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REVIEW ARTICLE

Factors that influence bone mass of healthy children and adolescents measured by quantitative ultrasound at the hand phalanges: a systematic review☆

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KEYWORDS
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Abstract
Objective: To analyze the main factors that influence bone mass in children and teenagers assessed by quantitative ultrasound (QUS) of the phalanges.
Data source: A systematic literature review was performed according to the PRISMA method with searches in databases Pubmed/Medline, SciELO and Bireme for the period 2001-2012, in English and Portuguese languages, using the keywords: children, teenagers, adolescent, ultrasound finger phalanges, quantitative ultrasound of phalanges, phalangeal quantitative ultrasound.
Data synthesis: 21 articles were included. Girls had, in QUS, Amplitude Dependent Speed of Sound (AD-SoS) values higher than boys during pubertal development. The values of the parameters of QUS of the phalanges and dual-energy X-ray Absorptiometry (DXA) increased with the increase of the maturational stage. Anthropometric variables such as age, weight, height, body mass index (BMI), lean mass showed positive correlations with the values of QUS of the phalanges. Physical activity has also been shown to be positively associated with increased bone mass. Factors such as ethnicity, genetics, caloric intake and socioeconomic profile have not yet shown a conclusive relationship and need a larger number of studies.
Conclusions: QUS of the phalanges is a method used to evaluate the progressive acquisition of bone mass during growth and maturation of individuals in school phase, by monitoring changes that occur with increasing age and pubertal stage. There were mainly positive influences variables of sex, maturity, height, weight and BMI, with similar data when compared to the gold standard method, the DXA.

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PALAVRAS-CHAVE
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Densidade óssea

Fatores que influenciam a massa óssea de crianças e adolescentes saudáveis mensurada pelo ultrassom quantitativo de falanges: revisão sistemática

Resumo
Objetivo: Analisar quais os principais fatores que influenciam na massa óssea de crianças e adolescentes avaliada pelo ultrassom quantitativo (QUS) de falanges.
Fonte de dados: Foi realizada revisão sistemática da literatura, de acordo com o método Prisma, com buscas nas bases de dados do Pubmed/Medline, Bireme e Scielo, referente ao período de 2001 a 2012, nos idiomas inglês e português, utilizando os descritores *children, adolescent, ultrassonography finger phalanges, quantitative ultrasound of phalanges, phalangeal quantitative ultrasound*.
Síntese dos dados: Foram incluídos 21 artigos. As meninas apresentaram no QUS valores de Amplitude Dependent Speed of Sound (AD-SoS) superiores aos meninos durante o desenvolvimento puberal. Os valores dos parâmetros do QUS de falanges aumentaram com o incremento do estádio maturacional, assim como ocorre com o Dual-energy X-ray Absorptiometry (DXA). Variáveis antropométricas, como idade, peso, estatura, índice de massa corporal (IMC) e massa magra, demonstraram correlações positivas com os valores do QUS de falanges. A atividade física também demonstrou estar positivamente relacionada ao aumento da massa óssea. Fatores como etnia, genética, ingestão calórica e perfil socioeconômico ainda não mostraram relação conclusiva e necessitam um número maior de estudos.
Conclusões: O QUS de falanges é um método indicado para avaliar a progressiva aquisição da massa óssea durante o crescimento e a maturação dos indivíduos em fase escolar, por acompanhar as alterações que ocorrem com o aumento da idade e do estádio puberal. Observou-se influência positiva, principalmente das variáveis de sexo, maturação, estatura, peso e IMC, sendo seus dados semelhantes quando comparados ao método padrão-ouro, o DXA.

Introduction

Childhood and adolescence are important phases for the development of peak bone mass, as it is the time when there is a gradual increase in bone tissue, with the predominance of formation in relation to absorption.[1] Several aspects may influence the process of increasing bone mass, such as genetic, hormonal, and nutritional factors, as well as physical activity.[1,2]

There are several methods to measure bone mass in pediatric age ranges, which are different regarding the techniques and assessed anatomical sites, and all present advantages and disadvantages. The method considered to be the gold standard is dual-energy x-ray absorptiometry (DXA),[3] but this method is influenced by changes in bone size during growth and may underestimate bone mineral density (BMD) in small individuals and overestimate it in larger individuals, in addition to not providing information regarding bone quality.[2] In recent years, quantitative ultrasound (QUS) of the phalanges has been widely used as it is an easily accessible, low-cost, non-invasive, non-ionizing, and portable technology,[4-6] which uses the speed of sound as a principle to assess bone mass in the proximal phalanges of the hand, a site sensitive to bone alterations that occur during growth[7-9] and is less influenced by bone size.[9,10]

