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Diagnosis of Osteoporosis in Children

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Abstract

Since the endorsed use of pediatric bone software to assess bone mass through DXA in the 1990s, some concepts have been established to arrive at a correct interpretation of bone mineral density in this population. This review describes all elements that should be considered when diagnosing bone mineral density diminished for age. The use of the Z-score instead of the T-score and the history of bone fractures (only fractures of long bones and vertebral crushing are considered clinically relevant) are discussed. The evaluation of BMD (Bone Mineral Density) values by DXA according to pubertal stage, sex, and bone age is clarified. In addition mention is made of diseases which must be ruled out by clinical and biochemical parameters; the latter vary according to age and sex, so that the normal reference value for adults should not be used.

Keywords: Osteoporosis; Bone mineral density diminished for age; Children; Diagnosis

Introduction

In the 90s the use of a pediatric software for the evaluation of bone by densitometry (DXA) in children was recommended [1-4]. DXA assesses areal bone: bone mineral density (BMD) is calculated based on the content of bone mineral per bone area (g/cm^2), without evaluating bone volume, which is influenced by bone size and length.

Based on these concepts we shall begin to describe the various elements that have to be considered when evaluating bone health in the pediatric population, in an attempt to make a correct diagnosis of decreased BMD.

Key points

The diagnosis of osteoporosis in children requires: history of fracture and low bone mass.

- Low bone mass by densitometry is defined by the Z-score at or below-2.0 (adjusted for age, sex and height).
- You can use the terminology low BMD for chronological age if the Z-score is less than -2.0.
- In children therapeutic interventions should not be instituted only by measuring BMD.
- The lumbar spine and whole body are preferred sites for evaluation; hip BMD is not recommended.

One element that must be considered when performing osteologic evaluation in the pediatric population is the concept of peak bone mass. This represents the highest BMD, which is achieved between the second and third decades of life. It varies at different skeletal sites; for example that of the vertebrae is achieved around 20 years, whereas at the cortical bone it is achieved about 10 years later.

Obtaining optimal peak bone mass during adolescence is critical; it determines, together with the rate of bone loss in adult life, bone resistance and the susceptibility to fracture.

In order to achieve an optimal peak bone mass, an adequate calcium intake during childhood and adolescence is needed, along with physical exercise and sufficient sun exposure, to avoid vitamin D deficiency.

Table 1 shows the factors that modulate peak bone mass in adolescence [5,6].

Nutrition (calcium, protein)
Mechanical load
Environmental
Genetic (80%)
Hormones and growth factors

Table 1: Determinants of peak bone mass in adolescence.

For a proper interpretation of a bone densitometry report two concepts must be kept in mind: T-score and Z-score. The T-score compares the BMD of the patient with the mean value found in healthy adults aged 20 years; and Z-score compares the patient's BMD with that of his/her peers; i.e. healthy subjects of the same age and sex (Figure 1).

It follows that BMD in children and adolescents should be defined in terms of standard deviations from the mean observed in a control group of the same age and sex (Z-score) and not compared to the average of adults 20 years (T-score), since the child is in a process of gaining bone mass, which has not yet reached its peak [7]. Figure 2 shows the difference between a pediatric densitometry report of and one of an adult.

