FACTORS INFLUENCING CALCANEUS QUANTITATIVE ULTRASOUND MEASUREMENTS IN AN URBAN POPULATION

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Short running title:

Factors influencing QUS
Abstract

Objective: To estimate the effect of demographic, social, behavioural and anthropometric factors on quantitative ultrasound (QUS) parameters, in an urban population.

Methods: Cross-sectional evaluation of consecutive subjects selected as part of the EPIPorto study, Portugal. Information was obtained on demographic, social, clinical and behavioural characteristics using a standard protocol. Calcaneus QUS parameters (Broadband Ultrasound Attenuation – BUA and Speed of Sound - SOS) were obtained for men and women, stratified by age group. Comparisons according to exposure levels were done using the Kruskal-Wallis test and the multivariate effect on QUS parameters was estimated by linear regression.

Results: 1482 consecutive subjects (1010 females and 472 males), aged from 18 to 92 years. Higher levels of QUS parameters were found in the younger groups and progressive decrease with age were reported. Men showed higher values as compared to women in all parameters and differences between them increased with age. Differences were significant for BUA after the age of 39 and for SOS after the age of 59. In women, the multivariate model showed that age, body mass index (BMI) and smoking status were independent predictors of BUA and SOS. In men, age, BMI and calcium intake were significantly associated with BUA and SOS.

Conclusion: The reference values in our Portuguese population are similar to other obtained in Southern European countries. In the Portuguese population QUS parameters have age, sex and BMI as its major determinants. In addition, BUA and SOS may reflect specific bone characteristics influenced by a different set of independent determinants.
Keywords:
Calcaneus Quantitative Ultrasound; Reference values; Osteoporosis; Portugal; Risk factors
Introduction

Osteoporosis (OP) is a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration, predisposing to an increased fracture risk (1). In the absence of non invasive methods to measure bone quality, the diagnosis of OP is based on low bone mineral density (BMD) measured by dual X-ray absorptiometry (DXA) (2). However, there is only a moderate correlation between BMD and bone strength. The recognition that new methods for assessment of bone quality are needed has motivated the development of complementary techniques to DXA.

The propagation of ultrasounds (US) through bone is dependent on bone mass, bone structure and bone material properties. The quantitative measurement by ultrasounds (QUS) can capture indirect information from bone quality. QUS is a portable, non invasive method for the evaluation of peripheral bones and does not use radiation (3). The localization usually chosen is the calcaneus, a predominantly trabecular bone (>90%) with parallel surface trabeculae and located in an anatomic region easy to position and scan (4).

In Portugal, as in other countries, the use of QUS of the calcaneus has quickly spread. Reference values for QUS are available for several populations (5,6,7), and we have recently determined the precision, accuracy and normal values for QUS in the Portuguese population (8). Despite risk factors for low BMD are well known (9,10) few data are available about the factors that influence QUS parameters (11,12).

The objective of this study was to estimate the effect of demographic, social, behavioural and anthropometric factors on QUS parameters, in a Portuguese population.
Material and methods

Cross-sectional evaluation of non-institutionalised Caucasian adults, selected as part of the EPIPorto study, a health and nutrition survey of a representative sample of the inhabitants of Porto, Portugal (13). Participants were selected by random digit dialling using households as the sampling frame. Residences were sampled, and in each residence a single adult was selected by simple random sampling. The selected person was invited to visit the Department and an appointment was scheduled. The proportion of participation was 70%. Refusals were not replaced and participants did not differ significantly from non-participants in age, gender, education and in selected cardiovascular risk factors (14).

The age and gender distribution in the EPIPorto cohort is overall similar to the last census results for the city of Porto, though women over 74 years-old were comparatively underrepresented in our sample. The study was approved by the Ethics Committee of São João Hospital and all the participants gave written informed consent. A questionnaire for the characterization of demographic, social, clinical and behavioural data was completed by a trained interviewer (13). For each subject, socio-demographic, anthropometric and lifestyle variables were collected (sex, age, education, height, body mass index (BMI), alcohol intake, smoking status, physical activity), as well as gynaecological and obstetric history in women. Total caloric, calcium and vitamin D intakes were assessed by using a semi-quantitative food frequency questionnaire, which was developed for use in the Portuguese adult population and was previously validated in this population (15). The questionnaire comprises 86 food or food group items. Frequency of consumption is recorded as a categorical variable with nine pre-specified categories from “never or less
than once per month” to “six or more times per day”. Pre-specified portion sizes were allocated to each food item. Dietary intake was estimated by multiplying the frequency of intake for any given item by its respective portion size, in grams, and by a seasonal variation factor for foods consumed only in some seasons. The Food Processor Plus® version SQL (ESHA Research, Salem, Oregon) was used to convert food intakes from the questionnaire to nutrient intakes. This database was supplemented with nutritional composition of Portuguese foods and recipes, using data from Portuguese food composition databases (16, 17) and from national and international publications that analyzed Portuguese foods (18, 19, 20, 21, 22, 23, 24, 25). For some dishes with unknown nutritional composition, this was estimated directly on the basis of their culinary recipe.