Understanding the factors that determine the process of acquisition during bone tissue maturation and which techniques can be used to properly assess bone mass allows for the creation of strategies for intervention and prevention of disorders and alterations in that tissue, preventing early onset of osteogenic diseases. However, it is yet to be determined which factors are more important or show more interference during these periods. Thus, this study aimed to analyze the main factors that influence bone mass in children and adolescents assessed by QUS of the phalanges.

Methods

This is a systematic review of the literature on the QUS of the phalanges method in healthy children and adolescents. The Prism Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISM) [11] method was used as a reference.

Initially, it was done an article research in PubMed, Bireme, and SciELO databases, between 2001 and 2012. The search was performed by two authors (TK and EMG) at different times, guided by a librarian, in English and Portuguese. The keywords used for the search were: children, adolescent, ultrasonography finger phalanges, quantitative ultrasound of phalanges, phalangeal quantitative ultrasound, using “and” or “or”.

Based on the analysis of titles and abstracts, 69 articles were identified in the databases, of which 48 were excluded and 21 were included in this study. The inclusion criteria for selecting the articles were: studies with QUS of

the phalanges with healthy children and/or adolescents in Portuguese or English, from 2001 to the date of the survey.

The criteria for excluding articles were: studies with individuals with disorders or diseases (n=33); in languages other than English or Portuguese (n=04); assessing individuals outside the specified age range, such as newborns and adults (n=3), or with physical disabilities (n=1); review articles (n=1); response letters (n=1); and others who did not meet the inclusion criteria (n=5), as shown in Fig. 1.

Results and Discussion

The summaries of the articles are presented in Table 1. All selected articles were published between 2001 and 2012. These articles showed an association between ultrasound parameters and variables such as gender (10), physical activity (one), ethnicity (two), genetics (two), anthropometric data (21), caloric intake (two), socioeconomic profile (two), and pubertal stage (10).

Gender

Most of the studies reported measures of amplitude-dependent speed of sound (AD-SoS) that were higher for females when compared to males.[4,5,8,10,12-15] These differences are mainly found between 11 and 16 years.[4,5,7,8,10,16] Studies comparing pubertal development using the pubertal stage also observed higher values of AD-SoS for females at stages II, III, IV,[5,10,12] and V[16] when compared to males. Moreover, females aged 11-13 years had higher values of bone transmission time (BTT)[5,14] when compared with males of the same age. However, males showed higher BTT values at ages 6-8, 15-21,[14] and at 18 years;[10] regarding pubertal development, males showed higher values at stages I, II, and V.[14]

