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REGULAR ARTICLE

Cohort study shows that peripheral dual-energy X-ray absorptiometry is of limited epidemiologic use in prepubertal children

Ana Martins[1,2], Teresa Monjardino[1,2], Helena Canhão[3], Raquel Lucas (rlucas@med.up.pt)[1,2]

1.EPIUnit-Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal
2.Department of Clinical Epidemiology, Predictive Medicine and Public Health, Faculdade de Medicina, Universidade do Porto, Porto, Portugal
3.EpiDoC, CEDOC, Nova Medical School, NOVA University, Lisbon, Portugal

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Correspondence
R Lucas, Instituto de Saúde Pública da Universidade do Porto (ISPUP) Rua das Taipas, 135 4050-600 Porto, Portugal.
Tel: +351 222 061 820 |
Fax: +351 222 061 821 |
Email: rlucas@med.up.pt

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ABSTRACT

Aim: Peripheral methods are increasingly used to assess bone health, despite little evidence on their predictive ability. We aimed to evaluate the usefulness of forearm dual-energy X-ray absorptiometry in prepubertal children, by estimating the agreement between peripheral and central measures and the ability to predict fracture history.

Methods: In 2012/2014, we assessed 1177 seven-year-old children from the Generation XXI cohort who were recruited at birth in all five public hospitals with maternity wards in Porto, Portugal. Subtotal and lumbar spine bone mineral density (BMD) and content, left-arm BMD and peripheral forearm BMD were measured. Parents reported the child's lifetime fracture history. We estimated agreement using Bland–Altman's method and Cohen's kappa. Fracture prediction ability was calculated using area under the receiver operator characteristic curve (ROC-AUC).

Results: The limits of agreement were very wide, ranging from −2.20/2.20 to −1.87/1.87 standard deviations for the comparison between peripheral and central measures. Categorical agreement was also poor, with all kappa values below 0.40. In addition, none of the measures predicted fractures, because all the ROC-AUCs were close to 0.50.

Conclusion: This study suggests that forearm BMD has limited use for bone health research or as a basis for clinical decisions in prepubertal children.

INTRODUCTION

In both clinical and research settings, dual-energy X-ray absorptiometry (DXA) remains the gold standard method for assessing bone physical properties – bone mineral density (BMD) and bone mineral content (BMC) – in adults and children (1). In clinical settings, paediatric DXA has mostly been used to assist in the diagnosis and monitoring of primary and secondary osteoporosis. In research, paediatric DXA scans have been increasingly used due to their tempting availability, safety, ease of use and ability to estimate body composition. Conceptually, investigating bone quality in generally healthy children follows the life course premise that childhood and adolescence are sensitive periods for bone mass acquisition and consequent bone health in adulthood (2).

Dual-energy X-ray absorptiometry measures can be obtained for the whole body or for axial or peripheral sites, with the latter including the forearm and calcaneus. Peripheral devices are portable, which makes them particularly valuable for improving research participation rates (3). Also, peripheral scans take substantially less time, which is rather helpful when evaluating young children. Thus, when the aim is to quantify physical properties of the bone, the practical advantages of peripheral measures would, in theory, make them ideal. Yet, epidemiological

Abbreviations
95% CI, 95% Confidence interval; AUC, Area under the curve; BMC, Bone mineral content; BMD, Bone mineral density; cm, Centimetre; DXA, Dual-energy X-ray absorptiometry; g, Gram; ROC curve, Receiver operator characteristic curve; SD, Standard deviation.

Key notes

- Peripheral methods are increasingly used to assess bone health, despite little evidence on their predictive ability.
- We assessed the usefulness of forearm dual-energy X-ray absorptiometry in 1177 seven-year-old prepubertal children and found little agreement between forearm and central bone mineral density (BMD) measures.
- Our findings show that forearm BMD has limited use for bone health research or as a basis for clinical decisions in prepubertal children.

classifications and subsequent clinical decisions demand that such a substitution is supported by good agreement. Previous investigations on agreement between peripheral and central bone physical properties have shown disappointingly low agreement. However, these studies evaluated small sample sizes and/or wide age ranges and may have lacked the power to detect a true effect at any given age (3,4).

