2/28/94

STUDY OF OSTEOPOROTIC FRACTURES (V4)

Quantitative Ultrasound (QUS) of Bone

1. Introduction/overview of ultrasound measurements in SOF

Bone mass explains 30-90% of the variance in bone strength determined in vitro. However, bone mass is not the only determinant of bone strength: the geometry and quality of bone play vital roles Current methods of assessing bone health are inadequate. Parfitt postulated that bones are weakened by accumulation of fatigue damage, including microscopic fractures, as bone ages. In support of this hypothesis, Parfitt observed that women with vertebral fractures had greater bone age than women without fractures who had similar degrees of osteopenia.

The strength of trabecular bone also depends on the number and integrity of connections between trabecular rods and plates. Loss of these connections (decreased "connectivity") accounts for about 40% of the decrease in trabecular bone mass with aging in women. For the same bone mass, the strength of trabecular bone will vary inversely with its connectivity.

Ultrasound may be a useful measure of both the quality and quantity of bone. Two quantitative ultrasonic measurements in particular, sound velocity and broadband ultrasonic attenuation (BUA), may correlate with bone fragility. Ultrasonic transmission velocity, or speed of sound (SOS), is related to both the mass density and modulus of elasticity of a substance. The elastic modulus of a material depends upon a number of physical properties, and is believed to reflect fatigue damage and the size and spatial orientation of bone microstructure. BUA is thought to measure the attenuation of sound energy from scattering and absorption for a spectrum of frequencies (typically 0.2-0.6 MHz), but the exact correlates of BUA in bone remain unclear. Both SOS and BUA measurements correlate with bone strength in vitro, but in vivo the two measurements are not highly correlated with BMD at other sites, nor are they highly correlated to each other.

Clinical studies indicate these measures are lower in women who have osteoporotic fractures. Case-control and cross-sectional studies have found that women with hip, vertebral, and wrist fractures have lower calcaneus BUA results than normal controls. A single prospective study demonstrated that elderly women with lower BUA had a greater risk of hip fracture; whether ultrasound added information about the quality of bone in addition to measuring bone mass could not be determined as no measurements of bone mass were made. Heaney et.al. have reported that, compared to normal controls, speed of sound in the patella was significantly lower in women with vertebral fractures, and the difference was about as great as for bone density of the lumbar spine by antero-posterior (AP) dual photon absorptiometry of the spine. Unfortunately, this and other clinical studies of ultrasound were too small to determine whether ultrasound added to the prediction of fracture based on BMD alone, and no study has directly compared the predictive accuracy of ultrasound and BMD at the same site.

Besides its potential for assessing bone quality, quantitative ultrasound has several practical advantages over densitometry: it is quicker, less expensive, entails no radiation exposure, and portable devices may soon be available. Both ultrasonic velocity and BUA measurement are sufficiently reproducible, generally 0.5-1.0% and 2-4%, respectively, for clinical applications. If ultrasound predicts hip and other types of fractures as well as measurements of bone mass, it would be the best approach to screening women to assess their risks of fracture.

2. Equipment:

Quantitative ultrasound (QUS) measurements are carried out using the Walker Sonix UBA 575+ device (Walker Sonix Inc., Worcester, MA 01606). After taking a baseline reference measurement the subject's foot is placed in a water bath. After a wait period of about 5 minutes which serves to dissolve air bubbles and to thoroughly wet the skin of the heel to optimize coupling, the actual scan is taken. A matrix of 3x3 locations is measured and the final results are obtained by averaging of these 9 measurements which in turn are averages of signals obtained in the left-right and right-left ultrasound propagation directions.

The scanner allows for assessment of BUA as well as velocity parameters. BUA reflects the frequency dependence of ultrasound attenuation. Two different velocity parameters are calculated: Speed of Sound (SOS) and Ultrasound Velocity through Bone (UVB). (In our proposal, we refer to UVB as "velocity"). Whereas SOS measurements include a portion of ultrasonic velocity through soft tissue, UVB solely reflects ultrasound velocity when passing through the largely trabecular calcaneal bone. In addition the Walker Sonix device allows to store the raw data sampled by means of Fourier analysis from the transmitted ultrasound pulse. These raw data would enable us to calculate and investigate additional ultrasound parameters such as the average attenuation of ultrasound in the frequency range of 228-577 kHz based on the average absorption at 27 equidistant frequencies within that range.