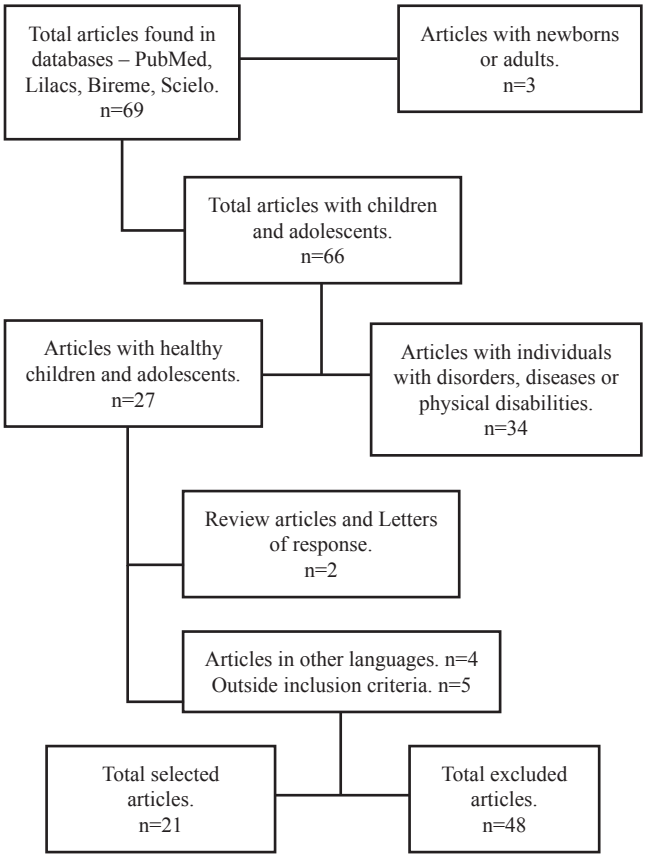

Figura 1 Prisma Fluxograma

In contrast, studies with DXA presented higher BMD values primarily in males, who had higher values at the femoral neck, full body, hip, and arm,[17-20] whereas females presented higher BMD values for the lumbar spine.[18,20] After the end of the growth phase, with increasing age, the curve obtained by DXA is significantly higher for males, with higher BMD values after the age of 19 years.[21]

It was observed that females often showed higher values of AD-SoS compared to males at ages where there is greater influence of puberty. At the observed ages, the former are usually at the stage of early development due to the earlier start of the maturation process,[22-24] which may explain the results obtained by phalanges QUS, as this bone site is sensitive to changes in growth and maturation.

Maturation

Maturation assessment through the stages of pubertal development is divided into pre-puberty (stage I), puberty (stages II and III), and late puberty (stages IV and V).

Most studies evidenced an increase in bone mass according to pubertal development. Females showed an increase in AD-SoS values at all pubertal stages[7,10,14,23] or at least from one stage to another.[5,12,24,25] As for BTT, most studies showed an increase in relation to all pubertal stages.[5,10,14] In males, AD-SoS progressively increased with puberty[10,25] or at some stage.[5,7,12,24] BTT increased significantly in all pubertal stages,[10,14] in stages I through IV,[5] and in late puberty.[24] Only two studies found no association between pubertal stages and QUS parameters.[15,26]

Regarding maturational stages, the results of DXA are quite similar to those of the BTT. In all pubertal stages, males present higher BMD values than females for total body, radio, hip, and femur.[18]

When the groups were compared by pubertal stage, females showed higher values of AD-SoS in stages III and IV when compared to males. This result can be explained by the fact that the period of childhood and adolescence is characterized by a high rate of bone formation and, therefore, by gain in the amount of bone tissue. As the phalanges are more sensitive to general hormonal and osteometabolic changes for having large amounts of trabecular bone,[16]the fact that females mature earlier can directly influence the results found in studies with QUS of the phalanges.

The results of the ultrasound are similar to those found by DXA when comparing the maturational stages between individuals of the same gender. BMD progressively increases between maturational stages in both genders in the different sites analyzed, such as the lumbar spine, femur, and whole body,[19,20,27-29] corroborating the results of the QUS. That is, the data indicate that pubertal development is one of the factors that influence bone mass, and is positively associated with age, weight, height, and BMI, confirm-

Table 1 Main characteristics and results of articles with quantitative ultrasound (QUS) of the phalanges.

