World Journal of Surgery and Surgical Research

Research Article
Published: 02 Apr, 2021

# Ultrasound and Bone Disease: A Systematic Review

***Sara Behforootan[1]*, Oliver Boughton[1], Ulrich Hansen[2], Justin Cobb[1], Peter Huthwaite[2] and Richard Abel[1]***

*[1]Department of Surgery and Cancer, MSK Lab, Imperial College London, Sir Michael Uren Hub, White City Campus, UK*

*[2]Department of Mechanical Engineering, Imperial College London, UK*

## Abstract

Over the last five decades bone ultrasound has been extensively used to give new understanding into bone. However, the actual contribution of ultrasound to bone disease treatment in clinical practice remains relatively limited.

This review aims to resolve why ultrasound has not been established as a clinical tool to diagnose or treat bone disease. An overview of published ultrasonic techniques used on bone at key sites in osteoporosis and osteoarthritis is provided to investigate applicability of ultrasound in a clinical setting.

An electronic literature search was conducted *via* MEDLINE and Embase to identify publications utilizing bone ultrasound. After removing duplicates, abstracts of 2,951 articles were screened, and 64 articles that met the inclusion criteria, based on abstracts, were selected. Full text of all selected articles was evaluated based on inclusion criteria and ten articles met the inclusion criteria.

Even though a substantial amount of research has been conducted in the field of bone ultrasound, these techniques are not frequently used in clinical practice. The published literature comprises an inclusive toolbox for future work towards clinically applicable ultrasonic techniques, yet no integrated ultrasonic technique exists that could be directly utilized in the clinic at all bone disease critical sites. The ultimate challenge for the implementation of ultrasonic techniques on the key sites is to adapt the current techniques to *in-vivo* measurements and to ensure that they can produce reliable results for different population groups. Accordingly, this highlights the necessity of extensive validation of each specific integrated system and rigorous clinical trials.

**Keywords: Ultrasound; Bone; Osteoporosis; Osteoarthritic; Diagnosis; Treatment**

**OPEN ACCESS**

****Correspondence:***
*Sara Behforootan, Department of Surgery and Cancer, MSK Lab, Imperial College London, Sir Michael Uren Hub, White City Campus, 86 Wood Lane, London W12 0BZ, UK,*
*E-mail: s.behforootan@imperial.ac.uk*

**Received Date**: *01 Mar 2021*
**Accepted Date***: 30 Mar 2021*
**Published Date***: 02 Apr 2021*

***Citation:***
*Behforootan S, Boughton O, Hansen U, Cobb J, Huthwaite P, Abel R. Ultrasound and Bone Disease: A Systematic Review. World J Surg Surgical Res. 2021; 4: 1296.*



## Introduction

Assessing bone quality is one of the key factors in the diagnosis and treatment of different bone disease including osteoporosis and osteoarthritis. Mechanical behavior of bone (i.e. bone stiffness, bone brittleness, bone porosity) and geometrical characteristics of bone (i.e. cortical thickness, femoral neck length) are the most important factors to measure in assessing bone strength [1,2].

Osteoporosis is a debilitating disease that makes bones to become weak and fragile and affects 200 million people worldwide [3,4]. Unfortunately, half of people with osteoporosis are only diagnosed and treated because they suffer a fracture, which could have been potentially prevented by earlier diagnosis and treatment. The Dual X-ray Absorptiometry (DXA) Bone Mineral Density (BMD) criteria for diagnosing osteoporotic patients are not sensitive enough, as more than 50% of old women with osteoporotic fractures do not encounter the BMD criteria measurements for osteoporosis [5-9]. It is clear that there are important factors for assessing bone health that are not part of DXA measurements, which include structural parameters such as cortical thickness and porosity, together with material properties [10,11].

Bone health assessment, especially at the femur, is important for decision making in osteoarthritic patients. Osteoarthritis (OA) which affects the hips is the most common form of arthritis [12]. In some people, the harm and pain in the hip may be extremely severe to permit hip replacement surgery. In cementless joint replacement, the stiffness and strength of bone are critically important. An implant must be inserted with enough force to ensure a stable "press-fit", without too much force that could fracture the bone. Both the stability of the press-fit and the likelihood of fracture are dependent on the bone quality [13-15]. In addition, in the longer term after the operation, differences in the stiffness of the implant and bone can cause thinning of the bone around the implant, a process called stress shielding [16]. Therefore, assessing the bone mechanical properties can improve the outcome of orthopedic operations in the short-term and long-term and reduce the risk of failure [17].

Ultrasound is an imaging technique which is non-invasive and portable with low machine manufacturing costs [18]. Utilizing ultrasound for bone assessment has been discussed since the 1950s [19]. Ultrasonic wave speed and attenuation are affected by the medium they travel through [20]. Therefore, the geometrical and mechanical properties of bone can, in theory, be quantified by a pair of transducers which respectively emit and receive the ultrasonic waves [21,22], although the complexity of the interaction means that the relationship between the measured signal and the underlying properties is not straightforward, making extracting the bone properties a challenge.

Characterizing the bone quality using ultrasound has been investigated extensively at different sites, especially at the calcaneus. A number of quantitative ultrasound techniques at the calcaneus are being utilized in a number of clinics for assessing fracture risk, where DEXA is not available [23]. However, this method is not recommended as a diagnosis tool yet, according to the NICE guidelines in the UK [24]. Bone mechanical properties can be different at various sites [25]. Therefore, there is a need for a device to accurately measure the bone strength at high risk sites in bone disease (i.e. the forearm, proximal femur and vertebrae).

