Editorial

Ultrasonic bone assessment: "The time has come"

Bone is unique in its ability to maintain its strength in the presence of constant turnover. It has been established that there is gradual and relatively complete removal and replacement with new bone several times in a lifetime. The reparative pattern is constantly changing in order to maintain strength and is influenced by changes in general health, the presence of disease, and the degree of physical activity. To date, no method has been developed to measure the nature of lifetime changes in patterns during childhood and throughout older age [1]. Often the first indication that a problem exists is the occurrence of a fragility fracture, which is often associated with a high degree of morbidity and mortality.

Fracture risk is dependent on the strength of bone as well as other factors including tendency to fall. This latter aspect may be related to poor balance and eyesight, or to environmental obstacles like stray wires, defective pavements, and edges on carpeting [2]. Inherent strength of bone depends upon a host of multi-factorial components. Dual-energy X-ray absorptiometry (DXA), which measures the mass of the mineralized matrix at a given site (e.g., hip, spine, forearm) is currently the accepted indicator used to assess bone strength. It has been shown that bone mass has about the same predictive value for fracture as blood pressure has for stroke [3]. Stages of bone turnover have been studied by analysis of biochemical markers as bone is removed and reformed [4]. But there is as yet no reliable clinical method to assess the status of the internal trabecular structure of bone which normally contributes significantly to strength.

Notwithstanding the fact that X-ray densitometry is reasonably effective in bone mass assessment, osteoporosis remains one of the most prevalent undiagnosed and under-diagnosed diseases in the world today [5]. Among the reasons for this is that densitometry (i.e., DXA) is not a standard tool in a primary care physician's office. It does not lend itself to routine screening because of expense, inconvenience, and reticence concerning X-ray exposure, particularly in young adults and children.

It is estimated that approximately 20% of women with osteoporosis have unrecognized or untreated conditions that are capable of causing absorption of bone ("secondary osteoporosis") [6]. These may include thyroid, parathyroid, gastrointestinal disease, may be drug related or associated with a whole host of other possibilities [6]. Similarly for example, in adolescents and children, bone loss may be associated with metabolic conditions including hypogonadism, malnutrition, bulimia, and medication [7]. The ability to screen the quality of bone at any age would be expected to serve as preventive medicine by uncovering unrecognized causes and permit treatment of these conditions as well as to institute early appropriate therapy for osteoporosis.

In an attempt to address many of the above issues, ultrasound has been proposed as an alternative to DXA. It was first described for clinical bone assessment in 1984 by Langton et al. [8] although other researchers previously had studied the interaction of ultrasound with bone *in vitro* [9–13]. The great promise of ultrasound is related, in part, to the fact that as a mechanical wave it is affected by the biomechanical and biophysical properties of a bone through which it propagates. Prior research and recent observations have enlarged the scope of ultrasound's capability for detecting changes in bone and measuring a variety of features, including architectural structure of bone and mass. In view of these and other emerging observations to be mentioned regarding the application of ultrasound to assess bone quality in diagnosis, screening, and monitoring the course of osteoporosis, the time has come for greater focus on clinical and experimental research.

A number of studies have shown that both mass and architecture affect the propagation of ultrasound through bone [14–16]. In particular, it is reasonably well-established that the fundamental parameters associated with ultrasound measurement of bone, namely the velocity (e.g., speed of sound or SOS) and frequency-dependent attenuation (e.g., broadband ultrasound attenuation or BUA), are each mass and architecture dependent [14–19]. This is notable since the vast heterogeneous trabecular structure accounts for a significant part of the strength of bone and its ability to counter multidirectional stress [20]. Since osteoporosis is a surface absorptive phenomena, the earliest stages of trabecular bone loss are generally associated with trabecular discontinuity and thinning that alters the internal structure of bone [21]. Together, these facts imply that ultrasound may have the potential to provide a better estimate of bone strength beyond consideration of mass alone [16,22].

The frequency-dependent attenuation (such as characterized by BUA) is sensitive to both mass and structure [14]. Indeed BUA has been shown to be exquisitely sensitive to the architectural orientation of trabeculae, which after mass

is the main component of bone strength, explaining up to 35% of the observed variations [14,22,23]. The study by Gluer et al., for example, demonstrated about a 50% change in BUA solely by changing the direction of ultrasound propagation through a trabecular bone sample from along the axis of the compressive trabeculae to an axis which was orthogonal [23].

Notwithstanding the sensitivity of the acoustic parameters to architectural structure, ultrasound is also an excellent proxy for bone mass. Fig. 1 shows the correlation of an ultrasound based estimate of bone mass with a DXA determined estimate of bone mass at the calcaneus [18,19]. As may be seen from this clinical study involving 86 adult females, ultrasound is presently able to afford a high degree of correlation ($r = 0.88$, $P < 0.001$) with DXA determined BMD.

