Review

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Imaging methods for bone mass evaluation during childhood and adolescence: an update

DOI 10.1515/jpem-2016-0252
Received June 27, 2016; accepted January 31, 2017; previously published online March 22, 2017

Abstract: The objective of the work was to prepare an update on imaging methods for bone evaluation during childhood and adolescence. The text was based on original and review articles on imaging methods for clinical evaluation of bone mass in children and adolescents up to 20 years old. They were selected from BIREME and PUBMED by means of the following keywords: bone density; osteoporosis/diagnosis; densitometry; tomography; ultrasonography; magnetic resonance imaging; and radiogrammetry and published in Portuguese or English, in the last 10 years (2006–2016). The article was organized into topics with the description of peculiarities, advantages and disadvantages of each imaging method and their possible clinical applicability. Despite the emergence of new technologies, dual energy X-ray absorptiometry (DXA) remains the gold standard method for low bone mass diagnosis in all age groups. However, interpretation is complex in children and adolescents and demands skilled people. Quantitative computed tomography (QCT) [central QCT, peripheral QCT (pQCT) and high resolution-pQCT (HR-pQCT)] and magnetic resonance imaging (MRI) evaluate real bone density, but are not yet available for routine use. Quantitative bone ultrasound (QUS) shows good perspectives for its use in primary prevention actions. Automated radiogrammetry shows promise as a method able to flag individuals who might benefit from a complete bone assessment, but the clinical value of the measures still needs to be established.

Keywords: bone density; children; densitometry; magnetic resonance imaging; osteoporosis/diagnosis; radiogrammetry; tomography; ultrasonography.

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Introduction

The interest in studying children's and adolescents' bone health has increased in recent years. Identify individuals with low bone mass in early life may be an important strategy so that preventive and therapeutic measures can be taken to promote a healthy growth of the skeleton [1–8].

The most appropriate technique for bone mass evaluation in children and adolescents is still a matter of great discussion [9–12]. A good method is not always available or standardized for use in clinical practice and the findings may bring more doubts than clarifications. In addition, other aspects such as the cost and use of ionizing radiation should be considered in children, especially if the exam has preventive purposes.

Dual energy X-ray absorptiometry (DXA), the most commonly used method to assess bone mineral density (BMD) and bone mass or bone mineral content (BMC), is considered the gold standard in all age groups, including childhood [13]. Central quantitative computed tomography (central QCT), peripheral QCT (pQCT), high-resolution pQCT (HR-pQCT), bone quantitative ultrasound (QUS), magnetic resonance imaging (MRI) and automated radiogrammetry are methods that can provide important additional information regarding bone strength: size, geometry, micro-architecture and/or bone quality [14–16].

There are several peculiarities in the assessment of children and adolescents' bone mass that make it a challenge and need to be recognized and discussed. One of

them is that skeletal growth should be considered for the correct interpretation of the tests, making the evaluation more complex in this age group [17]. In 2013, the International Society for Clinical Densitometry (ISCD) reviewed specific guidelines for DXA performance and interpretation in children and adolescents [9, 18–21], in order to improve the quality of the assessments.

Faced with the increasing indications for bone mass investigation during childhood and adolescence, the purpose of this review was to show the particularities, advantages and disadvantages of each imaging method in these age groups, summarizing and discussing the literature findings to date. A better understanding of these methods can help to identify their roles and stimulate advances to their applicability in clinical practice.

Materials and methods

The publications examined for this review were on imaging methods for clinical evaluation of bone mass in children and adolescents up to 20 years of age, in English or Portuguese, in the last 10 years (2006–2016). The literature search was conducted in the Regional Library of Medicine – BIREME, and in PUBMED, using the following keywords: bone density; osteoporosis/diagnosis; densitometry; tomography; ultrasonography; magnetic resonance imaging; and radiogrammetry in various possible combinations, always including the first or second terms. The original and review articles selected addressed the methods characteristics to assess bone mass in the age groups of interest. Some studies considered relevant for the topic presentation, published before the period cited, were also included.

Results

Currently, the following imaging methods can be used for bone mass evaluation in childhood and adolescence: DXA, central QCT, pQCT, HR-pQCT, QUS, MRI and automated radiogrammetry.

