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Peak Bone Mass and Quantitative Ultrasound Bone Properties in Young Adulthood: A Study in the PEAK-25 Cohort of Women

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Running title: QUS and body composition at peak bone mass

Abstract

Introduction: Peak bone mass is normally reached in the third decade. Previously we demonstrated that bone mineral density (BMD) in the population-based PEAK-25 cohort is comparatively high, therefore this study aimed to determine if calcaneus microarchitecture mirrored this. In the process we describe normative quantitative ultrasound (QUS) values for 25 year old women and the relationship between extremes of body weight and QUS.

Methodology: QUS variables speed of sound (SOS), broadband ultrasound attenuation (BUA) and stiffness index (SI) were measured in PEAK-25 (n=1061; age 25.5±0.2). Young adult values were based on the manufacturer supplied QUS reference values. Analyses were performed in the cohort as a whole and additionally, to understand the relationship between body weight and QUS in young women, they were categorized into octiles for weight or body mass index (BMI) and the lowest and highest compared.

Results: In the cohort SOS, reflecting bone density, was higher (108±18%), while BUA, reflecting bone complexity, was lower (90±14%) compared to the young adult reference population. SOS did not correlate with body weight or BMI. In the cohort overall correlations between BUA, weight and BMI were small and positive (Pearson's r coefficients 0.261; 0.197 respectively; p<0.001) although in the low-weight group, r-coefficients were higher (r values 0.313; 0.268; p<0.05). In contrast, in the high-weight group correlation with BUA tended to be small, negative and non-significant. Correlation between QUS and DXA measured BMD was low to moderate and significant at all skeletal sites (r-values 0.37 - 0.52) whereas coefficients tended to be higher in the low-weight group, while the reverse was apparent for low-BMI.

Conclusion: In these 25-year old women, a comparatively high DXA measured bone mass is offset by less complex bone structure assessed by QUS. This may have implications for later osteoporosis assessment and future fracture risk.

Introduction

Peak bone mass (PBM) is the highest bone mass acquired when normal growth is completed, supposedly during the third decade of life and prior to age associated bone loss [1]. PBM is also used as a comparative denominator for the diagnosis of osteoporosis. Higher young adult bone mass may contribute to a lower risk of fragility fractures later in life [2]; simulations suggest that the diagnostic threshold for osteoporosis could be postponed by up to 13 years among individuals whose PBM is ten percent above average [3]. However, bone strength depends not only on bone mineral density (BMD), but also on the microarchitecture and composition of bone, often alluded to as 'bone quality'. Unlike dual x-ray absorptiometry (DXA) quantitative ultrasound (QUS) can provide information on these aspects [4] and has been shown to predict hip and osteoporotic fractures independent of BMD [5]. Although it may only be an indirect representation of micro-architectural properties compared to other methods, QUS still has the possibility to contribute to our understanding of future fracture risk.

Previously we demonstrated that in the PEAK-25 cohort BMD measured by DXA is comparatively high [6]. We hypothesized that the bone microarchitecture would consequently be more complex. The aim of the current study was to investigate this hypothesis and in the process, because of the sample size, describe normative QUS values for 25 year old women. Establishing regional and ethno specific normative data is necessary since peak bone mass varies between populations due to genetic variation and differences in life style [7]. Several such studies have been performed for DXA [8]. While studies to establish population specific QUS data have also been performed [9-21], these have involved children, adolescents or the elderly, but to our knowledge no one has investigated QUS specifically with regard to peak bone mass in young adult women. Finally, we wanted to extend our

understanding of the relationship between QUS and body weight, by investigating extremes of body weight in an age group closely representing peak bone mass.

Materials and Methods

Participants

The PEAK-25 cohort consists of 25 year old women (25.5 $\pm$ 0.2) living in Malmö, Sweden. Of 2394 invited, 1166 accepted the invitation. By design, women who were or had been pregnant in the previous 12 months, or those outside the age limit were excluded, leaving 1061 attending the baseline investigation during 1999-2004 [6].

The investigation included BMD measurement using dual-energy x-ray absorptiometry (DXA) (Lunar Prodigy, Lunar Corporation, Madison, USA). The absolute precision errors (CV %) were 0.90% (femoral neck) and 0.65% (lumbar spine). Reproducibility was monitored by daily use of a manufacturer-supplied phantom [22]. Information on lifestyle factors was collected via questionnaire but not used in the analyses reported here.

The study was approved by the Ethics Committee of Lund University and the Swedish Data Inspection Board. The Study was performed according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Quantitative Ultrasound Measurements

Baseline QUS measurements of the calcaneus were available, for technical reasons, from 908 women, using the Achilles Insight (GE Medical systems, Madison, USA).

