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Topography of Acoustical Properties of Long Bones: From Biomechanical Studies to Bone Health Assessment

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Abstract

The article presents a retrospective view on the assessment of long bones condition using topographical patterns of the acoustic properties. The application of ultrasonic point-contact transducers with exponential waveguides on a short acoustic base for detailed measurements in human long bones by the surface transmission was initiated during the 1980s in Latvia. The guided wave velocity was mapped on the surface of the long bones and the topographical patterns reflected the biomechanical peculiarities. Axial velocity profiles obtained in vivo by measurements along the medial surface of tibia varied due to aging, hypokinesia, and physical training. The method has been advanced at Artann Laboratories (West Trenton, NJ) by the introduction of multifrequency data acquisition and axial scanning. The model studies carried out on synthetic phantoms and in bone specimens confirmed the potential to evaluate separately changes of the bone material properties and of the cortical thickness by multifrequency acoustic measurements at the 0.1 to 1 MHz band. The bone ultrasonic scanner (BUSS) is an axial mode ultrasonometer developed to depict the acoustic profile of bone that will detect the onset of bone atrophy as a spatial process. Clinical trials demonstrated a high sensitivity of BUSS to osteoporosis and the capability to assess early stage of osteopenia.

I. INTRODUCTION

The rationale for obtaining the ultrasonic profiles of long bones is based on 3 premises: 1) spatial heterogeneity of the mechanical properties and nonuniform deposition of the bone substance are natural characteristics of bones related to their structure and function; 2) vital changes such as those occurring due to pathologies, aging, and adaptation to loads are spatially developing processes based on the volume of bone; and 3) ultrasound velocities related to different wave modes and obtained in multiple locations along the bone can reflect changes associated with the elastic properties and the cortical thickness as the spatially or, particularly, axially developing processes.

Long bones are well-optimized biological constructions with substance organization. The Roux' "minimum-maximum" principle that stipulates the maximum load-bearing capacity with the most economic deposition of the substance [1] is used as a guide. Classic studies in bone biomechanics emphasized effective adaptation of bone to mechanical loads at every level of its hierarchical structure, starting from the collagen/mineral complex to the levels of tissue and the whole organ [2], [3]. Factors determining bone strength can be divided into 2 groups related to the geometrical and material properties [4], [5]. The first factors imply the cortical thickness and the amount of bone substance. Prevalence of resorption over new bone formation during the bone atrophic process, particularly in age-related osteoporosis, results in thinning of the cortex due to the enlargement of the interosseous channel that leads to degradation of the bone strength. Determinants of the mechanical properties of bone material are mineralization of bone matrix, inner porosity, microdamages, and cortical bone architecture.

Mineralization or the mass fraction of minerals in the mineral/organic substance in the solid bone matrix has a nonlinear effect on the bone strength. The lack of mineralization or a great amount of poorly mineralized matrix as observed in the growing children's bones and in the pathologic condition called osteomalacia causes softening, while hypermineralization results in hardening and brittleness. The elastic modulus and strength of bone decline with growth of porosity as stiffness falls rapidly with small changes of inner porosity in the solid bone substance. The material properties are also affected by different factors related to microstructure [6], such as accumulation of microdamages as a consequent of mechanical fatigue, size of crystallites, and percentage of the osteonic and lamellar structures. Adaptation to spatially directed loads results in anisotropy of the structure and mechanical properties [7].

Diverse mechanical properties of bones investigated from biomedical and material aspects, have demonstrated a wide spectrum of variations caused by biological, structural, and compositional factors [8]. The elastic and strength parameters were determined as functions of location with emphasis on the influence of regional differences of structure and microstructure [9]–[12]. Although axial nonuniformity of the elastic modulus, strength, and hardness of cortical bone was shown to be a characteristic feature of long bones with the maximum values in diaphysis and the lowering slope toward epiphyses [10], [13], there is a lack of studies providing detailed spatial patterns of the stress-strain properties of bones. This would present them as rationally designed, complex, and nonuniform load-bearing constructions.

Application of ultrasonic waves as a noninvasive characterization of the bone's mechanical status has a long-standing history resulting in the development of several diagnostic technologies of quantitative bone ultrasound [14]. Ultrasound velocities of the longitudinal and shear waves were documented along the main axes of symmetry of the osteonic structure, allowing us to consider the compact bone as either a transverse isotropic [15] or an orthotropic [16] solid. In normally mineralized compact bone specimens, the velocity of the longitudinal wave measured by the through transmission along osteons in a low megahertz frequency band varies from 3.7 to 4.3 km/s [17]. In bones in vivo examined in a broader frequency band, from 100 kHz to 1 MHz, at different anatomical locations, the range of ultrasonic longitudinal wave velocity is broader, initially 2.8 km/s and even smaller values while not exceeding 4.3 to 4.4 km/s. Sensitivity of ultrasonic propagation parameters have been linked to changes of important properties defining bone quality, including elastic properties [18], [19] and thickness [20], [21]. Although several studies have demonstrated topographical differences of ultrasound velocity in long bones and a decreasing slope from diaphysis toward epiphyses [22], [23], these regularities have not been properly interpreted, nor have they been exploited as a diagnostic feature. Attempts to use shear and surface waves for mapping ultrasonic properties were done using the critical-angle reflectometry [24].

Detailed assessment of the topographical patterns of ultrasound velocity in long bones was motivated by the use of point-contact transducers on a short acoustic base. The method was introduced and widely applied in the 1970s at the Non-Destructive Testing Laboratory of the Riga Technical University (RTU) headed by V. Dzenis for testing concrete, cement, ceramics, brick, and other nonmetal building materials [25] or materials whose structural heterogeneity may lead to defects or failure. Applied transducers operating in the 50 to 200 kHz band were designed as exponential waveguides-concentrators with thin tips to provide point contact with testing objects; see Fig. 1(b). The transducers allowed for fast measurements at multiple locations in geometrically nonuniform objects with rough surfaces. At the same time, investigations conducted in the Biomechanics and Biomaterials Department of the Latvian Institute of Traumatology and Orthopedics (LITO) headed by H. Yansons and in the Biomechanics Lab of the Latvian Science Academy Polymer Mechanics Institute headed by I. Knets attempted to study bone structure and function interaction from biomedical [26] and

material science [11] viewpoints, respectively. The studies conducted at LITO with in-house designed ultrasonic devices and transducers, as shown in Fig. 1(a)–(c), were focused on the topography of acoustical properties of long bones [27]–[32]. Most of these studies were conducted using slow propagating guided waves at 100 kHz. These waves are similar to the Lamb waves in plates, whose velocity depends both on material stiffness and plate thickness.