Dual energy X-ray absorptiometry (DXA)

The advantages of DXA are that scanners are widely available, scanning is fast and precision is good. The three main limitations of the method in children and adolescents are: (1) lack of robust reference databases, especially in younger children; (2) lack of significant clinical outcomes related to densitometric measurements; and (3) inaccuracies and artifacts due to changes in body size and composition, related to growth [12]. Furthermore, it uses ionizing radiation (although at low levels) and demands that the individual remain still during the procedure, which is difficult in children under 4 or 5 years, without using sedatives.

DXA measures areal bone mineral density (aBMD), a two-dimensional measure, and not true volumetric density. aBMD (g/cm^2) consists of bone mass or BMC per bone area of a tridimensional structure. The third dimension, depth, cannot be measured directly once it has the same direction as the X-ray beam [22]. Unlike adults, the child's bones grow with time and this increase is not uniform in all three dimensions. As skeletal growth leads to a much higher increase in volume than in bone area [23], young children have a proportionately larger area in relation to bone volume compared to older children [24]. Therefore, aBMD underestimates the real bone density in smaller children and overestimates it in larger ones [25, 26]. This is noticed from the fact that aBMD increases with age throughout childhood, whereas the volumetric bone mineral density (vBMD), measured by computed tomography, remains relatively constant until puberty [27, 28]. For this reason, aBMD measured by DXA is difficult to compare in children, in which there is a wide variation of height and bone size. In a study by Wren et al., on average, three times more children with low BMD were identified by DXA than by tomography. The majority of children identified only by DXA had a chronic disease and a short stature, indicating that the method underestimates the BMD in these individuals [29].

Various adjustments of densitometric measurements have been proposed, taking into account bone size and shape, height, height age, bone age, pubertal stage and/or the lean body mass of the child [23, 30–35], but there is no consensus so far on the best way to do it. The fact is that these corrections to the child's size, though necessary, add great complexity to the studies [33].

Mathematical models were developed to estimate vBMD from the densitometric measurements in children, assuming that the lumbar vertebrae has a cylindric [36] or a cuboid [23] format, although there is a discussion of the validity of the assumptions made about bone shape. One of the most commonly used models is the estimation of bone volume from its area, assuming that the vertebrae have a cuboid shape. Then, the lumbar spine vBMD (LS vBMD) is calculated, in g/cm^3, by the formula LS vBMD = LS BMC ÷ LS area [1, 5–23].

Molgaard et al. [30] proposed a three-step approach to understanding the possible causes of low BMC for age in the total body assessment: short bones (height for age);

narrow bones (bone area for height) and light bones (BMC for bone area). Crabtree et al. [31] evaluated the relationship between muscle and bone mass and proposed an algorithm in two stages to understand if the cause of the bone deficit is primary or secondary to sarcopenia, in children with chronic diseases. The first step assesses whether there is sarcopenia through the relationship between total body lean mass (TBLM) and height and the second assesses whether there is osteopenia, through the relationship between BMC and TBLM. TBLM measured by DXA has proven to be one of the main predictors of BMC in healthy population [32].

The study of BMC is considered one of the preferred methods for bone status assessment due to its reproducibility, reliability, accuracy and lack of errors related to the aBMD. BMC measured by DXA showed strong correlation with BMC evaluated by QCT ($r = 0.94$) [33]. A study proposed that BMC and bone area assessed for height were the measures that most closely correlated to bone strength parameters measured by pQCT [34].

Although DXA evaluates regions consisting primarily of cortical bone (total body) and trabecular bone (lumbar spine), it is not able to obtain cortical and trabecular aBMD separately, once aBMD is the result of the relationship between the amount of bone beneath the periosteal envelope and bone size.

DXA has been used to rule out asymptomatic vertebral fractures in patients at high risk of bone fragility, such as those receiving long-term glucocorticoid therapy. Newer software may provide sufficient image quality to screen for these spine fractures with far less radiation than conventional radiography. It can be performed at the same time as the routine DXA assessment [19].