In addition, studying peripheral DXA as a research tool should extend beyond agreement with central measures and include its accuracy to predict the most relevant clinical outcome, that is fracture. Although some studies have shown a statistical association between fractures and DXA measurements (5,6), the few formal estimates of clinical accuracy have shown surprisingly low predictive ability (7). In addition, little is known about this relationship in prepubertal children, because most studies have been conducted during or after the growth spurt period (5,6,8).

Therefore, we used data from a large cohort of seven-year-old children, to assess the clinical and epidemiological usefulness of forearm BMD by estimating the agreement between peripheral and central DXA measures. We also assessed the ability of peripheral DXA to predict fracture history.

METHODS

Participants

This study was conducted as part of the Generation XXI population-based birth cohort, which was launched in 2005/2006 in the five public level three maternity units that covered all six municipalities in the metropolitan area of Porto, Portugal. In the 24–72 hours following delivery, 91.4% of the women who delivered a live-born infant with a gestational age above 23 weeks agreed to participate in the cohort study and this resulted in 8647 infants recruited at baseline. Between April 2012 and April 2014, 6889 children, who comprised 79.7% of the initial sample, were re-evaluated at the age of seven years. The detailed methods have previously been described (9). The protocol was approved by the University of Porto Medical School ethics committee. Written, informed consent was obtained from the parents or legal guardians of all participants, according to the Declaration of Helsinki.

Peripheral and whole-body dual-energy X-ray absorptiometry

Of all children who participated in the evaluation at the age of seven, we used data from a subsample of 1177 (51% girls) with valid peripheral and whole-body DXA scans. Eligibility for the DXA scans was based on the project timeline and equipment availability and defined regardless of the children's characteristics. Peripheral bone mass was estimated through areal bone mineral density (g/cm^2) at the distal radius of the non-dominant forearm with a Peripheral Instantaneous X-ray Imager device (GE Medical Systems, Madison, WI, USA). If a previous fracture of the non-dominant arm was reported, the dominant arm was the one assessed. Whole-body scans were performed with a Discovery QDR 4500W device (Hologic Inc, Bedford, MA, USA), from which we extracted BMC (g) and BMD (g/cm^2) for the subtotal – total body minus the head – and the lumbar spine regions, and BMD for the left arm.

Fracture assessment

The lifetime fracture history of each child was reported by the parents in response to a structured questionnaire applied by a trained interviewer. The anatomical site of the fracture, the number of fractures and the age at the first fracture at each anatomical site were recorded.

Statistical analysis

To harmonise measurements between different anatomical sites and devices, we computed sex-specific BMC and BMD *Z*-scores and used them as continuous variables for agreement analysis with the Bland–Altman method. Mean differences and limits of agreement were estimated, because assumptions were met (10). Also, *Z*-scores were categorised using cut-offs at each unit of standard deviation (SD) to estimate concordance between the categories. Observed agreement (%) was calculated as a measure of overall concordance, and Cohen's linear weighted kappa (κ) with 95% confidence intervals (95% CIs) was estimated to account for the agreement expected by chance.

Receiver operator characteristic (ROC) curves were plotted, and the areas under the curves (AUC) with their 95% CIs were calculated to assess the accuracy of measures to predict fracture. Likelihood ratios with 95% CIs were computed for *Z*-score categories. For this particular analysis, two children with missing information for lifetime fracture history were excluded. We also excluded 16 fractures that occurred up to two years of age, which are usually thought to result from severe trauma, regardless of bone quality, such as delivery injuries, child abuse or accidental falls due to the caregiver's negligence (11,12).

The statistical analysis was performed using Stata version 11.2 for Windows (Stata Corp LP, College Station, TX, USA).

RESULTS

Descriptive results

Children included in this study were slightly younger (7.1 versus 7.2 years, $p < 0.001$), heavier (27.0 versus 26.0 kg, $p < 0.001$) and taller (124.0 versus 123.6 cm, $p = 0.029$) than the remainder of the cohort. Nevertheless, the lifetime fracture prevalence in this subsample was similar to that in the remaining cohort (6.7% versus 6.3%, $p = 0.577$).