Recently, multiple attempts to differentiate cortical thickness as an important factor of bone strength by means of guided waves at low frequencies (0.1–0.3 MHz) have been undertaken [32]–[38]. Studies conducted in specimens and bones in vitro revealed the possibility to detect slow guided waves and correlate the velocity with bone thickness. The velocity of guided waves showed sensitivity to osteoporosis [33] and to the status of growing bones [38] due to a higher velocity than that of the longitudinal wave evaluated from the first arriving part of the transmitted ultrasonic signal.

The technology incorporating guided waves and assessment of topography has been further advanced at Artann Laboratories (West Trenton, NJ) by introducing several innovations: multifrequency data acquisition based on the implementation of broadband transducers run by a programmable waveform generator with stepped switching of frequency; multiparametric data analysis gaining information differentially at low and high frequencies; and axial-stepped scanning along the bone [39]. These principles were implemented in the bone ultrasonic scanner (BUSS) [40] illustrated in Fig. 1(d). The theory forming the basis of BUSS technology and used for relating the data obtained by BUSS to the material properties and geometrical features of bone is given in the classical monographs of Viktorov [41] and David and Cheeke [42].

The purpose of this article is to review findings from the studies started in LITO to the latest results obtained by Artann Laboratories' novel technology capturing acoustic heterogeneity of long bones, axial profiles of ultrasound velocity, and their diagnostic value.

II. ULTRASONIC MEASUREMENTS ON THE SURFACE OF LONG BONES BY POINT-CONTACT TRANSDUCERS AND TOPOGRAPHIC MAPPING OF ULTRASOUND VELOCITY

Ultrasonic transducers based on the exponential waveguides-concentrators, which were used in the early studies [27]–[31], had numerous advantages. The main advantage was that they served as a point source of acoustic waves, at the frequencies on the order of 100 kHz, providing a sufficiently high amplitude signal necessary for reliable measurement of ultrasound propagation parameters. The transducers with waveguides-concentrators, shown in Fig. 1(b), and Fig. 4(a), had a stem with a decreasing diameter concluded by a point contact tip. Such transducers with a quasi-point contact area of about 1 mm^2 allowed close rapprochement of the tips and measurements on acoustic bases in the 0.5 to 2.0 mm range without additional liquid or gel lubrication. The waveguide length was equated to a whole number of half-waves along the stem and the cross section of the waveguide changed axially by exponential law.

By measurements of a constant acoustic base L , the distance between the centers of emitting and receiving transducers' tips, the ultrasound velocity C was determined as $C = L/(T - \Delta\tau)$, where T and $\Delta\tau$ were propagation time and a constant time delay in transducers determined for the same reference point of the signal. The determination of $\Delta\tau$ is crucial in velocity estimations. It was defined by building the velocity hodograph, a linear time-base $(T - L)$ slope graph formed by the measurements of T during stepped increase of L . Interference of bulk, guided, and reflected waves, as well as dispersive properties of the medium, produce transformations of ultrasonic signals with increasing L . It was experimentally shown that at a frequency of 100 kHz on short acoustic bases ranging from 6 to 15 to 20 mm, hodograph plots for the first-

arriving peak of propagated ultrasonic signals were linear within the measurement accuracy. The wave type responsible for these peaks corresponded to the slow-type guided wave with the velocity ranging from 0.6 to about 1.8 km/s depending on the bone thickness. In a bone model with a thickness of greater than 8 to 10 mm, the velocity approaches that of a Rayleigh surface wave. Although the fast longitudinal wave stands out from the entire wave packet in the application of point-contact transducers, its amplitude is many times smaller than that of the flexural and surface Rayleigh waves.

For a detailed mapping of the velocity on the surface of long bones, an accumulation of elementary measurement cells was compiled, as shown in Fig. 2(a), composed of 630 (30×21) rectangular zones in cross sections. The acoustic base was oriented parallel to the bone axis. The determination of the anisotropy coefficient as an informative anatomic variable was completed by measurements and by orienting the base transversally to the bone axis in relatively flat plots of bone surface. The largest human long bones of the tibiae, femurs, and humeral bones for in vitro studies were obtained at LITO from donors who had died in catastrophes or from amputations.

Velocity of the ultrasonic flexural wave C_f was found to be in a broad range from 600 to 1800 m/s, depending on the anatomical location. The lowest values were obtained in the epiphyses, in zones close to the joints, and the highest ones corresponded to the diaphysis. Statistically significant differences were found between average values in epiphyses, metaphyses, diaphyses (Table I), or in the bone lengths, as well as between several specific anatomical zones in cross sections, such as between the surface and the marginal zones in the tibia diaphysis or between the neck and trochanters in the proximal femur. The highest values corresponded to anatomical areas with the thickest cortical layer and conversely.

Each bone type of a tibia, femur, and humerus has its characteristic topographical pattern of C_f . The common features are: 1) location of the highest values in diaphysis, where the cortical layer is the thickest; 2) the most expressed gradient of C_f reaching and even exceeding 200 m/s per 1 cm of length in the metaphyseal zones, i.e., in the plots, where the cortical thickness sharply grows from the epiphysis toward the diaphysis; and 3) the highest nonuniformity of C_f in regions of in epiphyses and metaphyses that are fortified compact bone with neighboring areas of prevailing trabecular structure, for example, in proximal femur and in distal humerus.

From the analysis of the iso-velocity maps, several topographical peculiarities subordinated to bone construction were revealed [27]–[31]. Fig. 2(b) illustrates iso-velocity maps of the tibia.

