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Menarchal status and calf circumference predict calcaneal ultrasound measurements in girls

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Abstract

Purpose— The purpose of this study was to predict calcaneal QUS measurements in healthy adolescent females as a function of anthropometric measures, pubertal stage and menarchal status.

Methods— This was a secondary data analysis from a two-year intervention designed to increase bone accretion. Simple Pearson correlation and Spearman's rank correlation analyses, followed by linear stepwise regression analyses were conducted. Setting: 12 middle schools. Participants: 672 female students, baseline; 587 students at 18 months. Main outcome measure: Calcaneal stiffness index (SI) by quantitative ultrasound.

Results— Eighty percent of the subjects were premenarchal at baseline; 33% at 18 months. Although SI correlated with self-assessed pubic hair ($\rho = 0.21$) and menarchal status ($\rho = 0.23$, $p < 0.01$ for both) at baseline, the model for predicting SI included menarchal status, not pubic hair, and calf circumference, controlling for BMI ($R^2 = 0.22$, $P < 0.01$). At 18 months, SI correlated with self-assessed pubic hair ($\rho = 0.21$) and menarchal status ($\rho = 0.25$, $p < 0.01$ for both). The best model to predict SI included calf circumference and pubic hair stage ($R^2 = 0.14$, $p < 0.01$), and not menarchal status as 67% of the subjects at 18 months were postmenarchal.

Conclusions— In research assessing calcaneal SI in groups of adolescents, assessment of pubertal stage could be replaced with menarchal status and calf circumference when the majority of subjects are premenarchal. When the majority is postmenarchal, pubic hair stage and calf circumference together may be used to assess for pubertal maturation without menstrual status.

Keywords

female; puberty; self-assessment; IMPACT

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Introduction

Ten million Americans have osteoporosis, characterized by compromised bone strength predisposing to fracture. Another 18 million have reduced bone mass making them at risk for osteoporosis.¹ An osteoporotic hip fracture is associated with increased mortality or a significantly reduced quality of life.² Osteoporosis is a disease manifest primarily of the elderly yet its onset may be in the second decade of life if optimal peak bone mass is not achieved.^{3–5} During adolescence, 50% of adult bone mass is accumulated. Bone mass, as assessed by bone mineral density (BMD) measurements, correlates better with pubertal stage than chronologic age.⁷ Bone mass is also a function of body weight and regional muscle mass, which increase during puberty.⁵ A relationship between calf muscle area and changes in BMD of the lower extremities in peripubertal children, and calf circumference and calcaneal ultrasound measurements in elderly females has been reported.^{5,6} In published reports relating bone mineral measurements to pubertal stage, there is no consistency in the assessment of pubertal stage.⁸ Nine reports related bone mineral measurements to estimates of pubertal stage, and each had a unique method of categorizing pubertal stage 3,5,7,9–14 including: composite scores from self-assessment of pubertal stage, 7,12–14 composite scores from both self-assessment and clinician examination, 9 use of age range only and not pubertal assessment, 3 no report of pubertal stage, 10 and a physical examination.^{5, 11} There is a need to improve the description of the relationship between bone mineral measurements, pubertal stage and anthropometric measurements in females.

Methods to measure the effects of interventions on bone mineralization include dual-energy x-ray absorptiometry (DXA), peripheral quantitative computerized tomography (Pqct), and quantitative ultrasound (QUS) measurements. Each method has advantages and disadvantages.¹⁵ Calcaneal QUS measurements can predict the risk of osteoporotic fracture in postmenopausal women as well as DXA bone mineral density (BMD) measurements.¹⁶ Calcaneal QUS measurements correlate with BMD and Pqct measurements and are related to the strength of trabecular bone in adults. 9,10,17 QUS appears to measure components of bone strength and structure, such as elasticity and trabecular separation that are independent of BMD.^{17,18} QUS measurements are inexpensive; the equipment is portable, easy to use, and does not involve ionizing radiation, making this method attractive for studying large groups of subjects. Of the eight studies referred to in the previous paragraph, two report related pubertal stage to calcaneal QUS measurements.^{9, 10} One report, in abstract form, combined males and females. The other used an unconventional method of estimating pubertal stage: breast stage and pubic hair stage were self-assessed and combined into one stage. When there was discrepancy between the pubic hair and breast stage, greater emphasis was placed on the breast development. Neither included menstrual status of the subjects. In longitudinal studies, the peak accrual of bone mineral in pubertal females occurs in the perimenarchal period.^{4,7,19} There is a need to describe QUS measurements as a function of pubertal stage that includes menstrual status.

