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Commentary

Ultrasound imaging and regulated mechanotransduction for characteristics, regeneration, and therapeutics of bone

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ABSTRACT

Ultrasound imaging has been widely used in clinical diagnoses, such as B-mode and M-mode ultrasound imaging for cardiovascular, abdomen, OB-Gyn, and other soft tissue and organs in clinical diagnoses. Ultrasound imaging has traditionally been limited in its application to bone because of the high acoustic impedance and density of trabecular and cortical bone structure and density alterations, high wave reflection, absorption, scattering, and low penetration, which result in significant reflection and attenuation of ultrasonic energy in such mineral tissues. Recent advancements in quantitative ultrasound technology have opened new possibilities for noninvasive characteristics of bone quality through transmitted or backscattered signals, offering a radiation-free alternative to traditional imaging modalities like dual-energy X-ray absorptiometry (DEX), X-rays, and CT scans. In addition, low-intensity ultrasound (LIUS) has been studied and applied to promote bone regeneration and fracture healing through induced mechanotransduction in tissue and cells. The field of bone ultrasound encompasses fundamental research on the interaction of elastic waves with cortical and trabecular bone microstructures, the development of innovative imaging methodologies and medical applications such as bone health assessment for osteoporosis diagnosis, therapeutic use of LIUS, and phase aberration correction inside the skull. This work has highlighted recent developments and advancements in ultrasound diagnosis and therapeutics, induced cellular and molecular pathways, and future directions using ultrasound as a promising imaging tool and treatment method.

1. Introduction

Musculoskeletal deterioration and associated complications (i.e., osteopenia, stress fracture, and non-union fractures) pose significant threats to human health and their resultant long-term bedrest impact on human quality of life. Osteoporosis, nonunion fracture, and disuse osteopenia are significant problems for human health. Healing fractured bone involves cellular and molecular proteins' spatial and temporal interconnected actions and expression of hundreds of gene factors that restore bone mass and integrity.[4] These bone disorder problems diminish bone structure and strength; each considered critical for skeletal tissues to resist fracture.[7] Such decayed alterations significantly compromise bone's ability for resistance to fracture; osteoporosis-induced vertebral and hip fractures severely threaten human health and quality of life.[27] Early diagnosis of such disorders can lead to prompt and optimized treatment that will dramatically reduce the risk of fracture and provide long-term benefits for human health.

At present, osteoporotic bone loss is commonly assessed by bone mineral density (BMD) measures that reflect in vivo bone mass conditions. Noninvasive measurements of BMD would be of value in predicting the risk of fracture, in assessing the severity of the disease, and in following response to treatment. Several methods are available for the measurement of bone mass, with the most commonly used methods being DXA and computed tomography (CT). DXA is currently a gold standard technique used because of its relative precision (~2 %), and whole body and/or multi-site imaging ability (spine, hip, wrist, and total skeleton). Current techniques, *apparently*, are insensitive to quantifying trabecular bone mass separately. Importantly, the measurements obtained do not provide information about the integrity of the trabecular architecture, nor the mechanical properties of bone. Physical methods include mechanical stimulation, electromagnetic fields, and low-intensity pulsed ultrasound (LIPUS/LIUS). Recent experimental studies have shown the efficacy of these physical methods; LIPUS is widely clinically used even though controversial results have been reported.[29]

1.1. Bone quality as a factor of assessment of fracture

If not only bone mineral density (BMD) but bone quality, e.g., stiffness and/or modulus, can be monitored or determined instantly during aging and disuse like a space mission, then one can better understand the

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skeleton adaptation daily. In the case of osteopenia and/or osteoporosis, fractures can occur without a singular traumatic event. While a formal definition of bone quality is somewhat elusive, at the very least it incorporates architectural, physical and biological factors that are critical to bone strength, such as bone morphology (i.e., trabecular connectivity, cross sectional geometry), the tissue's material properties, and its chemical composition and architecture (calcium concentration, collagen orientation, porosity, permeability). The ability to directly assess bone density and quality (i.e., strength) would greatly impact predicting the risk of fracture.