In the epiphyses and proximal metaphyseal zones featured by low C_f values, the transversal orientation of iso-velocity zones is prevalent. This can be a consequence of stiffer transversal bonds in these zones. Together with a high axial gradient of the stiffness (as also follows from C_f data), it is a logical constructional mechanism to react to high transient stresses from the joints and to serve as a dynamic force damper.

In diaphysis, the prevalent orientation of iso-velocity zones coincides with the longitudinal bone axis. Zones of lower and higher velocities are located relatively parallel to the stem, and the C_f gradient in a cross section is higher than by the length. According to ultrasonic data, the anatomical anterior margin and the posterior surface of the tibia are stiffer than the medial and lateral surfaces and are similar to reinforced load-bearing axial rods or columns. These zones are also characterized by the thicker cortex strengthening the bone in the walking plane. The highest stiffness accumulated in the midst of diaphysis is a measure to resist extreme bending forces experienced by the bone during physical loads.

In metaphyses, which are transitional zones from epiphyseal to diaphyseal structures, the iso-velocity patterns are tooth-shaped with inclinations of deep protuberances of higher velocity directed toward epiphyses along the anatomical margins.

Other types of long bones, femur and humerus, have the same types of iso-velocity zones in epiphyses, metaphyses, and diaphysis. Their specific peculiarities are related to increased velocities, which reflect their biomechanical roles, such as the femoral neck transmitting body weight to the lower extremities, in femur, and the medial and lateral margins acting like webbings in a lever construction, in the distal humerus.

A comparison of the iso-velocity and large muscle anchoring zones showed their coincidence for the most part; see Fig. 2(c). The relative acoustic plateau in the muscle anchoring zones provides indirect evidence of uniform physiological traction on the whole surface of the muscle belly fixation. Zones of the muscle anchoring generally correspond to zones of relatively lower ultrasound velocities and to lower bone stiffness, which provides to an extent softening of a sharp mechanical gradient between bone and muscle.

The acoustical anisotropy coefficient was determined as $K_C = C_0/C_{90}$, where C_0 and C_{90} were ultrasound velocities measured on bone surface corresponding at 0° and 90° to the bone axis. To account for topographical nonuniformity, measurements of 3×3 in axial and transversal directions were averaged, encompassing a bone surface cell with a square $1 \times 1 \text{ cm}^2$. It was found (Table I) that the degree of ultrasonic anisotropy is not a constant, but may alternate in a wide range depending on the anatomical region of the long bone. The coefficient K_C varied from 0.9 to more than 1.4, being close to 1 in epiphyseal zones and ranging from 1.15 to 1.4 in the diaphyseal stems. Maximum values of K_C were observed in those anatomical regions that are subjected to higher bending and tensile strains during physiological loading, e.g., the femoral neck and the distal third of tibia diaphysis. Remarkable differences between K_C can be observed at the same cross-sectional levels in the length of long bones, in regions differing morphologically and composed of different bone structures. Thus, K_C in the femoral neck reached values of more than 1.4, while in the neighboring regions of the same bone length girdle and in zones of the minor and major trochanters composed prevalently of the trabecular structure, the range was 0.9 to 1.1. Hence, biomechanical nonuniformity is manifested not only in topographical patterns of the velocity, but in the degree of acoustical anisotropy as well.

Pathological processes like severe arthritis are associated with a reduction in the normal level of loading, alterations of loading stereotypes, and disturbance of bone trophism. Such pathologies result in bone morphological and structural changes, consequently resulting in alteration of acoustical patterns. Fig. 3 presents an example of such alternations in the proximal femur in the case of severe cox-arthritis with necrosis of the femoral head compared with the healthy condition. The pathological process affecting the hip joint area is manifested not only in regions directly close to hip but also involved the whole proximal femur. Acoustical pattern demonstrated the lowering of the velocity in the femoral neck and in the cortex below it, as well as flattening of the natural velocity gradient between the neck and the minor trochanter.

III. ALTERATIONS OF AXIAL PROFILES CAUSED BY VITAL FACTORS

The medial surface of the tibia was chosen as a convenient site for *in vivo* studies due to the relatively thin layer of soft tissues along the entire length between the knee and the ankle. The tibia is one of the largest load-bearing bones with available regions of different structures such as compact, spongy, and combined. Axial profiles were obtained by discrete measurements along the tibia into 10 or 30 girdles of the bone length in the middle of the medial surface (Fig. 4). Point-contact tips of the transducers allowed compression of the skin and subcutaneous soft tissues while approaching the bone surface noninvasively.

To get reference data, a contingent of more than a 100 healthy people of both genders ranging in age from 6 to 74 years was examined [31]. Fig. 4 presents the age-related evolution of velocity profile graphs along the tibia. The youngest age group of 6 to 13 years old, in which the bone cortical layer was much thinner than in adults and had a greater percentage of non-mineralized osteoid tissue, displayed the lowest velocity values along the entire bone length. As further growth and maturation allow the compact bone to become stiffer and thicker, a rapid growth of the ultrasound velocity is observed, with the maximum at 23 years. In the middle of diaphysis, the ultrasound velocity growth is the most pronounced and the maximum values are gained just in this region of the thickest cortical layer and maximum bending stresses. Due to this, the profile graph in adult people ranging from 23 to 44 years old obtains the shape of a bent bow with decreasing gradients of the velocity toward the epiphyses. During further aging, there is some regress of the ultrasonic profiles that can be explained by osteopenic manifestations. In comparison to the data on ultrasound velocity in vitro, the coincidence of ranges was found only in the diaphysis and in the metaphyseal regions close to the diaphysis. The velocities were higher in vivo than in isolated bones and did not go below 1.2 km/s when approximately 15% of the bone length is taken from the proximal and distal ends in the epiphyses and proximal metaphyseal regions. The effect is presumably the result of the influence of the covering layer of soft tissue masking slow and highly attenuated waves in prevalent trabecular sites.

Maximal values of the flexural velocity revealed in the middle of diaphysis, location of maximum cortical layer thickness, can be indicative of load-resisting capacity of the bone, which achieves the highest values in high-level athletes such as runners and jumpers coping with intensive dynamical loads [43]. Assessment of metaphyses can present data sensitive to the development of bone's atrophic processes as bone loss in osteoporosis, because thinning of the cortex due to resorption will evoke the most expressed changes of the velocity in these regions, where the slope of the thickness-velocity dependence is the sharpest. Thus, total axial scanning has the capability to be a source of information on the bone biomechanical status.