In 2013, a group of experts from ISCD made the following recommendations for DXA performance and evaluation in children and adolescents:

1. The recommended sites for densitometric evaluation in children are the lumbar spine (LS) and the total body (TB) (preferably excluding the head in small children). Other sites may be useful depending on the clinical need. The hip is not a preferred measurement site in growing children because of variability in skeletal development [19]. In children under 3 years of age, only LS DXA should be performed (absence of reference values and difficulties in positioning for TB DXA in this age group) [18].
2. The densitometric variables should be expressed in standard deviations (Z scores rather than T scores, as in adults), indicating the difference from the average value of the healthy population of same age and gender [19].
3. Low BMC or BMD are diagnosed when the Z score is less than or equal to –2 standard deviations (SD) for age, gender, ethnicity and/or body size, when appropriate [19].
4. Osteoporosis diagnosis in children should not be performed based only on DXA results, i.e. in the absence of clinical evidence of bone fragility. If Z score is less than or equal to –2 SD, but there is no relevant history of fracture, the term low bone mineral content or low bone mineral density for age (or for height, when the adjustment is set), should be used. It is necessary to be careful in relation to this because, unlike in adults, it was not possible to correlate any densitometric variable with the risk of fracture in children [20].
5. A fracture history is considered clinically significant when at least one of the following criteria is fulfilled: two or more fractures of long bones until the age of 10; three or more fractures of long bones at any age up to 19 years; one or more vertebral compression fractures. The last criterion makes the diagnosis of osteoporosis regardless of DXA [20].
6. In children with growth disorders or delay in skeletal maturation, the densitometric measurements (BMC and aBMD of lumbar spine and total body) should be adjusted to prevent misinterpretations. For the spine, the adjustment should be done by estimating the vBMD or using the Z score for height. For the total body, the adjustment must be made using the Z score for height [19].
7. If a follow-up DXA scan is indicated, the minimum interval between scans is 6–12 months [19].

DXA is considered the gold standard method to assess bone mass in all age groups, once it is the most studied technique to date. In spite of being widely available in tertiary centers, there is still, even in these centers, little knowledge about the exam particularities in children and adolescents, which can lead to misinterpretation of results. Some factors to be considered and that limit its use are its high cost and the ionizing radiation, which preclude its application for large-scale preventive studies in this age group.

Quantitative computed tomography (QCT)

The term QCT describes the analysis of the computed tomography (CT) images using dedicated software to extract quantitative parameters. QCT has some important advantages over DXA once it allows a tridimensional study of bone. It can measure the true vBMD, in g/cm^3, a measure independent of bone size. It also assesses bone structure

and geometry, both determinants of bone strength, and analyzes cortical and trabecular bones separately [15, 37].

The types of CT scanners used in bone densitometry are: whole body general-purpose CT scanners and dedicated peripheral QCT (pQCT) and high-resolution pQCT (HR-pQCT) scanners that are smaller and less expensive. The term central QCT refers to the technique applied to the spine and proximal femur, using general-purpose CT scanners. pQCT is the application of QCT to appendicular skeletal sites (arms or legs), executed on dedicated peripheral or general-purpose CT scanners. HR-pQCT is also a pQCT method but refers to a technique with which trabecular and cortical architecture can be quantified [37].

Central QCT

Central QCT of the spine is a research application to obtain a measure of vBMD in the trabecular compartment of the child vertebral bodies. Trabecular bone is more metabolically active than cortical bone, and changes may be greater with time, disease, and treatment. Scan times on modern machines are rapid, and the child may be more comfortable in a supine position on a full length table, especially those with physical disabilities (e.g. cerebral palsy or Duchenne muscular dystrophy). The main disadvantage of this method is the high radiation dose required that makes it unsuitable for use in pediatric population [38]. Currently, adult scan protocols are being used and there is an urgent need for the development of pediatric protocols to minimize radiation dose [37].

Peripheral QCT (pQCT)

pQCT allows tridimensional analysis of some appendicular bones, primarily the radius and tibia, using lower doses of radiation when compared to central QCT. It provides analysis of cortical and trabecular vBMD and also specific geometric parameters of images obtained through cross-section (total area, cortical area, cortical thickness, periosteal and endosteal circumference, etc). A cross-sectional muscle area is also commonly reported. These parameters can be used to calculate an index of bone strength [39]. In spite of the advantages, there are unique difficulties in children. The smaller and thinner cortical bones are more subject to partial volume effects. Partial volume effects are a function of the resolution of the image (voxel size) and the size of the bone measured. They occur because the voxels located close to the bone edge are more likely to be comprised of both bone and soft tissue and will have a lower density value than the voxels that are attenuated only by bone. Smaller bones will have a higher proportion of voxels close to the bone edge and may thereby appear to have a lower cortical vBMD due to this artifact. Furthermore, the presence of epiphyseal plate and the variation of metaphysis size with growth make difficult to obtain measurements at the same location for longitudinal studies [40]. Although pQCT generates vBMD, a three-dimensional measure that is not confounded by body size, measures of cortical geometry and muscle area are proportional to the length of the bone and should be interpreted considering this variable. Therefore, the interpretation of this size-dependent pQCT measures in children with advanced or delayed growth is complex. Lastly, the method has not yet been standardized and lacks databases with reference values [41]. For these reasons, pQCT is not routinely used for clinical purposes, except in some local centers with appropriate expertise [37].