The purpose of this study was to predict calcaneal QUS measurements in healthy adolescent females as a function of anthropometric measures, pubertal stage and menarchal status.

Methods

Study design

This paper is a secondary analysis from the IMPACT study (Incorporating More Physical Activity and Calcium in Teens), a two-year, school-based health education intervention designed to increase bone accretion by promoting calcium containing foods and physical activity in middle school girls. IMPACT made use of a group randomized cohort design where sixth grade girls were assessed at baseline and 18-months after completion of the intervention.²⁰ For the present analyses, we utilized data from girls in both treatment and control conditions, making adjustments to the 18-month results to account for treatment effects. The results of treatment intervention are presented elsewhere.²¹ The results presented here focus on the relationship between QUS measurements and estimates of pubertal stage and menstrual status.

Seven hundred eighteen girls in sixth grade from 12 middle schools were enrolled at baseline with 72% non-Hispanic white, 12% Hispanic, 5% African-American and 4% Asian. After enrollment, students were excluded from having a QUS measurement if they had a medical condition or were using a medication that interfered with bone accretion, or had a recent injury that kept them out of physical education class for > 2 weeks (see Figure). Six hundred seventy-two had valid QUS measurements. At 18 months, 606 subjects were contacted and 587 had valid QUS measurements. Parental consent and student assent were obtained before participation in the measurements. The study was approved by the Human Subjects Review Committees at the University of Texas-Houston, School of Public Health, and Baylor College of Medicine.

Anthropometric measures

Weight was measured using a top-loading digital scale (SECA 770 or Tanita BWB-800S), and height was measured with standard stadiometers. Calibration weights were used to calibrate the scales up to 200 lbs. before each set of measurements. The calf circumference was measured in centimeters, at the largest portion of the calf using a standard girth tape measure. The measurements were made in centimeters and the protocol was to conduct intra-rater and inter-rater reliability on students chosen randomly from those seen on a particular day at each school. The repeat measurements were not consecutive; the examiner measured at least five other students before the designated students underwent repeated measurements. Twenty-three subjects had repeat measurements. Thirteen of these assessed intra-rater reliability; 10 rated inter-rater reliability. The intra-rater correlation was 0.98 (mean difference = 0.0 cm, SEM 0.15 cm). The inter-rater correlation was 0.94, mean difference, 0.35 cm, SEM 0.45 cm). Body mass index (BMI) was calculated using the standard formula (kg/meters^2). Underweight was defined at BMI < 5%; normal 5–85%; at-risk for overweight 85–95%, and overweight > 95%.²²

Pubertal stage assessment, menarchal status, and age

The use of self-assessment of breast and pubic hair stage has been used for 26 years.⁸ One previous study demonstrated that older drawings of breast and pubic hair stages were not valid for self-assessment compared to physician rating of breast and pubic hair development.

Clearer drawings which one of the authors used in a previous project, were used in this study.^{23, 24} Self-assessment of breast and pubic hair stage was done using these line drawings of the five stages, with a text description under each drawing, and recorded as one of five breast stages and one of five pubic hair stages.^{23, 24} Menstrual status (premenarchal or postmenarchal) was reported in response to a question posed by a female research staff member during a one-on-one interview. Students provided demographic information and medication history during the interview.

Calcaneal QUS measurements

Calcaneal QUS measurements were obtained using a Lunar Achilles+ ultrasonometer (Lunar Corporation, Madison, WI). The Achilles+ ultrasonometer measured two primary variables: 1) the velocity (speed of sound, SOS in m/sec); and 2) frequency attenuation (broadband ultrasound attenuation, BUA in dB/MHz) of a sound wave as it traveled through the calcaneus and combined the SOS and BUA values to construct the Stiffness Index (SI). The SI is constructed by normalizing BUA and SOS through subtracting the lowest observable values (50dB/MHz and 1380 m/sec) from each and then scaling the resultant values. The SI is the sum of the scaled and normalized BUA and SOS values. The formula used was $SI = (0.67 * BUA + 0.28 * SOS) - 420.25$. The calcaneal SI correlates well ($r = 0.78$) with total body BMD in adolescents, with heel BMD ($r = 0.80$), and with spine BMD ($r = 0.77$).²⁶ The Achilles+ ultrasonometer has high precision ($CV = 2\%$) in adults and comparable precision in children ($CV = 1.8\%$).^{26, 27} Each student was measured once on the right heel. SI measurements that were either four standard deviations below or two standard deviations above (SI below 32 or above 132) the mean for young healthy women in the U.S., based on the manufacturer's reference data were excluded.^{25, 28}