Ultrasound techniques would appear to have many advantages over existing bone assessment techniques: They are relatively low in cost, non-invasive, portable and avoid ionizing radiation. However, despite a large amount of research and the release of several systems onto the market, ultrasound devices have not been adopted widely into healthcare [23,24]. Therefore, the aim of this review is to evaluate the technology readiness and effectiveness of the currently available ultrasound techniques in assessing bone health in clinically relevant scenarios.

## Method

An electronic literature search of all articles published up until January 2020 was conducted *via* MEDLINE and Embase to identify publications utilizing ultrasound for assessing the bone. The search included MEDLINE and Embase using the keywords (*ultrasound [Abstract] OR ultrasound [Abstract] OR ultrasound* [Abstract]) AND (*bone [Abstract] OR bone [Abstract] OR bone*) AND (*rigidity [Abstract] OR stiffness [Abstract] OR stiffness* [Abstract] OR *elasticity [Abstract] OR elastic it* [Abstract] OR *strength [Abstract] OR *thickness [Abstract] OR thickness [Abstract] OR porosity [Abstract] OR poros* [Abstract]) in December 2019. There was no limitation in terms of publication date. Only studies that full texts published in English are included in this search.

Ultrasound has been utilized extensively to assess bone quality at different bones in different parts of the body. However, site-specific measurements have been proven to have the highest predictive power [26]. Therefore, the focus of this review is on studies that have utilized ultrasonic techniques to assess the bone quality at the main sites for osteoporosis and osteoarthritis (i.e., hip, forearm, and vertebrae) [27]. Therefore, this review considered original papers on assessing bone quality using ultrasound at fracture sites including the forearm, femur and vertebrae. Studies that measured bone quality at other sites (e.g., calcaneus, tibia, etc) or from cadavers were excluded. Selected papers were assessed in terms of the ultrasound classes and the frequency range. Furthermore, the outcome of the studies and their applicability for utilizing as a clinical method and limitations were investigated.

## Results

A total of 1,711 articles were identified from MEDLINE and 2,383 articles from Embase. Duplicates were removed, abstracts of 3,029 articles were screened, and 69 articles that met the inclusion criteria based on abstracts, were selected (Figure 1). Full texts of all remaining articles were evaluated based on inclusion criteria. Only 10 articles met the inclusion criteria (Table 1). The included papers covered a range of studies utilizing both transverse transmission and axial transmission techniques at the forearm and femur. Eight studies measured bone quality at the forearm and two studies determined bone quality at the femur using *in vivo* ultrasound. Four studies utilized axial transmission techniques whereas six studies used transverse transmission techniques. Three studies investigated the geometrical parameters of bone and six studies explored the material properties of bone.

### Transmission techniques

Based on the included studies, ultrasound techniques can be broadly divided into two classes by their specific arrangement of transducers: Transverse transmission techniques and axial transmission techniques. In transverse transmission techniques, a pair of transducers typically faces each other on two positions of a skeletal site and the mechanical behavior of the skeletal site is estimated based on the Broadband Ultrasonic Attenuation (BUA) and Speed of Sound (SOS) [28-31]. The signal transmission through the bone in response to an ultrasonic excitation is compared against a calibration signal which has been transmitted through water or any other known reference medium and the speed of sound is measured.

Axial transmission techniques or guided wave techniques utilize a specific configuration of transducers placed along the long bone axis. Transducers generate and receive guided waves through the cortical bone [1,32,33]. Guided waves are mechanical stress waves that propagate through the long bones within the structural boundaries and are, in some cases, highly sensitive to changes of cortical thickness.

