

Quantitative Ultrasound at the Calcaneus in Premenopausal Women and Their Postmenopausal Mothers

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The aim of the study was to establish a relationship between mothers' and daughters' bone status. Forty-eight postmenopausal women and their 48 premenopausal daughters were evaluated. The analysis was made for the whole group and for two subgroups: 27 healthy mothers and their 27 daughters; and 21 fractured mothers and their 21 daughters. The subgroups were matched for age and years since menopause (YSM), and height, weight, and body mass index (BMI) did not differ significantly. Bone status was evaluated by ultrasound measurement at the heel using the Achilles system (Lunar, Madison, WI), which measures speed of sound (SOS [m/sec]) and broadband ultrasound attenuation (BUA [dB/MHz]). The Achilles software also calculates a stiffness index (SI [%]). Ultrasound values for BUA, SOS, stiffness index, and Z score were significantly lower both in mothers with previous fractures and in their daughters, compared with respective values in mothers without fractures and their daughters. Future values in daughters were predicted using a stepwise, multiple regression analysis separately in the whole group and in the two subgroups. Future values were predicted in two models taking into consideration mothers' present SOS, BUA, and age or present SOS, BUA, and YSM. In both models, daughters' present SOS, BUA, age, height, and weight were taken into consideration. Predictive values were found to be high for daughters of women having had fractures ($r = 0.72-0.87$, $p = 0.015-0.00007$, $SEE = 6.0-15.8$) and lower for all daughters studied ($r = 0.38-0.62$, $p = 0.03-0.0001$, $SEE = 8.8-21.5$). In daughters of mothers without past fractures, prediction was not possible. Heritability of ultrasound values in daughters of women with past fractures ranged between 52% and 76%, whereas in the whole group the range was 14%–40%. In conclusion, the data indicate that, as a group, the daughters of women with osteoporotic fracture are likely to be at an increased risk for fractures because they have relatively low ultrasound values. Their future ultrasound values can be predicted on the basis of a single ultrasound evaluation with the condition that there is a history of maternal past fracture. (Bone 29:79–83; 2001) © 2001 by Elsevier Science Inc. All rights reserved.

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Introduction

Osteoporosis is a disorder characterized by low bone density, microarchitectural deterioration in bone tissue, and a consequent increase in fracture risk.² Bone mass depends on several factors, including genetic predisposition, diet, physical activity, diseases known to affect bone metabolism, certain drugs, caffeine and alcohol intake, and smoking. Genetic factors play an important role in the pathogenesis of osteoporosis, and studies of twins^{4,15} and families^{13,16} suggest a strong genetic effect on bone mineral density (BMD) in adults. BMD in adults is under a genetic influence with up to 80% of the variance in BMD at the lumbar spine and femoral neck attributable to genetic factors.¹⁵

Some studies of mothers and daughters have shown the presence of a major genetic influence on bone mass.^{13,16} Bone densitometry methods, generally used in clinical studies, include dual-photon absorptiometry (DPA) and dual-energy X-ray absorptiometry (DXA). In the present study, bone status was assessed by quantitative ultrasound (QUS). This method has several advantages (lack of ionizing radiation, portable machines, relatively low costs) and provides data on bone mass and bone quality.^{5,12} Heritability of QUS parameters was evaluated in mother-daughter pairs by Danielson et al.,³ and in mono- and dizygotic twins by Howard et al.⁸ and Arden et al.¹ The aforementioned studies showed, in different degrees, heritability in QUS values.

If a strong relationship between the bone status in mothers and their daughters is confirmed by QUS measurement, the data obtained can be used to predict future ultrasound parameters in daughters. This hypothesis was evaluated in the present study. The aim of the study was to establish a relationship between the bone status of the mother and daughter.

Subjects and Methods

Subjects

The subjects studied were selected from 85 mother-daughter pairs who underwent ultrasound measurements in the outpatient osteoporotic clinic in the years 1994–1997. Prior to and during QUS measurements, none of the subjects was on medical therapy for osteoporosis (hormonal replacement therapy, calcitonin, bisphosphonates, fluoride), with the exception of vitamin D (400–1200 IU daily) and calcium supplementation. All women were interviewed by a physician to exclude subjects with diseases (hyperthyroidism, chronic liver or kidney disorders, stomach surgery) or on medication (corticosteroids, thyroid hormones, antacids, anticonvulsants) known to affect bone metabolism. Twenty-five mother-daughter pairs were excluded