The mean (SD) subtotal BMD was 0.626 (0.057) g/cm^2, and the mean (SD) subtotal BMC was 606.1 (86.6) g. Regarding the lumbar spine, the mean (SD) BMD was 0.679 (0.066) g/cm^2 and the mean (SD) BMC was 18.8 (3.6) g. Peripheral BMD was 0.260 (0.034) g/cm^2, and the mean (SD) left-arm BMD was 0.470 (0.058) g/cm^2. A total of 79 children were reported by parents to have sustained at least one fracture, corresponding to a total of 91 fractures. The majority of fractures occurred in the upper limb (71.4%),

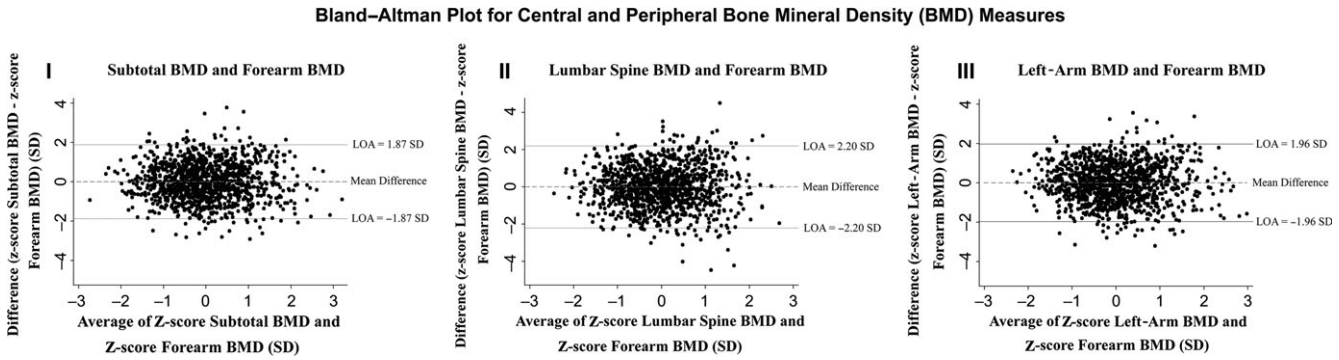

Figure 1 Bland–Altman plot of the difference (*y*-axis) against the average (*x*-axis) of central and peripheral bone mineral density (BMD) measures. I – subtotal BMD and forearm BMD; II – lumbar spine BMD and forearm BMD; III – left-arm BMD and forearm BMD.

followed by the lower limb (18.7%) and the remaining fractures, were in other or unspecified anatomical sites. In addition, more than half of the fractures (56%) happened from the age of four onwards.

Agreement between peripheral and central measures

Figure 1 plots the difference against the average of peripheral and central BMD *Z*-scores. Limits of agreement were remarkably wide for the comparison of BMD *Z*-scores between measures derived from peripheral versus whole-body scans: −1.87 SD to 1.87 SD for forearm versus subtotal measures, −2.20 SD to 2.20 SD for forearm versus lumbar spine measures and −1.96 SD to 1.96 SD for forearm versus left-arm BMD. The agreement between forearm and central measures beyond chance was weak, with kappa values below 0.40. In particular, the observed agreement between central and peripheral measures among those with low central BMC/BMD for chronologic age (*Z*-score < −2 SD) was <20%.

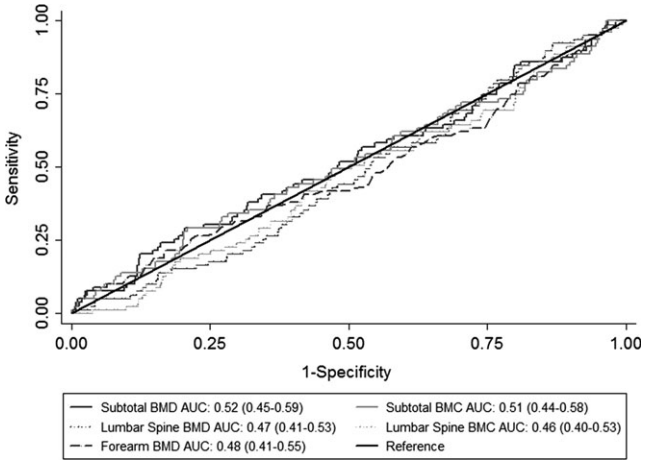

Figure 2 Receiver operator characteristic (ROC) curves for peripheral BMD and central BMC and BMD. AUC, area under the curve; BMD, bone mineral density; BMC, bone mineral content.