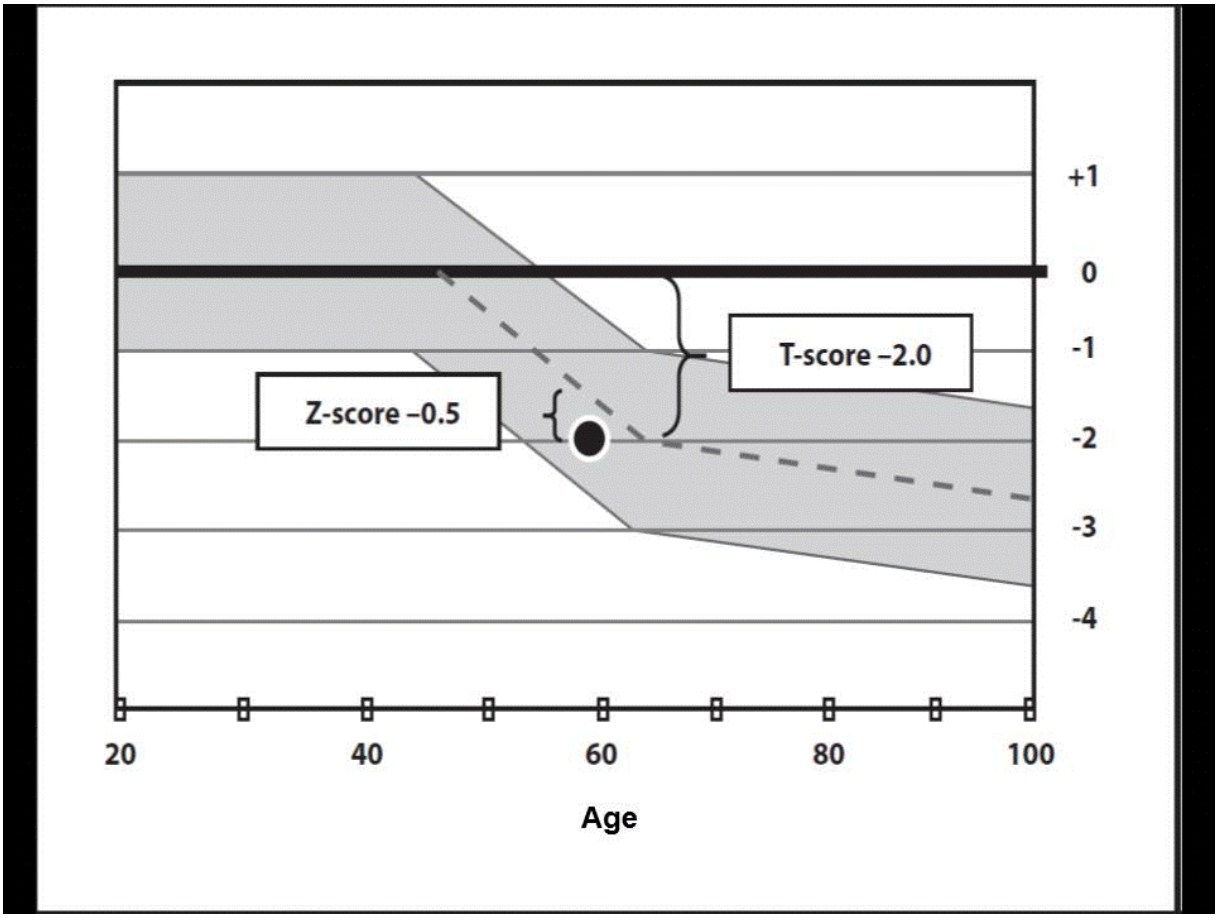

Figure 1: T-score or Z- score.

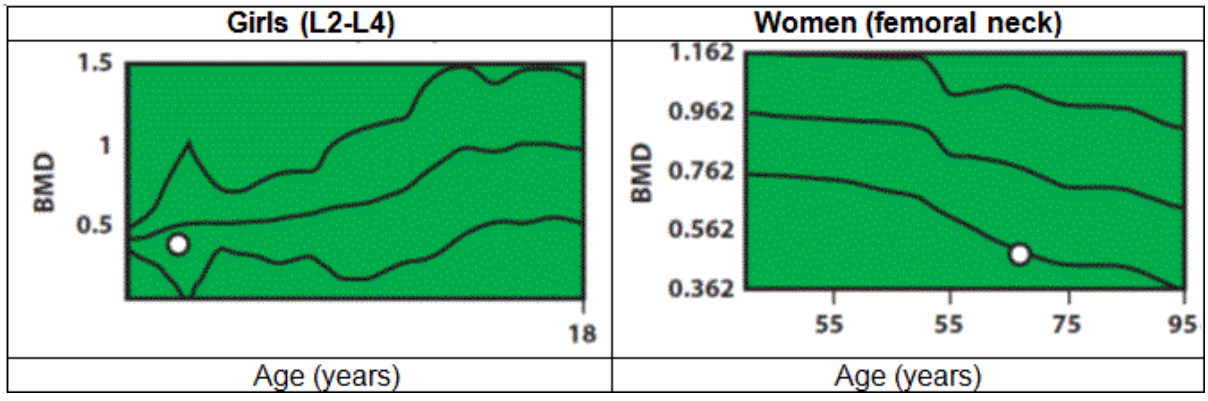

Figure 2: Important graphical difference between pediatric and adult densitometries.

Each equipment has its own reference values, which is another element to be considered when analyzing densitometry reports and especially when comparing two densitometries made with different equipments; direct comparison of absolute values should not be made, since there are systematic differences between densitometers made by different manufacturers.

When reading a densitometry report we must consider first the absolute value in g/cm^2 of the region under study, which allows comparison between two studies and infer whether the patient has improved or not; secondly we have to observe the value of the Z-score.

In children and adolescents it is recommended to order whole body bone densitometry, quite useful for monitoring treatment, or

densitometry of the lumbar spine, rich in trabecular bone, which metabolically more active. Hip densitometry is not recommended, since that area is more influenced by mechanical factors.

