# Bone health in children and adolescents: the available imaging techniques

**Stefano Stagi**[1]
**Loredana Cavalli**[2]
**Chiara Iurato**[1]
**Salvatore Seminara**[1]
**Maria Luisa Brandi**[2]
**Maurizio de Martino**[1]

[1] Department of Health's Sciences, Anna Meyer Children's University Hospital, Florence, Italy
[2] Department of Surgery and Translational Medicine, Bone Diseases Unit, University of Florence, Florence, Italy

Address for correspondence:
Loredana Cavalli, MD
Bone Metabolism Diseases Unit, Careggi Hospital
Largo Palagi 1
50139 Florence, Italy
Phone: +39 055 7946303
Fax: +39 055 794 8053
E-mail: loredana.doc@gmail.com

## Summary

**Many clinical conditions affecting children can be associated with a loss of bone mass and quality, leading to an increased risk of fracture over the life. Actually, different techniques are available to assess bone density and/or bone quality, but their employment in children and adolescents requires the acknowledgement of their characteristics and reference values, as well as of age, sex and pubertal stage of the patient. In this paper, the main densitometric techniques are described, and the principal conditions potentially affecting bone health in young people are indicated, with the intention of providing a small guide to prevent fractures in people at risk.**

*KEY WORDS: densitometry; bone mineral density; bone quality assessment; children; DXA; pQCT; QUS.*

## Introduction

From the birth, bone mass shows a progressive increase until about the third decade of life, when it reaches a maximum value defined "peak bone mass". The achievement of this value appears to be influenced by genetic, nutritional, endocrine and mechanical factors, as well as the accumulation of microdamage, turnover rate, architecture, degree of mineralization, in addition to the properties of collagen and bone matrix (1).
Any modification of each of the above factors may be the basis of a reduction, more or less important, of the skeletal quality and resistance, with obvious pathological consequences (2).

Many scientific evidences document an altered bone density and/or quality affecting not only the adult but also the childhood and adolescence. Primary task of the Practitioner or the Specialist is to make the earliest diagnosis as possible of an alteration of bone structure, in order to examine every condition potentially associated with it, so that the appropriate measures can be established in time for the prophylaxis of the debilitating complications (3).
The diagnosis must always be based, other than on clinical criteria and/or laboratory, on an accurate assessment of bone mineral density (BMD) through densitometric methods, that allow to identify reduction in bone mineral content (BMC) around 3-4%, thus quite slighter than that shown by the traditional radiography (4, 5).
The result of bone densitometry in children and adolescents, however, requires a very accurate clinical interpretation, taking into account the specific characteristics of the different densitometric methods, to reduce the risk of erroneous diagnosis of altered density and/or bone quality. For example, Dual-X-Rays Absorptiometry (DXA), despite being the "gold standard" technique for the evaluation of bone mineral density and the assessment of fracture risk in adults, it is still burdened by the use of radiation, as well as by restrictions on short- term reproducibility. In contrast, a quantitative ultrasonometry (QUS) can give skewed results if, for example, the patient has recently presented a fracture or an inflammatory process at the level of the segment studied (4-7).
So, when it is necessary to carry out a densitometric examination, it should be clear the problem affecting the patient, the need of a follow-up, the age of the patient to be studied (4).

## Methods of evaluation

Over the past 25 years, different densitometric techniques have been developed for the non-invasive measurement of bone mass (Table 1) (4-7).
Bone densitometry allowed us to deepen the knowledge on the complex bone structure highlighting the different response of trabecular and compact bone to biomechanical, hormonal and nutritional stimuli. In fact, BMD is one of the most important factors that contribute to the mechanical strength and stiffness of bone, even if other factors, such as

Table 1 - Main densitometric techniques for non-invasive measurement of bone mass.