Propagation of the QUS signal is influenced both by the structure and mineral content of the bone. The QUS variables measured included speed of sound (SOS, m/s), broadband ultrasound attenuation (BUA, dB/MHz) and the composite stiffness index (SI). SOS is thought to reflect BMD, since studies show that 88-93% of the variance is explained by BMD alone [23, 24]. BUA by comparison may be considered to primarily reflect the microarchitecture, with studies demonstrating an approximate 50% change in BUA depending on the trabecular orientation through which the propagated ultrasound signal passes [25].

The right calcaneus was measured unless a previous fracture or injury occurred on that side. The coefficient of variation (CV) was 1.5% for derivatives of BUA and SOS [26]. Daily calibrations were performed. To compare each individual to the reference population, QUS measurements are standardized into a sex and age matched percentage value (AM %) and to the young adult percentage value (YA %) which is a comparison with a population assumed to have peak bone mass. These estimates were obtained from the QUS device internal reference population (based on 214 women, 20-35y, from four locations in the USA) [27].

To provide a wider perspective on our results and illustrate the relatively few published studies on normative QUS data corresponding to peak bone mass, we have also made a non-systematic review of available publications.

Statistical Analysis

Analyses were performed in the population as a whole and additionally into categories in order to understand the relationship between weight at the extremes of the distribution curve and QUS. Since quartiles were too broad to explore our question the women were categorized into octiles for weight or BMI, with statistical comparison made between the lowest and highest.

To explore the contribution of skeletal size and body weight to bone strength we sought to describe the characteristics of young women who had 'better or 'poor' bone based on DXA measured bone mass and QUS measured bone structure. Women in the highest 10% of femoral neck BMD values and had a correspondingly high QUS-SI value were defined as having 'better' bone (n=40). The 'poor' bone group contained women in the lowest 10% of femoral neck BMD values and a correspondingly low QUS-SI value (n=36).

Descriptive data are presented as mean (standard deviation). Correlation between QUS, weight and BMI was estimated by Pearson's correlation coefficient (r). Differences between high and low categories were identified using one-way ANOVA and presented uncorrected. The data was analyzed using IBM SPSS v22 (SPSS Inc., Chicago, IL). P-values <0.05 were considered nominally significant.

RESULTS

Women in the PEAK-25 cohort are all the same age. More than half of the participants were non-smokers and <10% had children. Height was normally distributed while there were a number of outliers with high weight. All three QUS variables were normally distributed.

Firstly we describe the distribution of QUS values in young adult women. According to the age matched and young adult values (based on the built-in QUS reference population), the PEAK-25 participants have values for SOS approximately 8% above the expected range for age, which is in line with the previously observed higher BMD measured by DXA. Conversely, values for BUA (ostensibly reflecting bone structure) are 10% lower than the reference population. Individual SI values were similar to the expected range (Table 1).

In terms of producing normative data of QUS values for peak bone mass, the PEAK-25 cohort is the most extensive study (Table 2). Compared to Caucasians measured with an Achilles device, the PEAK-25 participants have not dissimilar QUS values. The scarcity of studies published in equivalently aged women [11-14, 16, 17, 21, 28-31] is apparent and direct comparison with other studies is not possible however due to the use of different devices, and ethnicities.

Examining the opposite ends of the distribution curves for body weight and BMI can reveal additional, valuable information regarding the relationship between body weight and QUS. We report the QUS values for women in the lowest and highest octiles of weight (Table 3A) and BMI (Table 3B). As expected, QUS values for all three variables were higher among women in the high category for weight and BMI, but only BUA and SI were statistically different between the high and low categories (p<0.001). In terms of the relationship with bone mass, SOS values appeared to be little influenced by being very underweight or overweight and were, again above the expected range for age (3-8%). BUA, as observed in the population overall, was lower than the reference population. However, regarding the relationship with BUA as an indirect measure of bone microarchitecture, body weight appeared more influential; young women in the high weight or BMI category had values 5% lower than average while women with the lowest weights or BMI <20 were almost 18% below the expected range for age.

Correlation between QUS, body weight and BMI

Having shown that the population average may not provide the full picture across a spectrum of weight distributions, we looked at the correlation between body weight and BMI and QUS variables in the total population and in the high-low categories of body weight

and BMI in young adult women. In the total population, the correlation with BUA was positive, small but significant, and stronger for weight (r=0.261) than BMI (r=0.197) (Table 4A). Similarly in the low-weight category, however notably with larger coefficients than observed in the population overall (weight r=0.313; BMI r=0.268) (Table 4B). In the high weight category, the correlation coefficients for all QUS variables tended to be negative, small and non-significant. SOS was not correlated with either weight or BMI in the population overall or the high-low categories.