Norland Reference Values, Lumbar Spine (L2-L4)				
	Females		Males	
Age	Mean	2 SD	Mean	2 SD
3	0.42	0.08	0.48	0.14
4	0.45	0.18	0.47	0.14
5	0.52	0.48	0.50	0.2
6	0.54	0.18	0.54	0.18
7	0.52	0.2	0.56	0.24
8	0.55	0.28	0.59	0.2
9	0.59	0.26	0.59	0.24
10	0.62	0.44	0.61	0.32
11	0.65	0.48	0.63	0.32
12	0.72	0.46	0.62	0.46
13	0.87	0.56	0.71	0.42
14	0.90	0.52	0.79	0.66
15	0.95	0.42	0.96	0.48
16	1.0	0.48	1.01	0.36
17	1.01	0.46	1.06	0.5
18	0.97	0.46	1.09	0.7

Table 2: Reference values of lumbar spine BMD (L2-L4) in normal Argentinean children of both sexes (ages 3-18 years) studied with a Norland DXA equipment (modified from Zanchetta et al.).

BMD increases with age [8] (Table 2 and Table 3); that is why we need the reference values. They are different for each year of life. It is useful to have reference values for each equipment, which allows the calculation of the Z-score by age and gender when it is not present in the report (Z-score=Patient's BMD-mean BMD of the control group/ standard deviation of the control group).

Gender also makes a difference, with prepubertal boys having slightly higher values than girls; in the pubertal period girls have higher values than boys, and then again in the post-pubertal period males have higher values than women.

During pubertal development, the reference values increase as seen in Table 4 [9,10]. This increase is progressive and more marked from Tanner stage III onwards. This applies to the lumbar spine and whole body.

Reference Values in Young Adults (Norland)			
	Age (years)	Mean	2 SD
Lumbar Spine (L2-L4)			
Women	20	1.040	0.246
Men	20	1.138	0.287
HIP			
Trochanter Women	20	0.773	0.228
Femoral Neck Women	20	0.950	0.212
Trochanter Men	20	0.866	0.266
Femoral Neck Men	20	1.040	0.224

Table 3: DXA reference values for lumbar spine and hip; young adults, Norland (SD: standard deviation).

Tanner stage/Perc.	Minimum	25	50	75	Maximum
Women					
I	0.648	0.722	0.795	0.889	1.103
II	0.623	0.854	0.975	1.024	1.101
III	0.836	0.998	1.070	1.111	1.249
IV	0.960	1.090	1.184	1.243	1.453
V	0.971	1.087	1.115	1.239	1.364
Men					
I	0.569	0.665	0.743	0.819	1.052
II	0.687	0,872	0.895	1.010	1.104
III	0.742	0,897	0.946	1.007	1.291

Table 4: BMD of lumbar spine (L2-L4) according to Tanner stage in women and men; values in percentiles (modified from Bianculli et al.).

Another parameter to be considered when interpreting a densitometry in a child, is bone age; children with diseases causing delayed bone age (growth hormone deficiency, hypothyroidism, etc.) should have their BMD compared with reference values stratified for bone age and not for chronological age.

In 2007 the International Society for Clinical Densitometry released its official position regarding the use of densitometry in the pediatric population and the appropriate terminology [11].

It is not appropriate to use the term osteopenia in the pediatric population, the proper denomination is "low bone mass for chronological age". Low bone mass can be defined when the BMD Z-score is equal to or less than-2.0 adjusted for age, sex, and body size. And the term osteoporosis should not be used only on the basis of the densitometry report; the past history of fractures should be considered as well.

In children there is no a “threshold” BMD value that can predict the risk of fracture. One or more of the following fractures are considered clinically significant:

- A fracture of the long bones in the lower limbs.
- Vertebral compression fracture.
- Two or more fractures of the long bones in the upper limbs.

It is advisable to evaluate pediatric patients by whole body densitometry and/or densitometry of AP spine before indicating specific medical treatment. Response to treatment should be monitored with a repeat densitometry BMD after a minimum interval of 6 months. There is no sufficient evidence in the literature yet to support the clinical use of peripheral quantitative computed tomography (pQCT) for the diagnosis of low bone mass in the pediatric population.

Table 5 shows some of the situations in which bone densitometry should be requested in children and adolescents [5,7,12-17].

Radiological abnormalities - Osteogenesis Imperfecta - Idiopathic juvenile osteoporosis - Chronic renal failure - Prolonged immobilization (cerebral palsy) - Ehlers-Danlos syndrome - Bruck syndrome - Marfan syndrome	**Estrogen or androgen deficiency** - Turner syndrome - Amenorrhea - Klinefelter syndrome - Hypogonadism - Anorexia nervosa
Endocrine disorders - Cushing syndrome - Growth hormone deficiency - Diabetes mellitus - Hyperparathyroidism - Hyperthyroidism - Pubertal delay - Hyperprolactinemia - Acromegaly - Adrenal insufficiency - Alterations in the metabolism of vitamin D and phosphorus - Other	**Use of drugs** - Corticosteroids - Methotrexate - Heparin - Anticonvulsants - GnRH agonists - Medroxyprogesterone - Cyclosporine - High-dose levothyroxine - Other
Other causes - Celiac disease - Leukemia - Rheumatic diseases - Cystic fibrosis - Hematologic: leukemia, hemophilia, thalassemia - Infectious: HIV infection - Other	

Table 5: Indications for densitometry in children and adolescents.