| |
|---|
| Plain radiography |
| Qualitative morphometry |
| Quantitative morphometric techniques |
| Dual-energy X-ray absorptiometry (DXA) |
| Peripheral quantitative computed tomography (pQCT) |
| Bone Quantitative Ultrasonometry (QUS) |
| Quantitative Magnetic Resonance (QRM) |

the alterations of trabecular number, thickness and spatial distribution, play an important role in determining bone tissue resistance (8, 9).
With the exception of QUS, densitometric techniques are based on the absorption and interaction with the bone tissue of incident photons (X-rays) (4).
In particular, projective techniques, such as Dual energy X-ray Absorptiometry (DXA or DEXA), providing a two-dimensional representation of bone structure examined, do not allow to obtain volumetric data.
The information derived from bone densitometry are:
- the measurement of bone mineral content (BMC), expressed in g/cm;
- the measurement of bone mineral density in an area (BMD), in g/cm$^2$ (10);

Central and Peripheral QCT, thanks to their three-dimensional approach, also allow to monitor bone mineral density in a given volume (vBMD expressed in mg/cm$^3$) (11).
In adults, DXA-derived BMD is significantly correlated with bone strength and consequently with the risk of fractures. Therefore it is essential to assess BMD, but it would be important to evaluate the peak bone mass reached and the rate at which it increases or decreases over the years, so as to obtain also a dynamic information, similarly to the curves used in auxology representing the speed of growth (12).
Actually the research is also directed towards the development of new non-invasive technologies, based on energy sources other than ionizing radiation (used in DXA, QCT and pQCT), such as bone quantitative ultrasonometry (QUS) and Quantitative Magnetic Resonance (QMR), which provide data not only on bone mass but also on bone quality (4).

**Conventional radiology**

In traditional radiographic study, attention should be directed not only on the semiquantitative evaluation of bone density (subjective criterion, influenced by the implementing rules of the examination or the quality of the image), but also to the morphological study of the bone with the analysis of the cortical compartment (endosteum thickness, homogeneity of compact bone to recognize the potential increase in intracortical striae) and cancellous compartment (distribution of the trabecular beams, their architecture, density and thickness). In this regard, it must be remembered that conditions of increased bone resorption or reduced bone synthesis are greater when turnover is elevated, i.e. at the level of spongeous (4).
Thus, osteopenia is radiologically characterized by: 1) higher bone radiolucency due to the reduction of the trabecular thickness; 2) a thinning of cortical bone.
Typical exams for this assessment are the scan of the hand and the morphometric study of the spine.
The use of conventional radiology in the study of osteopenic syndromes still presents limitations, especially in the initial stages of these diseases, since, in order to appreciate radiological signs of reduction in bone density, a loss in the amount of mineralized bone of 30-40% is needed. Furthermore, these methods providing a semiquantitative evaluation present the limit of a high intraoperative variability (4).
The morphometric analysis, however, overcomes the limitations related to the evaluation of the operator as it allows, in a reliable manner, to measure the heights of the vertebral bodies, so as to recognize vertebral fragility fractures (4).

**Densitometry X-ray dual-energy**

Dual energy X-ray absorptiometry was introduced in 1987 and is constituted by a radiation source, the system which allows the separation of the two energy levels and a digital detector (10).
The source of X-radiation is located under the bed and moves synchronously with a system of detectors placed above the patient. While scanning, the computer reconstructs, pixel by pixel, the image of the section under consideration, after the operator has manually placed one or more regions of interest (ROI), the unit provides data of BMC and BMD of each district examined (Figure 1).
With second-generation scanners a lateral projection of lumbar spine is also possible, thus excluding from the densitometric analysis structures such as ossificated ligaments and aortic wall calcifications, which can artificially increase BMD value (10).
After scanning, the values obtained are reported automatically on a reference curve normalized for age and sex, which is necessary for the diagnosis (8, 9).
The assessment of BMD in children still shows, however, some technical difficulties related to the method, which can lead to a false interpretation of the result:
- auxological parameters, such as height or weight, may influence the evaluation of BMD. A smaller bone, in fact, can have a falsely reduced density (g/cm$^2$), since, with a non-volumetric method, it is impossible to directly calculate bone thickness.
- Pubertal development. This phase of the development strongly influences the peak bone mass. For this reason, a reduction of BMD should be evaluated with caution in the course, for example a delay of puberty.
- Radiation dose. The dose supplied by DXA is inferior to 10 mSv, relatively small compared to 700 mSv of a radiograph of the lumbar spine or 50 mSv an anteroposterior X-Ray chest scan (8, 9).

