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Ultrasonic Bone Density Measurement: A Biomedical Engineering Victory By A Medical Intervention

[1-]Ali Mohammad Al Senan , [2-]Jasser Saleh Alabbas , [3-]Masoud Mohammad Al Senan , [4-]Hussein Mohammad Al Senan , [5-]Saeed Mohammad Al Senan

Abstract
The broadband ultrasonic attenuation (BUA) and speed of sound (SOS) are commonly used to assess bone density. However, because earlier research has shown that the BUA is sensitive to movement and soft tissue, measurement repeatability will be challenging to obtain. Secondary osteoporosis is a significant co-morbidity associated with inflammatory rheumatic disorders that is caused by a variety of variables such as inflammatory cytokines, inactivity, and glucocorticoid medication. Because of its capacity to identify bone density as well as bone quality, quantitative ultrasonography (QUS) has been used in osteoporosis research. The purpose of this research is to look at the therapeutic potential of deep-sea water (DSW) for osteoporosis. We previously created ovariectomized senescence-accelerated mice (OVX-SAMP8) and demonstrated substantial osteoporosis healing using stem cells and platelet-rich plasma (PRP). The MTT assay revealed a considerable increase in osteoblastic cell (MC3T3) proliferation in deep sea water with a hardness (HD) of 1000. After a 4-month deep sea water therapy, bone mineral density (BMD) was dramatically raised, followed by significantly increased trabecular numbers by micro-CT examination, and biochemistry investigation revealed that blood alkaline phosphatase (ALP) activity was lowered. Bone marrow-derived stromal cells (BMSCs) were collected and studied for stage-specific osteogenesis. Workforce aging is becoming a major public health issue as a result of the growth of age-related disorders such as osteoporosis. Osteoporosis prevention and early identification are critical for avoiding bone fractures and their associated socioeconomic impact. Parkinson's disease (PD) is a prevalent neurological condition among the elderly, with a significant risk of falling. There is a lot of research on the link between Parkinson's disease and osteoporosis. The goal of this study is to use calcaneal ultrasound to describe the bone quality of a population with Parkinson's disease and compare it to a healthy control, while accounting for possible gender differences.

Keywords: *Radius Quantitative ultrasound (QUS), osteoporosis, bone mineral density.*

1. Introduction

The growing number of older people around the world increases the likelihood of osteoporosis and bone fractures (Llopis, Escrivá, Navarro-Illana, & Benlloch, 2022). This issue has recently prompted the creation of a technique for evaluating bone condition and forecasting bone fracture risk. Dual-energy X-ray absorptiometry (DEXA) is currently the most essential and widely accepted technology for detecting bone in hospitals. However, it is not frequently utilized due to the high cost, inconvenience, and patient apprehension about X-ray exposure, particularly in young adults and children. Because of its tiny wavelength, ultrasonic frequencies can penetrate the bulk and provide diagnostic capabilities for tissue monitoring. Nondestructive testing (NDT), tissue healing, and fetal health monitoring are among its diagnostic capabilities (Chen, Xu, Ma, & Sun, 2010).

Quantitative ultrasonography (QUS) has emerged as an essential technique for assessing osteoporosis state and estimating the risk of osteoporotic fracture. Because of the combination of ultrasonic contrast agents and ultrafast imaging, the recent introduction of ultrasound localization microscopy (ULM) solved the conceptual trade-off between spatial resolution and penetration depth while boosting sensitivity. ULM is based on the same notion that underpins photo-activated localization microscopy3 and stochastic optical reconstruction microscopy (Demené, Robin1, Alexandre, & Heiles, 2022).

In contrast to through-transmission applications, the axial transmission approach has been found to be suitable for analyzing long bones such as the tibia and radius (Kaufman, Luo, & S. Siffert, 2007).

Osteoporosis is characterized by decreased bone mass and microarchitectural degeneration of bone tissue, resulting in bone fragility and fracture susceptibility.