For equipment or repair problems related to the UBA 575 system, the contacts at Walker Sonix are Phil Townsend (General Manager), and Jane Roach. They may be reached at (508) 752-1653.

3. Subject preparation

SOF participants should be informed that a painless, radiation-free measure of heel bone integrity will be done during Visit 4. The test will require removing the shoe and sock or stocking, placing the heel in a room temperature water bath, and then sitting quietly for approximately five minutes.

Each participant should be told not to use lotions, creams, powders or ointments on the lower extremities the day of her visit.

4. Measurement Procedure:

The protocol for obtaining BUA measurements is detailed in the Walker Sonix User's Manual, Section 3. Turn on the UBA 575 at least 15 minutes before performing any patient scans. Be sure to use only "All" liquid detergent in the water bath. It is preferable to prepare the water bath the day before it is use, but at the very least it should be prepared 30 minutes before use. Keep the water bath temperature at room temperature. It is not necessary to use a thermometer, but do check the temperature with your hand.

We will obtain ultrasound measurements on the same side as the SPX (Osteon) measurement performed at this visit. Each participant will have two measurements of the same heel. The foot should be removed from the water bath and repositioned between measurements. *If the second measure differs by more than ten units, obtain a third measurement.*

Some participants will want to know the results of their test and its interpretation. Indicate that low ultrasound measurements may be an indication of poor bone quality, but the exact meaning is unclear. It is important to emphasize that ultrasound measures of bone are still experimental and that we hope to determine the relationship between ultrasound measures and subsequent fractures in this study. Refrain from discussing the exact meaning of a specific BUA value. The vast majority of physicians, even those who are

knowledgeable about osteoporosis, will not be able to interpret the meaning of a specific BUA level.

5. Data storage and backup

a. Participant Identification.

Each SOF participant will be identified by her name (last name, first name, middle initial) and SOF ID number. Participant date of birth and female sex ("F") must also be entered, but the other patient identification fields (height, weight, address, etc.) found under "Patient Record" may be left blank.

b. Data Collection and Storage

If the machine is used for more than one study, be sure to maintain a unique identifier for each study in the patient ID field or some other field. You must be able to sort the participants by study.

Save the hard copy generated at the time the examination is done and place it in the participants folder. The current BUA reading, and any previous readings, are automatically stored in the system computer.

Record the two scores in the designated place on the participant's Visit 4 exam form.

c. Data Backup and Transfer

Back up the stored data base on floppy disk once a week. Follow the instructions given in Section 5 of the UBA 575 User's Manual.

Once a month, copy the entire SOF database onto a floppy disc and forward it to Katie Stone at the coordinating center.

6. Quality Control

a. Training and Certification of Operators

Although BUA measurements are relatively simple compared to SPA, to obtain reproducible results considerable attention must be paid to preparing the participant and positioning the foot. All trained staff who wish to be certified to perform BUA measurements on SOF participants must complete the following:

- Carefully read this section and the Walker Sonix operations manual
- Receive training from the SOF QC Officer or the designated staff who attended the central training session at the coordinating center
- Practice scanning with the acoustic phantoms, then on other staff or volunteers
- Perform at least one scan on a participant while being observed by the SOF QC Officer or designate

b. Phantom Scans

Each site will receive a set of acoustic phantoms from Walker Sonix. Phantom scans must be done in duplicate. Turn on the UBA 575 at least 15 minutes before performing the QC scans. Keep the water bath temperature roughly constant, preferably lukewarm, although room temperature is acceptable. Is is not necessary to use a thermometer, but do check the temperature with your hand.

In order to establish the site-specific error margins for your system, perform the following procedure during the first four weeks:

- For the first four weeks, scan the acoustic phantoms twice weekly. Over the four week period, a total of 32 scans will be obtained (two phantoms each scanned twice two times a week for four weeks)

- FAX the data (just the 32 BUA values and the dates obtained) to Claus Gueer, PhD, at (415) 502-2663.

