

Heel Ultrasound as a Predictor of Appendicular Bone Mineral Density

Rebecca G. Frederick, Louisiana State University, Baton Rouge, LA

E. Barry Moser, Louisiana State University, Baton Rouge, LA

Ellen R. Brooks, Northwestern University Medical School, Chicago, IL

And Woman's Health Research Institute, Woman's Hospital, Baton Rouge, LA.

Abstract

Emerging medical technologies for use in the area of skeletal assessment of bone mineral density (BMD) are on the rise, while at the same time the aging population and the incidence of osteoporosis both increase. A new technology, quantitative peripheral heel ultrasound (Sahara Clinical Bone Sonometer, Hologic), measures variables related to sound transmission through the calcaneus. This study evaluates the utility of heel ultrasound in predicting appendicular BMD as determined by dual energy x-ray absorptiometry (Hologic QDR 4500) at the hip in Caucasian females, 65-81 years old. Computations were performed on an IBM 300PL personal computer with Microsoft® Windows NT® Workstation and SAS® software. Proc Reg was used for variable selection and model building, while Proc CanCorr provided canonical correlations of the data. There is an adequate correlation that exists for predicting the T-score (a diagnostic criterion of the World Health Organization) for the total femur (hip) and the femoral neck (hip) of women using the heel ultrasound T-score, broadband attenuation of sound waves (BUA), speed of sound (SOS), stiffness index (QUI), age and body mass index (BMI). This paper discusses the selection of predictor variables and the evaluation of the model.

Introduction

The measurement of bone mineral density (BMD = gm/cm³) and bone mineral content (BMC = grams) using dual energy X-ray absorptiometry (DXA), is a widely accepted technology that affords low radiation exposure, quick scanning time, and quantitative data from which to rule out bone loss (Genant, et al, 1996). Two anatomical sites, the lumbar spine and proximal femur (hip) are usually measured using DXA.

Although the DXA has been accepted as the gold standard for evaluating area bone density, other methods have more recently been developed that may provide additional information on bone microarchitecture. This information is particularly significant with respect to ascertaining fracture risk. Quantitative peripheral heel ultrasound of the calcaneus (heel) uses imperceptible sound waves that are passed through the heel. This equipment is portable, whereas DXA is not, and may therefore make heel ultrasound a useful tool for mass (community-based) screening of the high-risk postmenopausal population. Further, it may be a more cost-effective means for identifying those individuals who should be referred for detailed osteoporosis evaluation (Sim, Stone, Johansen, and Evans, 2000; Stewart, 2000). Since the diagnostic criterion for osteoporosis is based upon DXA, further evaluation of the relationship between the variables measured with the two differing technologies is warranted.

Purpose

The purpose of this investigation was to assess the strength of the predictive relationship of heel ultrasound for variables from hip DXA scanning, particularly the T-score. Our specific focus was on the older Caucasian postmenopausal female (aged 65-81 years), since older women are at high risk for continued slow bone loss (Riggs, Khosla, and Melton, 1998).

Methods

The Institutional Review Board approved this study and the informed consent of all subjects was obtained. One hundred and sixty-seven women were enrolled in this study. Anthropometric data that included height, weight, and body mass index (BMI = wt in kg/ht in m²) were measured. Age was also included as an explanatory variable, since it is a potentially confounding variable due to the decline that occurs in bone density with aging.

DXA scanning of the hip and heel ultrasound measurements were performed on the same day. Since the left hip was scanned by DXA, all duplicate heel ultrasound measurements were made using the left heel. The left lower leg (and thus heel) was positioned, using a goniometer, such that there was a 90 degree angle at the knee.