Osteoporosis is one of the most common skeletal illnesses, with 10 million Americans being diagnosed and 2 million experiencing osteoporotic fractures each year (Khosla & Naik, 2019).

Pathologically, radiographic imaging in osteoporosis plays a role in identifying early bone weakening and evaluating patterns of bone changes (Llopis, Escrivá, Navarro-Illana, & Benlloch, 2022).

Osteoporosis, a widespread illness characterized by abnormal bone remodeling, is a worldwide public health issue. Patients with osteoporosis frequently experience pain, incapacity, and a deterioration in quality of life, as well as an increase in mortality and a depletion of municipal health care budgets (Maneerat, Visitsattapongse , & Pintavirooj, 2021).

In many nations, workforce aging is becoming a substantial occupational health issue. As a result, age-related disorders and diseases are rapidly appearing in the workplace, posing a threat to workers' physical functions and productivity. Osteoporosis is an example of one of these conditions. This illness affects about 200 million individuals globally, and the burden of osteoporosis is expected to rise significantly in the near future, with negative consequences in terms of bone fractures, death, quality of life decreases, chronic pain, autonomy loss, and social costs (Min Oo, Naganathan, Thae Bo, & Hunter, 2018).

Parkinson's disease is the most common neurodegenerative disorder among the elderly, with a frequency in developed nations ranging from 0.3% to 1% in people over the age of 60, reaching 3% in people over the age of 80 (Yu Liu, Che Liu, Wang, & Hong Chen, 2013).

Other approaches, such as guided waves or axial transmission, can also be used to examine bone condition in addition to the mode of transmission used here. The emitter and receiver are on the same side of the specimen in the later approach (Min Oo, Naganathan, Thae Bo, & Hunter, 2018).

Musculoskeletal degeneration and its related consequences, such as disuse osteopenia and muscle atrophy, pose serious risks to astronauts and increase the chance of fractures during a long-term space mission, such as remaining in the space station or traveling to Mars. Data has shown that space flight, particularly long-term missions, has a negative impact on the musculoskeletal system (Xu, Xu, Chen, & Ding, 2016).

Wolff's law describes how bone tissue rapidly adapts to changes in its functional environment to ensure that sufficient skeletal mass is suitably distributed to withstand the regions of functional activity (Siffert & Kaufman, 2007).

The inherent strength of bone is determined by a number of multi-factorial factors, one of which is the amount of mineralized matrix. The acknowledged indication of bone strength and fracture risk is radiological densitometry, which measures (areal) bone mineral density (BMD) at a specified site (e.g., hip, spine, forearm) (Siffert & Kaufman, 2007).

Bone is exceptional in its ability to preserve strength in the face of continual turnover. It has been established that bone is gradually and relatively completely removed and replaced with new bone multiple times during one's lifetime. To sustain strength, the reparative pattern is always changing and is impacted by changes in general health, the presence of disease, and the level of physical activity. To yet, no mechanism for measuring the nature of lifelong changes in patterns during childhood and later age has been developed (Khosla & Naik, 2019).

Osteoporosis is characterized by a loss of bone mass and an increased risk of fractures. Osteoporotic fractures cause greater pain and disability, as well as death. Postmenopausal women, elderly adults of both sexes, and people taking bone-depleting drugs such as corticosteroids and heparin are at higher risk. The goal of bone density testing is to identify people who have low bone mass and treat them with medications that slow or reverse bone loss in an effort to prevent fractures (Rinaldi, Bortoluzzi, Airoldi, & Leigheb, 2021).

Osteoporosis is frequently a hidden disorder that exposes affected individuals to increased fracture risk and, as a result, reduces their quality of life, for example, by reducing mobility and autonomy. For example, someone in the world suffers an osteoporosis-related fracture every three seconds (Llopis, Escrivá, Navarro-Illana, & Benlloch, 2022).

The basic unit of the human skeletal system that provides the framework and bears the weight of the body, protects the important organs, and supports mechanical movement of the human body is the bone. Bone is made up of the protein collagen, which is the fiber link, and a calcium phosphate salt, which is a chemical that strengthens bones (Qin, Xia, Muir, & Lin, 2019).