Table 1. Clinical characteristics of subgroups studied

| | All mothers (n = 48) | Unfractured mothers (M-1) (n = 27) | Fractured mothers (M-2) (n = 21) | All daughters (n = 48) | Daughters of unfractured mothers (D-1) (n = 27) | Daughters of fractured mothers (D-2) (n = 21) |
|--------------------------|-------------------------|--|--|---------------------------|--|--|
| Age (years) | 70.9 ± 5.2 | 71.0 ± 4.5 | 70.8 ± 6.1 | 43.2 ± 5.7 | 42.6 ± 6.2 | 44.0 ± 5.0 |
| Weight (kg) | 64.0 ± 11.6 | 66.8 ± 10.3 | 60.4 ± 12.4 | 65.6 ± 12.5 | 65.9 ± 13.9 | 65.1 ± 10.8 |
| Height (cm) | 154.0 ± 4.9 | 155.1 ± 3.8 | 152.6 ± 5.8 | 161.0 ± 12.5 | 161.6 ± 4.6 | 160.3 ± 5.6 |
| BMI (kg/m ²) | 26.8 ± 4.3 | 27.5 ± 4.3 | 25.8 ± 4.4 | 25.3 ± 5.0 | 25.2 ± 5.5 | 25.3 ± 4.0 |
| YSM (years) | 20.1 ± 6.3 | 20.2 ± 5.2 | 19.8 ± 7.5 | — | — | — |

KEY: BMI, body mass index; YSM, years since menopause.

None of the variables studied differed significantly between groups of mothers (M-1 vs. M-2) and between groups of daughters (D-1 vs. D-2).

for any of the aforementioned reasons, and 12 other pairs were excluded for purposes of studying groups that were comparable in terms of age and years since menopause (YSM). The excluded mothers and daughters were significantly younger than the study population, and none had experienced previous fracture. Height, weight, and body mass index (BMI) did not differ significantly between excluded and included mother-daughter pairs. The remaining 48 pairs were accepted for further evaluation. All mothers had had natural menopause and all daughters were premenopausal. Each mother had one daughter without any problems affecting bone metabolism. The subjects were divided into two subgroups: 27 mothers without fracture and their daughters (subgroup M-1/D-1); and 21 mothers with past fracture and their daughters (subgroup M-2/D-2). All fractures (n = 44) were the result of minimal trauma involving a fall from a standing height or less during normal daily activity (wrist 18 cases, spine 10, shank 6, rib 5, foot 2, humerus 2, clavicle 1). All spine fractures were confirmed by radiography. Vertebral fracture was defined as a decrease in vertebral height of between 15% and 25% in either the anterior, central, or posterior height of the vertebral body.¹⁰ There were four wrist fractures in daughters (one daughter of a woman without fracture and three daughters of women with fractures). Clinical characteristics of the whole group and mother-daughter pairs are presented in **Table 1**. Further analysis of the population studied was performed in the whole group and in subgroups separately. The study was approved by the local ethics committee and informed consent was obtained.

Methods

Evaluation of the skeletal status was based on ultrasound measurements of the right (dominant) heel. In the case of a previous fracture within the lower extremity, the opposite calcaneus was measured. Speed of sound (SOS; m/sec) and broadband ultrasound attenuation (BUA; dB/MHz) were measured with the Achilles system (Lunar, Madison, WI). The Achilles software calculates a stiffness index (SI [%]) = $[0.67 \times \text{BUA} + 0.28 \times \text{SOS}] - 420$ that does not express biomechanical stiffness but rather is an attempt by the manufacturer to derive a clinically useful index combining BUA and SOS.⁶ Z score was derived from the value of SI and expressed as the number of standard deviations (SDs) from the mean value for an age-matched population.

The device was calibrated daily in accordance with the manufacturer's recommendations. All measurements were made by the same operator. Short-term in vivo precision was established on the basis of 60 measurements in ten healthy women (five premenopausal and five postmenopausal women). In each of them, five measurements with repositioning of the calcaneus were made. The percentage coefficient of variation (CV%) and standardized (sCV%) values were: 4.25% and 12.85% for BUA;

0.37% and 4.23% for SOS; and 3.12% and 4.86% for SI, respectively. CV% and sCV% were calculated using the following formulas, respectively: $\text{CV\%} = (\text{SD}/\text{mean}) \times 100$; $\text{sCV\%} = \text{CV\%}/(4 \text{ SD}/\text{mean})$.