Study	Sample	Design	Parameters	Hand	Results
04	1,328 Germans (M/F) - 3 to 17 years	Cross-sectional	AD-SoS BTT	Right	Both increased with age and height. Higher values of AD-SoS in females.
10	256 Lebanese (M/F) 11 to 18 years	Cross-sectional	AD-SoS BTT	Non-dominant	Increased with age and pubertal stage, positive correlation with age, height, and lean mass. Higher AD-SoS in females
12	1,083 Italians (M/F) 3 to 21 years	Cross-sectional	AD-SoS	Non-dominant	Increased with age and pubertal stage. Higher values in females.
13	1,020 Polish (M/F) 7 to 19 years	Cross-sectional	AD-SoS	Dominant	Increased with age. Higher values in females.
15	245 Spanish (M/F) 4 to 16 years	Cross-sectional	AD-SoS	Non-dominant	Higher values in females. Increased with age.
05	1,227 Italians (M/F) 3 a 16 years	Cross-sectional	AD-SoS BTT	Non-dominant	Increased with age and pubertal stage. Higher values in females.
08	150 Polish (M/F) 14 to 19 years	Cross-sectional	AD-SoS	Dominant	Higher values for females. Positively correlated with age, height, and pubertal stage.
14	3,044 Italians (M/F) 2 to 21 years	Cross-sectional	AD-SoS BTT	Non-dominant	Both increased with age, weight, height, BMI, and pubertal stage. Higher AD-SoS in females and BTT in males.
16	267 Brazilians (M/F) 8 to 18 years	Cross-sectional	AD-SoS	Non-dominant	Positive correlation with age, weight, height, BMI, lean mass, waist circumference, and hip circumference. Negative correlation with waist-to-hip ratio.
25	1,775 Brazilians (F) 8 to 17 years	Cross-sectional	AD-SoS BTT	Non-dominant	Increased with age and pubertal stage. Positive correlation with age, height, and pubertal stage.
30	2,850 Polish (F) 7 to 77 years	Cross-sectional	AD-SoS	Dominant	Significant increase from 11-16 years. Peak at 19 years. From 7 to 11 years, age and height positive and weight negative. From 12 to 19 years, is age-dependent.
32	1,175 Polish (M) 7 to 80 years.	Cross-sectional	AD-SoS	Dominant	Significant increase after 13 years. Correlation with weight and height. From 14 to 28 years, it is highly dependent on age.
38	106 Monozygotic twins (M/F) - 5 to 71 years	Cross-sectional	AD-SoS, UBPI SDy, BTT	Non-dominant	Age and height are predictors of differences between pairs.
31	83 mono and dizygotic Polish twins (M/F)- 15 to 23 years	Cross-sectional	AD-SoS	Dominant	Stronger correlation in monozygotic twins. Intra-pair difference influenced by age.
35	226 Polish Karate fighters and 44 sedentary individuals (M) - 8 to 62 years	Cross-sectional	AD-SoS T-Score Z-Score	Dominant	Higher values in karate fighters.
26	38 preterm and 50 full-term Polish (M/F) - 9 to 11 years	Cross-sectional	AD-SoS	Dominant	There were no statistical differences between groups.
40	1,356 Brazilians (M/F) 6 to 11 years	Cross-sectional	AD-SoS	Non-dominant	Increased with age. Higher values in white females.
23	1,356 Brazilians (M/F) - 6 to 11 years	Cross-sectional	AD-SoS UBPI	Non-dominant	Increased with age and pubertal stage. Both higher in white females than African-descendants. UBPI higher in whites females than in African-descendants.
33	50 Austrians with fractures and 154 with no fractures, (M/F) - 8 to 12 years	Cross-sectional	SOS	Dominant	Lower value in the fracture group. In the control group, higher values in females.
24	662 Italians (M/F) - 3 to 16 years	Longitudinal	AD-SoS BTT	Non-dominant	Increased with age and pubertal stage. Higher values in males with delayed puberty.
07	269 Polish (M/F) 7 to 12 years	Longitudinal	AD-SoS	Dominant	Higher values in females. Increased significantly after 1 year. Increased with pubertal stage.

AD-SoS, amplitude dependent speed of sound; UBPI, ultrasound bone profile index; BTT, bone transmission time; SDy, dynamics of ultrasound signal; M, Male; F, Female

ing that the development and increase of bone mass are directly associated with maturation and growth aspects.

The studies also demonstrated that, after a period of increase in peak bone mass, males showed higher values of the ultrasound parameters, indicating greater amount of bone mass, as observed in studies using DXA.

Anthropometrics and body composition

Studies have demonstrated that both AD-SoS and BTT increased progressively with age and height in both genders.[4,10,12-14,23,25,30] Studies have also reported a positive correlation between AD-SoS and anthropometric variables, such as weight and height,[4,13,15,16,25,31-33] BMI,[15,16] mean width of the fingers,[12] waist and hip circumference,[16] lean body mass,[10,15] fat mass, fat mass index, and body fat percentage.[16] BTT showed a positive correlation with age, weight, height, BMI,[5,14,25] and lean mass.[10] Likewise, studies that analyzed the association between BMD, evaluated at several sites using DXA and anthropometric parameters (age, weight, height, and BMI), observed a positive correlation in both genders,[19,21,27] noting that lean mass exerts influence on BMD of the lumbar spine[20] and is related to the BMD of arms and legs in both genders.[34]

Physical activity

Only one study observed that the values of AD-SoS, T-score, and Z-score were significantly higher for men who practiced karate, and AD-SoS positively related them to time and weekly frequency of training.[35]

In a similar study using DXA, a group of wrestling athletes had higher BMD values of the whole body, lumbar spine, legs, and arms than the sedentary group.[34] When assessing physical activity and bone mass by DXA, physical activity has a positive correlation with BMD of the femoral neck, hip, and whole body[29] . Studies with children and adolescent athletes suggest that physical exercise is positively associated with the individuals' BMD results.[36,37]

Due to the scarce number of studies that address the assessment of QUS with physical activity, it is not possible to establish parameters concerning the data presented. Therefore, more studies are necessary involving physical activity and QUS evaluation of phalanges to elucidate the reliability of its use.

