed to improve the precision of the measured modes. An inversion scheme was developed for determining the plate thickness from the measured velocity. Experiments were performed on free and immersed plates, mimicking bone without and with an overlying tissue. With group velocity filtering, modes could be identified reliably with precise phase velocities and thicknesses. These methods were essential for the immersed plates and they should lead to more reliable in vivo measurements.

*M. Muller, P. Moilanen, E. Bossy, P.H.F. Nicholson, V. Kilappa, J. Timonen, M. Talmant, S. Cheng, P. Laugier, "Comparison of three ultrasonic axial transmission methods for bone assessment", Ultrasound Med Biol, 31: 633-642, 2005.*

This study compared three approaches to bone assessment using ultrasonic axial transmission. In 41 fresh human radii, velocity of the first arriving signal was measured with a commercial device (Sunlight Omnisense) operating at 1.25 MHz, a prototype based on 1-MHz bidirectional axial transmission and a low-frequency (200 kHz) prototype, also measuring the velocity of a slower wave. Cortical and trabecular bone mineral density, cortical thickness and cross-sectional area were determined by peripheral quantitative computed tomography. Significant but modest correlation between velocities reflects differences in the nature of the propagating waves and methodological differences. Of the higher frequency devices, bidirectional measurements provided stronger correlations with bone properties than did conventional measurements. High-frequency devices were less sensitive to cortical thickness than was the low-frequency device, because higher frequency waves interrogate thinner cortical layers. The results suggest that different axial transmission approaches reflect different bone properties. Therefore, a multifrequency technique might be useful in probing different bone properties.

*P. Moilanen, V. Kilappa, P.H.F. Nicholson, J. Timonen, S. Cheng, "Thickness sensitivity of ultrasound velocity in long bone phantoms", Ultrasound Med Biol 30: 1517-1521, 2004.*

One approach to bone disease diagnosis such as osteoporosis is to measure the velocity of ultrasound propagating axially along long bones. In this study, the variation in velocity as a function of radial position was assessed using two polyvinyl chloride (PVC) bone phantoms with cross-sectional geometry similar to the human tibia but differing in medullary cavity diameter. Two ultrasonometers were used: these were a commercial device operating at a relatively high frequency (HF) of 1.25 MHz and a prototype low frequency (LF) device operating at approximately 200 kHz. The LF measurements showed a larger variation with radial position, with changes in velocity of up to 20% occurring around the phantom compared with changes of only 4% at most for HF. The LF velocity correlated strongly with local thickness (r(2) = 0.81) but HF velocity did not. The results demonstrate that LF measurements have a greatly enhanced thickness sensitivity. Using LF, it may therefore be possible to assess bone thickness as a function of radial position and hence to determine the distribution of bone around the long axis.

*P. Moilanen, P.H.F. Nicholson, T. Kärkkäinen, Q. Wang, J. Timonen, S. Cheng, "Assessment of the tibia using ultrasonic guided waves in pubertal girls", Osteoporos Int, 14: 1020-1027, 2003.*

The purpose of this study was to compare low frequency ultrasonic guided wave measurements with established ultrasound and bone density measurements in terms of their ability to characterize the tibia in pubertal girls. Subjects were 12-14-year-old girls (n=106) who were participating in a calcium and vitamin D intervention study. A prototype low frequency pulse transmission device consisting of a uniaxial scanning mechanism and low frequency transducers orientated perpendicularly to the limb was used to measure two ultrasound velocities in the tibia. The first velocity, V1, was that of the first arriving signal, similar to that measured by existing commercial tibial ultrasound devices. The second velocity, V2, was that of a slower wave propagating at 1,500-2,000 m/s, which has been shown elsewhere to be consistent with the lowest order antisymmetric guided mode in the bone. In addition, commercial ultrasound devices (Omnisense, Sunlight Ltd.; QUS-2, Quidel Corp.) were used to measure the speed of sound (SOS) in the tibia and the radius and attenuation (BUA) in the calcaneus. Cortical bone cross-sectional area (CSA), mineral density (BMD) and cortical thickness (cTh) of the tibia were measured using pQCT, site-matched to the ultrasound measurements. Both V1 and V2 correlated significantly with cortical BMD and with cTh and CSA. On the other hand, tibial SOS correlated with BMD, but not with cTh and CSA. These results indicate that the prototype device using guided waves captures aspects of tibial cortical bone geometry in addition to bone density, thereby potentially offering increased diagnostic information compared to existing tibial ultrasound devices.

*P.H.F. Nicholson, P. Moilanen, T. Kärkkäinen, J. Timonen, S. Cheng, "Guided ultrasonic waves in long bones: modelling, experiment and in vivo application", Physiol Meas, 23: 755-68, 2002.*

Existing ultrasound devices for assessing the human tibia are based on detecting the first arriving signal, corresponding to a wave propagating at, or close to, the bulk longitudinal velocity in bone. However, human long bones are effectively irregular hollow tubes and should theoretically support the propagation of more complex guided modes similar to Lamb waves in plates. Guided waves are attractive because they propagate throughout the bone thickness and can potentially yield more information on bone material properties and architecture. In this study, Lamb wave theory and numerical simulations of wave propagation were used to gain insights into the expected behaviour of guided waves in bone. Experimental measurements in acrylic plates, using a prototype low-frequency axial pulse transmission device, confirmed the presence of two distinct propagating waves: the first arriving wave propagating at, or close to, the longitudinal velocity, and a slower second wave whose behaviour was consistent with the lowest order Lamb antisymmetrical (A0) mode. In a pilot study of healthy and osteoporotic subjects, the velocity of the second wave differed significantly between the two groups, whereas the first arriving wave velocity did not, suggesting the former to be a more sensitive indicator of osteoporosis. We conclude that guided wave measurements may offer an enhanced approach to the ultrasonic characterization of long bones.