2. Ultrasound imaging for bone density and architecture assessment

2.1. Quantitative ultrasound (QUS) to assess bone quality

Recently, new methods in QUS have emerged with the potential to estimate cancellous bone modulus more directly. The primary advantage of ultrasonic techniques (UT) is its capability to measure not only bone density but also bone quality, i.e., bone's structural and mechanical properties. Over the past two decades, many technologies have been developed to quantify bone mass and structural stiffness using UT. The major drawbacks of current ultrasound osteometers are their limited resolution and lack of physical interrelation with meaningful bone strength, e.g., providing qualitative measurement, not the true prediction of bone's strength properties, only on the peripheral sites. Therefore, UT remains a screening tool in the peripheral skeletal sites.[19] This situation was changed when the scanning quantitative ultrasound was developed.[23–25] The new design of a scanning confocal acoustic navigation (SCAN) system is intended to provide true images reflecting bone's structural and strength properties, which will be a real-time diagnostic tool (instead of just for screening) that not only assesses BMD, but also further predicts the structural and strength properties of bone. The study used SCAN to evaluate trabecular bone quality in 60 cubic trabecular samples harvested from adult sheep; it showed that ultrasound image precisely predicts bone's structural and strength properties, which μCT and compressive mechanical testing validated. Strong correlations were observed between ultrasound velocity (UV) and bone's mechanical strength and structural parameters, i.e., bulk Young's modulus ($R^2 = 0.67$) and BV/TV ($R^2 = 0.85$). The bone density and mechanical strength predictions were significantly improved by using a linear combination of BUA and UV, yielding $R^2 = 0.92$ for BV/TV and $R^2 = 0.71$ for bulk Young's modulus.[23] These results imply that quantitative ultrasound can characterize trabecular structural and mechanical properties through measurements of particular ultrasound parameters and potentially estimate bone's structural integrity.[24,30]

2.2. QUS parameters

Ultrasound may be applied to bone using many fundamental physical mechanisms: ultrasonic wave propagating velocity (UV) or speed of sound (SOS), sound energy attenuation (ATT), broadband ultrasound attenuation (BUA), and critical angle ultrasound parameters (Fig. 1). Large prospective studies have confirmed that QUS measurements of BUA and UV can identify those individuals at risk of osteoporotic fracture as reliably as BMD.[5,24] It has been shown that both BUA and UV are decreased in individuals with risk factors for osteoporosis, i.e., primary hyperparathyroidism,[6] kidney disease, and glucocorticoid use. The potential sources contributing to the attenuation include absorption, scattering, diffraction, and refraction. While absorption predominates in cortical bone attenuation, the mechanism of BUA in cancellous bone is believed to be scattering.[19] The strength of trabecular bone is an important parameter for bone quality. *In vitro* studies have correlated the UV with stiffness in trabecular bone samples.[15] This indicates that ultrasound has the potential to be advantageous over the X-ray-based absorptiometry in assessing the quality of bone in addition to the quantity of bone. By determining the wave velocity through bone, the elastic modulus of bone specimens can be estimated, and through determining the ultrasound phase tracking.[1,15,14,24]

QUS can predict the principal structural orientation of trabecular bone; this orientation is highly correlated with the mechanical strength of trabecular bone. The irregular shape of bone, however, would increase variation in such a prediction, especially under human *in vivo* measurement.[11,12,31] QUS, mechanical testing, and micro-computed tomography (μCT) scanning were performed on trabecular bone cube samples harvested from a bovine distal femur to obtain the mechanical and structural parameters (Fig. 1). Analysis of covariance showed that the combined transmission-reflection modes improved prediction for the structural and