**Quantitative Computed Tomography**

Quantitative Computed Tomography (QCT) is the only non-invasive technique that measures the real density of bone tissue in a given volume (mg/cm$^3$), without the superimposition of other tissues (unlike the projective methods such as DXA) (4, 11).
Moreover, providing information of a three-dimensional entire region of the body (usually the lumbar spine and femoral

Figure 1 - DXA procedure.

neck), QCT allows to differentiate the trabecular and the cortical components (4, 11).
Peripheral quantitative computed tomography (pQCT) requires dedicated equipments for the scan of superior or inferior limbs. Similarly to the study of the lumbar spine, pQCT exam of forearm starts with a scout view centering, in which precise points of reference are located proximally at 4% and 66% of the distance between the ulnar styloid and the olecranon apophysis, subsequently acquired a single axial scan of the radius and then a program of automatic processing allows to separate the trabecular from the cortical component and gives the corresponding BMC and vBMD. Moreover, by pQCT is possible to evaluate *in vivo* geometrical parameters, such as marrow and cortical cross-sectional area (CSA), cortical thickness, periosteal and endosteal circumference, as well as biomechanical parameters, like cross-sectional moment of inertia, indicating bending strength, polar moment of inertia, which is a measure of bone strength in torsion, and Strength Strain Index. An important but not largely studied peculiarity of pQCT is that also CSA of muscle and fat can be extracted (4, 11).
The relationship between pQCT parameters of healthy subjects and the changes observed with increasing age has been the object of several publications, which have shown a correlation between changes in bone mass at the peripheral level and age of the subject. Very little is known, however, on different aspects of this technique, such as BMD reference limits and behaviour of the different variables in many pathologies of the elderly.

**Quantitative Magnetic Resonance**

As above mentioned, BMD is correctly assessed both with QCT and DXA, however, equally important factors for mechanical strength are the changes in bone micro-architecture. In this regard, QRM (Quantitative Magnetic Resonance imaging) is a new non- invasive technique able not only to evaluate the alterations described above, but also to highlight subtle fracture lines (not yet detectable with other methods, which appear as lines hypointense in RM T1-weighted images and hyperintense on T2-weighted images), and to make a differential diagnosis between traumatic and pathological fractures, including malignant and benign vertebral collapse.
The evaluation of compact bone tissue with the RM is not easy, but it can be used for the quantitative characterization of the trabecular bone structure, exploiting the inhomogeneous magnetic field caused by the different magnetic properties of bone tissue and bone marrow. The most studied sites with QRM are the heel, the phalanges and the distal radius.
The progress of MRI imaging techniques have potential applications both in the *in vivo* and *in vitro* study of trabecular bone architecture and its biomechanical properties in the evaluation of osteoporosis and prediction of fracture risk.
The non-invasiveness of MRI along with its ability to obtain 3D images suitable for the quantitative evaluation of the trabecular bone structure makes this technique particularly useful for the *in vivo* study, however, the QRM, at the moment, is only used in research (4, 13).

**Quantitative ultrasound (QUS)**

Quantitative bone Ultrasonometry (QUS) has been introduced in clinical practice for several years, since this method is fast to execute, reliable, inexpensive and does not use ionizing radiation. Moreover, QUS is extremely suitable for screening and follow-up of children and adolescents as it is painless, fast to execute, completely free of contraindications, so as it guarantees a good compliance by the pediatric patient (4).
The ultrasound techniques are based on the measurement of the degree of attenuation (broadband ultrasound attenuation [BUA]) or ultrasound velocity (speed of sound [SOS], amplitude-dependent speed of sound [AD-SoS], and bone transmission time [BTT]) during the crossing in the transverse direction of the bone segment under examination (e.g. phalanges of the hand, calcaneus) or on the measurement of the speed of the ultrasonic wave after transmission along the longitudinal axis of the bone examined (e.g. medial portion of the tibia) (4).
Given the physical characteristics of ultrasound, these methods can provide useful information, not only on the density, but also on structure and mechanical properties of the bone segment in question. The ultrasound methods, however, show specific characteristics in relation to the parameters examined, the procedures for data acquisition, and seat skeletal evaluation. Hence, these factors make the various methods of bone ultrasonometry completely different from each other (14).
The sites normally analyzed are:

- the phalanges of the non-dominant hand: distal metaphyseal ends of proximal phalanges of all the fingers except for thumb contain both trabecular and cortical bone, therefore are characterized by high turnover and sensitivity to changes in the metabolism due to both physiological (e.g. growth) and pathological conditions (such as hyperparathyroidism);
- the heel: almost entirely constituted by trabecular bone, it has the advantage of having an homogeneous and parallel outer surfaces flat, therefore suited to the geometry of propagation of the ultrasound beam, the region of interest analyzed represents only a small part of the calcaneous, as the size of the calcaneous are superior to those of the ultrasound beam (15).

The reference values for measurements at phalanges of the hand, heel and tibia are available for subjects in childhood, although, for the Italian population, only phalangeal QUS reference values are currently available (Figure 2).
Numerous clinical studies have demonstrated a statistically significant correlation between ultrasonometric and densitometric values; however is not sufficient to be able to trace in a reliable manner the value of BMD through the QUS results. These observations demonstrate that QUS cannot replace bone densitometry, but can be integrated to it (4, 16).

**Interpretation of densitometric data**

In children and adolescents, when a physician diagnoses a low bone density and/or quality, the first step to take should be to find the causal factors, the second to promote proper bone growth, if possible before puberty, in order to establish measures necessary for the achievement of peak bone mass to prevent or reduce the risk of osteoporosis in adulthood.
Etiopathogenetic bases of osteoporosis are in fact recognized in the early stages of life, since a sub-optimal bone growth in the infancy seems to be at least as important as the loss of bone mass occurring in adulthood. So, to build a strong and healthy skeleton during childhood and adolescence and to learn a correct life style in this period can be the best defense against the insurgence of osteoporosis.

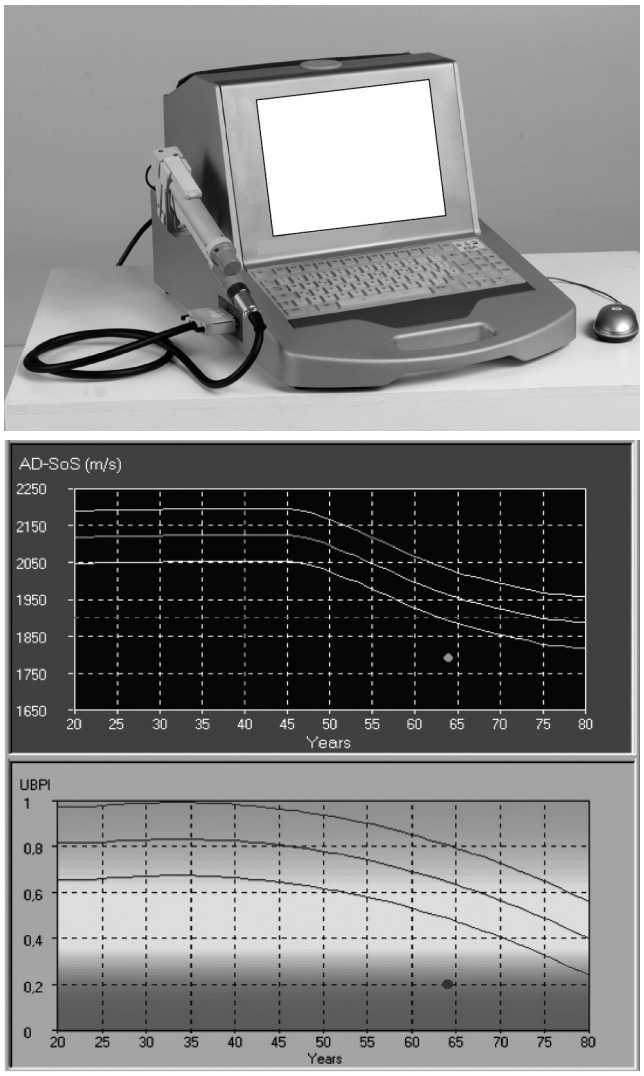


Figure 2 - QUS device and references curve for AD-SoS and BTT.