In the last two decades, research into characterizing bone strength

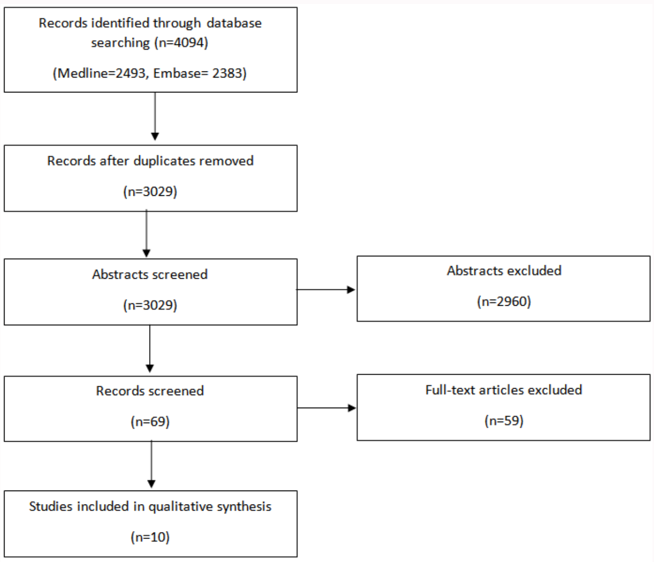


**Figure 1:** Review flow chart (Prisma 2009).

**Table 1:** Included studies, methodologies, measured values, and disadvantages of the method.

| Reference | Method (Numerical/ Experimental/Both) | Experimental method | Wave type | Frequency | Anatomical position | Outcomes | Limitations |
|---|---|---|---|---|---|---|---|
| [32] | Experimental | Phantom/*In-vivo/Ex-vivo* | Guided waves | 0.4-1.6 MHz | Radii | Introduced a new technique that utilised inversion method based on genetic algorithm using multi-mode guide waves with blind mode-order. | Their algorithm does not work in the case of soft tissue thickness is more than 10 mm. The probe should be perfectly aligned with long bone. |
| [1] | Experimental | Phantom/*In-vivo* | Guided waves | 0.4-1.6 MHz | Radii | Introduced new technique to measure the thickness and porosity of cortices in long bones. | Their algorithm does not work in the case of soft tissue thickness is more than 10 mm. The probe should be perfectly aligned with long bone. |
| [45] | Experimental | *In-vivo* | Guided waves | 0.4-1.6 MHz | Radii | Technique which was introduced in [1] was utilised to assess the relationship of ultrasound results on Radii with traumatic and non-traumatic fractures and BMD. | Their algorithm does not work in the case of soft tissue thickness is more than 10 mm. The probe should be perfectly aligned with long bone. Although there are significant differences between the results of traumatic fractured, non-traumatic fractured and healthy participants, the average values are not very different. More studies with bigger sample size are necessary to validate the predictability of the device. |
| [33] | Experimental | *In-vivo* | Guided waves | 400 kHz | Tibiae/Radii | This study discriminated subjects with fracture history from non-fractured by introducing a low frequency axial transmission ultrasound. The study showed that speed of the sound in axial transmission can better distinguish fractured with non-fractured subjects compared to other techniques such as DXA and peripheral Quantitative Computed Tomography. | Data are not on bone status at the fracture time. Fractured group was very small. |
| [47] | Experimental | *In-vivo* | Transverse waves | 5 MHz | Femora | Utilised radiography to measure the thickness of cortex and the estimate the mechanical properties based on Time of Flight (ToF). | The method needs radiography which is invasive and not accessible in all health centres. The thickness measurement with radiography may not be very accurate. The effect of accuracy in the thickness measurement on characterised bone material properties should be investigated. |
| [29] | Experimental | *In-vivo* | Transverse waves | 600/550 kHz | Femora | A QUS device was developed in order to measure bone quality in-vivo at the proximal femur. QUS measured transmitted and reflected signals. Furthermore, scattered signals from the inner layers of the bone were measured. Though, validity of these signals has not yet been assessed. The quantified material properties were validated against BMD results from DEXA which is not accurate in all cases. | Device is very big which is not clinically applicable in this setting. Device includes water bath, which can be replaced with ultrasonic gel which is more clinically applicable. The device was able to assess the trabecular properties of femoral head. Therefore, cortical bone thickness and material properties were not considered. The quantified material properties were validated against BMD results from DEXA which is not accurate in all cases. |
| [30] | Experimental | *In-vivo* | Transverse waves | Not mentioned | Tibiae/Radii | The speed of sound in tibia and forearm was compared between normal and obese children which was not significantly different between two groups. Bone strength that was measured with developed QUS was lower in children with obesity. However, the severity of obesity did not affect the results. | Bone strength was just considered as the only factor which affects the speed of sound; however, different factors (e.g. cortical thickness, cortical properties and trabecular properties) are the factors that affect both bone strength and speed of sound. The device specifications were not mentioned comprehensively in the manuscript. |
| [31] | Experimental | *In-vivo* | Transverse waves | 5 MHz | Radii | Elasticity of cortical bone was calculated using speed of sound. | It is necessary to measure BMD using DEXA as well as speed of sound with ultrasound. It is necessary to have radiography from the same patients in order to measure the geometry of cortical bone. Method is not validated. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| [28] | Experimental | *In-vivo* | Transverse waves | 5 MHz | Radii | The validity of the previous study [10] was assessed. The combination of speed of sound and BMD works better in discriminating healthy with patients with osteoporosis or metabolic bone disease than any of these parameters alone. | It is necessary to measure BMD using DEXA as well as speed of sound with ultrasound. It is necessary to have radiography from the same patients in order to measure the geometry of cortical bone. |
| [46] | Experimental | *In-vitro*/*in-vivo* | Transverse waves (pulse echo) | 2.25 MHz | Tibiae and Radii | An *in vivo* ultrasonic method was employed to measure the cortical bone thickness. Furthermore, the appropriateness of two different signal processing methods (the envelope and cepstral methods) was compared. A fairly small variation in the SOS among participants was found in this research. | The material properties of cortical bone were assumed to be constant in different subjects. However, this could be different as a result of aging or disease. |

has increasingly focused on pulse-echo techniques [29,34], i.e., those where an ultrasonic wave is both transmitted and received at the same location. This is in part due to the successful use of parameters that are based on ultrasound reflections. Since ultrasound waves are easily scattered by small particles, the inhomogeneous structure reflects ultrasound to an extent that is significantly dependent on its structure [35]. In a study by Barkmann et al. [29] a pulse-echo technique was utilized to assess the mechanical properties of trabecular bone at the femoral head and the results were compared against BMD.

The transverse transmission technique has been utilized in cancellous bone at the distal radius and a pulse-echo technique has been utilized more recently in order to evaluate the quality of bone at the femoral head [36,37]. Amplitude and Time of Flight (TOF) of the transmitted signals were measured to analyze the density and elasticity of the bone at the femoral head and echo signals were analyzed to calculate bone thickness and soft tissue thickness [37,38].