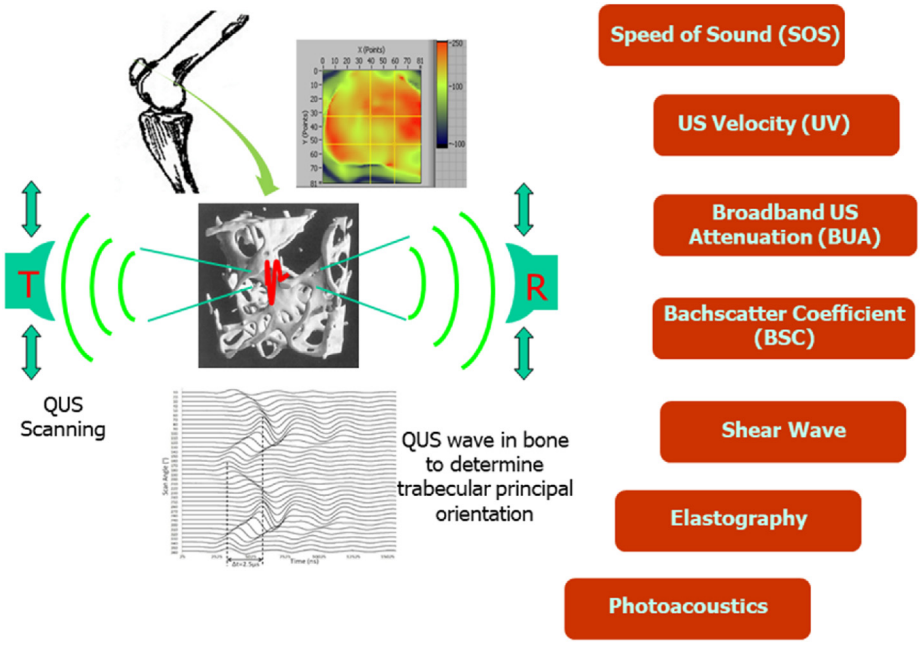

Fig. 1. Quantitative ultrasound imaging transmits waves into bone to assess density and structure of trabecular and cortical bone quality. QUS scanning of trabecular bone can reveal the bone's structure and principal strength orientation. Ultrasound parameters in bone include the speed of sound (SOS), wave velocity (UV), broadband ultrasound attenuation (BUA), and backscatter coefficient (BSC) for bone density and strength predictions. The QUS formats can formulated by ultrasound shear wave, elastography, photoacoustics, etc.

Young's modulus of bone in comparison to the traditional QUS measurement performed only in the medial-lateral orientation. Significant improvement was found in ATT vs structural model index (SMI) ($p < 0.01$), ATT vs bone volume fraction (BV/TV) ($p < 0.01$), ATT vs modulus ($p < 0.001$), UV vs SMI ($p < 0.01$), UV vs BV/TV ($p < 0.05$), and UV vs modulus ($p < 0.01$).[11,13] The 3-D trabecular principal structural and strain direction between QUS prediction and μCT measurements showed less than 5° (Fig. 1), suggesting that the combined transmission-reflection QUS method can provide information more relevant to trabecular bone's structural and mechanical properties.

2.3. Strategy for further development of QUS imaging for bone quality assessment

Non-invasive trabecular bone strength and density assessment is critical in predicting patient fracture risk. QUS has emerged with the potential to detect trabecular bone strength directly. To overcome the current hurdles, such as soft tissue and cortical shell interference, improve the "quality" of QUS, and apply the technology for future clinical applications, the development of image-based ultrasound system will concentrate on several main areas: (1) increasing the resolution, sensitivity, and accuracy in diagnosing osteoporosis to improve signal/noise ratio, and through extracting bone surface topology; (2) increasing BUA accuracy by incorporating cortical shell attenuation; (3) validation of structural and strength properties using micro-CT, nanoindentation, and mechanical testing; and (4) predicting local trabecular bulk stiffness and microstructure of bone, and identifying risk region of fracture.

3. Low-intensity ultrasound for bone regeneration and fracture healing

3.1. Osteogenesis induced by mechanotransduction

Load-induced interstitial fluid flow by ultrasound and other physical stimuli and induced mechanical influence on bone morphology has become a basic tenet of bone physiology.[20] The advantage of acoustic radiation force (ARF) by ultrasound and induced dynamic fluid flow within the callus would be a unique stimulus for enhancing fracture healing via generated mechanotransduction at bone and fracture sites.