High-resolution pQCT (HR-pQCT)

HR-pQCT scanner has recently been introduced. It measures three-dimensional bone microarchitecture and vBMD in cortical and trabecular compartments of the distal radius and tibia, with accuracy previously unachievable and with relatively low-dose radiation. HR-pQCT is currently a research tool and shows promise for describing the changes in bone architecture with skeletal maturation. Many outcome measures are provided, some of which have been derived to be equivalent to histomorphometric parameters: trabecular number (Tb.N), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), cortical thickness (Ct.Th), cortical porosity (Ct.Po), bone volume/total volume (BV/TV), cortical, trabecular and total bone area, cortical and trabecular vBMD. The proper positioning of the patient is crucial to accuracy and reproducibility. Because it has a high resolution and relatively long scan times (3 min) it needs a secure fixation of the limb and a quiet scanning environment to minimize movement artifacts [42].

Bone quantitative ultrasonography (QUS)

The recent interest in QUS is due to the fact that the method provides a new way to evaluate bone tissue. QUS exploits bone quantitatively and qualitatively, assessing connectivity, elasticity and architecture, in addition to mineral density, thus providing a measure of “bone quality”, currently used as an overall indicator of bone strength [43].

It consists of a safe, easy to use and cost effective technique. The reproducibility is high, the devices are portable and only a few minutes are required to perform measurements, in addition to not use radiation. These features are particularly interesting to assess bone mineral status in children and adolescents [14, 44], and sets QUS as a viable method for primary prevention studies in this age group.

When a sound wave propagates through a medium, gradual changes of its shape, intensity and speed are influenced by the physical properties of the medium [45]. Based on this principle, the transmission speed and the amplitude of the ultrasound signal reflect bone tissue characteristics, while propagating through it [46]. Although the potential clinical application of this technique has already been shown in a large number of diseases that affect bone health [44, 47–53], this method is still little studied and used.

There are several QUS devices available in the market, evaluating different peripheral skeletal sites and providing specific ultrasonographic parameters. Those which may be employed in children are described in Table 1.

The ultrasound equipment consists of two transducers, a transmitter and a receiver. At the heel and phalangeal sites, the transducers are placed on opposite sides of the bone with a variable distance among them according to the bone plus soft tissue thickness. The ultrasound wave produced by the transmitter crosses the medium and is received by the second transducer [14]. Soft tissue (like subcutaneous fat or edema) should be minimal because it affects the velocity and attenuation of the signal. Alternatively, a multisite device, which accesses the radius and the tibia, combine the transmitter and the receiver at a fixed distance in only one probe, positioned on one side of the bone, and can be used to measure the ultrasound velocity longitudinally along the cortical bone [14].

Calcaneal QUS, the most widely validated technique, assesses predominantly trabecular bone and has been recognized by the ISCD, in 2007, as a technique that can be used for low bone mass screening in postmenopausal women and men over 65 years. According to this society, calcaneal QUS, in conjunction with clinical risk factors, can be used to identify a population at a very low fracture probability in which no further diagnostic evaluation may be necessary [54].

Two main variables are provided by this device: the speed of sound (SoS), expressed in meters per second (m/s), and the sound wave attenuation (BUA – broadband ultrasound attenuation), expressed in dB/MHz. SoS is calculated as the ratio of the distance traveled by the impulse (the distance between the probes) and the time taken by the signal to travel that distance (Figure 1). The accuracy of the variable SoS in children is described as being better than that of BUA, as well as in the adult [55]. Foot placement is a main cause of inaccuracy of the latter measure, which can be a limiting factor in longitudinal studies [56].

A more recent technique, the phalangeal QUS, has been studied for assessment of bone mineral status in children and has shown great accuracy and reproducibility [14]. It examines the distal end of the dyaphysis of the proximal phalanges of the 2nd to the 5th fingers of the non-dominant hand, in which two transducers, an emitter and another receiver, are positioned. The anatomic region of interest contains approximately 60% of cortical bone, in addition to trabecular bone and a small

Table 1: Characteristics of the main QUS methods available in the market to evaluate the child (adapted from Baroncelli) [14].