Data analysis

The Statistical Package for Social Sciences (SPSS for Windows, version 11.0.1, SPSS, Inc., Chicago, Ill.) was used for analyses. This analysis was exploratory, not hypothesis-driven. Descriptive statistics were calculated as mean $\pm$ SD or frequencies. Simple Pearson correlations were calculated between the dependent variable (SI) and key independent variables (anthropometric variables) for continuous variables, and Spearman's rank (ρ) correlations were calculated for categorical variables (pubertal stage, menstrual and treatment group status). Collinearity between independent variables was assessed using Pearson or Spearman's correlations. The independent variables were chosen based on their known association with bone density measurements in the literature (see Background and Discussion). Models to predict SI were constructed using linear regression with backward elimination and linear regression with forward inclusion. If it met criteria for elimination (0.1 probability of F), it was removed. After the first variable was removed, the variable with the smallest partial correlation with the dependent variable was considered next. The process was continued until no variable met the elimination criteria. The variables in the final analysis are those listed in Table 2. For analysis of the 18-month data, treatment condition (control or intervention status) was entered as a covariate in the model, to control for intervention differences between the groups. Significance was defined as $p < 0.05$.

Results

Baseline

Baseline key independent variables and the SI (mean and SD) are in Table 1. Valid QUS measurements were obtained for 672 subjects (see Figure). The largest percentage of subjects was in stage 2, as expected, based on chronologic age. The number of subjects with valid QUS measurements was 677.

Calf circumference and BMI correlated with each other ($r=0.89$, $p < 0.01$), and with SI ($r=0.45$, 0.40 , respectively, $p<0.01$ for both). SI was related to self-assessed pubic hair ($\rho = 0.21$), self-assessed breast development ($\rho=0.19$), and menstrual status ($\rho = 0.23$, $p<0.001$). Menstrual status predicted SI ($p<0.01$) while adjusting for BMI. The best model for predicting SI included menarchal status and calf circumference, controlling for BMI and age ($R^2 = 0.22$, $P < 0.01$, see Table 2). SI was unrelated to treatment status group assignment ($p=0.93$). The results of the forward regression analyses are shown in Table 2. Similar results ensued from the backward regression analysis. The final model used includes those variables listed in Table 2. The only significant predictor variables for SI were calf circumference and menstrual status.

18-month follow-up

Pearson correlations between pubertal variables, age, height, weight, calf circumference, and BMI were similar to those at baseline and are not included here. The Spearman rank correlations between SI and menarchal status, self-assessed pubic hair and breast stage were: $\rho = 0.21$, $\rho = 0.25$, and 0.17 , respectively, $p<0.001$ for all. Regression analyses showed that the best predictors of SI at 18 months, when 67% of the subjects were postmenarchal, were calf circumference, self-assessed pubic hair stage, and treatment group status ($R^2 = 0.14$, $p<0.001$). When self-assessed pubic hair and intervention group were excluded from the analysis, the best model to predict SI included calf circumference and menarchal status ($R^2 = 0.11$, $p=0.015$).

Discussion

This study demonstrates that menstrual status has higher levels of predictive power in the assessment of bone mass by ultrasound than pubertal stage when the majority of subjects are premenarchal and a lower predictive power when the majority of subjects are postmenarchal. In the latter, menarchal status was still predictive of SI, albeit less so than estimated pubic hair stage. Because of the high correlation between pubertal stage and menarchal status, investigators can consider selecting one or the other in regression modeling because of multicollinearity.