Predictive ability for fracture

Forearm BMD lacked predictive ability for fractures at all sites as all cut-off values originated likelihood ratios that were not significantly different from one. Concordantly, the AUC for forearm BMD was low (0.48, 95% CI: 0.41–0.55) as shown in Figure 2. In a sensitivity analysis, forearm BMD was not predictive of upper limb fractures (0.44, 95% CI: 0.34–0.54). Low predictive ability for fractures was also observed for central measures (Fig. 2).

DISCUSSION

Our study argues against the use of forearm BMD as a proxy for central measures or as a fracture predictor in prepubertal children, suggesting a limited use for peripheral measures in population-based research on skeletal development. Low agreement between peripheral and central measures has been reported in previous literature, either as wide limits of agreement (3) or as kappa values below 0.6 (4). Our study extended the existing knowledge to a large population-based sample of children before the growth spurt period. An additional concern raised by our findings was the poor agreement between whole-body derived left-arm BMD and peripherally measured forearm BMD. Greater agreement was expected because these measures have high anatomical correspondence and previous studies reported reasonable agreement between these measures (3,4). With regard to clinical applications, peripheral BMD measures were also not accurate in identifying children with low BMD for chronologic age (*Z*-score < −2 SD) when using central measures as a reference. Surprisingly, peripheral and central measures were not concordant, even when ranking children in BMD *Z*-score distributions. Indeed, children were classified differently, depending on the measure chosen, which also hampered the creation and interpretation of reference curves from peripheral measures in children.

The lack of agreement between peripheral and central measures may be the result of the pre-test variability related to the method. It has been shown that whole-body DXA has

good reproducibility, whereas forearm DXA repeatability has been shown to be poor (1). Thus, the lack of agreement found in our study may have been partly a result of poor peripheral DXA reproducibility.

Importantly, neither central nor peripheral BMD and BMC predicted fractures in our sample. Even though current guidelines denote an association between DXA measures and fractures in children (1), individual studies have shown that DXA-derived measures have a low ability to predict fractures (7). This suggests that DXA measures may be particularly limited for fracture prediction when risk is mostly determined by trauma rather than underlying bone deficits, such as among the generally healthy prepubertal children in the Generation XXI cohort. Indeed, in our previous work on this cohort, we found that physical exertion was likely to play a central role in the association between bone physical properties and fracture history. We only estimated a protective effect of bone mineral density and content on the odds of fractures in children in the highest categories of physical activity (13). This suggests that the usefulness of peripheral and even central DXA in the generally healthy paediatric population may only be clearer in children with a higher exposure to regular trauma. However, these findings do not exclude the usefulness of bone densitometry when it comes to quantifying age-related osteoporosis in adults or secondary bone fragility in children with chronic conditions that influence bone metabolism (14).

Some limitations need to be addressed. The children's fracture history was reported by parents and was not confirmed with X-ray scans or clinical records and may therefore have been subject to recall bias. Nevertheless, our estimates were in agreement with a previous study, where the prevalence of fracture in slightly older children was 10% (15). Also, we were not able to study the reproducibility of DXA methods by conducting repeated measurements for each subject, which would have been useful to assess whether our findings resulted mainly from a lack of accuracy or precision.

CONCLUSION

This investigation showed that forearm BMD in prepubertal children had low agreement with central DXA measures. In addition, neither peripheral nor central measures were able to predict fracture risk in generally healthy prepubertal children. We feel that forearm BMD measurements have limited use for research on normal bone development or as a basis for clinical decisions.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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