Cognitive status was evaluated by Mini Mental State Examination, depressive symptoms using Beck Depression Inventory and quality of life was assessed by SF-36.

Calcaneus QUS were obtained from all subjects by the same device, a Sahara Clinical Sonometer® from Hologic. The QUS sonometer assesses two basic parameters: the broadband ultrasound attenuation (BUA, expressed in dB/MHz), a measurement of the differential attenuation of sound waves transmitted through the calcaneus and the speed of the sound (SOS, expressed in m/s) which translates the time necessary for US to travel through the calcaneus. The quantitative ultrasound index (QUI, expressed in %) and the estimated bone mineral density (EBMD, expressed in g/cm²) result from the combination of the two first parameters: QUI = 0.41 x (SOS + BUA) - 571; EBMD = 0.0025926 x (BUA + SOS) – 3.687. The QUI is highly correlated (r=0.83, p<0.01) with the Stiffness Index, which is a similar parameter calculated by the Achilles® Sonometers (26).
For quality control, the device was tested daily using the phantom supplied by the manufacturer. *In vitro* precision was established by five repeated evaluations of the phantom, during five consecutive days. *In vivo* precision was calculated performing six successive evaluations of the calcaneus of a 24 years-old Caucasian healthy woman and, as for the evaluation of *in vitro* precision, with new repositioning after each evaluation. *In vitro* and *in vivo* precision were expressed by coefficient variation (CV), defined as the ratio between the standard-deviation (SD) and the mean of the measurements, expressed in percentage (CV = SD/mean x 100).

BUA and SOS values were calculated separately for men and women, distributed in 6 age groups: 18-29, 30-39, 40-49, 50-59, 60-69 and more than 70 years and expressed in mean and standard-deviation.

Comparisons according to age-groups were done using the Kruskal-Wallis test. Multivariate linear regression was used to estimate the effect of exposures on QUS parameters. Variables were entered in the model if the corresponding p-value in univariate regression was equal to or under 0.1. The statistical analysis was performed with Stata software.

**Results**

Demographic data

1482 consecutive subjects were evaluated, 1010 females (68.15%) and 472 males (31.85%). The mean age was 50.8±15.9 years for women, with a minimum of 18 and a maximum of 92 years, and 50.3±16.9 years for men, with a minimum of 19 and a
maximum of 86 years. The BMI expressed in kg/m² was obtained in 1466 individuals. In females (n=996), mean BMI was 26.5±5.1 and in males (n=470) was 25.8±4.0.

Precision

In vivo precision (CV) was 5.5% for BUA and 0.4% for SOS. In vitro precision was 3.23% for BUA and 0.15% for SOS.

QUS parameters

Calcaneus QUS parameters (BUA, SOS, QUI and EBMD) were presented for women and for men (Table I), by age groups. Median values (interquartile range) were 68.8 (57.5-81.6) for BUA, 1547.6 (1529.4-1568.9) for SOS and 91.5 (80.3-105.3) for QUI. Higher values, for all parameters, in both sexes, were detected in younger groups. Increasing age, in both sexes, induced a significant reduction (p<0.001) of all parameters, with the exception of BUA values in males (p=0.06). Men presented higher values in all parameters, as compared to women, with a clearer cut difference in older age groups (Table I). Sex differences were statistically significant after 39 years for BUA and after 59 years for SOS (Figure 1).

In women, the multivariate model showed that age was independently associated with BUA and SOS. BMI (kg/m²) and smoking status also significantly influenced BUA and SOS (Table II). Duration of the reproductive period (years) was a determinant of SOS but not BUA. Education level, physical activity, caloric, calcium, vitamin D and ethanol intake, Beck depression inventory, SF-36, age at menarche and number of pregnancies showed no significant effect on QUS parameters (results not shown).
In men, age was found to be significantly associated with BUA and SOS (Table II). The multivariate model showed that BMI and calcium intake were significant BUA and SOS determinants. SOS was also significantly associated with total caloric intake (regression coefficient: 0.01, 95% CI: 0.00-0.01). Physical activity, vitamin D and alcohol intake, Beck depression inventory and SF-36 were not significantly correlated with male QUS parameters (results not shown).

Discussion

The role of QUS in OP assessment is still debatable but it has already been proved to be a useful tool for fracture risk assessment (27, 28, 29). Moreover QUS parameters might be particularly useful for screening for patients with a high risk for osteoporosis associated fractures secondary to inflammatory rheumatic diseases (30).

The aims of our study were to estimate the effect of demographic, social, behavioural and anthropometric factors on QUS parameters in a representative sample of urban Portuguese adults.

Our data depicted, for both sexes, a decrease of QUS parameters values with increasing age, although this reduction started earlier and was greater in women than in men. These findings in the Portuguese population were similar to others previously published in Southern European countries (5,6).