Skeletal site of measurement	Bone region of interest	Bone components at region of interest	Pathway of ultrasound transmission inside the bone	Main parameters obtained	Related CV, %
Heel	Midcalcaneus	Trabecular bone (>90%) with thin cortical shell	Transverse	SoS BUA SI and QUI	0.2–3.9 2.7–7.0 1.9–2.7
Proximal phalanges (fingers II–V) of the hand	Distal end of diaphysis below the condyles	Cortical bone (~60%) Trabecular bone (~40%) Small medullary canal	Transverse	AD-SoS BTT UPBI	0.3–0.9 1.0–3.5 2.85
Radius	Distal third	Cortical bone (>95%)	Axial	SoS	0.4–0.9
Tibia	Midshaft	Cortical bone (~100%)	Axial	SoS	0.3–1.0

QUS, bone quantitative ultrasound; CV, coefficient of variation; SoS, speed of sound; BUA, broadband ultrasound attenuation; AD-SoS, amplitude-dependent speed of sound; BTT, bone transmission time; UBPI, ultrasound bone profile index; SI, stiffness index; QUI, quantitative ultrasound index.

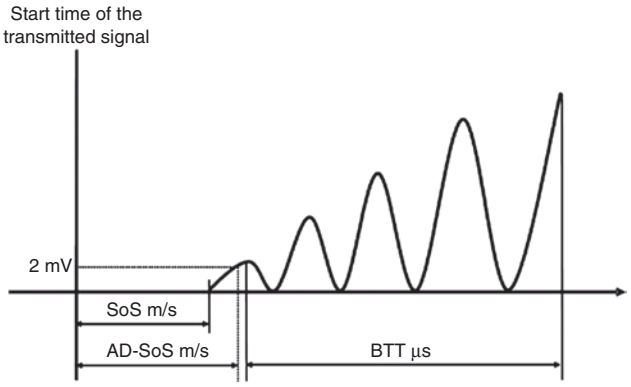

Figure 1: Analysis of the trace of the sound wave to calculate SoS, AD-SoS and BTT (adapted from Baroncelli) [14].

medullary canal [57], being sensitive to early changes in bone mass [41]. Two parameters are usually provided by phalangeal QUS in children and adolescents evaluation: the amplitude-dependent speed of sound (AD-SoS) and the bone transmission time (BTT). Bone measures are provided automatically by the device, from the average of 96 acquisitions of the four fingers, and are not observer-dependent [58].

AD-SoS is expressed in m/s and represents the speed of the sound that goes through the bone. The device calculates this parameter measuring the finger width (including the soft tissue) and dividing it by the trip time of the sound wave, defined as the time interval between the transmitted pulse and the received signal, considering the signal that reaches a minimum predetermined amplitude of 2 mV for the first time. Thus, unlike SoS, the calculated speed of sound is amplitude-dependent [58, 59] (Figure 1).

BTT is expressed in microseconds (µs) and represents the bone transmission time. It is calculated as the difference between the time taken for the first peak of the received signal to reach its maximum level in bone tissue and the time obtained when only soft tissue is present between the transducers (Figure 1). This parameter is calculated only from the phalanges II to IV and the transmission time in the soft tissue is measured between the base of the thumb and the index finger, during each session. BTT, therefore, unlike AD-SoS, only reflects the bone properties, regardless of the confounding effects of the soft tissue [58].

The variables AD-SoS and BTT from phalangeal QUS have shown to be highly correlated and appear to provide similar information [58]. Clinical and experimental studies indicate that these variables must reflect cortical mass and porosity [57], in addition to geometrical parameters such as cortical thickness [60] and area [57, 61].

Finally, the multisite quantitative ultrasound device measures SoS in axial transmission mode along the cortex of the mid-shaft tibia and the distal third of the radius [62]. SoS is also expressed in m/s (Figure 1) and is known to be dependent on several bone parameters, including cortical thickness, density; micro-structure, and elasticity. It has been proven that this type of dependency exists until the cortical thickness is greater than 4 mm [63].