In fact, several studies show that certain factors can cause a deficiency of bone mineralization still in the fetal and neonatal life (maternal deficiency of vitamin D, gestational diabetes, placental insufficiency, prematurity, breast- feeding without vitamin D supplementation, etc.). Then, a series of pathological conditions preventing proper bone maturation can add to these risk factors.

It would be important to know either the advantages and the limits of each available densitometric technique, and the reference values able to distinguish a pathological alteration from a condition at risk or a healthy one.

In fact, only in recent years a definition of osteopenia and of osteoporosis was reached for the childhood: in children and adolescents a reduction in BMD more than 2 SD lower than the mean for age and sex should be considered pathological, similarly to what is normally done for many auxological parameters. However, in addition to age, other variables such as race, height, weight and pubertal stage, may significantly interfere on the reference values (8, 9).

In adults, the parameters to be taken into consideration for a densitometric examination, are T-score and Z-score. However, it should be remembered that T-score is a parameter to use only in adult subjects.

The T-score is the number of standard deviations (SD) above or below the mean value of BMD in a population of healthy young adults of the same sex and ethnic group of the subject examined. The average value of this population is the value that the patient should have at the time of the peak, which is about 20- 25 years of age. In adults, for each standard deviation below the average, the risk of fracture doubles (e.g. T-score of -1 indicates a 2 times greater risk of fracture of a subject with a BMD corresponding to the average BMD of the healthy population). Values ranging between -1 and -2.4 SD are considered as belonging to an osteopenia, i.e. a reduced BMD; values of -2.5 SD or lower indicate osteoporosis.

Clearly, T-score cannot be used as an index of reduced bone density in children, and in any case before the age of twenty years, time of the achievement of physiological peak bone mass. Z-score, however, is the index used throughout the childhood and adolescence. It represents the number of SD above or below the average value of a group of healthy subject of the same age, other than ethnic group and sex, of the patient.

It should be noted that, until a few years ago, for the evaluation of pediatric patients, DXA Z-score was used with the same reference limits of T-score, although a correlation between low bone mass and risk of fracture has never been precisely defined for pediatric patients. For this reason, in 2004 the International Society for Clinical Densitometry (ISCD) has determined that the diagnosis of osteoporosis in children cannot be made solely on densitometric criteria, and the terms “osteopenia” and “osteoporosis” should not be used, while a condition of “reduced bone density according to chronological age”, is defined by Z-score inferior to -2.0 SD. The database pediatric reference for the interpretation of the Z score should be mentioned in the report.

**When a densitometric examination is useful**

In general, a densitometric evaluation, as well as depth to a question or clinical laboratory, should be performed in subjects that present the following risk factors (Table 2):

- Clinical or radiological findings of one or more fragility fractures, or history of multiple fractures in childhood caused by minimal trauma, or radiological findings of altered bone density;
- Chronic drug therapies (actual or planned): many drugs can interfere with the normal process of bone remodeling through 1) an increase in osteoclast activity, 2) a direct suppression of osteoblastic activity, or 3) inhibition of mineralization of the osteoid matrix. Among these drugs, especially important are anti-epileptics, whose chronic intake leads to a reduction in bone mineral density and an increased risk of fractures by about 34% in the adult population. Most of antiepileptic drugs interfere with the metabolism of vitamin D.
- Disorders associated with a reduced bone mass and/or quality, such as 1) endocrine diseases (primary or secondary amenorrhea, hypogonadism, hyperparathyroidism, hyperthyroidism, Cushing syndrome, acromegaly, GH deficiency, hyperprolactinemia, diabetes mellitus type 1). For example, in hypogonadism, in both male and female, estrogen deficiency leads to a reduction of bone formation, of the synthesis of active vitamin D, and of intestinal absorption of calcium, and an increased bone resorption, resulting in an altered density and bone quality; on the contrary a person with GH deficiency presents an alteration of densitometric parameters for a reduction of the formation and

Table 2 - Main conditions potentially causing an altered bone density and/or quality in childhood.