A special study [43] was devoted to the influence of intensive loads on the axial ultrasonic profiles in the tibia as indicators of the bone adaptation. Males 18 to 25 years old were examined with different level of physical training, including students not involved into any kind of sport, swimmers, biathlon skiers, runners, jumpers, and all-round track and field athletes. The latter group of athletes, associated with intense dynamic loads, demonstrated the highest average values and the most expressed peak in diaphysis. The lowest values were noted in the group of nontrained students and in swimmers. This study is one more illustration of influence of mechanical stimuli on bone formation, especially critical early in life. The results are consistent with later Japanese studies in athletes, in which similar regularities related to the cortical area were obtained using quantitative computed tomography [44].

Behavior of the ultrasonic profiles in the tibia were followed in patients with severe gonarthrosis during pre- and postoperation periods [45]. In the postoperation period, the velocity at injured sites decreased on an average of 1.5% as it increased by 5% of the initial values during the rehabilitation process.

The remarkable opportunity to investigate the influence of unloading of the ultrasonic profiles in the tibia was presented in experiments on long-term antiorthostatic hypokinesia, ANOG-120 (120-d bed rest) and ANOG-370 (370-d bed rest) conducted in the Institute of Medical and Biological Problems (Moscow) in the 1980s [46]. Volunteers were divided into groups of control, physical therapy, pharmacological therapy, and combined therapy. Ultrasonic profiles were recorded once a month in parallel to estimations of the bone mineral content (BMC) by the photon absorptiometry in the proximal third of the tibia. Despite a wide range of individual variations in ultrasound velocity values and "behavior trends," common flattening of axial

velocity profiles accompanied by lowering shifts was observed during hypokinesia period. If BMC changes were shifted by a month relative to the ultrasound in the ANOG-120, a correlation of monthly changes of the ultrasound velocity with the same BMC changes improved from $r = 0.68$ to $r = 0.79$. A characteristic example of bone atrophic changes in the tibia of a volunteer during long-term hypokinesia manifested in the axial velocity profiles is shown in Fig. 5.

Possible short-term fluctuations of the ultrasound velocity in the compact bone under the influence of diverse impacts were evaluated. It was found that ultrasound velocity in the tibial diaphysis can increase by several percentage points during an intensive dynamic load (10–30 min of running) [47] and a 20-min static load [31]. Additionally, the tibiae diaphysis is accompanied by an increase in the blood flow to the extremity after the application of tourniquet [48]. Such an increase of stiffness in bone diaphysis during “warming up” can be a manifestation of an unknown adaptive mechanism to loading. Even though independent studies examining marathon runners have corroborated these changes, further systematic studies are needed [49].

IV. MULTIFREQUENCY SCANNING TECHNOLOGY

The method of ultrasonic axial profiles for the characterization of long bone condition was further advanced at Artann Laboratories. Initially, this was achieved by the introduction of multiparametric analysis based on multifrequency scanning and followed by the application of advanced data acquisition tools [39], [40]. This renewed approach is based on the measurement of ultrasound velocity at different ratios of wavelength to the bone thickness at various carrier frequencies ranging from 100 kHz to over 1 MHz. Different types of acoustic waves become apparent at different frequencies. They are identified as bulk waves, the fastest wave component at high frequencies, surface waves, the slower wave component of greater amplitude at high frequencies, and guided waves, the dominant wave component at low frequencies. The waves referred to as bulk, propagate in the sub-surface bone layer and are compression-dilatation waves with the velocity close to the bulk longitudinal waves in through transmission. The slower surface waves are similar to the Rayleigh waves propagating in a solid half-space. In bones, this condition is fulfilled, if the cortical layer is thicker than the ultrasonic wavelength. Guided waves are similar to the A_0 Lamb waves in plates or flexural waves and have strong dependence of the velocity on the cortical thickness. This complex approach allows an assessment of changes in both the material properties related to porosity and mineralization, as well as in cortical thickness influenced by resorption from inner layers. The developed method was validated in diverse model studies.

Tubular phantoms modeled the combined changes in material stiffness and the cortical thickness in midshafts of long bones. The specimens were made of available polymers and polymer composites ranging by longitudinal velocity from about 2200 m/s to 4400 m/s in the following order: ebonite, acrylic plastic, fiberglass, and carbon fiber plastic. The entire known range of ultrasound velocity from the poorly mineralized to hypermineralized bone was included. Wall thickness of the models was gradually increased from 1 to 6 mm to mimic the typical range in the variation of cortical thickness of different human long bones. The characteristic dependence of the velocity at a low frequency of 100 kHz on the thickness obtained in all phantoms was similar to the same dependence of the velocity of A_0 Lamb waves in plates, as shown in Fig. 6(a). At 100 kHz, the velocity slope is very steep with a velocity gradient of 200 to 400 m/s per 1 mm increment over the thickness range of 1 to 2.5 mm. Thus, at a measurement accuracy of 20 to 30 m/s, the thickness changes on the order of 0.1 mm can be revealed in the sites of thin cortex. In the thickness range of 2.5 to 6 mm, the gradient of the velocity slope decreases to 40 to 60 m/s per 1 mm. Even in this case, the method can be sensitive enough to discriminate bones with thinner or thicker cortex with resolution about of

0.5 to 1 mm. At a higher frequency of 500 kHz, the velocity did not change substantially with variation of the wall thickness in phantoms, being mostly a function of the material properties. The experiment demonstrated that the geometric dispersion phenomenon previously considered for plates, as shown in Fig. 6(c), can be extended for assessment of the cortical thickness in tubular bones using empirically established correlations. The earlier results obtained in bones in vitro at 0.1 MHz [29], shown in Fig. 6(b), showed the same character of the velocity-thickness dependence as that in the tubular phantoms.