Variables that were measured using the differing technologies are:

Table 1: Quantitative Heel Ultrasound

- Broadband attenuation of sound waves (BUA)
- Speed of Sound (SOS)
- Stiffness index of bone (QUI)
- T-score (World Health Organization diagnostic criterion for determination of a patients' current BMD versus their expected peak BMD. This comparison is delineated into three categories: normal, low BMD, or osteoporosis. The T-score criterion is based upon DXA data)

Table 2: DXA of the Proximal Femur-Hip

- Total Femur BMD, BMC, and T-score (defined above)
- Femoral Neck BMD, BMC, and T-score (defined above)

Analysis

Regression Methods

The data was imported into SAS from an Excel spreadsheet. Proc Univariate was used to review the data and identify any potential errors and outliers in data entry. Proc Reg, with the stepwise option, was then used to determine which DXA variable (of the hip) was most related to the heel ultrasound

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variables. These models used age and BMI. An example of a typical model was:

Exhibit 1: Typical Model of Data

Model	$Y = \beta_0 + \alpha_1 X_1 + \dots + \alpha_k X_k + \beta_2 X_2 + \beta_3 X_3 + \varepsilon$			
Where:				
Y	:	Hip Measurements		
β_0	:	Intercept		
$\alpha_1, \dots, \alpha_k$	:	Coefficients of Heel Measurements		
$X_1, \dots, X_k$	:	Heel Measurements		
β_2	:	Coefficients of Age		
X_2	:	Age of individual		
β_3	:	Coefficients of Body Mass Index		
X_3	:	Body Mass Index (BMI)		
ε	:	Error		

Stepwise regression, at the default significance level of 0.15, was performed to identify potential models of explanatory variables. A typical model statement was:

Exhibit 2: Hip Measurements of SAS Regression Procedure

```
Proc Reg;
Model LT_TOTF2 = US_T_S US_QUI US_BUA US_SOS BMI AGE
/ selection=stepwise;
Run;
```

Polynomial Interactions were also assessed, however, none were found to be statistically important for any of the explanatory variables using either heel measurement.

The results from the stepwise regressions did not identify the same model with respect to the heel measurements. The first explanatory measure, at $\alpha = 0.15$, selected the total femur T-score, then the BMI, and finally, age. For the femoral neck T-score, using BMI and age as covariates, the procedure selected heel BUA. The total model R^2 for total femur T-score was 0.4959, and for the femoral neck T-score was 0.3670.

Table 3: Hip Procedure for Regression with the Stepwise Option

Variable Entered	Partial R^2	Model R^2	F Value	Prob > F
Total Femur T-Score				
T-score	0.3012	0.3012	69.39	<.0001
BMI	0.1832	0.4844	56.86	<.0001
Age	0.0115	0.4959	3.26	0.0590
Femoral Neck T-Score				
BUA	0.2514	0.2514	54.06	<.0001
BMI	0.0906	0.3420	22.04	<.0001
Age	0.0250	0.3670	6.27	0.0133

Regression Diagnostics

Partial regression plots are used to assess the major role that an explanatory variable, X_k , plays in the model given that all of other explanatory variables under consideration are already in the model. Both the response variable, Y , and the explanatory variable, X_k , are regressed against the other explanatory variables in the model and the residuals are obtained from each fit. Thus, a partial regression plot for the total femur T-score, Y , and the heel T-score, X_1 , consists of a plot of the Y residuals, $\varepsilon(Y | X_2 X_3)$ against the X_1 residuals, $\varepsilon(X_1 | X_2 X_3)$ where X_2 and X_3 are BMI and Age, respectively. For the three-variable model there are three partial leverage plots of the residuals of the total femur T-score versus residuals from each of the predictors. These graphics appear in figure 1:

Figure 1: Partial Regression Plot 1 of T-Score

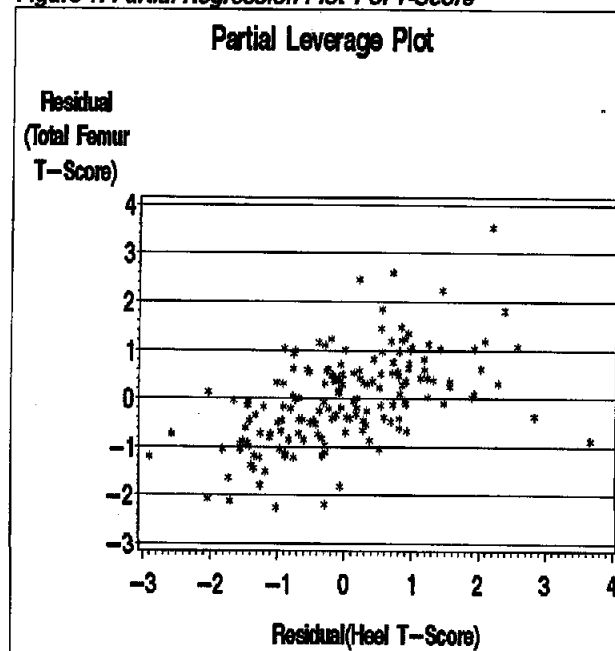


Figure 2: Partial Regression Plot 2 of Body Mass Index

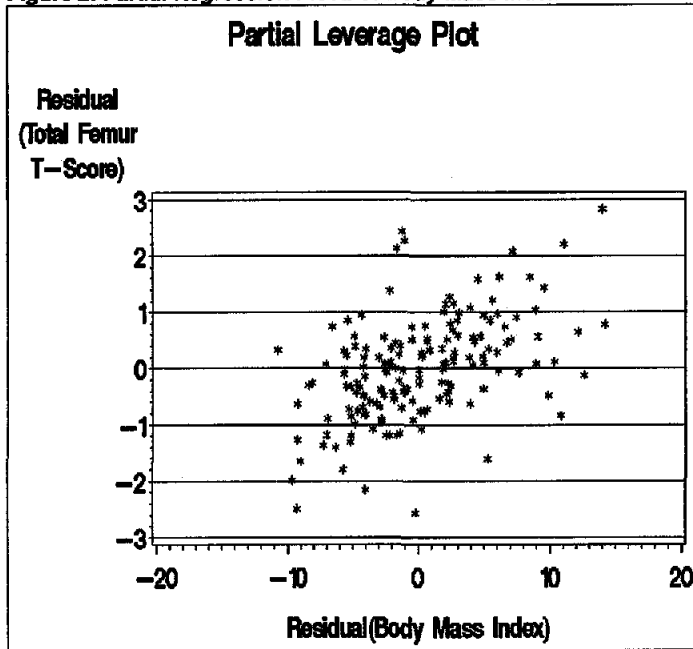
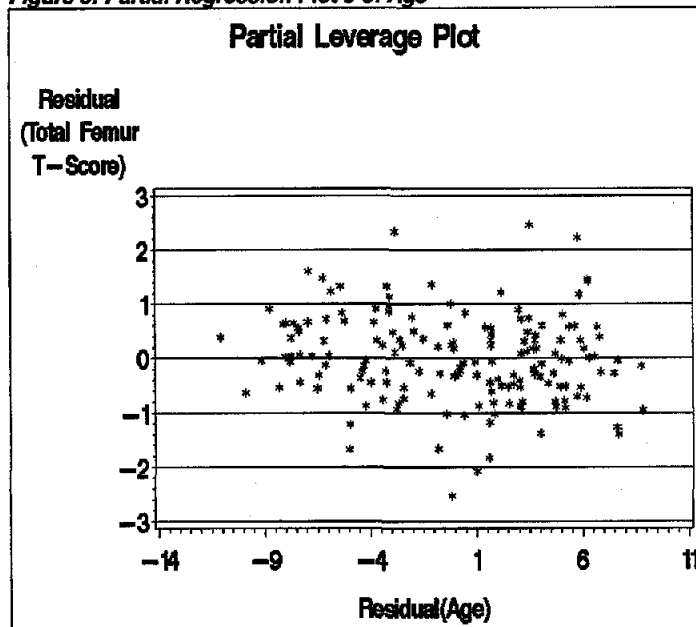


Figure 3: Partial Regression Plot 3 of Age



From the three partial regression plots, Figures 1-3, the T-score of the hip and the BMI support relationships with femur T-score. This occurred even when the other explanatory variables are in the model. Yet, age contributed little to no additional information for predicting femur T-score when the heel ultrasound T-score and BMI were in the model.

Canonical Correlation

Canonical correlation (CANCORR procedure) was used to perform canonical correlation, partial canonical correlation, and canonical redundancy analysis. It was used to analyze the relationship between two sets of variables (linear sets of both the

hip and heel measurements). Canonical correlation is a type of correlation that is a variation on the concept of multiple regression and correlation analysis. The procedure was written as:

Exhibit 3: SAS Procedure of Canonical Correlations

```
PROC CANCORR ALL
  Vprefix=Heel Vname="Measurement from the Heel"
  Wprefix=Hip Wname="Measurement from the Hip";
VAR US_T_S US_SOS US_BUA US_QUI;
WITH LT_TOTF2 LT_FEM_3;
RUN;
```

Proc CANCORR has an option ALL, (Exhibit 3) that displays the correlations among the original heel and hip measurements. The correlations within the heel measurement were in the range of 0.9978 to 0.9184. The correlation within the hip measurements was 0.8878. The procedure also displays the correlations between the set of X (heel) variables, and the set of Y (hip) variables. The correlations between the heel and hip measurements were smaller than the within set of correlations as expected.