| Endocrine diseases | Iatrogenic causes |
|---|---|
| Hypogonadism | Corticosteroids |
| Insensitivity syndrome of estrogen | Anticonvulsants |
| Panhypopituitarism; GH deficiency | Gonadotropin-releasing hormone analogue |
| Hyperthyroidism | L-thyroxine (high dose) |
| Cushing's syndrome | Antiretroviral drugs |
| Primary hyperparathyroidism | Anticoagulants |
| Primary hypoparathyroidism | Chemotherapeutic drugs |
| McCune Albright Syndrome | Aromatase inhibitor |
| **Genetic and metabolic diseases** | **Chromosomopaties** |
| Osteogenesis imperfecta | Turner syndrome |
| Homocystinuria | Klinefelter syndrome |
| Marfan syndrome; Ehlers-Danlos syndrome | 22q11 deletion syndrome |
| Menkes syndrome | Down syndrome |
| Lysinuric protein intolerance | **Malignancies** |
| Phenylketonuria | Leukemia |
| Gaucher's disease | Lymphoma |
| Cystic fibrosis | Solid tumors |
| **Nutritional problems** | **Chronic diseases** |
| Nervous anorexia | Rheumatic (juvenile idiopathic arthritis, systemic lupus |
| Lattose intolerance | erythematosus, dermatomyositis) |
| Deficiency of calcium, copper, etc. | Kidney disease (chronic renal failure, renal tubular acidosis, |
| Vegetarian diets | idiopathic hypercalciuria) |
| Malnutrition | Hepato-biliary (cholestatic forms) |
| Total parenteral nutrition | Gastrointestinal diseases (celiac disease, Crohn's disease, |
| **Other** | ulcerative Colitis) |
| Immobilization/little use | Heart disease (congestive heart failure) |
| Intense physical activity | Hematologic (thalassemia, hereditary hemochromatosis, |
| Post-transplant | hemophilia, sickle cell anemia) |
| Paget's disease of youth | Immunological (systemic mastocytosis, Hyper-IgE syndrome) |
| Juvenile idiopathic osteoporosis | Overweight/obesity |
| Prematurity | |

mineralization of bone tissue and renal excretion of calcium; in addition, a hyperthyroid subject may present an altered density and/or quality of bone due to an increase in bone resorption induced by IL-6 and IL-8. In a person with Cushing's syndrome, glucocorticoids excess mediates a decrease of osteoblastogenesis, osteoblast and osteocyte half-life, reduced intestinal absorption of calcium. Finally, a subject with type I diabetes may present an alteration in bone turnover and density due to the production of advanced products of glycosylation of collagen type 1.

- Conditions associated with a transient decrease in bone density as a constitutional delay of growth and puberty (delayed onset of secretion of gonadic steroids, transient GH deficiency). For the characteristics of bone turnover, densitometric examination should be carried out at the beginning and repeated over time to evaluate the evolution; changes in bone mineral content, in fact, are carried out rather slowly. A cycle of bone remodelling requires a period of 4-6 months, from its start to its completion, and for this reason the evaluation of bone density at intervals of less than 6 months has little clinical significance.

In general, for the follow up of a condition that is associated with reduction in bone density, an evaluation every 12 months is sufficient, while an evaluation every six months should be indicated only in the quickly ingravescent forms, such as those arising from the use of corticosteroids or high-dose chemotherapy in intestinal malabsorption or in situations of severe malnutrition, or to evaluate the short-term effect on bone mineralization of pharmacological treatments (bisphosphonates, gonadal hormones).

## Conclusions

A reduced density or bone quality may be quite frequent in children and adolescents. This seems to be due to different problems, such as inadequate calcium intake, low vitamin D levels, and a reduced rate of physical activity.

In the adult, osteoporosis is a skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in its fragility and susceptibility to fracture, often leading to disability. It is also a major cause of morbidity and mortality among the elderly.

Pathological alteration of the density and quality of bone, however, can also affect children. During childhood a reduced bone density and / or quality can be either primary or represent a complication of chronic diseases or treatments. In any case, as the majority of bone mass is reached at the end of the longitudinal growth of an individual, the growth of the skeleton during childhood and adolescence is a determinant of the osteoporosis risk.

Therefore, osteoporosis should be considered as a pediatric disease with geriatric consequences.

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