Correlation between QUS and BMD

To understand how QUS variables compare to BMD measurements in young adult women we investigated the correlation in the total population and in the high-low categories of body weight and BMI. In the total population, the correlation between QUS and DXA measured BMD was low to moderate and significant at all skeletal sites (r-values 0.37 - 0.52). As expected, the correlation between SOS and BMD was generally stronger at all sites (r-values 0.43 - 0.47) compared to BUA (r-values 0.37 - 0.38). This trend was also apparent in the low and high categories of weight and BMI. Interestingly, the coefficients for correlation between DXA and all QUS variables tended to be greater in the low weight compared to the high weight group, while in the low BMI group, the coefficients tended to be lower than in those high BMI group (**Table 5**).

A final, subsidiary aim of the study was to describe the characteristics of young women who had 'poor' or 'better bone with regards to their bone mass and structure (**Table 6**). There was a large (33.6%) difference in femoral neck BMD while QUS-SI was larger again (40%). BMI appeared to be more dependent on skeletal size. Those with the 'better bone' generally

had a higher BMI and weight ranged between 52-112 kg. Conversely, the weight range in the

"poor bone" category was 40kg-92kg, including only one woman with a BMI >30.

DISCUSSION

The object of this study was to determine if the previously observed higher bone density in the PEAK-25 cohort of 25 year old women was similarly reflected using QUS to provide an indirect representation of micro-architectural properties. In addition, we evaluated the relationship between body weight and QUS phenotypes.

In the present study we found that SOS (the QUS variable most equivalent to bone density) supported the original observation of high BMD in these women. Despite this implied higher BMD however, the BUA values indicated that the bone microarchitecture may be less complex, suggesting that already at this young age, when peak bone mass is assumed to have been reached, bone strength appears to be compromised. The implications for future fracture susceptibility are a concern.

In this study we also found that age matched and young adult QUS values were identical. In contrast, we previously reported that for DXA in this cohort at assumed PBM the age matched and young adult values were not identical [6]. A possible explanation for this may come from differences in the reference populations for the two methods. The QUS reference population is based on a substantial sample size (n=214) of women aged 20-35, while the precise number and age distribution used in DXA is less well described. Sample size and age category may be more relevant than geographical source. Making comparison with currently published studies is difficult however since the number of equivalently aged participants is very low and different QUS devices have been used [11-14, 16, 17, 21, 28-31]. However for those young adult cohorts that can be compared, it would appear that QUS values are not dissimilar. We can only speculate that in the other cohorts there may also be a tendency to poor bone structure, potentially a function of age and ethnicity.

Bone microarchitecture is influenced by biomechanical forces, therefore one can expect QUS values to differ at opposing ends of the weight distribution curve. We found that while the magnitude of the load appeared to influence the microarchitecture (BUA was highest in those with the heaviest body weight), this was not the case for SOS.

Most QUS studies indicate only that body weight is an important factor influencing QUS. In order to improve our understanding of the influence of body weight on bone properties we analyzed the correlation between weight and QUS variables in the population as a whole and at opposite ends of the weight distribution curve. The generally low coefficients indicate that other factors [22, 32], not explored in this study, may have a greater influence on bone structural properties. In the population overall, the strongest correlation observed was between BUA and weight rather than BMI. The relationship between weight and QUS appeared to be nonlinear however, such that the influence on QUS was not the same across the distribution curve. A positive correlation between QUS variables and weight is usually described but we found in the heaviest young women the correlation was negative, conversely in the lightest the correlations were positive and considerably higher than the population mean. This supports the idea that even though an increase in weight at low to moderate weights is generally considered to be positive for bone, some evidence suggests that beyond a certain threshold a further increase in weight is detrimental to bone strength [33].

The results from this study demonstrate that in young women assumed to have reached PBM, DXA measurements alone may not fully reflect bone strength and the potential for future fracture risk. Although verification of bone properties by other methods is not part of this study, longitudinal follow-up in this cohort is ongoing and in due course it will be

possible to evaluate prospectively the influence of our observations on fracture incidence. In this age group it will be important to identify the characteristics that contribute to 'better or 'poor' bone. Our preliminary data suggests that the most pronounced differences may be attributable to smoking habits [32] and having children; further analyses are ongoing.

