Elderly Cohort Study Subjects Unable to Return for Follow-up Have Lower Bone Mass than Those Who Can Return

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Longitudinal studies of osteoporosis in older persons may underestimate bone loss because of a lack of follow-up measurements on subjects too frail to return. The authors addressed this possible bias as part of the population-based Framingham Study; in 1996-1997, they used quantitative ultrasound to assess the bone status of elderly subjects regardless of their ability to return to the clinic. Broadband ultrasound attenuation (BUA) and speed of sound of the calcaneus (heel) were measured in 433 subjects at the Framingham, Massachusetts, clinic and in 167 subjects at their homes or nursing homes. All ultrasound parameters were measured with intramachine coefficients of variation of <6.0%. The mean BUA for those subjects evaluated at the clinic was higher than for those measured at home (9.2% higher for men, p = 0.081; 8.6% higher for women, p = 0.034). After adjustment for age and weight, the differences in BUA were no longer significant. Among the elderly subjects participating in this longitudinal cohort study, those who were unable to return for follow-up were older, weighed less, and had a lower BUA than those who did return, suggesting that longitudinal studies of changes in bone mass with aging may underestimate the true population values.

Recent longitudinal studies have estimated that bone loss progresses unabated as persons continue to age (1-5). However, the bone loss estimates from these studies assume that the rates of change for those persons lost to follow-up are similar to the rates for those retained in the study. One major reason for loss to follow-up, particularly among elderly subjects, may be increased frailty leading to an inability to return to a clinic site. If these subjects have lower bone mass or greater rates of bone loss than those who are able to return, biased estimates of the rate of bone loss may result.

The availability of portable technologies to measure bone mass, such as quantitative ultrasound, affords the opportunity to perform measurements on persons who might otherwise be lost to follow-up in a longitudinal study. To test the hypothesis that subjects unable to return for follow-up visits have lower bone mass than those who are able to return, we used quantitative ultrasound of the calcaneus (heel) to compare bone status in a population-based group of elderly subjects who attended the Framingham, Massachusetts, clinic versus subjects who were unable to attend.

MATERIALS AND METHODS

Study sample

The Framingham Study began in 1948 with the primary goal of longitudinally evaluating risk factors for heart disease. A population-based, one-third sample of Framingham adults aged 28-60 years has been followed biennially for over 50 years (6-8), and nearly two-thirds of the original cohort members have died. The age and sex of surviving subjects follow the same proportions as those in the general Framingham population (1). Between 1996 and 1997, quantitative ultrasound measurements of the calcaneus were made on 446 of 605 clinic attendees (74 percent); 159 had no measurements taken because their regular Framingham clinic appointment preceded installation of the ultrasound equipment. In addition, 196 subjects had ultra-
sound measurements taken in their home or nursing home because of physical or cognitive limitations. Study subjects \( n = 19 \) for whom a valid weight was unattainable were excluded from the analysis; therefore, the final sample included 445 subjects from the clinic and 178 from homes or nursing homes. This study was approved by the appropriate institutional review board, and written informed consent was obtained for all study subjects.

**Ultrasound measurements**

In this study, ultrasound measurements were performed on the right calcaneous by using a Sahara clinical bone sonometer (Hologic, Inc., Bedford, Massachusetts), a water-free ultrasound device that contains a motorized caliper mechanism with a pair of sound transducers. Two of the parameters that the device measures are the velocity of the ultrasound signal as it passes through the heel (speed of sound (SOS), m/second) and the broadband ultrasound attenuation (BUA, dB/MHz). SOS is defined as the distance between the two opposing transducers divided by the time it takes for the signal to pass from one transducer, through the heel, to the other transducer. In the frequency range commonly used to assess bone (0.1–1 MHz), the total attenuation is approximately linearly proportional to the frequency.

BUA is defined as the slope of this attenuation versus frequency curve (9). For certain persons, the linear relation between frequency and attenuation, which is used to indicate the technical quality of the BUA measurement, is violated. A third parameter reported by the Sahara device, the quantitative ultrasound index (QUI), is a linear combination of the SOS and BUA measurements. Higher values for all three ultrasound measures indicate greater bone mass.