The results of this study suggest that the two-category, menarchal status (pre vs. post-menarchal) simplifies the description of maturational processes in adolescent girls, while still significantly predicting SI. The implications for research in assessment of calcaneal SI in pubertal females are considerable: methods to assess pubertal maturation could be reduced to asking about menarchal status and measuring an anthropometric variable, such as calf circumference; consent forms could be simplified, avoiding the delicate subject of

assessment of breast and possibly pubic hair staging; and data collection time and costs could be reduced by eliminating the need for one-on-one interviews. In doing so, participation rates may be enhanced; in addition, it could be easier to conduct such studies in more public health settings such as schools. The model presented here, if replicated, provides evidence for the use of menarchal status and calf circumference to predict calcaneal SI in studies involving large groups of adolescents. Specifically this could apply to research designed to study the effects of physical activity on the calcaneal SI of groups of pubertal subjects.

The finding of higher calcaneal SI measurements in postmenarchal versus premenarchal females was expected.^{13, 19, 29} The rates of BMD and calcium accretion are greatest in the perimenarchal period and may overshadow the increases that occur between each pubertal stage.^{4,6, 19, 27} Regarding the question of why there might be different models for predicting SI in pre and post-menarchal subjects, the effect of weight as a determinant of BMD may be tempered in mid to late puberty compared to early puberty.⁷ Serum estrogen concentrations are higher in postmenarchal females and the effect of estrogen on the periosteal sensitivity of bone to mechanical loading, and therefore bone apposition, may be a function of serum estrogen concentration, mediated by alpha and beta estrogen receptors and IGF-. Periosteal apposition of new bone may vary in early versus late pubertal subjects.³⁰ Finally, fractional intestinal calcium absorption differs in pre- and post-menarchal females.³¹

The higher correlation between calf circumference and SI measurements, compared to BMI, suggests that calf muscle mass, possibly as a reflection of increased weight-bearing physical activity, has a more specific mechanical impact on the calcaneus, than does body weight. Slemenda reported a relationship between calf muscle area and changes in BMD in peripubertal children.⁵ Stewart et al reported the functional significance of calf muscle mass related to time spent standing and a lower risk of falling in elderly females.⁶ The mechanostat theory posits that developmental changes in bone strength are secondary to increasing loads generated by larger muscle forces.³² As the gastrocnemius and soleus muscles insert as the Achilles tendon on the calcaneus, if the mechanostat theory is true, physical activity requiring repeated calf muscle force generation would expect to increase calcaneal SI measurements. Whether calf circumference and its relationship to bone mass/strength is a function of physical activity increasing the muscle mass, or genetically, those programmed to have greater muscle mass are likely to exert greater force on bone and therefore, have greater bone mass remains to be established. When controlling for lean mass, the effect of physical activity on femoral neck BMD was lost in a group of adolescents followed longitudinally.³³ Regarding the relative contribution of age, height, weight, BMI, calf circumference, menarchal, and pubertal stage to predicting SI, these variables are so highly intercorrelated it was expected that with one or two in the model the others would be insignificant, as they were.

This study has limitations, including the use of: self-reported data, ultrasound rather than DXA measurements, and a largely white non-Hispanic, healthy, female population. Caution is suggested in applying these models to more diverse ethnic groups and cannot be advocated for adolescent females with chronic illness. Self-reported data were used for

assessment of pubertal stage. The large number of subjects precluded clinician assessment of pubertal stage. Self-assessment can be valid in estimating breast and pubic stage, albeit not as accurate as direct assessment by a clinician, and has been used for 26 years.^{8, 24} The drawings used in this study for self-assessment were clearer to the investigators than those used previously by one of the investigators, however, the kappa coefficient for breast stage and pubic hair stage against direct physician assessment of breast and pubic hair stage were 0.34 and 0.37, respectively, in the authors' previous work.²⁴ The previous study included a multiethnic sample with 45% European-American, 40% African American, 10% Hispanic and 5% Asian subjects, unlike the current study group which was predominantly white non-Hispanic. The drawings to self-assess pubertal stage have not been validated on a group of predominantly white adolescents. Indirect assessment of sexual maturity stages remains a limitation in research involving pubertal subjects. Data from the current study are consistent with the type of pubertal stage distribution and menarchal status expected at this age.³⁴