To model the actual osteoporosis development in long bones, a series of layered specimens modeling gradual growth of porosity in the compact bone from the endosteum to the periosteum was used. This is the location where porosity grows from the endosteal surface causing trabecularization of the inner cortical layer and reducing the effective cortical thickness, reaching the periosteal layer only at the latest stages. Small submillimeter rubber particles with a bulk velocity of about 1500 m/s were used to build models mimicking porous bone. The rubber particles were incorporated in the homogeneous solid epoxy matrix with a bulk velocity of about 2700 m/s that mimicked the hard substance. Porosity progression was modeled by gradual incorporation of pores into upper layers of the cortex, thus decreasing the thickness of the solid nonporous layer from 7.5 mm to 0.5 mm step by step in the 8 mm thick phantoms. Dosed porosity content in different layers ranged from 20% to 50%, representing the initial stage and developed stages of osteoporosis, respectively. Fig. 7 displays the relative changes of the velocities at low and high frequencies in these layered porous phantoms. The velocity of 100 kHz steadily decreased from Phantom #1 (pure solid epoxy) to Phantom #6, in which porous inclusions almost reached the very upper surface. Decreasing the thickness of the intact layer by 1 mm led to a 50 m/s decrease in the velocity on average. A significant decrease in velocity at 500 kHz was noted only in Phantom #6, which imitated the final stage of porosity development. Thus, it was demonstrated that an ultrasonic guided wave at low frequency is able to provide information about deeper layers and its velocity could be highly sensitive to the porosity progressing from endosteum at early stages of osteoporosis. Simultaneous measurements at high frequencies can be helpful for assessment of the true material properties affected, for example, by mineralization degree.

Animal bone specimens were used for testing bone properties that were difficult to model in simple phantoms [39]. Porcine metacarpal bones taken from young and adult animals admittedly differed in both geometry and tissue material properties due to size and degree of ossification. The cortex in the adult animal bone was about 2 times thicker than in the young bone. The ultrasound velocities of guided wave and bulk wave differed not only in their magnitudes (2.5 to 3 times), but also by a different distribution pattern along the bones. The guided wave velocities ranging from 0.8 to 1.4 km/s were much lower in the young animal for any given bone site. Lowered bulk wave velocity was noted only in the physis zone of the young animal as a sequence of incomplete ossification in this area. In the diaphyseal part, the bulk wave velocities were at maximum about 4.0 km/s and equivalent in the adult and young animals, where the bone is completely mineralized and mature. The experiments with animal bones showed ability of the method to assess differentially cortical thickness and bone mineralization.

V. DUAL-FREQUENCY BONE SCANNER IN ASSESSMENT OF BONE CONDITION IN OSTEOPOROSIS USING 2-D WAVEFORM PROFILES

The BUSS developed by Artann Laboratories is an ultrasonometer based on multifrequency (or dual) acoustic evaluation of long bones; see Fig. 1(d) and Fig. 8. The BUSS was designed to obtain diagnostic information by a comprehensive analysis of acquired ultrasonic waveform parameters as a function of position along the bone and ultrasound frequency. Measurements in the axial transmission mode are realized by broadband transmitting and receiving transducers

placed unilaterally on the surface of the examined bone. A train of short ultrasonic enveloped burst pulses (at least, 2) with various carrier frequencies from 100 kHz to 1 MHz, is emitted and ultrasonic signals passed along the examined bone are acquired. Measurements are repeated at multiple points along the predetermined trajectory-of-scanning along the bone. The passed distance is controlled by a movement controller. Times-of-flight and various phase and amplitude characteristics for portions of ultrasonic signals related to ultrasonic bulk, surface, and guided waves are analyzed, and axial profile graphs are plotted for various spatiotemporal parameters of the received waveforms.

The BUSS software acquires raw data at successive discrete points along the scanning trajectory and forms a series of 2-D maps presenting the amplitude of the acquired signal as a function of position along the bone such as that shown in Fig. 9. A 2-D map is generated for every received frequency wave packet and is used for evaluation of axial profiles of various parameters of acquired ultrasonic waveforms. The parameters include amplitude and phase characteristics of received ultrasound pulses, the related values of velocity, and attenuation of different modes of acoustic waves. The axial profiles provide information on different structural components of bone due to the varying cortical thickness and compact and porous bone ratios. The algorithm illustrated in Fig. 9 is based on finding the most informative part of the received acoustic waveform to reveal the spatial features of the bone deterioration process. The spatio-temporal map of acquired signal is filtered and analyzed to determine the region with the most significant distortions, called the most informative fragment of signal (MIFS). After several further steps of image processing, the axial profile of acoustic wavefronts in the MIFS region is obtained.

Pilot clinical studies aimed to test the sensitivity of the spatiotemporal profiles produced by BUSS for early stage osteoporosis were conducted at the Robert Wood Johnson Medical Center of the University of Medicine and Dentistry of New Jersey. The proximal tibiae were tested by manual axial scanning the medial surfaces starting from the knee joint to the diaphysis. Examined contingent included about a hundred female patients at menopausal and postmenopausal age with overall skeletal status ranging from upper norm level to severe osteoporosis. The patients' population was divided into several groups according to dual-energy X-ray absorptiometry (DEXA) T-score in the hip, using standard definitions: "norm," "osteopenia," and "osteoporosis." The individual ultrasound data sets were processed for each patient separately and the averaged data sets were prepared for the predetermined patient groups.

Processing of 2-D spatiotemporal profiles of 100 kHz guided wave pulse waveforms revealed significant differences in the profiles of each group. The position of the pulse wavefronts shown in Fig. 10 corresponds to the time-of-flight of the pulse (a shift of the front to the right in patterns) and indicates a decrease of the ultrasound velocity. As it is clearly seen in Fig. 10, the onset of osteopenia results in slowing the guided waves in the tibial metaphysis and this change gradually expands along the length of the tibia from the metaphysis toward the diaphysis. BUSS demonstrated high sensitivity to the initial stages of bone atrophy. This was most notable within the norm group and between the norm and osteopenia groups. Changes between osteopenia and osteoporosis were smaller. Temporal shifts due to wave front at the same location along the bone reflect the slowing of the ultrasonic guided wave mainly due to the thinning of the cortical layer due to progressing resorption from the intramedullary canal. As shown by model experiments above, there is a steep slope of the velocity-thickness dependence at 0.1 MHz in the thickness range from 2 to 6 mm. Changes of the cortical thickness along the scanned area in the proximal tibia occur in exactly the same range.