Two machines were used for this study, one at the Framingham clinic and the other during nursing home and home visits. An anatomic phantom (Hologic, Inc.) was used to track the performance of the machines over time. A subject’s right heel was scanned by using standard positioning unless there was a history of amputation, deformity, or pain in the right foot. Valid ultrasound measurements could not be obtained for 23 participants (11 clinic, 12 nursing home or home) for various reasons (subject bedridden, subject unable to position the foot correctly, values out of the range of plausibility, violation of the frequency-attenuation relation (indicating an invalid result)). Therefore, 433 valid scans were performed at the clinic and 167 in nursing homes or homes.

We tested reproducibility between the instrument used during the nursing home or home visit and the one used at the clinic by measuring 27 subjects aged 20–93 years on both machines on the same day. The coefficients of variation showed high reliability for all measures: the intermachine coefficients of variation for BUA, SOS, and QUI were 7.9 percent, 0.5 percent, and 5.3 percent, respectively. Neither the mean BUA (73.15; standard deviation (SD), 20.49) nor the mean SOS (1,557; SD, 47) measured by using the clinic machine was significantly different from the mean BUA (75.28; SD, 19.78; \( p = 0.19 \)) or the mean SOS (1,556; SD, 43; \( p = 0.76 \)) measured by using the home or nursing home machine. Therefore, no adjustments for machine used were made in the analyses. Based on duplicate, same-day measurements on 29 subjects with the clinic machine and on 19 subjects with the home visit machine, the intramachine coefficients of variation for BUA, SOS, and QUI were 5.3 percent, 0.4 percent, and 4.3 percent, respectively, for the clinic machine and 5.8 percent, 0.3 percent, and 3.7 percent, respectively, for the home visit machine.

For those subjects seen in the clinic, weight was measured by using a balance beam scale. For those subjects visited in the home or nursing home, a portable electronic scale was used.

**Statistical analysis**

We examined the three ultrasound measures, BUA, SOS, and QUI, for men and women separately. Subjects’ characteristics were compared by using Student’s \( t \) tests. A linear regression model was used to examine the relation of the ultrasound measurements between participants who attended the clinic and those visited at their home or nursing home after adjustment for age and weight by using the least squares means PROC GLM procedure (SAS/STAT software). This paper presents adjusted mean ultrasound values and reports exact \( p \) values. For all statistical analyses, we used release 6.12 of the SAS/STAT component of the SAS System (SAS Institute, Inc., Cary, North Carolina).

Subjects in our study who were unable to attend the Framingham clinic for ultrasound assessment would have been lost to follow-up had we not used a portable device. Based on the number of nursing home and home visit subjects in our study and on the observed difference in ultrasound measures between those subjects assessed on-site and those measured in their place of residence, we estimated the difference between the observed ultrasound measurements (for all subjects regardless of where the measurements were performed) and those that would have been observed had subjects who were measured in their home or nursing home been lost to follow-up. We used equation 1 to calculate a weighted average, which was the expected BUA of the population, knowing that a certain number of subjects otherwise
would have been lost to follow-up and that those subjects would have had a different mean BUA than subjects who were followed.

\[
BUA_{\text{total}} = \frac{(n_{\text{followed}} \times BUA_{\text{followed}}) + (n_{\text{lost to follow-up}} \times BUA_{\text{lost to follow-up}})}{n_{\text{followed}} + n_{\text{lost to follow-up}}} 
\]

(1)

RESULTS

The mean age of study participants (83.4 years; SD, 5.1; range, 76–103 years) was, on average, 1 year younger than that of nonparticipants \((p < 0.01)\). The weight \((p = 0.33)\) and gender \((p = 0.23)\) distributions of participants and nonparticipants were similar. Compared with the 190 men in our study, the 410 women were older \((p = 0.01)\) and weighed less \((p < 0.01)\), and a greater percentage of their ultrasound measurements were performed in their home or nursing home \((p = 0.01)\). Therefore, all subsequent analyses were stratified by gender.