There are few published studies about factors that potentially influence QUS parameters (7,11,12, 31, 32).

In our work the multivariate model showed that age, BMI and smoking status in women were independent predictors of BUA and SOS. Additionally, the duration of the
reproductive period was associated with SOS. In men, age, BMI and calcium intake were found to be significantly associated with BUA and SOS. Total caloric intake exerted a significant effect only in some QUS parameters. Factors like education level, physical activity, vitamin D and alcohol intake, Beck depression inventory and SF-36 did not present any association with QUS values. The results here described are in accordance with other previous studies such as the ESOPO study, performed in Italian men and women (32). The effect of age and BMI on QUS parameters was expected as they are major determinants of bone mass (1). Smoking status is also a well known risk factor for OP and the reason for a lack of effect of this variable on QUS parameters in man is not clear. However in accordance with this, Kaji et al (33) using peripheral quantitative computed tomography found high correlation between smoking habits and volumetric bone mineral density in women although, in man, this correlation was not observed. In other hand, our findings might also reflect the decreasing smoking habits in Portuguese males as opposed to the increasing of smoking habits in women (34).

On the contrary, calcium intake did not influence QUS parameters in women, which might be explained by a more homogeneous calcium intake pattern in women, due to increase awareness of OP (34).

In our population, QUS parameters have age, sex and BMI as their major determinants. In addition, BUA and SOS may reflect specific bone characteristics influenced by a different set of independent determinants.
Acknowledgments

This work was funded by a grant from POCTI/ESP/35769/2000.
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Table I – BUA, SOS, QUI and EBMD values for women (above) and men (below), stratified by age. p-values refer to the non-parametric comparison of each ultrasound parameters across age-groups, at a 0.05 significance level.

BUA – broadband ultrasound attenuation; SOS – speed of sound; QUI – quantitative ultrasound index; EBMD – estimated bone mineral density.
| Variables       | BUASOSMen | Women | Men | Women | Univariate | Multivariate | Multivariate | Age (per year) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) | Education (years) |
|-----------------|-----------|-------|-----|-------|------------|--------------|--------------|---------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| (per year)      | -0.20     | -0.30 | -0.10 | -0.22 | -0.33 | -0.10 | -0.48 | -0.55 | -0.42 | -0.55 | -0.71 | -0.39 | -0.46 | -0.61 | -0.30 | -0.54 | -0.73 | -0.35 | -0.77 | -0.88 | -0.65 | -1.02 | -1.28 | -0.77 |
| (per kg/m²)     | 0.72      | 0.30 | 1.14 | 0.04 | 0.61 | 1.47 | 0.28 | -0.51 | -0.04 | 0.36 | 0.04 | 0.69 | 0.33 | -0.36 | 1.02 | 0.87 | 0.17 | 1.57 | -0.60 | -0.99 | -0.22 | 0.53 | 0.02 | 1.04 |
| Calcium intake (per mg/day) | 0.01 | 0.00 | 0.01 | 0.01 | 0.01 | 0.00 | 0.01 | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.00 | 0.00 | 0.00 |
| Vitamin D (per μg/day) | 0.16 | -0.51 | 0.84 | -0.48 | -1.18 | 0.23 | -0.12 | -0.57 | 0.34 | 0.03 | -0.57 | 0.64 | 0.17 | -0.94 | 1.27 | 0.92 | -2.06 | 0.23 | 0.40 | -0.34 | 1.15 | 0.27 | -0.56 | 1.22 |
| Ethanol intake (per g/day) | 0.00 | -0.07 | 0.06 | 0.01 | -0.05 | 0.07 | -0.12 | -0.23 | -0.02 | -0.02 | -0.13 | 0.09 | 0.03 | -0.12 | 0.06 | 0.01 | -0.09 | 0.11 | -0.17 | 0.18 | -0.34 | -0.01 | 0.00 |
| Smoker (yes/no) | 0.45 | -3.34 | 4.24 | -0.86 | -4.52 | 2.80 | 4.41 | 1.81 | 7.00 | 6.32 | 1.15 | -1.04 | 2.43 | -8.58 | 3.72 | 5.55 | -11.48 | 0.37 | 5.06 | (0.80, 9.32) | -17.81 | -1.26 |
| Reproductive period (per year) | 0.05 | -0.21 | 0.30 | 0.11 | -0.15 | 0.37 | 0.29 | -0.12 | 0.70 | 0.44 | (0.04, 0.85) | 0.10 | 0.90 | 0.11 | 0.14 |

* Multivariate coefficients were adjusted for all variables in the table.

Table II – Regression coefficients (95% confidence intervals) for the multivariate model for BUA and SOS in both sexes regarding anthropometric, social and behavioural factors.

BUA – broadband ultrasound attenuation; SOS – speed of sound
Figure 1 – Chart representing BUA (broadband ultrasound attenuation) and SOS (speed of sound) parameters, in both sexes, stratified by age group; * p < 0.05

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