To improve precision, some QUS devices provide additional variables such as the stiffness index (SI), the quantitative ultrasound index (QUI), or the ultrasound bone profile index (UBPI). SI and QUI are derived from the mathematical combination of both SoS and BUA, obtained from calcaneal QUS, and expressed as percentage. UBPI at phalangeal QUS is a measure that quantifies the characteristics of the sound wave transmission. The values given range from zero to one, and the higher the index the lower the probability of fracture. It seems to reflect properties more related to bone quality, as elasticity and microarchitecture, since it presented a different pattern from that of AD-SoS, with values independent of age up to 30 years [53]. The clinical usefulness of these QUS variables should be validated in children [14].

Some authors have reported that the ultrasonographic variables, as well as the densitometric measures, are correlated to height and that their interpretation must also be made with caution, taking into account this correlation [64, 65]. This is probably because the ultrasonographic variables do not merely reflect density (which remains relatively constant until puberty) [66], but also other bone resistance indicators [14, 43, 64]. Bone geometry, for example, is influenced by height, since the skeleton adapts to the biomechanical forces placed on it with growth [51]. Bone size can affect the ultrasonographic parameters mainly in the heel [67]. Regarding phalangeal QUS, it was estimated that only 6% of the AD-SoS values are related to the finger width, a minor confounder of this measure [68].

Moreover, some evidences indicate that the thickness of the surrounding soft tissues at the heel [69], proximal phalanges of the hand [70, 71] and tibia or radius [10, 72] may influence the QUS variables, underestimating them. To overcome this problem, phalangeal QUS device can perform an adequate correction for the overlying soft tissue with BTT, a more accurate parameter to assess bone mineral status particularly in obese individuals [14].

The higher the absolute value of the ultrasonographic variables SoS, BUA, AD-SoS and BTT to a certain age group, the better the bone mineral status. There are some pediatric reference curves, obtained with reasonable number of children and adolescents [58, 73, 74], and bone measurements are expressed in Z-scores for age, height and pubertal stage, according to the QUS device used. Just as in the interpretation of DXA in children, a measurement

below –2 SD identifies bone health impairment or "low bone mineral status" in relation to the anthropometric variable considered [14].

QUS at heel, phalanges and radius have been shown to be comparable to DXA in identifying postmenopausal women with vertebral fractures [75–78]. Fielding et al. [49], using the calcaneal QUS, managed to identify, with the same sensitivity of DXA, children with low-impact fracture history. Similar results were found by Baroncelli et al. [79], measuring AD-SoS in the phalanges of the hand and the LS aBMD and vBMD by DXA. Mussa et al. [80], assessing 1719 children with bone diseases, also demonstrated that phalangeal QUS managed to discriminate fractured and non-fractured patients, identifying specifically those with fractures related to bone fragility. It seems that calcaneal QUS predicts bone fragility regardless of BMD [81] and that the combination of DXA and calcaneal QUS data improves prediction of fracture [82].

Studies have shown a variable correlation (since no correlation to strong correlation), between the variables measured by QUS and DXA and/or pQCT [10, 47, 64, 83–86]. A weak, but significant, positive correlation ($r = 0.22$; $p < 0.05$), was found between SoS in the heel and vBMD in the radius, measured by pQCT [64]. Moderate correlation was found between AD-SoS, measured by phalangeal QUS, and forearm BMD, measured by DXA ($r = 0.66$; $p < 0.000001$), in children with genetic diseases [84]. Recently, Gonçalves et al. [86] also demonstrated a significant correlation (which ranged from 0.59 to 0.72; $p < 0.001$), between phalangeal QUS parameters and those of the DXA (from lumbar spine and total body), in Brazilian patients with congenital adrenal hyperplasia.

Discordant results between DXA, QUS and pQCT do not necessarily mean methodological error [54]. Indeed, if the methods do not assess the same bone tissue properties, they are not interchangeable and cannot identify the same patients [10]. Some authors consider that QUS can provide different and additional information in relation to DXA [53, 81]. BUA measured by calcaneal QUS, for example, is influenced by trabecular connectivity [87] and by changes in the organic compounds of bone tissue [88]. The SoS, on the other side, seems to be more related to bone density than to bone elasticity [89]. Furthermore, the use of different reference data for each method may be a cause for inconsistency. Anyway, more studies are needed to investigate the correlation and the agreement between the methods of bone mass evaluation.