With respect to fracture risk clinical data, a number of prospective studies have clearly demonstrated that ultrasound is capable of predicting fractures about equally well as DXA [24–26]. For example in the study by Hans et al., the relative risk of hip fracture for one standard deviation reduction in calcaneal BUA and femoral neck BMD was found to be 2.0 and 1.9, respectively [24]. In addition, it has been shown that ultrasound is predictive for fractures, even when adjusted for BMD [27]. Moreover, the recent increasing shift in emphasis, away from "T-scores" towards "risk-based" assessment provides further support of the value of ultrasonic techniques [28,29]. For example, in a recent study by Kanis et al., ultrasound measurements at the fingers, in conjunction with other risk factors (including age), provided excellent estimates of the 10-year probabilities of clinical vertebral fractures [30]. One key aspect requiring further study is to determine if individuals identified by ultrasound as "high risk" (e.g., those individuals in the lowest quartile in ultrasound measurements) will benefit significantly by treatment with antiresorptive or other medications. In a related topic, ultrasound may have a role to play in addressing a current paradox in osteoporosis research, namely that although treatment with antiresorptive drugs produces only relatively modest increases in BMD (as determined by DXA), it leads to much larger and incommensurate reductions in fractures [31–33]. Since ultrasound propagation is dependent on mass and structure, and because antiresorptive therapy may affect both, ultrasonic methods may help to explain this current paradox.

Since there are other factors besides mass and architecture which may influence osteoporotic fracture risk, it will be necessary to examine the role that ultrasound may have in their non-invasive identification [34–37]. For example, fatigue damage has been postulated to play a role in the incidence of osteoporotic fractures [38]. To date, there have been only four studies which have evaluated the capability of ultrasound to assess fatigue damage, three demonstrating a positive conclusion [39–41] and one indicating a negative result [42]. Another key challenge in the use of ultrasound, which must also be the subject of further investigations, is to improve its precision in order to be able to reliably monitor the effects of treatment over the course of time [43,44].

The practical implication for ultrasound technology which can be embodied in devices that are highly portable and relatively inexpensive, and which may be utilized in an office type setting, is the increasing expansion of clinical bone assessment to the population. This is considered to be a major health priority by the Surgeon General of the United States in order to deal appropriately with an aging population for which the incidence of osteoporotic fractures is expected to increase significantly over the coming decades [45]. Indeed, ultrasound technology may very well open the door to being able to measure changes in bone quality, including mass, safely through all stages of life, including childhood, adolescence, and pre-, peri-, and post-menopausal periods. It might also be able to be used to study factors affecting peak bone mass, to elucidate the natural history of osteoporosis, and to obtain a better understanding of secondary osteoporosis.

An ultrasound device is not yet available to provide quantitative clinical measurements of the hip or spine, although some initial *in vitro* work has recently been reported [46]. Nevertheless, it is becoming increasingly clear that since osteoporosis is a body-wide condition, it is reasonable to believe, and indeed it has been demonstrated, that measurements at appendicular sites can provide excellent estimates of fracture risk elsewhere [24–27,30,47,48].

Although a good deal of research regarding ultrasound interactions with bone has already been done, and a number of devices commercialized, there is, in our opinion, every reason to believe that vital advances can be realized through additional studies. Hence, at this time, the enormous practical potential for an inexpensive, convenient, non-radiological, and office compatible approach and device, we believe, demands greater, prompt, and expanded focus and attention to basic and translational clinical investigations of ultrasonic bone assessment.
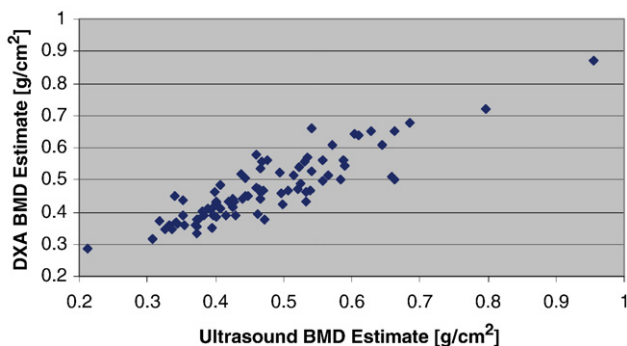
Fig. 1. Comparison of ultrasound BMD estimate with DXA BMD estimate.

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Robert S. Siffert
Jonathan J. Kaufman
Department of Orthopedics,
The Mount Sinai School of Medicine, New York, NY, USA

Jonathan J. Kaufman
CyberLogic, Inc., New York, NY, USA

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