In contrast to low frequency, the front arrivals at high frequency of 1 MHz changed little between norm and osteoporosis and were almost uniform on the bone length. At high

frequencies, the gradual lowering of intensity in MIFS was the established feature of osteoporosis. Increased inner porosity and enlargement of the natural pores within the compact substance result in the elevated attenuation of ultrasound at high frequency.

Both clinical and model experiment data unambiguously show that low and high frequency spatiotemporal profiles are carriers of different information about atrophic manifestations in bone.

VI. CONCLUSION

Topography of ultrasound velocity in long bones reflects biomechanical peculiarities related to distribution of bone substance and the material properties. Assessment of ultrasonic velocities in broadband frequency range related to different acoustic modes like bulk, surface, and guided waves present different information about the cortical thickness and the material properties that are equally important from the diagnostic point. Acoustic waveform profiles obtained by BUSS allow assessment of osteoporosis development at an early stage.

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REFERENCES

1. Frost HM. Vital biomechanics. Proposed general concepts for skeletal adaptation to mechanical usage. *Calcif. Tissue Int* 1988 Mar.;vol. 45:145–156. [PubMed: 3130163]
2. Currey JD. The many adaptations of bone. *J. Biomech* 2003 Oct.;vol. 36(no 10):1487–1495. [PubMed: 14499297]
3. Kummer, BKF. Biomechanics of bone; mechanical properties, functional structure, functional adaptation. In: Fung, YC.; Perrone, H.; Anliker, M., editors. *Biomechanics: Foundations and Objectives*. Englewood Cliffs, NJ: Prentice-Hall; 1972. p. 237-245.
4. Martin RB. Determinants of the mechanical properties of bones. *J. Biomech* 1991;vol. 24:79–88. [PubMed: 1842337]
5. Turner CH. Bone strength: Current concepts. *Ann. N. Y. Acad. Sci* 2006 Apr.;vol. 1068:429–446. [PubMed: 16831941]
6. Augat P, Schorlemmer S. The role of cortical bone and its microstructure in bone strength. *Age Ageing* 2006 Sep.;vol. 35:ii27–ii31. [PubMed: 16926200]
7. Katz JL, Meunier A. The elastic anisotropy of bone. *J. Biomech* 1987 Nov.–Dec.;vol. 20(no 11–12): 1063–1070. [PubMed: 3323198]
8. Langton, CM.; Njeh, CF., editors. *The Physical Measurement of Bone*. Bristol, UK: Institute of Physics Publishing; 2003.
9. Kimura T, Amtmann E. Distribution of mechanical robustness in the human femoral shaft. *J. Biomech* 1984 Jan.;vol. 17(no 1):41–46. [PubMed: 6715387]
10. Pope MH, Outwater JO. Mechanical properties of bone as a function of position and orientation. *J. Biomech* 1974 Jan.;vol. 7(no 1):61–66. [PubMed: 4820652]
11. Knets, IV.; Pfafruds, GO.; Saulgozis, YZ. *Stress and Strain of Hard Biological Tissues*. Riga: Zinatne Publishers; 1980. (in Russian)
12. Hoc T, Henry L, Verdier M, Aubry D, Sedel L, Meunier A. Effect of microstructure on the mechanical properties of Haversian cortical bone. *Bone* 2006 Apr.;vol. 38(no 4):466–474. [PubMed: 16332459]

13. Yanson HA, Bite R, Knets IV, Saulgozis YZ. Hardness of the human tibia. *Mechanics Composite Materials* 1973 Nov.;vol. 9:966–971.
14. Njeh, CF.; Hans, D.; Fuerst, T.; Gluer, CC.; Genant, HK., editors. *Quantitative Ultrasound: Assessment of Osteoporosis and Bone Status*. London: Martin Dunitz; 1999.
15. Lang SB. Ultrasonic method for measuring elastic coefficients of bone and results on fresh and dried bovine bones. *IEEE Trans. Biomed. Eng* 1970 Feb.;vol. 17(no 2):101–105. [PubMed: 5422484]
16. Van Buskirk WC, Cowin SC, Ward RN. Ultrasonic measurement of orthotropic elastic constants of bovine femoral bone. *J. Biomech. Eng* 1981 Feb.;vol. 103(no 2):67–72. [PubMed: 7278184]
17. Nicholson, PHF.; Buxsein, ML. Ultrasonic studies of cortical bone in vitro. In: Njeh, CF.; Hans, D.; Fuerst, T.; Gluer, CC.; Genant, HK., editors. *Quantitative Ultrasound: Assessment of Osteoporosis and Bone Status*. London: Martin Dunitz; 1999.
18. Abendschein W, Hyatt GW. Ultrasonics and selected physical properties of bone. *Clin. Orthop. Relat. Res* 1970 Mar.–Apr.;vol. 69:294–301. [PubMed: 5445356]
19. Rho JY. An ultrasonic method for measuring the elastic properties of human tibial cortical and cancellous bone. *Ultrasonics* 1996 Aug.;vol. 34(no 8):777–783. [PubMed: 9010460]
20. 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. Amer* 2002 July;vol. 112(no 1):297–307. [PubMed: 12141355]
21. Prevrhal S, Fuerst T, Fan B, Njeh C, Hans D, Uffmann M, Srivastav S, Genant HK. Quantitative ultrasound of the tibia depends on both cortical density and thickness. *Osteoporos. Int* 2001 Nov.;vol. 12(no 11):28–34. [PubMed: 11305080]
22. Bensamoun S, Ho Ba Tho MC, Luu S, Gherbezza JM, de Belleval JF. Spatial distribution of acoustic and elastic properties of human femoral cortical bone. *J. Biomech* 2004 Apr.;vol. 37(no 4):503–510. [PubMed: 14996562]
23. Dubrov EI, Tarushkin OV, Zima LG. Ultrasonar diagnosis in bone injuries and bone diseases. *Khirurgiya (Mosk)* 1972 Apr.;vol. 48(no 4):61–66. (in Russian). [PubMed: 5057521]
24. Mehta S, Antich P. Measurement of shear-wave velocity by ultrasound critical-angle reflectometry (UCR). *Ultrasound Med. Biol* 1997 July;vol. 23(no 7):1123–1126. [PubMed: 9330455]
25. Dzenis, VV. *Application of Ultrasonic Transducers with Point Contact for Non-destructive Testing*. Riga: Zinatne Publishers; 1987. (in Russian)
26. Yanson, HA. *Biomechanics of Human Lower Extremity*. Riga: Zinatne Publishers; 1975. (in Russian)
27. Jansons HA, Tatarinov AM, Dzenis VV, Kregers AF. Constructional peculiarities of the human tibia defined by reference to ultrasound measurement data. *Biomaterials* 1984 Jul.;vol. 5:221–226. [PubMed: 6487702]
28. Yanson HA, Dzenis VV, Kregers AF, Oga MV, Tatarinov AM. Structural features of human tubular bones relative to ultrasound. *Mechanics Composite Materials*, New York 1983 Apr.;vol. 19(no 4): 542–549.
29. Tatarinov AM, Dzenis VV, Yanson HA. Role of compact bone tissue thickness in the investigation of tubular bones by ultrasonic exponential concentrators. *Mechanics Composite Materials*, New York 1985 Feb.;vol. 21(no 2):342–357.
30. Tatarinov AM, Dzenis VV, Yanson HA. Acoustic anisotropy of human tubular bones. *Mechanics Composite Materials*, New York 1985 Jan.;vol. 21(no 1):124–131.
31. Yanson, HA.; Dzenis, VV.; Tatarinov, AM. *Ultrasonic Investigations of Tubular Bones*. Riga: Zinatne Publishers; 1990. (in Russian)
32. Nicholson PHF, Moilanen P, Kärkkäinen T, Timonen J, Cheng S. Guided ultrasonic waves in long bones: Modelling, experiment and in vivo application. *Physiol. Meas* 2002 Nov.;vol. 23(no 4):755–768. [PubMed: 12450274]
33. Moilanen P, Nicholson PH, Kilappa V, Cheng S, Timonen J. Assessment of the cortical bone thickness using ultrasonic guided waves: Modelling and in vitro study. *Ultrasound Med. Biol* 2007 Feb.;vol. 33(no 2):254–262. [PubMed: 17306696]
34. Lefebvre F, Deblock Y, Campistron P, Ahite D, Fabre JJ. Development of a new ultrasonic technique for bone and biomaterials in vitro characterization. *J. Biomed. Mater. Res* 2002;vol. 63(no 4):441–446. [PubMed: 12115753]