A limitation of QUS, expressed by some authors, is that it does not analyze bone mass, density and geometry separately, only provides an integral estimation of bone mineral status [15]. Furthermore, QUS variables are still difficult to interpret and more studies are needed to assess the determinants of each variable. The reference curves are scarce in the pediatric age group and for the various ethnic groups. A study of over a thousand healthy Brazilian children and adolescents, of 6–17 years of age, was recently published [73, 90].

There are several types of QUS devices commercially available, which complicate the comparison of results between studies [60]. According to the ISCD, the variability of devices has hindered the method validation in clinical practice and standardization is required [54]. As a recommendation of this society, the method should not be yet used in clinical practice for the diagnosis of low bone mass in childhood and adolescence [18].

Magnetic resonance imaging (MRI)

MRI, like QCT, provides a volumetric measure of bone, but without use of ionizing radiation [91]. It enables the study of central or appendicular skeleton, providing information on bones and muscles in multiple anatomical planes without having to reposition the patient [8]. Application of full body MRI to bone structure quantification is limited by poor accessibility, but dedicated peripheral MRI (pMRI) units have been developed. In adults, pMRI has been used to demonstrate trabecular and cortical bone microstructure in the distal radius, distal tibia, calcaneus, and proximal femur at resolutions of 200 μm or higher [92]. The technique is a challenge to standardize, is not widely available, and has been applied infrequently in children. Accuracy is still being optimized. Other limitations of MRI are that the equipment is noisy for the subject being scanned and scan times are too long depending on the imaging sequence used, taking 20 to 30 min. As a consequence, keeping children still for this length of time is problematic with potential for more motion artifact. Lying in the long horizontal gantry of the scanner can be distressing to claustrophobic individuals. The environment of the scanner room may not be user friendly and parents cannot stay with the child during scanning. To date, MRI has been used only in research protocols; and its applicability in clinical practice has yet to be assessed [8].

Automated radiogrammetry

Radiogrammetry is the oldest method for quantitative assessment of the skeleton, and it is applied to a radiograph of the nondominant hand [93]. Metacarpal dimensions can be used to calculate various indices such as metacarpal

Table 2: Advantages, disadvantages and possible indications in clinical practice of the imaging methods for bone mass evaluation in children and adolescents.

Methods	Advantages	Disadvantages	Possible indications in clinical practice
DXA	Widely available in tertiary centers Most used, known and studied method (gold-standard) Short analysis time Good accuracy	Radiation is used, albeit in small doses: 6.7–31 μSv (with a multiple X-ray beam) Demands that the child remain still Bidimensional measure, providing only an estimate of bone mineral density Lack of robust pediatric reference curves High cost	Children and adolescents (0–19 years) with primary chronic bone disease or at risk of secondary bone disease (if an intervention to reduce fracture risk is potentially beneficial and DXA results can influence the management) [9] In children under 3 years, only lumbar spine DXA should be performed (no RV and positioning difficulties in total body DXA in this age group) [18] Vertebral fracture analyses in selected patients No indication for preventive studies
Central QCT	Measures cortical and trabecular volumetric bone mineral density	High dose radiation is used (50–100 μSv), which prevents routine use in children Non-portable machine, lack of accessibility and lack of RV High cost	No indication to date [18]
pQCT	Measures cortical and trabecular volumetric bone mineral density Use minimal dose of radiation (<2 μSv) Portable and less expensive machine	Difficult to correct positioning in children Cortical vBMD may be underestimated due to partial volume effects Not clinically available and lack of RV	No indication to date, except in some local centers with appropriate expertise [18]
HR-pQCT	Measures cortical and trabecular volumetric bone mineral density Use minimal dose of radiation (<2 μSv) Provides measures of microarchitecture Portable and less expensive machine	Difficult to correct positioning in children Not clinically available and lack of RV	No indication to date
QUS	Portable and practical device for use in primary care Measures are obtained quickly and easily No radiation is used Reduced cost High reproducibility Quantitative and qualitative bone evaluation	Less available, known and studied Uncertainty about what each variable does reflect. It does not assess bone mass, density and geometry separately Scarce reference curves There are several types of devices available, making it difficult to compare studies It cannot be done if there is history of previous fracture or deformity at the measurement site	Good perspective for use in primary prevention actions in 0–19 years individuals [14] There is no formal indication yet (from ISCD) for confirmation of low bone mass, monitoring and evaluation of response to treatment of this condition [18]
MRI	Measures cortical and trabecular volumetric bone mineral density	Difficult to correct positioning in children	No indication to date