3.2. LIUS enhanced tissue regeneration and fracture healing

LIUS has been shown to accelerate the healing of fresh fractures, and has a strong positive influence on each of the three key stages of the healing process (inflammation, repair, and remodeling) as it enhances angiogenic, chondrogenic, and osteogenic activity.[3] The mechanism of LIUS for fracture healing may relate to differential energy absorption of ultrasound that gives rise to acoustic streaming, and its resultant fluid flow as a mechanotransduction signal.[20] ARF-induced fluid flow, and canaliculi fluid shear stresses have been proposed as a mechanism by which bone perceives stimuli and serves as an essential mediator in cell sensing, signaling, and nutrient transport.[10,22,8]

4. Cellular and molecular pathways regulated by ultrasound mechanotransduction

Recent research has shed light on how LIUS influences bone cells, promotes regeneration, and modulates signaling pathways critical for bone healing. Cellular and molecular pathways are of great interest in elucidating how mechanical signals produce such observed effects, including reduced tissue mass loss, increased healing and formation, and cell differentiation through cellular and molecular interaction mechanisms, such as Piezo ion channels and Wnt signaling, immune response, neuron development, tissue adaptation and repair, and stem cell differentiation, leading to bone regeneration (Fig. 2).

4.1. Wnt signaling pathway

A number of studies demonstrate the proliferative expressive response of osteoblast-like cells to dynamic strains *in vitro* with various mechanosensory mechanisms (i.e., pressure, shear stress, gap junction, and cilia activity).[16] The Wnt/β-catenin signaling pathway is recognized as an important regulator of bone mass and cell function,[21,32] serving to stimulate the transmission of mechanical signals sensed by osteocytes to the surface of bone (Fig. 2). New data suggest that the Wnt/β-Catenin pathway in osteocytes may be triggered by crosstalk with the prostaglandin pathway in response to loading, which in turn leads to decreased expression of negative pathway regulators such as Sclerostin (Sost). Mature osteocytes produce Sclerostin and inhibit Wnt/β-catenin signaling by binding to LRP5 and preventing Wnt binding (Fig. 2). ARF can serve as a regulator for such a pathway at targeted sites, demonstrating utility for future clinical applications. Thus, sclerostin-neutralizing antibody (Scl-Ab) may increase bone mass. Our research team has evaluated the effects of Scl-Ab in mitigating bone loss in ovariectomized (OVX) rats with concurrent functional mechanical unloading via hindlimb suspension (HLS) in a rat model. A significant decrease in distal metaphyseal trabecular architecture integrity was observed with HLS, OVX, and HLS plus OVX, in which bone volume fraction (BVF) decreased by 29 %, 71 %, and 87 % respectively.[32] The mechanical regulation through acoustic force would promote fracture healing and attenuate bone loss by enhancing the Wnt signaling pathway. In addition, mechanotransduction can enhance stem cell homing and differentiation.[9,2] Promising results revealed that stem-like cells reside in tissues and contribute to tissue repair; and these cells are replenished by precursor bone marrow-derived cells. Dynamic ultrasound has shown significance in promoting cellular proliferation and mineralization under simulated microgravity and in bioreactors.[17,28]

Bone remodeling involves all related cell types, i.e., osteoblast, osteoclast, osteocyte, T-cells, B-cells, megakaryocyte, and lining cells. These cells respond to mechanical loading, and can express specific molecular pathways. Related molecular and gene factors are represented in this temporal sequence (Fig. 2). Damage to the mineralized bone matrix results in localized osteocyte apoptosis, reducing the local transforming growth factor β (TGF-β) concentration and its inhibition of osteoclastogenesis. Osteoblast expression of OPG is decreased, and the production of CSF-1 and RANKL is increased to promote the proliferation of osteoclast precursors and differentiation of mature osteoclasts (Fig. 2).