Statistical Analysis

All calculations were done using the Statistica program run on an IBM PC. Student's *t*-test was used to compare the mean values between the subgroups, and the unpaired Student's *t*-test was used to compare the values for mother-daughter pairs. To compare data between mothers and daughters varying in age or menopausal status, the Z score of the SI (the standard deviation from the expected population mean value of bone measurement) was used. Correlation coefficients were calculated using Pearson product-moment correlation. Multiple, stepwise regression analysis was used to predict future ultrasound values in daughters and to examine heritability of ultrasound parameters in daughters. Heritability was expressed in percent with the use of r^2 (e.g., if $r = 0.5$, then heritability was 0.25 or 25%).

Results

Ultrasound results are presented in **Table 2**. BUA, SOS, SI, and Z score were significantly lower in mothers with past fracture compared with mothers without fractures, and also in daughters of women with fractures compared to daughters of women without fractures.

For M-2/D-2 pairs, several significant (SI: $r = 0.48$, $p = 0.028$; Z score: $r = 0.51$, $p = 0.017$) and borderline significant coefficients of correlation (SOS: $r = 0.41$, $p = 0.066$; BUA: $r = 0.41$, $p = 0.067$) between values for mothers and daughters were obtained. In M-1/D-1 pairs, no significant coefficients of correlation for SOS, BUA, SI, and Z score were noted ($r = -0.03$ – 0.18 , $p = 0.36$ – 0.85). When all subjects were analyzed, mothers' BUA and SI correlated significantly with daughters' BUA and SI ($r = 0.42$, $p = 0.03$ and $r = 0.33$, $p = 0.02$, respectively), whereas SOS in mothers and daughters correlated only on borderline significant level ($r = 0.27$, $p = 0.057$).

To obtain models predicting future ultrasound values in daughters, multiple stepwise linear regression analyses were made using two different groups of variables. In the first model, daughters' SOS and BUA values were predicted with the use of mothers' present SOS, BUA, and age, and daughters' present SOS, BUA, age, height, and weight. In the second model, daughters' SOS and BUA values were predicted with the use of mothers' present SOS, BUA, and YSM, and daughters' present SOS, BUA, age, height, and weight.

Two significant equations were obtained in the first model and one equation in the second model for M-2/D-2 pairs (**Table 3**). In these predictive equations, mothers' ultrasound values and

Table 2. Ultrasound values (mean ± SD)

| | SOS (m/s) | BUA (dB/MHz) | SI (%) | Z-score |
|--|---------------|--------------|-------------|-------------|
| All mothers n = 48 | 1478.0 ± 22.6 | 95.9 ± 10.9 | 58.9 ± 14.0 | -1.3 ± 1.1 |
| Unfractured mothers (M - 1), n = 27 | 1484.3 ± 22.5 | 99.5 ± 9.5 | 63.7 ± 13.8 | -0.92 ± 1.1 |
| Fractured mothers (M - 2), n = 21 | 1469.7 ± 20.3 | 91.2 ± 11.1 | 52.7 ± 12.0 | -1.8 ± 1.04 |
| <i>p</i> ^a | <0.05 | <0.001 | <0.001 | <0.001 |
| All daughters n = 48 | 1526 ± 27.2 | 113.4 ± 11.4 | 83.2 ± 14.5 | -0.4 ± 1.3 |
| Daughters of unfractured mothers (D-1), n = 27 | 1536.4 ± 22.9 | 118.3 ± 9.7 | 89.0 ± 12.0 | 0.1 ± 1.2 |
| Daughters of fractured mothers (D-2), n = 21 | 1513.6 ± 27.4 | 107.1 ± 10.4 | 75.8 ± 14.3 | -1.1 ± 1.2 |
| <i>p</i> ^b | <0.01 | <0.001 | <0.01 | <0.01 |

KEY: BVA, broadband ultrasound attenuation; SI, stiffness index; SOS, speed of sound.

^aSignificant differences between groups of mothers (M - 1 vs. M - 2).

^bSignificant differences between groups of daughters (D - 1 vs. D - 2).

present age or YSM did not have a significant influence on future SOS and BUA values in their daughters. This indicates that, on the basis of these calculations, it is possible to predict future ultrasound values when there is a history of maternal osteoporotic fracture.

For M-1/D-1 pairs, no significant predictive equations were obtained. Future ultrasound values were also predicted for all daughters. The equations are given in **Table 4**. Predictability of SOS and BUA values was much lower for all daughters than for daughters of mothers with osteoporotic fractures. Contrary to equations obtained for the subgroup with fractured mothers, in equations calculated for the whole population studied, maternal age and YSM had a significant effect on daughters' future ultrasound values. It was found that future ultrasound values could be predicted in 52%–76% of daughters of women with past fracture, and in only 14%–40% of daughters from the whole population studied.