Osteoporosis is a metabolic bone disease that develops with age. Because to increased bone fragility and porosity, affected persons are at a significant risk of fracture. The World Health Organization (WHO) defines osteoporosis as having a bone mineral density (BMD) less than 2.5 standard deviations (SDs) below the young adult mean. However, most cases of osteoporosis go misdiagnosed until a fracture occurs, which is expensive to repair and has a high morbidity (Min Oo, Naganathan, Thae Bo, & Hunter, 2018).

2. The Objective

The goal of this study was to examine the dynamic time window method (DTWM) in vivo for measuring the speed of sound (SOS) at the 1/3 distal radius in ten human individuals. DTWM is a new approach for determining the precise time of flight (TOF) of the first arriving signal that is based on our patented probe (FAS). In this study, work will be done on ultrasound bone densitometry, which is considered the triumph of biomedical engineering through medical intervention, this work will assess the relationship between ultrasound reflection and bone density, where for example osteoporosis is a common chronic disease and a major known source of morbidity and mortality among the elderly. Low bone density also occurs in infants and young children during development and can be significantly excessive if the fetus has problems during pregnancy such as poor nutrition, vitamin D deficiency, and smoking.

Low bone density occurs during growth in newborns and small children and can be problematically excessive if the fetus suffers difficulties during pregnancy such as malnutrition, a lack of vitamin D, and smoking. Currently, the only methods for assessing prenatal bone density are Dual-energy X-ray Absorptiometry (DEXA) or Magnetic Resonance Imaging (MRI) (MRI). Both are affected by movement artifacts. DEXA exposes the individuals to substantial radiation and is therefore not recommended during pregnancy. Quantitative MRI is noisy, costly, and time-consuming (8-20 minutes), and the consequences of high field strengths on the developing fetus are unknown. As a result, the purpose of this research is to develop a quick, accurate, and non-ionizing method for assessing fetal bone density.

3. Related works

In (Khosla & Naik, 2019), they presented the study about "Measurement of Bone Density Parameters using Ultrasound and Hardware Development on bone Density Measurement", The suggested study presents ultrasound simulation in a 2-D bone model as well as hardware implementation. Because of the complexity of bone structures, a basic linear model consisting of both cortical and cancellous bone has been developed. To collect the signal, a broadband emitter with a central frequency of 1 Megahertz is utilized in the simulation, coupled with an array of receivers. Because of their short-wave duration, ultrasound waves can be used in tissue diagnostics and evaluation. When there is no volumetric data available, ultrasound simulations can be used to study and analyze different qualities at different sites.

In (Qin, Xia, Muir, & Lin, 2019), they proposed the study about "Quantitative ultrasound imaging monitoring progressive disuse osteopenia and mechanical stimulation mitigation in calcaneus region through a 90-day bed rest human study", The sensitivity of bone to mechanical impulses can be used to combat this degradation. The purpose of this study is to assess the longitudinal effect of a dynamic mechanical loading through the heel on human bone in vivo during 90 days of bed rest using quantitative ultrasound (QUS) imaging and dual-energy X-ray absorptiometry (DXA) in localized regions of interest, namely the calcaneus. A total of 29 bed rest persons (11 control and 18 treatment) were examined with a brief (10-minute) daily low-intensity (0.3g), high-frequency (30Hz) dynamic mechanical stimulation countermeasure via vibrational inhibition bone eroding (VIBE). Both QUS and DXA detected changes in bone density and quality over time. Ultrasound velocity (UV) dropped in the control group while increasing in the low-intensity loading group.