4.2. Piezo 1/2 in mechanosensory transduction

Piezo 1 and 2 ion channels significantly impact the mechanosensory mechanism, serving an essential role in all its manifestations for living organisms. This shines a spotlight on the role mechanoreceptors play in the sustainability of different life forms, in a variety of environments, including microgravity for human colonization of outer space. Mechanosensitive Piezo ion channels, including Piezo1/2, are evolutionarily conserved proteins; and they are critical for normal physiological processes in mammals.[18] Piezo1 is localized at or near the plasma membrane. In our recent study, it has been demonstrated that Piezo1 can transduce dynamic mechanical loading induced by local ultrasound stimulation into intracellular Ca^{2+}, and the Ca^{2+} acted as a second messenger to activate ERK1/2 phosphorylation and perinuclear F-actin polymerization in bone-like cells.[33] The results indicate Piezo1 as a potential novel therapeutic target for fracture healing. In the cardiovascular adaptation, it has shown that Piezo1 channels as sensors of frictional force (shear stress) and determinants of vascular structure in both development and adult physiology.[26] Global or endothelial-specific disruption of mouse Piezo1 profoundly disturbed the developing vasculature and was embryonic lethal within days of the heart beating.[26] Piezo1 is also highly expressed in the brain and involved in sensing changes in the mechanical microenvironment (Fig. 2). It has been shown that Piezo1-mediated mechanotransduction is closely related to glial cell activation and neuronal function.[34]