### Frequency range

Bone is a highly attenuating medium for ultrasonic waves. This means a gradual loss of flux in ultrasonic waves, which is high in bone compared to soft tissues. Therefore, most investigations utilized low-frequency ultrasound in the 400 kHz to 5 MHz range.

The sensitivity of for axial transmission measured parameters to different frequency ranges was assessed by Muller et al. [39]. They concluded that the nature of the propagating waves with different frequencies causes the difference in the parameters that they can identify. Bidirectional axial ultrasonic measurement showed stronger correlations with bone mineral density than conventional measurements in the higher frequency devices. Bidirectional axial transmission is an ultrasonic technique which utilizes ultrasonic pulses transmitted in two opposite directions on a bone surface and the signals are received at two ends [40]. Low-frequency devices have shown to be more sensitive to cortical thickness. These results show that different frequency ranges in axial transmission approaches imitate different bone properties [41,42].

A study by Eneh et al. [43] investigated the sensitivity of the speed of sound in a radial direction to the porosity using 2.25 and 5.00 MHz frequencies. Although the speed of sound was changed by porosity in both cases, ultrasonic waves with lower frequency (2.25 MHz) were more sensitive to change in porosity. Consequently, a multifrequency technique can be the way forward in imaging various bone properties. Multi-frequency approaches in pulse-echo technique can reduce the uncertainty in the bone assessment considerably [44].

### Measured parameters

The parameters measured vary in the included studies. The measurements include: Cortical thickness and cortical porosity at the forearm [1,32,45,46], cortical mechanical properties at the forearm [31,47], and trabecular porosity at the proximal femur [48]. Furthermore, three studies only compared the signals to find any significant difference between fractured and non-fractured groups [30], osteoporotic and healthy groups [28] and healthy and obese children [33].

## Discussion

Although bone ultrasound has been vastly researched in the last few decades, ultrasound techniques have not become well-established in clinical practice yet [23,24]. Only ten out of 3,029 articles focused on assessing bone health at critical sites using *in vivo* techniques. This highlights the slow translation these techniques into clinical practice.

### Targeted away from key sites

Ultrasound has been utilized extensively to assess bone quality at different bones in different parts of the body. However, site-specific measurements (i.e. hip, forearm, and vertebrae) [43], have been proven to have the highest predictive power [26]. Hip and vertebral fractures need a long time of care after fracture and cause life-long disabilities in many cases [27,49]. Hip bone health is also key in decision making in osteoarthritis. However, studies focused on the most common fracture sites/key arthritis site are few.

Eight out of ten studies in this review characterized the material or geometrical parameters of the forearm and two studies characterized the material parameters of proximal femur. Although vertebral fracture needs a long time of care after fracture and cause life-long disabilities in many cases, no study in the literature investigated bone quality in vertebrae using ultrasound [27,49], probably due to the practical difficulty in applying ultrasound techniques to the spine.

**Proximal femur:** Although proximal femoral fractures have the highest morbidity and mortality of osteoporotic fractures [27], the proximal femur has been investigated less using ultrasound than other sites. This is likely due to the proximal femoral shape being irregular and the bone being bounded by a huge amount of soft tissue. Therefore, wave propagation through the proximal femur is much more complex than through other critical sites. Consequently, more advanced signal processing techniques are required to calculate ultrasonic properties [50,51], and regular signal processing techniques to measure Quantitative Ultrasound (QUS) variables fail as a result of multipath transmission [50,51].

Assessing bone at the femoral neck is important in osteoporosis diagnosis. However, the femoral neck has an irregular shape and is not very accessible. Therefore, assessing bone at the femoral shaft would be more feasible. Alternatively, geometrical parameters of bone at the femoral neck do not necessarily correlate with the femoral shaft. The mechanical properties of bone are different in the femoral shaft and femoral neck [52].

Therefore, the relationship between the changes in mechanical and geometrical properties of bone at the femoral neck and femoral shaft needs to be investigated. If biomechanical changes at the femoral neck and femoral shaft follow similar trends, monitoring bone properties at the femoral shaft could be helpful in assessing the risk of hip fracture. Otherwise, there is a need for techniques that are able to capture the femoral neck for diagnosing osteoporosis.

Pulse-echo techniques have been utilized to directly measure the Speed of Sound (SOS) through the proximal femur [29,34,48]. The measurement principles were similar to the other technologies such as forearm calcaneus ultrasound, with the size and precise structure of the device modified to the femur. The device includes a large water bath with an adaptable C-arm which surrounds the femoral area [29,47]. The results of this system for characterizing the mechanical behavior of the femur were compared against DXA measurements, which may not have been sensitive enough measurements of bone quality to compare against [53]. There is increasing evidence that cortical thickness and porosity, measured by computed tomography, are more reliable metrics of bone quality [54], and perhaps these should have been the metrics for ultrasound to be compared against in this study.

There were some other limitations of this device. The device required a water bath, which makes using this as an everyday clinical tool more challenging. Furthermore, the device is designed to assess the mechanical behavior of the trabecular bone at the femoral head, whereas the strength of the bone is also dependent on the cortical properties in the femoral neck [55].

**Vertebrae:** Osteoporotic fractures commonly occur in the vertebrae; however, ultrasound techniques have been rarely used to characterize the geometrical and material properties of vertebrae. Vertebrae have an irregular shape which makes diagnosing osteoporosis and fractures using ultrasound techniques challenging [56]. Pulse-echo techniques can potentially be utilized on the lateral side of vertebrae however, the complex shape of the vertebrae, especially centrally, makes signal processing more difficult [57].