In (Kaufman, Luo, & S. Siffert, 2007), they discuss the study about "A PORTABLE REAL-TIME ULTRASONIC BONE DENSITOMETER", The link between NTD and BMD was investigated using computer models of ultrasonic propagation. The simulations utilized micro-CT scans of ten calcaneal bone cores, which were then morphologically processed to yield a collection of thirty-six 'samples' with BMDs ranging from 0.25 to 1.83 g/cm2. The NTD and BMD were discovered to be substantially associated (r = 0.99), confirming the NTD's high sensitivity to bone mass. An IRB-approved clinical study assessed the heels of 85 adult women. DXA was used to measure BMD at the same time. A linear regression utilizing NTD yielded a linear correlation coefficient of 0.86, a significant improvement over current ultrasound bone densitometers but not nearly as good as the simulation results.

In (Albuquerque, Cruz, Carvalho, & Mayrink, 2022), they included the study about "A method based on non-ionizing microwave radiation for ancillary diagnosis of osteoporosis: a pilot study", Diagnostic devices used to assess this condition (e.g., dual-energy X-ray absorptiometry) are now prohibitively expensive, making it impossible to meet the demand for testing in most countries. As a result, we proposed a preclinical validation of a prototype dubbed Osseus in order to improve osteoporosis screening tests and reduce their costs. Osseus is a gadget designed to aid in the classification of bone mineral density. It incorporates a microcontroller into other peripheral devices in order to measure attenuation at the middle phalanx of the middle finger using two antennas operating at 2.45 GHz. We performed experiments on plaster, poultry, and porcine bones.

In (Demené, Robin1, Alexandre, & Heiles, 2022), they conducted the study about "Transcranial ultrafast ultrasound localization microscopy of brain vasculature in patients", Brain angiograms, which are commonly conducted using computed tomography or magnetic resonance imaging, have a resolution of millimeters and are insensitive to blood-flow dynamics. We show that ultrafast ultrasound localization microscopy of intravenously injected microbubbles allows for microscopic transcranial imaging of deep vasculature in the adult human brain as well as assessment of hemodynamic parameters. Using adaptive speckle tracking to correct for micrometric brain-motion artifacts and ultrasonic-wave aberrations caused by transcranial propagation, we were able to map the vascular network of tangled arteries to functionally characterize blood-flow dynamics at a resolution of up to 25 m and detect blood vortices in a patient's small deep-seated aneurysm.

In (Maneerat, Visitsattapongse , & Pintavirooj, 2021), they presented the study about "Bone Mineral Density Screening System Using CMOS-Sensor X-ray Detector", By optically linking a CMOS sensor with an image on an intensifying screen, an indirect X-ray detector is created. As an X-ray source, a dedicated microcontroller X-ray equipment is utilized to collect two energy level X-rays of the middle phalanges bone of the middle finger. To compute bone mineral density, the collected image is processed using a modified Beer-Lambert law. The area of the phalanges bone is also determined using active contour to calculate bone mineral content. The suggested bone mineral density (BMD) and bone mineral content (BMC) assessment device is low-cost and can thus be disseminated at district hospitals for osteoporosis screening. In comparison to BMD measurements from commercial models, BMD measurements from our system have a linear relationship with R2 equal to 0.969.

In (Yang, Chen, Zhang, & Wei, 2021), they proposed the study about "Diagnosis of Bone Mineral Density Based on Backscattering Resonance Phenomenon Using Coregistered Functional Laser Photoacoustic and Ultrasonic Probes", Early identification of osteoporosis, in conjunction with BMD and CC, will increase predictability of fracture risk. Backscattering resonance (BR) occurs in both ultrasound (US) and photoacoustic (PA) signal transmissions through bone, and the peak frequencies of BR can be altered by BM and CC. The creation of standing waves within the pores can explain this phenomenon. The same bone CT images were then simulated, and the resulting resonance frequencies were found to match those anticipated by the standing wave hypothesis. Experiments were carried out on the same bone sample, with an 808 nm laser serving as the PA source and a 3.5 MHz ultrasonic transducer serving as the US source. In the transmitted waves, the backscattering resonance effect was detected.

4. Materials and Methods

For the assessment of FAS TOF, this study compared DTWM to three common methods: threshold value method, first of maxima technique, and zero-crossing method.