35. Lee KI, Yoon SW. Feasibility of bone assessment with leaky Lamb waves in bone phantoms and a bovine tibia. *J. Acoust. Soc. Amer* 2004 June;vol. 115(no 6):3210–3217. [PubMed: 15237845]
36. Muller M, Moilanen P, Bossy E, Nicholson P, Kilappa V, Timonen J, Talmant M, Cheng S, Laugier P. Comparison of three ultrasonic axial transmission methods for bone assessment. *Ultrasound Med. Biol* 2005 May;vol. 31(no 5):633–642. [PubMed: 15866413]
37. Bossy E, Talmant M, Laugier P. Three-dimensional simulations of ultrasonic axial transmission velocity measurement on cortical bone models. *J. Acoust. Soc. Amer* 2004;vol. 115(no 5 pt 1):2314–2324. [PubMed: 15139643]
38. Moilanen P, Nicholson PH, Kärkkäinen T, Wang Q, Timonen J, Cheng S. Assessment of the tibia using ultrasonic guided waves in pubertal girls. *Osteoporos. Int* 2003 Dec.;vol. 14(no 12):1020–1027. [PubMed: 14564455]
39. Tatarinov A, Sarvazyan N, Sarvazyan A. Use of multiple acoustic wave modes for assessment of long bones: Model study. *Ultrasonics* 2005 Aug.;vol. 43(no 8):672–680. [PubMed: 15982472]
40. Sarvazyan, A.; Tatarinov, A. Method and device for multiparametric ultrasonic assessment of bone conditions. U.S. Patent. 6 468 215 B1. 2001.
41. Viktorov, IA. Rayleigh and Lamb Waves, Physical Theory and Applications. New York: Plenum Press; 1967.
42. David, J.; Cheeke, N. Ultrasonic Waves. Boca Raton, FL: CRC Press; 2002.
43. Shumskii VV, Merten AA, Dzenis VV. Effect of the type of physical stress on the state of the tibial bones of highly trained athletes as measured by ultrasound. *Polymer Mechanics*, New York 1978 May;vol. 14(no 5):711–715.
44. Liu L, Maruno R, Mashimo T, Sanka K, Higuchi T, Hayashi K, Shirasaki Y, Mukai N, Saitoh S, Tokuyama K. Effects of physical training on cortical bone at midtibia atastarinov and sarvazyan: topography of acoustical properties of long bones 1297 sessed by peripheral QCT. *J. Appl. Physiol* 2003 Jan.;vol. 95(no 1):219–224. [PubMed: 12598486]
45. Dzene IY, Dzenis VV, Petukhova LI, Tatarinov AM, Yanson AY. Human tibia in the presence of coxarthrosis and fracture using exponential ultrasonic concentrators. *Mechanics Composite Materials*, New York 1980 June;vol. 16(no 6):724–728.
46. Tatarinov AM, Dubonos SL, Ianson KA, Oganov VS, Dzenis VV, Rakhmanov AS. Ultrasonic diagnosis of the changes in human tibia during 370-day antiorthostatic hypokinesia. *Biol Aviakosm Med* 1990 Mar.–Apr.;vol. 24(no 2):29–31. (ann. in English) (in Russian).
47. Dzenis VV, Merten AA, Shumskii VV. Effect of dosed physical loads on the state of the tibia of athletes according to ultrasound measurements. *Mechanics Composite Materials*, New York 1980 Sep.;vol. 15:570–574.
48. Merten AA, Dzenis VV, Tatarinov AM, Vitola MK, Shumskii VV. Influence of blood flow on the ultrasound velocity in the tibial bone. *Mechanics Composite Materials*, New York 1982 Oct.;vol. 18 (no 10):165–168.
49. Rubin CT, Pratt GW, Porter AL, Lanyon LE, Poss R. The use of ultrasound in vivo to determine acute change in the mechanical properties of bone following intense physical activity. *J. Biomech* 1987 July;vol. 20(no 7):723–727. [PubMed: 3308891]