## Important parameters

A few studies demonstrate that cortical thickness and porosity at fracture sites such as the femoral neck and forearm can improve the identification of individuals with high fracture risk [36,58-60]. However, there is no assessment of the importance of each parameter (cortical thickness, cortical porosity, trabecular porosity and mechanical properties) in bone strength. The strength of any structure (e.g. bone) is dependent on both material and geometrical properties. Measuring either the material properties or geometrical parameters can add valuable information on bone quality.

To validate the significance of quantifying the mechanical or geometrical properties of the bone in assessing bone quality, it is necessary to investigate the effect of these parameters on bone strength. Therefore, a parametric study on the effect of various material and geometrical parameters on bone strength is necessary. This can be performed by a numerical or finite element study on a validated model at various fracture sites.

Ultrasound could be useful for collecting geometrical and material parameters that would aid assessment of bone health [61,62].

**Failure in measuring geometrical parameters:** Cortical thickness has been recently highlighted as a key determinant factor of bone strength [36,58], and it has been suggested that it should be included in evaluation of bone quality [59]. Guided wave ultrasound techniques have been recently developed which aim to quantify the cortical thickness and porosity of forearm [1]. The guided wave technique involves propagating waves in long bones [63]. Therefore, the method is not applicable on vertebrae.

Furthermore, soft tissue thickness more than 10 mm can create difficulties in the optimization techniques being used [1]. Soft tissue thickness at the femur is normally higher than 10 mm; therefore the method is difficult to apply at the femur. Optimization methods need to be improved to be able to deal with a wider range of geometry.

**Failure in measuring material properties:** Bone Mineral Density (BMD) measurements of bone from DXA scanning are indicators of the material properties of bone in different subjects [64]. However, bone elasticity, fragility and strength are not just dependent on BMD [65]. Therefore, there is a need for a method to consider the material properties of bone (i.e. elasticity, fragility and strength), in addition to BMD measured by DXA.

Ultrasound can measure the elasticity of bone based on wave speed and density. A number of studies utilized this method to calculate the material properties of cortical bone at the forearm [28,31]. The geometry of the radius is assumed to be a cylinder. DXA and radiography have been utilized to measure BMD and thickness of cortical bone, respectively. These data, along with the speed of sound measured by ultrasound were utilized to assess the mechanical properties of cortical bone [28,31]. The results were compared against published values of *in vitro* studies, where the results in 60% of a diverse group of patients with bone and joint symptoms showed a broader range of results than results of 90% of volunteers without symptoms. The necessity to utilize radiography and DXA, in addition to ultrasound, makes this method more difficult to implement as a clinical technique.

**Compromising between material and geometrical properties?** New techniques have been developed to address the challenge of measuring both material and geometrical properties applying multi-variable optimization algorithms. This has been achieved by different approaches, including pulse-echo [66-68], and multi-site axial techniques [69-71]. These techniques have been demonstrated *ex vivo* and have to be adopted for clinical applications to be utilized as *in vivo* techniques.

## Potential solutions to the challenges

Although extensive research has been performed on the mechanical characterization of bone, there is still more fundamental research required on the bone characterization. Finite Difference Methods (FDM) and Finite Element Methods (FEM) can be cost-efficient ways to investigate the best transmission techniques, wave modes and wave frequencies for characterizing the material and structural parameters of bone structure at fracture sites. Furthermore, parameter analysis on FDM/FEM will allow us to have better understanding of the effectiveness of different parameters in bone strength (i.e. structural and material parameters).

Micro-cracks in bone have come to attention recently as an important parameter in bone fracture risk in patients with bone disease [65]. Micro-cracks in bone are made by daily cyclic loading [72]. The density of cracks typically increases exponentially with age and significantly increases with the beginning of menopause [73]. The quantity of microcracks has a significant effect on the mechanical properties of bone including its stiffness [74], strength [75], and toughness [76]. Currently there is no clinically applicable available method for quantifying micro-cracks. It is worth investigating whether ultrasound techniques could be used to quantity micro-cracks.

## Conclusion

Bone strength has been investigated using ultrasound in many studies in the literature. However, few of these studies focused on techniques that can be used for the diagnosis of osteoporosis, fracture risk prediction and decision making in osteoarthritic treatment. Studies often focused on sites that are easy to measure rather than the key fracture sites. Ultrasonic technology has not developed enough yet to assess bone at key sites (i.e. femoral neck and vertebrae) in bone disease.

Optimization techniques have to be improved to enable them to be applied to the proximal femur, a site important in both osteoporosis and osteoarthritis. Furthermore, wave transmission techniques need to be improved in order to transmit better through the soft tissue. There is also a need for an ultrasonic method that can cope with the complicated geometry of vertebrae and the femoral neck.

Most of the methods in the literature are only applicable *in vitro* and are not clinically applicable *in vivo*. Many techniques are relatively new and need further validation. Overall, the techniques have to be moved towards more clinically applicable and cost-effective methods.

## Acknowledgement

This study was supported by Sackler charity fund.