Although higher frequencies would be preferable to reduce the impact of cortical thickness and improve the precision of TOF measurements, FAS attenuation in bone rises with frequency, preventing frequencies much higher than 1 MHz from being used. A commercial device (Sunlight OmnisenseTM, 1.25 MHz), as well as a bi-directional axial transmission prototype, have successfully utilized frequencies around 1 MHz in axial transmission devices (1 MHz)

Calibration of the probe is required for precise knowledge of the position of the receivers, which improves SOS determination.

The electrical system was programmed to set different system delay times (system = 0, 1, 2, 3, 4, and 5 ls). The SOS values in volunteers were measured at various system delays. To assess the efficacy of DTWM, we looked at the repeatability of SOS.

We did a cross-sectional survey with 20 participants working in five Italian healthcare facilities. A self-administered online questionnaire including all known osteoporosis risk factors was

developed. We conducted cognitive interviews to confirm that the items were understood correctly by the respondents, and we ran a test on a population sample of four people.
Each individual had two ultrasonography evaluations of the calcaneus, with the mean of both readings afterwards determined. To eliminate bias in data collection, all ultrasound measurements were done by the same operator. To gain bone mass, the manufacturer's recommendations were followed, including treating the calcaneus area with 70% alcohol and carefully positioning the foot. The nondominant foot was usually used for measurements.
During the bed rest phase, the VIBE group received a daily low-intensity vibration (LIV) treatment (10 min/day, 30 Hz, 0.3 g). LIV was applied to the subjects while they were supine, utilizing a vest and spring system that loaded the individual to the vibration platform on the moveable support at the foot of the bed.
A set of computer simulations of ultrasonic propagation were performed using a set of 3D bone scans, as shown below. A commercially purchased 1.4 cm diameter core was drilled from the posterior area of 10 human calcanei. They were then scanned with a micro-CT at a resolution of 40 micrometers, and each 3D image voxel was divided into bone or soft tissue using simple grey-level thresholding. The steps as the following:
(1) We create a dedicated microcontroller digital X-ray equipment that can be interfaced with other devices.
(2) We create a low-cost upgradeable indirect X-ray detector by mounting a CMOS sensor in a light-protective casing and capturing images on an X-ray phosphor enhance screen.
(3) When compared to commercial products, our bone mineral measurement device is less expensive and can be utilized as a screening test for bone mineral deficiency at a district hospital.
(4) We optimized the X-ray exposure parameters so that the proposed dual energy X-ray bone mineral density assessment system gives a minimal dosage to the subject.
(5) The dual energy X-ray-based portable bone mineral density measurement equipment is redesigned.
The proposed method of measuring bone density is based on the use of dual-energy X-rays. We created a dedicated microprocessor-controlled 50-mA 100-kVp stationary-anode X-ray system that can be operated via serial transmission by a personal computer. The two-dimensional X-ray detector is built on an indirect X-ray detector with a CMOS sensor.

5. Results and Discussion

The strongest correlation between SOS and BMD was reported in the 10 human individuals who used DTWM (RDTWM = 0.81, p 0.005) rather than the three standard approaches (R = 0.37-0.41, p [0.05]). To assess the reproducibility of our method, we employed the individual short-term coefficient of variation (CV, ranging from 0.07 to 0.27) and the Root-Mean-Square (RMS) of the average CV (CVRMS, 0.18). (DTWM).
Clinical investigations have shown that the ultrasonic velocity, as assessed by the FAS TOF, is highly related to bone status.
We previously demonstrated the osteogenic regeneration process in OVX-SAMP8 mice using stem cells and platelet-rich plasma.
The prospective benefits of DSW on bone regeneration in osteoporosis recovery were explored in this study; we discovered that DSW enhanced osteoblast viability, raised BMD scores, trabecular bone numbers, and alleviated osteoporosis symptoms.
Patients with clinically substantial bone loss who were unaware of their condition This diagnostic foresight is a key component of value for the project, particularly for the workers, because of the avoided poor consequences caused by the fractures, but also for the employer and society in general, because of the associated avoidable expenses.