Table 2 (continued)

Methods	Advantages	Disadvantages	Possible indications in clinical practice
	No radiation is used Provides measures of microarchitecture	Long scan times High potential for motion artifact Lack of accessibility and lack of RV High cost	
Automated radiogrammetry	High precision Low dose of ionizing radiation Low cost Good potential to be widely available Can be used in primary care environments	Clinical value of measures still needs to be established Limited reference values	No indication to date

DXA, dual energy X-ray absorptiometry; central QCT, central quantitative computed tomography; pQCT, peripheral quantitative computed tomography; HR-pQCT, high-resolution pQCT; QUS, bone quantitative ultrasonography; MRI, magnetic resonance imaging; ISCD, International Society for Clinical Densitometry; RV, reference values; vBMD, volumetric bone mineral density.

cortical thickness and the pediatric bone index. Pediatric bone index is calculated using the three middle metacarpals by a formula containing the average values for transverse cortical area (A), bone width (W), and bone length (L): pediatric bone index = A/(W 1.33 L 0.33) [94]. Measurements by radiogrammetry are most sensitive to cortical bone changes (periosteal apposition and endosteal resorption) and provide useful information on bone changes during growth and aging [8]. Despite its wide availability and relatively low cost, the poor precision when manual calipers were used limited its use as a clinical or research tool. The potential value of radiogrammetry for assessing bone status has progressed with the application of computer-aided analysis. Now it uses computer image processing to automating the location of the regions of interest for analysis, which improves precision [93]. Automated radiogrammetry has proved to be a useful tool in adults as a predictor of bone fragility [95]. In children, there are reference data published [96, 97], the technique has been applied to identify individuals with increased fracture risk [97], to study normal bone growth and development [98], and differences between patient groups and healthy children [99]. More recently, it has been combined with automated bone age assessment in the BoneXpert system [99]. Radiogrammetry currently remains a research tool [8].

Table 2 summarizes the advantages, disadvantages and possible indications in clinical practice of the methods of bone mass evaluation in children and adolescents. We found a great methodological variation and much progress is still needed before the use of each of these techniques becomes viable. The tomographies (central QCT, pQCT and HR-pQCT) and the MRI, despite having the advantage of assessing the real bone mineral density, are not available yet for use in clinical practice [18]. Central QCT is harmful due to high radiation dose. The absence of radiation and technical practicality are attributes that bring good prospects for QUS use in the evaluation of children and adolescents considered, so far, "healthy" and those with chronic diseases potentially harmful to the skeleton [14, 73]. More studies are needed for standardization and definition of the parameters that will allow the use of this method for low bone mass diagnostic confirmation and for follow-up of children with this condition [18]. Automated radiogrammetry shows promise as a method able to flag individuals who might benefit from a complete bone assessment, but the clinical value of the measures still needs to be established [95]. Insufficient reference data for the pediatric population are a common limitation to all methods, including DXA. Caution should be taken in interpreting the results and ideally the patient should be compared to local data. Osteoporosis diagnosis in this age group should be made only if a clinical evidence of bone fragility is present because, unlike in adults, it was not possible to prove a correlation of any bone measure with the risk of future fracture [20].

Conclusions

The reviewed studies show that, despite the emergence of new technologies, DXA remains the gold-standard exam for diagnostic confirmation of low bone mass in all age groups, being a possible indication for evaluation

of children and adolescents (0–19 years) with primary chronic bone disease or at risk of secondary bone disease. The correct interpretation of the results requires adequate knowledge of its characteristics and limitations. In children and adolescents, the problems imposed by the skeleton growth should always be considered and provide greater complexity to the evaluation. Ideally, the normal values of bone measures should be defined taking into account not only age, gender, and ethnicity, but also stature and pubertal stage. Appropriate local reference curves are essential for correct evaluation of these patients in clinical practice.

Author contributions: Isabela Leite Pezzuti: literature review, text editing, approval of the final version of the text. Juliana Albano de Guimarães: literature review, text editing, approval of the final version of the text. Isabela Alves Campos de Lacerda: literature review, text editing, approval of the final version of the text. Maria Tereza Filgueiras: literature review, text editing, approval of the final version of the text. Adriana Maria Kakehasi: literature review, text editing, approval of the final version of the text. Ivani Novato Silva: literature review, text editing, approval of the final version of the text. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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