Discussion

The present study demonstrates the possibility of predicting future values of QUS parameters in daughters of women with a history of osteoporotic fracture. This prediction is the most important finding derived from the study.

As expected, lower QUS values were noted in fractured compared with unfractured mothers. The values were also found to be lower in daughters of fractured mothers compared with daughters of healthy mothers. The findings are similar to those reported by Seeman et al.¹⁶ In that study, BMD in healthy mothers had higher values in comparison to women with osteoporosis of the lumbar spine, femoral neck, and femoral midshaft by 33%, 24%, and 15%, respectively. When compared with normal premenopausal women, the daughters of women with osteoporosis had lower BMD at these sites by 7%, 5%, and 3%, respectively (the difference was significant only for spine BMD).

In contrast, Hansen et al.⁷ observed no significant difference in bone mass at any skeletal site between daughters of women with either peripheral or spinal fractures and daughters of women without fractures. These investigators concluded that peak bone mass is hereditary in the distal forearm, lumbar spine, and proximal femur, but mother-daughter similarities could account for only 16% of the variability in daughters' bone mass. Ulrich et al.¹⁷ evaluated BMD in mother-daughter pairs in relation to lifetime exercise, lifetime milk consumption, and calcium supplements. There were no significant correlations between paired mothers' and daughters' BMD when crude data were analyzed (similar to our correlation analysis in mothers without fracture and their daughters), but after adjustment for mothers' age, body weight, and hormone replacement therapy, and daughters' lifetime weight-bearing exercise, peripheral BMD was positively correlated within pairs ($r = 0.44$, $p < 0.05$). No significant correlation was observed for total body BMD and axial BMD. These findings suggest that some environmental factors, such as calcium consumption, hormone therapy, or exercise level, may change the genetic relationship in mother-daughter pairs.

In our study we did not analyze the influence of the aforementioned factors, but such investigations are necessary in the future. In a study by Jouanny et al.,⁹ children's BMD was assessed in relation to parents' BMD and environmental factors. Children's BMD was significantly correlated with BMD in mothers, fathers, and both parents. The child's BMI, father's BMD, and daily calcium intake, and mother's BMD, BMI, and body fat accounted for 41.4% of the variance in the child's BMD. Lutz and Tesar¹⁴ compared BMD in daughters and their pre- and postmenopausal mothers. Several coefficients of correlation between mother-daughter pairs were obtained, and when mothers were classified as pre- or postmenopausal, these relationships were stronger for premenopausal mothers and their daughters than for postmenopausal mothers and their daughters, except for the trochanter. It is not possible to compare their results with our

Table 3. Equations predicting future ultrasound values in daughters of mothers with past osteoporotic fractures

| Regression equation | <i>r</i> | <i>p</i> | SEE |
|--|----------|----------|------|
| First model: $SOS/FD = 769.1 + 0.68 \times SOS/D - 1.17 \times BUA/D - 1.03 \times height/D - 0.59 \times age/D$ | 0.72 | 0.015 | 15.8 |
| First model: $BUA/FD = -168.7 + 0.28 \times SOS/D - 0.84 \times height/D - 0.57 \times age/FD + 0.19 \times weight/D$ | 0.87 | 0.00007 | 6.0 |
| Second model: $BUA/FD = -100.6 + 0.25 \times SOS/D - 1.08 \times height/D - 0.15 \times YSM/FD + 0.29 \times weight/FD - 0.57 \times age/FD$ | 0.87 | 0.0004 | 6.4 |

First model: Prediction of daughter's future (FD) ultrasound value taking into consideration mother's age; second model: prediction of daughter's future (FD) ultrasound value taking into consideration mother's YSM. SOS/FD and BUA/FD: predicted daughter's future ultrasound values; age/FD and YSM/FD: daughter's age or YSM in the future for which ultrasound values can be predicted; SOS/D, BUA/D, height/D, weight/D, age/D: daughter's present values. See Tables 1 and 2 for abbreviation.