In terms of the characteristics that may influence the disease, clear epidemiological and clinical variations in Parkinson's disease patients have been identified. Men are more likely to develop the condition, while women have a greater fatality rate, as well as faster progression and a worse prognosis.

In Parkinson's disease patients, the QUS method of the calcaneus appears adequate for these results. On a practical level, the findings suggest that the QUS technique is an appropriate tool for measuring bone density in Parkinson's disease patients.

The SOS and BUA values were determined using the methodology described above. In simulation, there was a difference in BUA levels between osteoporosis and normal samples. Furthermore, variations in BUA values were observed in the experimental setup with and without soft tissue.

Osteopenia and osteoporosis are systemic skeletal illnesses, and prolonged bed rest resulted in widespread bone loss. One of the key metrics used to examine changes in bone quantity and quality is the calcaneus QUS. Previous bed rest investigations, as well as DXA technology before and after space voyages, have looked into bone loss at the heel.

The statistics show that the novel device and its associated ultrasonic parameter, the NTD, are extremely sensitive to bone mass as determined by DXA scanners. In contrast, the findings demonstrate that ultrasonic velocity is substantially less linked with BMD; this is due to individual differences in underlying soft tissue thickness and calcaneus thickness.

Osseus' initial studies established its usefulness in detecting bone mineral density in animal models, demonstrating that it can handle the complexity of the tissues inside bones.

Predicting osteoporotic risk groups may help to reduce the significant financial burden of osteoporotic fractures on health-care systems. Given that the pattern of change in BMD with age is reasonably well understood and that the absence of an independent contribution of BMD to fracture risk is required to link it to somatic factors, several methods combine artificial intelligence with risk factors to screen groups at higher risk for osteoporosis or fractures.

We demonstrate that not only can ULM be performed transcranially in human adults, but that at this low ultrasound frequency, with an expected low SNR, and in the presence of motion, we can achieve resolutions of the order of 25 m, far exceeding the typical 1 mm resolution of functional ultrasound imaging. t-ULM is highly likely to become very important for the therapy of cerebrovascular illnesses in the future because it reveals both the human brain vascular structure and flow dynamics at microscopic scales.

The purpose of this study is to design and build a low-cost bone mineral density measurement device based on dual energy X-ray. The X-ray source in our study is a dedicated microcontroller X-ray equipment that communicates with a personal computer via serial connection.

The distribution has the shape of a skewed Gaussian distribution centered on 0.6 mm, which was the most frequent value. Because this is a histogram, the value 0.6 mm is the bin value rather than the actual value of the inter-trabeculae. The real numbers would be in the 0.56-0.65 mm range.

Local resonance features occur in cancellous bone in PA and US. The laser is absorbed not just by collagen in bone tissue cells, but also by inorganic calcium bone tissue. Light energy is absorbed by various bone tissues and transformed into ultrasonic waves that travel through the multilayer bone structure.

The previous simulations' results revealed a strong relationship between the US resonance frequencies and the first harmonic frequencies of standing waves created in the most frequently occurring inter-trabeculae distances. Experiment results revealed the occurrence of the BR phenomena in both US and PA signal transmissions via the bone. These findings supported our theory that the resonance effect can be detected in both US and PA signal transmissions through the bone, which might be explained by standing wave creation.

6. Conclusion

Despite the small sample size, the findings imply that DTWM increases the accuracy of SOS detection in vivo and could be used to improve the clinical assessment of long cortical bone osteoporosis and fracture risk profile.

The experimental results showed that DTWM effectively minimized system interference noise or latency, and hence has the ability to measure bone state in vivo, preferably in a special population (with BMI [25 kg/ m2].

Bone mineral loss is common in inflammatory rheumatic disorders. Although QUS may provide some additional benefits to fracture risk prediction models, current research does not support the use of QUS instead of DXA in the diagnosis and monitoring of osteoporosis in rheumatic illnesses. Confocal scanning ultrasound imaging can quantify bone density in the ROI, which can be utilized to anticipate bone loss changes in long-term bed rest simulations and potentially future space missions.

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