## References

1. Bochud N, Vallet Q, Minonzio J-G, Laugier P. Predicting bone strength with ultrasonic guided waves. Sci Rep. 2017;7:43628.
2. Krieg MA, Barkmann R, Gonnelli S, Stewart A, Bauer DC, Barquero LDR, et al. Quantitative ultrasound in the management of osteoporosis: The 2007 ISCD Official Positions. J Clin Densitom. 2008;11(1):163-87.
3. Epidemiology, International Osteoporosis Foundation. 2017(2).
4. Melton LJ, Clinic M, Infirmary R. International original article hip fractures in the elderly : A world-wide projection. Osteoporos Int. 1992;2:285-9.
5. Simonelli C, Adler RA, Blake GM, Caudill JP, Khan A, Leib E, et al. Dual-energy X-ray absorptiometry. J Clin Densitom. 2008;11(1):109-22.
6. Bolland MJ, Siu ATY, Mason BH, Horne AM, Ames RW, Grey AB, et al. Evaluation of the FRAX and garvan fracture risk calculators in older women. J Bone Min Res. 2011;26(2):420-7.
7. Fraser L, Langsetmo L, Berger C, Ioannidis G, Goltzman D, Adachi JD, et al. Fracture prediction and calibration of a Canadian FRAX® tool: A population-based report from CaMos. Osteoporos Int. 2011;22(3):829-37.
8. Leslie WD, Lix LM, Langsetmo L, Berger C. Construction of a FRAX® model for the assessment of fracture probability in Canada and implications for treatment. Osteoporos Int. 2011;22(3):817-27.
9. Cronin H, O'Regan C, Kearney P, Walsh JB. Under-diagnosis and under-treatment of osteoporosis in a random sample of community-dwelling Irish adults; results from the first pilot of the Irish longitudinal study on ageing (TILDA). Age Ageing. 2011;40(Suppl 1):S24.
10. Dagan N, Cohen-Stavi C, Leventer-Roberts M, Balicer RD. External validation and comparison of three prediction tools for risk of osteoporotic fractures using data from population based electronic health records: Retrospective cohort study. BMJ. 2017;356:i6755.
11. Aspray TJ. Fragility fracture: Recent developments in risk assessment. Ther Adv Musculoskelet Dis. 2015;7(1):17-25.
12. Breedveld FC. Osteoarthritis — the impact of a serious disease. Rheumatology. 2004;43(1):4-8.
13. Macdonald W, Carlsson LV, Charnlcy GJ, Jacobsson CM. Press-fit acetabular cup fixation: Principles and testing. Proc Inst Mech Eng Part H J Eng Med. 1999;213(1):33-9.
14. Winter W, Karl M. Basic considerations for determining the amount of press fit in acetabular cup endoprostheses as a function of the elastic bone behavior. Biomed Tech. 2014;59(5):413-20.
15. Boughton OR, Ma S, Zhao S, Arnold M, Lewis A, Hansen U, et al. Measuring bone stiffness using spherical indentation. 2018;1-18.
16. Sumner DR. Long-term implant fixation and stress-shielding in total hip replacement. J Biomech. 2015;48(5):797-800.
17. Arnold M, Zhao S, Ma S, Giuliani F, Hansen U, Cobb JP, et al. Microindentation – a tool for measuring cortical bone stiffness? Bone Jt Res. 2017;6(9):542-9.
18. Ranganathan K, Santy MK, Blalock TN, Hossack JA, Member S, Walker WF. Direct sampled I/Q beam forming for compact and very low-cost ultrasound imaging. IEEE Trans Ultrason Ferroelectr Freq Control. 2004;51(9):1082-94.
19. Siegel I, Anast GT, Melds T. The determination of fracture healing by measurement of sound velocity across the fracture site. Surg Gynecol Obs. 1958;107(3):327-32.
20. O'Brien WD. Ultrasound—biophysics mechanisms. Prog Biophy Mol Biol. 2007;93(1–3):212-55.
21. Grimal Q, Grondin J, Guerard S, Barkmann R, Engelke K, Gluer C-C, et al. Quantitative ultrasound of cortical bone in the femoral neck predicts femur strength: Results of a pilot study. J Bone Miner Res. 2013;28(2):302-12.
22. Kilappa V, Xu K, Moilanen P, Heikkola E, Ta D, Timonen J. Assessment of the fundamental flexural guided wave in cortical bone by an ultrasonic axial-transmission array transducer. Ultrasound Med Biol. 2013;39(7):1223-32.
23. Hans D, Baim S. Quantitative Ultrasound (QUS) in the management of osteoporosis and assessment of fracture risk. J Clin Densitom. 2017;20(3):1-12.
24. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N. UK clinical guideline for the prevention and treatment of osteoporosis. 2017;12(1):43.
25. Areeckal AS, Kocher M, David S. Current and emerging diagnostic imaging-based techniques for assessment of osteoporosis and fracture risk. IEEE Rev Biomed Eng. 2018;12(c):254-68.
26. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. 1996;312(7041):1254-59.
27. Foundation IO. Key statistics for Six European Countries Osteoporosis - Incidence and burden. 2017.
28. Gneenfield A, Craven JD, Huddleston A, Wishko D, Ph D, Stern R, et al. Measurement of the velocity of ultrasound in human cortical bone *in vivo*. Estimation of its potential value in the diagnosis of osteoporosis and metabolic bone disease. Radiology. 1981;138(5):701-10.
29. Barkmann R, Laugier P, Moser U, Dencks S, Klausner M, Padilla F, et al. A device for *in vivo* measurements of quantitative ultrasound variables at the human proximal femur. IEEE Trans Ultrason Ferroelectr Freq Control. 2008;55(6):1197-1204.