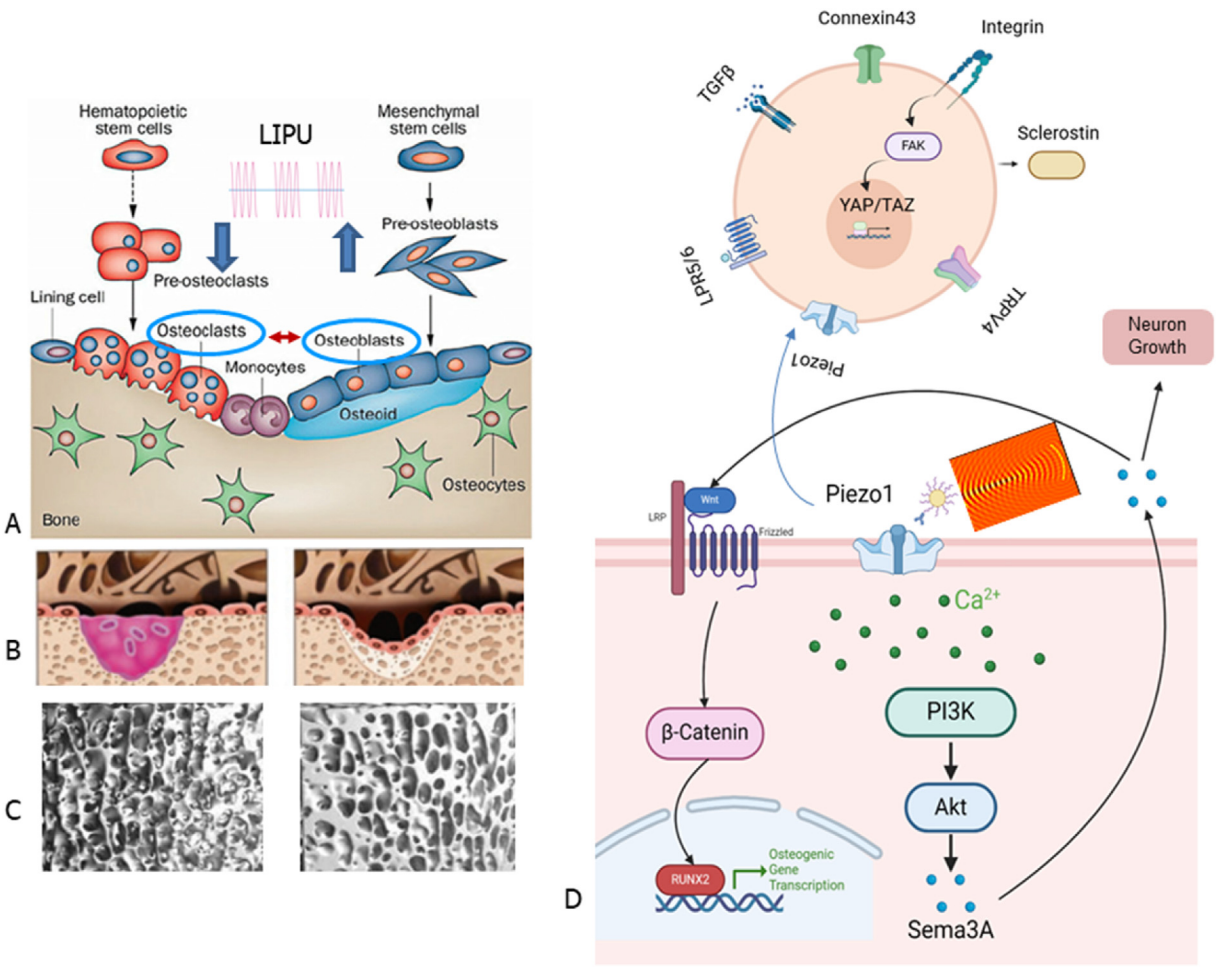

Fig. 2. Mechanical signals induced by low-intensity ultrasound can regulate bone cell differentiation and adaptation, such as promoting osteoblastogenesis (A,B&C, right) and mitigating osteoclastogenesis (A,B&C left). LIUS directs MSC differentiation towards the osteogenic lineages ((A), and enhance RUNX2 and YAP expression (D). Ultrasound induces Wnt signaling and b-Catenin activation, and regulates Piezo-1 ion channel activation to promote calcium exchange (D). The phosphoinositide 3-kinase (PI3K)/Akt pathway is activated by LIUS, promoting osteogenic differentiation, and enhancing TGF-β/Smad pathway. Piezo1 transduces LIUS loading to stimulate intracellular Ca^{2+}, and the Ca^{2+} acted as a second messenger to activate ERK1/2 phosphorylation and perinuclear F-actin polymerization (D). LIUS can enhance Semaphorin 3A (Sema3A) expression to promote bone formation and reduce bone resorption (D) (Courtesy for Biorender for illustration of the figure).

5. Future directions

The effects of mechanobiology induced by mechanical force, such as noninvasive ultrasound, may be one of the most intriguing aspects of living tissue, which has been harnessed in such a way that physical regulation and stimulation can act as a mechanobiological mediator in various cells, tissues, and organ, as well as scaffolds, to regulate cellular and tissue regeneration and proliferation. QUS imaging has the potential to become a promising diagnostic tool for the noninvasive measurement of bone quality and early assessment of bone loss. Substantial evidence has shown that mechanotransduction plays critical roles in cell-cell communication, normal and disease adaptation and progress, embryonic development, tissue homeostasis, tissue engineering and regeneration, and immune response as new therapeutics for osteoporosis and acceleration of healing. Future research will likely involve molecular and generic mechanisms identification, enhance our knowledge to develop novel ultrasound technology and treatment, and explore drug delivery and clinical applications. Further development of mechanobiology with advanced topics may be innovative for the following areas: 1) unraveling of molecular and genetic mechanisms, 2) localized treatment at the cellular and regional area for healing with new and innovative ultrasound technologies, 3) synthetic biology approach development and single-cell and RNA-seq technologies for ultrasound mode/signal optimization, and 4) clinical translation and applications. Further understanding of multiple imaging technologies, e.g., ultrasound and laser, cell-tissue communication, and sensing of mechanical cues, will have promising potential to develop novel ultrasound imaging and interventions for both diagnosis and therapeutics for musculoskeletal diseases.

CRediT authorship contribution statement

Yi-Xian Qin: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.

Ethical approval

This study is a perspective review, and does not contain any active studies with human or animal subjects performed by any of the authors.

The ethical approval is not applicable to this submission.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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