The unadjusted mean values of age, weight, and the three ultrasound measures for men and women are shown in table 1. Men visited in their home or nursing home were significantly older \((p < 0.01)\) and weighed less \((p = 0.04)\) than men seen in the clinic. They also tended to have lower ultrasound measures, although these differences were not statistically significant \((p \text{ for BUA difference } = 0.08)\).

Women visited in their home or nursing home were also older \((p < 0.001)\), weighed less \((p < 0.001)\), and had 9 percent lower BUA measures \((p = 0.034)\) than women seen in the clinic. The multivariate model showed significant contributions by both age \((p < 0.05)\) and weight \((p < 0.001)\) and greatly reduced the differences between the two visit groups in the BUA measures among the women (table 1). Women measured at the clinic also had a higher mean SOS and mean QUI; however, these differences were not statistically significant.

The 28 percent of the study population whose ultrasound measurements were performed in their place of residence rather than at the clinic (21 percent of the men, 31 percent of the women) would have been lost to follow-up had our study used nonportable methods of bone assessment. Those who attended the clinic had a 9 percent higher mean BUA than those measured in their residence (men, \(p = 0.081\); women, \(p = 0.034\)). Based on the BUA differences and as a result of using equation 1, we estimate that had the home and nursing home participants not been followed, we would have overestimated the bone mass of the men by approximately 2 percent and that of the women by about 3 percent.

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<tr>
<th>TABLE 1. Characteristics of the ultrasound study sample by sex, according to whether ultrasound was performed at the clinic vs. at home or a nursing home, Framingham Study, Framingham, Massachusetts, 1996–1997</th>
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* \(p < 0.001\).
† SE, standard error; BUA, broadband ultrasound attenuation; SOS, speed of sound; QUI, quantitative ultrasound index.
‡ Clinic, \(n = 151\); nursing home or home visit, \(n = 39\).
§ 1 pound = 0.45 kg.
¶ Clinic, \(n = 282\); nursing home or home visit, \(n = 128\).
DISCUSSION

To our knowledge, this is the first study to measure bone mass in subjects participating in a cohort study regardless of their ability to return to a central facility for follow-up. Among the men and women who had calcaneal ultrasound measurements, those visited in their home or nursing home were older, weighed less, and had a lower BUA than those seen at the clinic. Because of a smaller sample of men, the differences did not reach statistical significance. Moreover, after adjustment for the effects of age and weight, the two groups visited did not show statistically significant differences regarding any of the ultrasound measures.

Previously, studies of longitudinal bone loss have had to rely on the use of nonportable measures of bone mass that require the patient to travel to a central site. Thus, some participants may be lost to follow-up because of their inability to return to the site. Past studies either have assumed that the amount of bone loss in subjects not returning for follow-up is similar to that in subjects who are followed or they have ignored this potential bias altogether. If the characteristics of subjects lost to follow-up differ significantly from those followed (e.g., lower bone mass), incorrect estimation of disease prevalence may result (10–12). Our study confirmed this hypothesis that older persons who are unable to leave their residences have lower BUA values than those who are able to attend a clinic. Therefore, longitudinal studies in which nonportable bone densitometry devices are used may be underestimating the true rate of bone loss in the elderly over time. The finding that BUA, but not SOS, differed between the two groups was not expected; however, the two parameters may be measuring different qualities of bone (13).

Based on the age and frailty of our cohort, a significant number of elderly subjects were not able to return for follow-up. Heel ultrasound parameters would have been overestimated in our cohort had we not captured these subjects. The 2–3 percent overestimation of bone mass that we found between those subjects who returned and those potentially lost to follow-up represents large, clinically meaningful differences. Similar projections could be used in other studies to determine how losses to follow-up might affect their estimates of bone loss. If the expected rate of attrition and the expected difference in bone density between those who are and are not followed are known, the weighted average can be used to estimate the effect of losing these subjects on the rate of loss of bone density.

The advent of portable, peripheral bone assessment technologies makes it feasible to assure more complete follow-up of subjects in cohort studies, and it minimizes potential biases from differential follow-up. Our findings suggest that bone loss may exceed that reported in previous studies, because subjects who are not followed up have lower bone mass than those who comprise the actively followed group.

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REFERENCES