30. Eliakim A, Nemet D, Wolach B. Quantitative ultrasound measurements of bone strength in obese children and adolescents. J Pediatr Endocrinol Metab. 2001;14(2):159-64.

31. Greenfield MA, Craven D, Wishko DS, Huddleston AL, Friedman R, Stern R, et al. The modulus of elasticity of human cortical bone: An *in vivo* measurement and its clinical implications. Radiology. 1975;115(1):163-6.

32. Bochud N, Vallet Q, Bala Y, Follet H, Minonzio J-G, Laugier P. Genetic algorithms-based inversion of multimode guided waves for cortical bone characterization. Phys Med Biol. 2016;61(19):6953-74.

33. Moilanen P, Maatta M, Kilappa V, Xu L, Nicholson PHF, Alen M, et al. Discrimination of fractures by low-frequency axial transmission ultrasound in postmenopausal females. Osteoporos Int. 2013;24(2):723-30.

34. Barkmann R, Dencks S, Laugier P, Padilla F, Brixen K, Ryg J, et al. Femur Ultrasound (FemUS)-first clinical results on hip fracture discrimination and estimation of femoral BMD. Osteoporos Int. 2010;21(6):969-76.

35. Hoffmeister BK, Johnson DP, Janeski JA, Keedy DA, Steinert BW, Viano AM, et al. Ultrasonic characterization of human cancellous bone *in vitro* using three different apparent backscatter parameters in the frequency range 0.6-15.0 MHz. IEEE Trans Ultrason Ferroelectr Freq Control. 2008;55(7):1442-52.

36. Holzer G, Von Skrbensky G, Holzer LA, Pichl W. Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength. J Bone Miner Res. 2009;24(3):468-74.

37. Fellah ZE, Chapelon JY, Berger S, Lauriks W, Depollier C. Ultrasonic wave propagation in human cancellous bone: Application of Biot theory. J Acoust Soc Am. 2004;116(1):61-73.

38. Hosokawa A, Otani T. Ultrasonic wave propagation in bovine cancellous bone. J Acoust Soc Am. 1997;101(1):1-5.

39. Muller M, Moilanen P, Bossy E, Nicholson P, Kilappa V, Timonen J, et al. Comparison of three ultrasonic axial transmission methods for bone assessment. Ultrasound Med Biol. 2005;31(5):633-42.

40. Bossy E, Talmant M, Defontaine M, Patat F, Laugier P. Bidirectional axial transmission can improve accuracy and precision of ultrasonic velocity measurement in cortical bone: A validation on test materials. IEEE Trans Ultrason Ferroelectr Freq Control. 2004;51(1):71-9.

41. Bossy E, Talmant M, Laugier P. Effect of bone cortical thickness on velocity measurements using ultrasonic axial transmission: A 2D simulation study. J Acoust Soc Am. 2002;112(1):297-307.

42. Sarvazyan A. Diversity of biomedical applications of acoustic radiation force. Ultrasonics. 2010;50(2):230-4.

43. Eneh CTM, Malo MKH, Karjalainen JP, Liukkonen J, Toyras J, Jurvelin JS. Effect of porosity, tissue density, and mechanical properties on radial sound speed in human cortical bone. Med Phys. 2016;43(5):2030-9.

44. Eneh CTM, Afara IO, Malo MKH, Jurvelin JS, Toyras J. Porosity predicted from ultrasound backscatter using multivariate analysis can improve accuracy of cortical bone thickness assessment. J Acoust Soc Am. 2017;141(1):575.

45. Minonzio JG, Bochud N, Vallet Q, Ramiandrisoa D, Etcheto A, Briot K, et al. Ultrasound - based estimates of cortical bone thickness and porosity are associated with nontraumatic fractures in postmenopausal women: A pilot study. J Bone Miner Res. 2019;34(9):1585-96.

46. Karjalainen JJ, Riekkinen O, Toyras J, Kroger H, Jurvelin J, J K, et al. Ultrasonic assessment of cortical bone thickness *in vitro* and *in vivo*. IEEE Trans Ultrason Ferroelectr Freq Control. 2008;55(10):2191-7.

47. Gneenfield A, Craven JD, Huddleston A, Wishko D, Ph D, Stern R, et al. Measurement of the velocity of ultrasound in the human femur *in vivo*. Med Phys. 1980;138(4):324-30.

48. Barkmann R, Laugier P, Moser U, Dencks S, Klausner M, Padilla F, et al. *In vivo* measurements of ultrasound transmission through the human proximal femur. Ultrasound Med Biol. 2008;34(7):1186-90.

49. Reginster JY, Burlet N. Osteoporosis: A still increasing prevalence. Bone. 2006;38(2 Suppl 1):1998-2003.

50. Dencks S, Barkmann R, Padilla F, Haıat G, Laugier P, Gluer CC. Wavelet-based signal processing of *in vitro* ultrasonic measurements at the proximal femur. Ultrasound Med Biol. 2007;33(6):970-80.

51. Dencks S, Barkmann R, Padilla F, Laugier P, Schmitz G, Gluer CC. Model-based estimation of quantitative ultrasound variables at the proximal femur. IEEE Trans Ultrason Ferroelectr Freq Control. 2008;55(6):1304-15.