Genetics

Two studies involving genetic factors were retrieved. Drozdzowska *et al*[31]and Guglielmi *et al*[38] found that the differences between monozygotic and dizygotic twins are influenced mainly by environmental factors and lifestyle, and that AD-SoS significantly increased with age for both genders. The authors also observed that the intra-pair correlation coefficient of AD-SoS is stronger in monozygotic than in dizygotic twins.

When DXA was used, similar results were found, with a higher correlation of BMD among monozygotic twins and a lower correlation between parents and children, showing that 51% to 76% of the variation in BMD is hereditary.[39] More studies are needed in relation to genetic factors, as there is an apparent genetic affinity in relation to bone mass in monozygotic and dizygotic twins, and differences are predicted by anthropometric variables.

Ethnicity

Regarding ethnic classification, two studies showed differences between the groups classified as blacks or whites. When divided into blacks and whites, regardless of gender, the former showed lower values of AD-SoS. When divided by ethnicity and gender, white females had higher values of AD-SoS than the other three groups. White males showed higher values of AD-SoS when compared to black males.[23,40]

Differently from the results of QUS of the phalanges, Fonseca *et al*[27] observed a negative correlation of BMD with skin pigmentation in adolescent females. However, the author reports that this correlation is incorrect, because of the great diversity of the Brazilian population. Another study demonstrated that white, non-Hispanic individuals are more likely to have fractures than non-white individuals with lower BMD values of whole body, lumbar spine, forearm and femur. Furthermore, studies present significantly higher BMD values in black males when compared to whites.[41,42]

Additionally, in studies with DXA, it was observed that Asians had lower BMD values than whites of similar age and gender.[43] However, the differences found in the results may be more related to hereditary and environmental factors, as the studies were conducted in different countries and ethnic groups, with great diversity in the gene pool of populations, preventing comparisons.

Socioeconomic profile

Two studies assessed the socioeconomic profile, but the classification was used solely to describe the groups, not comparing with the QUS parameters.[16,23] Thus, further studies using the QUS of phalanges to assess bone mass in different socioeconomic profiles are suggested, as the DXA results demonstrated that groups of lower socioeconomic status had lower BMD.[18]

Nutrient intake

Two studies assessed the association between caloric intake and the parameters of QUS of the phalanges. Dib *et al*[10] evaluated the intake of calcium and vitamin D and found no significant correlation between calcium intake and ultrasound parameters in both genders. Lavado-Garcia *et al*[15] demonstrated that AD-SoS was negatively correlated with the intake of calcium, iron, magnesium, and calcium/protein ratio in females, with no association between nutrient intake and ultrasound parameters in males.

Although nutrition has great influence on bone health of individuals, there have been few studies investigating

the association between caloric intake and parameters of QUS of the phalanges. The authors suggest further studies in this area.

Limitations and conclusions

The first important limitation is that the studies included in this systematic review were mostly cross-sectional, and only two were longitudinal studies, with a follow-up of one and two years. Furthermore, the studies differed regarding the dominance of the evaluated limb and had different numbers of evaluated subjects, which may be a bias in their findings.

Despite the limitations described above, it can be concluded that the QUS of phalanges is a good method to evaluate the progressive acquisition of bone mass during the growth and maturation of school-age individuals, by monitoring alterations that occur with increasing age and pubertal stage. A positive influence was observed, especially of the variables gender, maturation, height, weight, and BMI, and data was similar when compared to DXA, which is the gold standard method. However, there is only a small number of studies that compared both methods. The scientific literature is scarce regarding physical activity, hormone levels, ethnicity, genetics, and caloric intake, and therefore it is not possible to clarify the influence of these factors on the parameters of QUS of the phalanges.

Moreover, there were few studies comparing the QUS and DXA methods, without clarifying the difference in results when comparing the parameters of bone mass in relation to gender.

Despite the advantages already described for the QUS of the phalanges, and the fact that it is an accessible, low cost, portable, and non-invasive method, further studies are needed regarding its use in regular bone assessment of children and adolescents.

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Conflicts of interest

The authors declare no conflicts of interest.

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