A major strength of this study is that the cohort includes only 25-year olds. Furthermore, because PEAK-25 is population-based, selection bias is reduced; although the response rate was 49% (not untypical for this age) we have not identified any pattern for non-participation. A limitation of the study is the absence of other quantitative methods of measuring bone micro-architectural properties since QUS can only be considered indirect. Additional studies in other cohorts and with other methods will be necessary to confirm our observations. In addition, clinically, QUS is not routinely used diagnostically due to its technical limitations which should be considered when interpreting the data e.g. in the heaviest women ultrasound transmission may differ in individuals with more soft tissue surrounding the calcaneus [34]. However, our conclusions are mainly based on BUA and studies indicate that it is less affected by variation in soft tissue thickness [35], we therefore assume the impact of this to be negligible. Whether the results of this study are applicable to other populations remains to be seen. Due to technical errors there are some missing QUS data; however with 908 women measured in our cohort it is still considerably larger than most studies with similar objectives.

In summary, our results suggest that in women at age 25 a comparatively high bone mass may be offset by less complex structural properties as measured by QUS. This may have additive implications for future fracture risk.

Acknowledgements

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Table 1. Descriptive data for the PEAK-25 cohort of young adult women

	Mean ± SD	Range
Anthropometric		
Age (y)	25.5 ± 0.2	25.0-26.0
Height (cm)	168 ± 6.1	149.6-186.5
Weight (kg)	64.7 ± 11.4	40.0-141.0
BMI (kg/m^2)	23.0 ± 3.81	15.2-51.2
Quantitative Ultrasound*		
SOS (m/s)	1574 ± 32	1498-1705
SOS-AM%	108 ± 18	65-181
SOS-YA%	108 ± 18	65-181
BUA (dB/MHz)	117 ± 11	59-149
BUA-AM%	90 ± 14	12-132
BUA-YA%	90 ± 14	12-132
SI	99 ± 15	42-151
SI-AM%	102 ± 15	44-173
SI-YA%	99 ± 15	42-151
Recreational Activity Level **		
High	529 (49.5%)	
Low/moderate	525 (49.9%)	
Smoking Status		
Current	276 (26%)	
Former	187 (18%)	
Never	591 (56%)	

Measurements available for QUS (n=908 (85.3%))

**Physical activity is based on a scale where 1 represents 'virtually no exercise' and 6 is 'high activity level on a regular basis'. The cutoff between high and low/moderate levels is ≥4 [22].*

Table 2 Summary of QUS values from the Peak-25 cohort and other QUS studies in comparably aged cohorts

	Reference	Country	Age	N	QUS Device	BUA	SOS	SI
PEAK-25 Cohort		Sweden	25	908	Achilles Insight	117 (11)	1574 (32)	99 (15)
Zanovec *et al*. 2011	21	USA	20–29	219	Achilles Insight	-	-	104 (19)
Scheffler *et al.* 2014	29	Germany	19-24	50	Sonost 3000	73 (13)	1531 (14)	-
Zhang *et al.* 2004	30	Japan	20-34	33	A-1000 Express	117 (-)	1597 (-)	104 (-)
		Mongolia	20-34	44	A-1000 Express	114 (-)	1576 (-)	96 (-)
Landin-Wilhelmsen *et al.* 2000	11	Sweden	25-34	45	Lunar Achilles	114 (11)	1545 (28)	-
Saadi *et al.* 2003	31	United Arab Emirates	20-29	213	Sahara	74 (15)	1522 (31)	83 (17)
Madimenos *et al.* 2011	14	Ecuadorian Shuar	21-30	38	Sahara	83 (17)	1578 (28)	-
		Ecuadorian Colonos	21-30	22	Sahara	80 (16)	1564 (25)	-
Magkos *et al.* 2004	16	Greece	26-29	129	Sahara	74 (17)	1561 (27)	99 (18)
Maasalu *et al.* 2002	12	Estonia	20-29	32	Lunar Achilles	116 (14)	1556 (33)	93 (16)
Shin *et al.* 2005	17	Korea	20-29	55	Achilles Insight	113 (14)	1556 (28)	91 (15)
Liu *et al.* 2006	13	China	20-29	100	Lunar Achilles	113 (14)	1583 (31)	98 (14)
Heldan de Moura Castro *et al.* 2000	28	Brazil	20-24	42	Lunar Achilles	115 (10)	1587 (25)	101 (12)
			25-29	33	Lunar Achilles	117 (11)	1570 (28)	97 (14)

Few studies are published in equivalently aged young women. Direct comparison between them is not possible due to the use of different devices, populations and age groups

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