Biographies

Alexey Tatarinov graduated from the Riga Technical University in 1980 and received a Ph.D. degree in biomechanics in 1989 at the Latvian Institute of Traumatology and Orthopedics (Riga, Latvia) for his work devoted to ultrasonic studies of long bones. In 1999, he joined Artann Laboratories (West Trenton, NJ) holding a position of senior research scientist and collaborating in projects supported by the NIH and NASA aiming development of new ultrasonic instrumentation for assessment of the bone condition. Recent years' activities also include application of ultrasound for monitoring the tissues hydration status and experiments

with ultrasonic standing waves in colloids in small volumes. He has published more than 30 scientific papers in the field of ultrasonic assessment of the skeletal system.

Armen Sarvazyan received a Ph.D. degree in biophysics in 1969 and a D.Sc. degree in bioacoustics in 1983 at the Institute of Biophysics of the USSR Academy of Science. From 1992 to 1998, he was a research professor in the Chemistry Department of Rutgers University, New Jersey. In 1995, he founded Artann Laboratories, a research company with the mission of early stage development and validation of original technologies and devices. Currently he is the chief scientist of Artann Laboratories and an adjunct professor in the Surgery Department at Robert Wood Johnson Medical School of the University of Medicine and Dentistry of New Jersey.

His current research interests include medical imaging, ultrasonic assessment of the skeletal system, nondestructive testing, and time reversal acoustics. He developed a new method of medical imaging termed mechanical (or tactile) imaging based on the reconstruction of internal tissue structures using surface stress data and another medical diagnostic technology, Shear Wave Elasticity Imaging, based on the use of the radiation force of focused ultrasonic beams for remotely testing tissue elasticity.

He holds more than 90 international patents on ultrasonic and biomechanical methods of medical diagnostics, has edited 6 books, and has published more than 200 research papers.

Fig. 1. Experimental ultrasonic setups and transducers used for obtaining axial velocity profiles in tibia. (a), (b), and (c) ultrasonic velocimeter UVM and point-contact transducers developed in RTU-LITO (Latvia) in 1980s; (d) BUSS, with manual scanning probe developed by Artann Laboratories.

Fig. 2. Topographical mapping of flexural wave velocity on unfolded surface of human tibia. (a) measurement scheme; (b) iso-velocity regions (see text); and (c) iso-velocity zones compared with muscles anchoring areas. [Reprinted from H. A. Yanson, V. V. Dzenis, and A. M. Tatarinov, *Ultrasound Investigations of Tubular Bones*. Riga: Zinatne Publishers, 1990, with permission from Zinatne Publishers.]

Fig. 3. Topographical maps of flexural wave velocity in proximal femurs of (a) 25-year-old male without pathology; (b) 56-year-old female with necrosis of the femoral head accompanying severe coxarthrosis; (1) area of femoral neck and (2) area of minor trochanter

Fig. 4.

In vivo testing of tibia by medial surface. (a) application of point-contact transducers with exponential waveguides on a fixed acoustic base; (b) acquisition by the length zones; and (c) axial velocity profiles evolving with human aging (according to data of [31]).

Fig. 5.

An example of bone atrophic changes in volunteer's tibia during prolonged antiorthostatic hypokinesia experiment ANOG-370 as revealed by flexural velocity profiles: 1-2-3—examination results at the beginning, in the middle, and at the final term of the experiment [Reprinted from H. A. Yanson, V. V. Dzenis, and A. M. Tatarinov, *Ultrasound Investigations of Tubular Bones*. Riga: Zinatne Publishers, 1990, with permission from Zinatne Publishers.

Fig. 6.

Dependence of flexural wave velocity on phantom thickness. (a) Results obtained at 100 kHz in tubular phantoms made of different polymers and modeling combined changes of material stiffness and the cortical thickness [Reprinted from A. Tatarinov, N. Sarvazyan, A. Sarvazyan, "Use of multiple acoustic wave modes for assessment of long bones: Model study," *Ultrasonics*, vol. 43, no. 8, pp. 672–680, 2005, with permission from Elsevier]; (b) experimental data dispersion corridor in human bones in vitro according to data of [29]; and (c) theoretical velocities ratio of flexural and Rayleigh waves C_f/C_R as function of thickness to wavelength ratio H/λ , where 1 to 4 are calculations for Poisson ratio gradually varied from 0.1 to 0.4.

Fig. 7.

Relative changes of flexural and longitudinal velocities at 100 and 500 kHz, respectively, in phantoms mimicking increasing porosity from the inner layer of compact bone. Measurement error is shown by rectangles height on the graphs. [Reprinted from A. Tatarinov, N. Sarvazyan, and A. Sarvazyan, "Use of multiple acoustic wave modes for assessment of long bones: Model study," *Ultrasonics*, vol. 43, no. 8, pp. 672–680, 2005, with permission from Elsevier.]

Fig. 8.

A block-diagram illustrating general principle of dual-frequency scanning bone ultrasonometer applying different wave modes identified as bulk longitudinal (L), surface (S), and guided (G).

Fig. 9.

Formation of 2-D waveform profile by processing signals acquired by axial scanning: (1) compilation of signals set as a video image in gray scale; (2) filtering and normalization; (3) selection of MIFS; and (4) enveloping and setting of thresholds applied to MIFS.

Fig. 10.
Changes of low frequency 2-D waveform profiles in tibia from norm to osteoporosis.

TABLE I

Flexural Wave Velocity C_F and Acoustical Anisotropy Coefficient K_C in Different Anatomical Regions of the Tibia.

Parameter	Anatomical region		
	Proximal metaphysis 3–15% length	Diaphysis 15–85% length	Distal metaphysis 85–97% length
C_f , km/s	0.99 ± 0.35	1.64 ± 0.18	1.10 ± 0.28
K_C	1.04 ± 0.14	1.26 ± 0.06	1.16 ± 0.15