The model proposed here (i.e. calf circumference and menarchal status) accounted for 22% and 11% of the variance in calcaneal SI at baseline and 18 months, respectively. One other model to predict calcaneal ultrasound measures is reported: Lehtonen-Veromaa et al reported a model that accounted for 12 and 8% of calcaneal bone ultrasound attenuation and speed of sound, respectively.⁹ Other authors have reported a higher variance accounted for in their prediction models of bone mineral measurements using DXA. Horlick, et al developed a model that included age, ethnicity, height and weight and accounted for 96% of the variance in total body bone mineral content measured in 578 girls ranging from pubertal stages 1–5.¹² With these variables included, pubertal stage did not significantly contribute to the variance. Boot, et al using forward regression analysis and independent variables similar to those described here, reported that weight and pubertal stage accounted for 80% of the lumbar spine and 85% of the total body BMD variance in females aged 4–20 years.¹³ Other investigators have reported similar results.³⁵ Ultrasound has developed increased acceptance in evaluating bone strength and density, as investigators have verified its applicability in assessing bone health in pediatrics.^{27,36, 37} Although the other models account for a larger variance of the bone mineral measurement using DXA, this model offers an improvement over the previous model to predict calcaneal SI as discussed above. The magnitude of the relationships between SI and the predictor variables is modest, and future models should attempt to improve the prediction of SI. To the extent that calcaneal SI assesses components of bone strength and structure, such as elasticity and trabecular separation that are independent of BMD, then models to improve prediction of calcaneal SI can add to the our overall understanding of factors that influence bone health in healthy adolescent females.

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Baseline

18 months

Figure.
Flow diagram of the number of study participants.

Table 1

Mean (SD) values for SI by baseline and follow-up characteristics.

	Baseline		Follow-up	
Variable	n	SI mean $\pm$ SD	n	SI mean $\pm$ SD
Overweight status (BMI)				
Underweight	26	63.12S SD=10.37	15	71.87 SD=9.15
Normal (5–85 th)	476	71.41 SD=13.22	421	85.87 SD=14.91
At-Risk for Overweight	100	79.49 SD=15.05	85	89.65 SD=16.14
Overweight	69	86.05 SD=17.68	60	92.09 SD=15.97
Pubertal Pubic Hair Stage				
1	70	70.21 SD=13.80	1	70.05 SD= -
2	251	70.44 SD=13.94	45	75.58 SD=11.45
3	192	75.83 SD=13.42	132	84.74 SD=15.67
4	127	78.43 SD=16.12	264	87.08 SD=14.29
5	23	76.83 SD=21.26	142	91.22 SD=16.37
Pubertal Breast Size				
1	141	69.27 SD=14.21	9	77.86 SD=12.23
2	389	73.63 SD=14.10	185	82.99 SD=14.73
3	111	79.11 SD=15.89	281	88.25 SD=15.39
4	13	74.90 SD=20.66	78	88.55 SD=16.17
5	7	79.53 SD=17.20	31	91.64 SD=14.34
Menarche Status				
Premenarchal	544	72.08 SD=13.77	189	81.81 SD=13.38
Postmenarchal	124	80.66 SD=17.25	397	88.96 SD=15.78
Age (years)				
10	14	69.25 SD=17.78	-	
11	557	73.84 SD=14.84	-	
12	98	74.12 SD=14.91	195	84.82 SD=15.79
13	2	75.11 SD=19.27	378	87.42 SD=14.97
14	1	70.79 SD= -	12	93.90 SD=19.10
15	-		1	68.16 SD= -
16	-			
Ethnicity/Race				
White	480	73.14 SD=14.29	423	86.18 SD=14.98
Hispanic	79	73.80 SD=16.18	73	83.17 SD=14.34
Black	37	82.04 SD=16.95	25	98.68 SD=14.34
Asian/PI	25	72.79 SD=16.94	22	87.45 SD=18.72
Native American	6	80.97 SD=18.97	5	87.19 SD=18.96
Other	44	72.92 SD=13.56	38	89.63 SD=16.73

SI = Stiffness Index

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Table 2

Baseline Regression Analysis of the relationship between Stiffness Index and key Independent Variables

Variable	Standardized Beta	t	Sig
Calf circ. ^a	0.464	13.3	<0.000
Calf circ. ^b	0.434	12.0	<0.000
Menses	0.102	2.8	0.005
Age	0.001	−0.37	0.97
BMI	−0.032	−0.43	0.67
Pubic hair stage ^c	0.058	1.5	0.13

^aLinear regression with only calf circumference in the model.^bLinear regression with those variables listed used in the model.^cIdentical results were obtained when breast stage was substituted for pubic hair stage.