The largest correlation was between the heel BUA and the hip T-score ($r=0.5391$). The smallest correlation was between the heel SOS and the T-score for the femoral neck ($r=0.4443$). The correlations for the within and between measurements are shown below:

Table 4: Correlations Within the Heel Measurements

	T-score	SOS	BUA	QUI
T-score	1.0000	0.9893	0.9659	0.9977
SOS	0.9893	1.0000	0.9184	0.9876
BUA	0.9659	0.9184	1.0000	0.9638
QUI	0.9977	0.9876	0.9638	1.0000

Table 5: Correlations Within Hip Measurements

	Total Femur T-Score	Femoral Neck T-Score
Total Femur T-Score	1.000	0.8878
Femoral Neck T-Score	0.8878	1.000

Table 6: Correlations Between Heel and Hip Measurements

	Total Femur T-Score	Femoral Neck T-Score
Heel T-score	0.5195	0.4717
SOS	0.4894	0.4443
BUA	0.5391	0.4893
QUI	0.5154	0.4673

Table 7: Canonical Correlations & Multivariate Statistics

	Canonical Correlation	Eigenvalue	Probability > F	Wilks' Lambda
1	0.556299	0.4490	<.0001	<.0001
2	0.026812	0.0007	0.9898	

As seen in Table 7, the first canonical correlation was 0.556 ($p < 0.0001$), which indicates a definite linear association between hip and heel measurements, however the magnitude of the correlation was not very high, indicating that predictions would not be precise. Since the measurements were in the same units, the standardized coefficients were almost equivalent to the raw coefficients (Tables 8 & 9).

Table 8: Standardized Canonical Coefficients for Heel Measurements

	Heel 1	Heel 2
Heel T-score	13.2139	-37.8835
SOS	-8.7556	18.1880
BUA	-3.8424	10.5013
QUI	0.0934	9.9315

Table 9: Standardized Canonical Coefficients for Hip Measurements

	Hip 1	Hip 2
Total Femur T-score	0.8973	1.9790
Femoral Neck T-score	0.1141	-2.1700

Since canonical variable 1 was significant, it was interpreted. The standardized canonical heel measurement variable 1 was a weighted difference between T-score with SOS and BUA:

- a very strong positive value of T-score = 13.2139
- a strong negative value of SOS = -8.7556
- a negative value of BUA = -3.8424
- a very small positive value of QUI = 0.0934.

The first canonical variable of standardized hip measurements was largely dominated by the femoral neck T-score since we have:

- a positive value of total femur T-score = 0.897
- a small positive value of femoral neck T-score = 0.114

The canonical redundancy analysis did not indicate a good relationship between the opposite canonical variables and their own canonical variables (the hip and heel measurement). The standardized proportion of variance that explained the heel and hip measurement was 0.2553 and 0.2844, respectively. Even after they were added together, the cumulative proportions were only 0.2554 and 0.2845, respectively.

Table 10: Canonical Redundancy Analysis

	Standardized Variance of Heel Measurement		Standardized Variance of Hip Measurement	
	Proportion	Cumulative Proportion	Proportion	Cumulative Proportion
1	0.2553	0.2553	0.2844	0.2844
2	0.0000	0.2554	0.0001	0.2845

Conclusion

The strongest correlation relationship observed between the heel and hip, using differing technologies, was between the total femur T-score and heel BUA. Bone is known to attenuate high frequency (ultrasonic) sound waves, with those patients who are older and are osteoporotic, such that a lower BUA reading is obtained. Consistent with this, we were able to demonstrate that a direct correlation existed between the hip T-score and heel BUA measurement. Simply stated, the lower the hip T-score, the lower the heel BUA measurement.