Table 4. Equations predicting future ultrasound values in all daughters

| Regression equation | <i>r</i> | <i>p</i> | SEE |
|--|----------|----------|------|
| First model: $SOS/FD = 1282.0 + 0.29 \times SOS/D - 1.17 \times height/D - 0.88 \times age/M$ | 0.43 | 0.03 | 21.1 |
| First model: $BUA/FD = 57.1 + 0.1 \times SOS/D - 0.74 \times age/M - 0.63 \times height/D + 0.35 \times BUA/D$ | 0.63 | 0.00015 | 8.8 |
| $BUA/FD = 32.8 + 0.11 \times SOS/D - 0.72 \times height/D - 0.34 \times YSM/M + 0.31 \times BUA/D - 0.30 \times age/D$ | 0.62 | 0.00095 | 9.1 |
| Second model: $SOS/FD = 1257.8 + 0.27 \times SOS/D - 1.17 \times height/D$ | 0.38 | 0.03 | 21.5 |

First model: Prediction of daughter's future (FD) ultrasound value taking into consideration mother's age; second model: prediction of daughter's future (FD) ultrasound value taking into consideration mother's YSM. SOS/FD and BUA/FD: predicted daughter's future ultrasound values; age/FD and YSM/FD: daughter's age or YSM in the future for which ultrasound values can be predicted; SOS/D, BUA/D, height/D, weight/D, age/D: daughter's present values; age/M and YSM/M: present age or YSM in mother. See Tables 1 and 2 for abbreviations.

data because we studied only postmenopausal mothers. However, the results suggest that the nature of inheritance of bone mass in women may have at least two components, one influencing the level of peak bone mass and one related to bone loss at menopause. Krall and Dawson-Hughes¹¹ analyzed familial similarity in BMD among 160 adult members of 40 families consisting of both parents, one son and one daughter. Correlation coefficients between midparent Z score and offspring Z score of BMD ranged between 0.22 and 0.52 for daughters and 0.27 and 0.58 for sons. Adjustment of bone density for age, height, weight, and significant lifestyle or environmental factors yielded heritability of between 0.46 and 0.62, which means that 46%–62% of the variance in bone density was attributable to heredity.

In a study by Danielson et al.³ the familial resemblance was examined in 207 mother-daughter pairs using BMD and QUS measurements. Three groups of daughters were recruited based on their maternal history of fracture, low BMD without fracture, or normal BMD. Total hip and femoral neck bone mass was significantly lower among daughters, particularly in premenopausal daughters of mothers with established osteoporosis, as compared with daughters of mothers at lower risk of osteoporosis, and calcaneal BUA did not differ across daughter groups. The investigators found evidence of heritability for calcaneal BUA (53%) only among postmenopausal daughters, which is different from other data suggesting stronger familial relationships between younger (i.e., premenopausal) women.

Heritability of ultrasound values in our study varied from 14% to 76%, and was in the range of values obtained for BMD measurements by other investigators.^{7,9,14,17} In a study by Danielson et al.,³ conducted using quantitative ultrasound, heritability for calcaneal BUA (53%) was also evident among postmenopausal daughters. They made no attempt to predict future ultrasound values in daughters. They merely established correlations between mother-daughter pairs and heritability, expressed as percentages. We tested a hypothesis that future values in daughters can be predicted when there is a strong relationship between the values in mothers and daughters. The hypothesis was confirmed in several equations (Tables 3 and 4).

Lack of correlation between ultrasound values in healthy mothers and their daughters and the presence of such correlation between fractured mothers and their daughters indicate a stronger genetic relationship in the latter subgroup, which was also confirmed by equations predicting future bone status in daughters. It was not possible to obtain any significant equation for daughters of healthy mothers. No equation revealed a significant influence of mothers' age, YSM, or ultrasound values on daughters' future SOS and BUA values. It thus appears that future ultrasound values can be predicted on the basis of a single ultrasound evaluation in daughters of women with osteoporotic fractures. It is difficult to explain why strong relationships exist only between mothers with past fractures and their daughters. It

could be due to differences in so-called genes candidates (i.e., in the different potential genes that have been associated with osteoporosis). Several genes are involved in the process controlling bone status,¹⁸ and in our study no genetic testing was done, so this hypothesis cannot be confirmed. Despite this limitation, it can be pointed out that strong relationships existing in fractured mothers and their daughters confirm the need for detailed, clinical evaluation of daughters with a maternal history of fractures because of the high risk of future osteoporotic fracture in this population.

Conclusions

The data indicate that, as a group, daughters of women with osteoporotic fractures are likely to be at increased risk for fractures because they have relatively low ultrasound values. Their future ultrasound values can be predicted using equations that carry clinically and economically valuable information. The data obtained need to be confirmed prospectively and further investigations are in progress. Currently, however, equations predicting future values of ultrasound parameters provide a unique potential for improving the clinical evaluation of daughters of women with past osteoporotic fractures.

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