52. Brown CU, Yeni YN, Norman TL. Fracture toughness is dependent on bone location - A study of the femoral neck, femoral shaft, and the tibial shaft. J Biomed Mater Res. 2000;49(3):380-9.

53. Provyn S, Clarys JP, Wallace J, Scafoglieri A, Reilly T. Quality control, accuracy, and prediction capacity of dual energy X-ray absorptiometry variables and data acquisition. J Physiol Anthropol. 2008;27(6):317-23.

54. Boughton OR, Ma S, Cai X, Yan L, Peralta L, Laugier P, et al. Computed tomography porosity and spherical indentation for determining cortical bone millimetre-scale mechanical properties. Sci Rep. 2019; 1-15.

55. Wear KA, Member S. Autocorrelation and cepstral methods for measurement of tibial cortical thickness. IEEE Trans Ultrason Ferroelectr Freq Control. 2003;50(6):655-60.

56. Lewiecki M, Lane NE. Common mistakes in the clinical use of bone mineral density testing. NIH Public access. 2008;4(12):667-74.

57. Conversano F, Franchini R, Greco A, Soloperto G, Chiriaco F, Casciaro E, et al. A novel ultrasound methodology for estimating spine mineral density. Ultrasound Med Biol. 2015;41(1):281-300.

58. Zebaze RM, Ghasem-Zadeh A, Bohte A, Iuliano-Burns S, Mirams M, Price RI, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet. 2010;375(9727):1729-36.

59. Bala Y, Zebaze R, Seeman E. Role of cortical bone in bone fragility. Curr Opin Rheumatol. 2015;27(4):406-13.

60. Bala Y, Zebaze R, Ghasem-Zadeh A, Atkinson EJ, Iuliano S, Peterson JM, et al. Cortical porosity identifies women with osteopenia at increased risk for forearm fractures. J Bone Miner Res. 2014;29(6):1356-62.

61. Stone K, Seeley D, Lui L, Cauley J, Ensrud K, Browner W, et al. Osteoporotic Fractures Research Group. BMD at multiple sites and risk of fracture of multiple types: Longterm results from the Study of Osteoporotic Fractures. J Bone Min Res. 2003;18:1947-54.

62. Cranney A, Jamal SA, Tsang JF, Josse RG, Leslie WD. Low bone mineral density and fracture burden in postmenopausal women. Cmaj. 2007;177(6):575-80.

63. Schneider J, Ramiandriosa D, Iori G, Grasel M, Barkmann R, Raum K, et al. Cortical thickness and porosity assessment on *ex-vivo* tibiae using axial ultrasound transmission. Biomed Tech. 2017;62(1):S253.

64. Mittra E, Rubin C, Gruber B, Qin Y-X. Evaluation of trabecular mechanical and microstructural properties in human calcaneal bone of advanced age using mechanical testing, microCT, and DXA. J Biomech. 2008;41(2):368-75.

65. Ma S, Goh EL, Jin A, Bhattacharya R, Boughton OR, Patel B, et al. Long-term effects of bisphosphonate therapy: Perforations , microcracks and mechanical properties. Nat Publ Gr. 2017;7:1-10.

66. Longo R, Grimal Q, Laugier P, Vanlanduit S, Guillaume P. Simultaneous determination of acoustic velocity and density of a cortical bone slab: Ultrasonic model-based approach. IEEE Trans Ultrason Ferroelectr Freq Control. 2010;57(2):496-500.

67. Loosvelt M, Lasaygues P. A wavelet-based processing method for simultaneously determining ultrasonic velocity and material thickness. Ultrasonics. 2012;51(3):325-39.

68. Litniewski J, Tasinkevych Y, Podhajecki J, Falin K, Y T, J P, et al. Simultaneous estimation of cortical bone thickness and acoustic wave velocity using a multivariable optimization approach: Bone phantom and *in-vitro* study. Ultrasonics. 2016;65:105-12.

69. Barkmann R, Kantorovich E, Singal C, Hans D, Genant H, Heller M, et al. A new method for quantitative ultrasound measurements at multiple skeletal sites. J Clin Densitom. 2000;3:1-7.

70. Weiss M, Ben-Shlomo A, Hagag P, Ish-Shalom S. Discrimination of proximal hip fracture by quantitative ultrasound measurement at the radius. Osteoporos Int. 2000;11(5):411-6.

71. Hans D, Srivastav S, Singal C, Barkmann R, Njeh C, Kantorovich E, et al. Does combining the results from multiple bone sites measured by a new quantitative ultrasound device improve discrimination of hip fracture? J Bone Min Res. 1999;14(4):644-51.

72. Chapurlat RD, Arlot M, Burt-Pichat B, Chavassieux P, Roux JP, Portero-Muzy N, et al. Microcrack frequency and bone remodeling in postmenopausal osteoporotic women on long-term bisphosphonates: A bone biopsy study. J Bone Min Res. 2007;22(10):1502-9.

73. Schaffler MB, Choi K, Milgrom C. Aging and matrix microdamage accumulation in human compact bone. Bone. 1995;17(6):521-5.

74. Schaffler MB, Radin EL, Burr DB. Mechanical and morphological effects of strain rate on fatigue of compact bone. Bone. 1989;10(3):207-14.

75. Burr D. Microdamage and bone strength. Osteoporos Int. 2003;14(0):67-72.

76. Zioupos P. Accumulation of *in-vivo* fatigue microdamage and its relation to biomechanical properties in ageing human cortical. J Microsc. 2001;201(2):270-8.