- You will receive a QA log form on which you can enter your subsequent QA data, both in numeric as well as graphic form. This will also indicate the error margins and describe procedures if unforeseen problems occur.

After the initial four week period, both phantoms should be scanned on a weekly basis (two scans for each phantom each week) the results recorded in the QC log maintained at the site.

c. Cross Calibration

A study wide ("gold standard") phantom will be circulated to each site with instructions on it's use. The phantoms will be circulated periodically during the course of the the study as well.

d. Instrument quality control

The stability of the performance of the 575+ device will be monitored by phantom and patient scans. For both the standards and the subjects we will determine the normal and acceptable ranges of variability of QUS parameters over time. The centers are requested to repeat any measurement on the next day for which a deviation by more than three standard deviations of the mean has been observed. If the error remains the coordinating center and the manufacturer needs to be contacted. On a monthly basis the coordinating center will review the quality assurance data. Analyzing them through Shewhart charts will allow us to test violations of a subset of Western Electric rules. These rules are considered industry standards in the area of quality assurance of processes that need to be monitored for stable random performance over time [Nelson]. We have selected and slightly adapted a subset of four rules applicable to bone scanners:

1. One measurement beyond the three standard deviation confidence limit.
2. Two out of three measurements beyond the two standard deviation confidence limit on the same side of the mean.
3. Four out of five measurements beyond the one standard deviation confidence limit on the same side of the mean.
4. Nine consecutive measurements on the same side of the mean.

Any violation of these rules will lead to a maintenance check of the equipment by the manufacturer.

e. Reproducibility

In our cohort, long-term reproducibility obtained on 12 subjects with 5-8 measurements each over a period of 1 week to 1 month was 5.8% for BUA and 2.8% for UVB. Averaging the 2-3 measurements obtained on the same day improved precision to 4.0% for BUA and 2.0% for UVB. Reproducibility errors were defined as root mean square average of standard deviations (SD) of repeated measurements with interim repositioning.

7. Equipment maintenance

Routine maintenance of the UBA 575 is discussed in detail in the Walker Sonix UBA 575 Operations Manual, Section 8.

8. General remarks

Unlike bone densitometry, ultrasound scanners are fairly new devices and there is not much knowledge about what kind of problems will be encountered. Therefore, we encourage you to call not only Walker Sonix, but also the coordinating center when problems arise. Both Claus Glueer (415) 476-5551 and Doug Bauer (415) 597-9289 will be available to help you.

Oct 8, 1992

To: SOF and FIT sites performing quantitative ultrasound measurements

From: Doug Bauer, UCSF Coordinating Center

Re: Update on protocol

Several issues have come up during the first month of ultrasound scanning. The following protocol amendments (which apply to both SOF and FIT participants) are intended to improve the reproducibility of the measurement. Please review the following suggestions and discuss with the clinic staff performing the ultrasound exam.

1. If the first two measurements differ by more than 10 units, obtain a third measurement. Record the third measurement on the data collection form (the SOF form has a space for the third measurement, it should be recorded in the "comments" section of the FIT form). It is not necessary to obtain more than three measurements on a participant.

2. Except under usual circumstances, do not change the water bath after each participant. Sites which have changed the water bath for each participant (even if the water was set out overnight) have significantly greater problems with reproducibility than those sites where the water is changed on a daily basis. The only reason to change the water after each participant is hygienic and this concern may be addressed by the following procedures:

    a. Clean off the foot of each participant with a wet towel prior to scanning.
    b. Participants with open sores or wounds should not be scanned
    c. If asked, inform the participant that a disinfectant (detergent soap) is added to the water.
    d. Make up the water bath (including detergent) the night before it is used.
    e. If a participant insists on new water in the bath, make sure it stands for at least 20 minutes before using.

3. Remember to send your ultrasound data (including any QC phantom scans) to the coordinating center each month. We prefer that you send us an ASCII file which can be generated by entering the "Database" and then "Summary report" functions. Copy your data onto a formated disk and send to Katie Stone at the CC by the the fifth of each month.

4. QC logs are being developed and will be forwarded to each site when available.