Although a statistical relationship existed between variables from the heel and hip, using diverse technologies, a statistically robust predictive relationship was not observed. Anatomic site discordance in BMD, using DXA, is a well-known phenomenon that has made DXA interpretation for diagnosis somewhat confusing to the clinician (Mulder, Michaeli, Flaster, Siris, 2000; Faulkner, von Stetten, Miller, 1999). This problem was therefore already an issue (we assessed heel and hip) and confounded further by the use of different technologies to quantify the BMD.

Although two ultrasound variables (BUA and SOS) explained some of the variance in the hip data, BMI and age were also selected in the stepwise regression model for the total femur T-score. Both weight (reflected in the BMI ratio) and age were known to have an effect on BMD. When we controlled for age and BMI, BUA was the strongest predictor for the femoral neck T-score.

Quantitative peripheral ultrasound does not strongly explain and account for the variance in the total femur and femoral neck T-score, as quantified by DXA. Further studies are required to better understand the biological, corresponding statistical relationship, the clinical utility and interpretation of quantitative peripheral ultrasound of the heel and how those results relate to the gold standard, DXA.

References

- Borland, Russell. Running Microsoft® Word for Windows® 95, Microsoft Press, A Division of Microsoft Corporation, 1995.
- Faulkner, K.G., von Stetten, E., Miller, P. Discordance in patient classification using T-scores. *Journal of Clinical Densitometry*. 2:343-350, 1999.
- Genant, H., Engelke, K., Fuerst, T., Gluer, C., Grampp, S., Harris, S.T., Jergas, M., Lang, T., Lu, Y., Majumdar, S., Mathur, A., Takada, M. Non invasive assessment of bone mineral and structure: state of the art. *Journal of Bone and Mineral Research*. 11:707-730, 1996.
- Microsoft® Windows® 95 Resource Kit, Microsoft Press, A Division of Microsoft Corporation, 1995
- Mulder, J.E., Michaeli, D., Flaster E.R., Siris, E. Comparison of bone mineral density of the phalanges, lumbar spine, hip, and forearm for the assessment of osteoporosis in postmenopausal women. *Journal of Clinical Densitometry*. 3:373-381, 2000.
- Riggs, B.L., Khosla, S., Melton, L.J. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. *Journal of Bone and Mineral Research*. 13:763-773, 1998.
- SAS Institute, Inc. SAS/INSIGHT® User's Guide, Version 6, Second Edition. Cary, NC: SAS Institute, Inc., 1993.
- SAS Institute, Inc. SAS/GRAPH® Software: Usage, Version 6 Edition, First Edition. Cary, NC: SAS Institute, Inc., 1991.
- SAS Institute, Inc. SAS/STAT™ Guide for Personal Computers, Version 6 Edition. Cary, NC: SAS Institute, Inc., 1987.
- SAS Institute, Inc. SAS® Procedures Guide for Personal Computers, Version 6 Edition. Cary, NC: SAS Institute, Inc., 1985.
- SAS Institute, Inc. SAS® Online Doc, Version 8 Edition. Cary, NC: SAS Institute, Inc., 1999.
- Sim, M.F., Stone, M., Johansen, A., Evans, W. Cost effectiveness analysis of BMD referral for DXA using ultrasound as a selective pre-screen in a group of women with low trauma Colles' fractures. *Technology and Health Care Journal*. 8:277-284, 2000.
- Stewart, R.A. Quantitative ultrasound or clinical risk-factors-which best identifies women at risk of osteoporosis? *British Journal of Radiology*. 73:165-171, 2000.
- Virgile, Robert. Efficiency—Improving the Performance of Your SAS® Applications, Cary, NC SAS Institute, Inc., 1998.

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Contact Information

Your comments and questions are valued and encouraged. Contact the authors at:

Rebecca Frederick or E. Barry Moser

Louisiana State University
Dept. of Experimental Statistics
161 Agric. Admin. Bldg.
Baton Rouge, LA 70803
Work Phone: 225-578-8303
Fax Phone: 225-578-8344
Email: rfrederi@lsu.edu
bmoser@lsu.edu

Ellen R. Brooks, Ph.D.

Northwestern University Medical School-Division
of Cardiology and Department of Preventive
Medicine,
Chicago, IL 60611
Work Phone: 312-908-0020
Fax Phone: 312-908-0031
Email: e-brooks3@northwestern.edu