Laboratory Studies

Regarding which laboratory studies are needed to study a child or teenager diagnosed with low BMD for chronological age or osteoporosis, we must consider:

- Clinical evaluation by history and physical examination, in order to rule out secondary causes of osteoporosis. Specific analyses can then be requested according to the suspected pathology.
- Laboratory determinations of calcium and phosphorus in serum and urine, along with regulatory factors (e.g. PTH, 25-hydroxyvitamin D, etc.) and bone turnover markers.
- It is important to be aware of reference values appropriate for to the patient's age, since some of values may vary with age (as discussed below).

Table 6 lists the laboratory determinations needed for assessing calcium andphosphorus metabolism.

Serum and urine calcium
Serum and urine phosphate
Serum and urine creatinine
Serum and urine magnesium
PTH
25(OH)vitamin D
Alkaline phosphatase and its bone Isoenzyme
Osteocalcin
Urinary deoxypyridinoline
Serum collagen telopeptides: NTX, CTX
Tubular reabsorption of phosphorus

Table 6: Laboratory to evaluate mineral metabolism.

Table 7 shows suggested reference values for usual laboratory determinations detailed by age and sex. The physician should consult the reference values provided by his laboratory, since they vary with different biochemical methods.

Serum calcium Newborn (1-3 weeks): 7.6-11.4 mg/dL 4 weeks to 8 years: 8.5-10.5 mg/dL 9 to 16 years: 9.1-10.4 mg/dL
Ionized calcium: 4.6-5.6 mg/dL (1.15-1.4 mmol/l)
Serum phosphorus Newborn, premature: 6.7-9.1 mg/dL Newborn, term: 4.5-7.5 mg/dL Children and adolescents: 3.0-6.5 mg/dL Adults: 2.0-4.6 mg/dL
Serum magnesium: 1.6-2.4 mg/dL
Urinary calcium: <4.0 mg/kg.24 hs
Tubular reabsorption of phosphorus (TRP): 85-95% Phosphorus (urine) × Creatinine (serum)/Phosphorus (serum) × Creatinine (urine) (All concentrations in mg/dL)
Parathormone (IRMA o ILMA) - Intact (PTH 1-84): 10-65 pg/mL
Vitamin D - Serum 25(OH)vitamin D: 16-74 ng/mL - Serum 1,25$(OH)_2$-vitamin D: 18-62 pg/mL Infants: up to 120 pg/mL Teenagers: 40-90 pg/mL

Table 7: Laboratory mineral metabolism: benchmarks.

During childhood and puberty, longitudinal growth involves active bone formation, and so the specific markers have greater values than in adults and vary with age (Table 8).

Age (years)	**Total alkaline phosphatase (UI/L, X ± DE)**		**Bone alkaline phosphatase (IRMA) (µg/L, X ± DE)**		**Bone alkaline phosphatase (ELISA) (UI/L, X ± DE)**	
	F	M	F	M	F	M
5-9.9	297 ± 74	262±81	65±18	51 ± 22	95 ± 26	79 ± 33
10.0-14.9	304 ± 108	385 ± 102	52 ± 22	69 ± 18	87 ± 36	124 ± 38
15.0-19.9	124 ± 53	148 ± 56	15 ± 8	12 ± 3	23 ± 11	22 ± 56

Age (years)	**Osteocalcin (µg/L)**
1-10	10-50
10-15	10-100
15-20	10-50
21-30	4-20

Age (years)	**FD-Pyr X ± DE (nmol/24 hs)**	**FD-Pyr/body weight X ± DE (nmol/kg.day)**

Female		
4.0-10.0	130 ± 45	4.8 ± 1.6
10.1-12.0	146 ± 66	4.0 ± 1.2
12.1-14.0	191 ± 67	3.8 ± 1.8
14.1-16.0	119 ± 53	2.0 ± 1.1
16.1-19.0	94 ± 84	1.5 ± 1.3
Male		
4.0-10.0	113 ± 48	4.7 ± 1.9
10.1-12.0	243 ± 152	5.5 ± 1.5
12.1-14.0	287 ± 139	5.8 ± 1.7
14.1-16.0	301 ± 79	5.3 ± 2.0
16.1-19.0	133 ± 62	1.8 ± 1.0

Table 8: Laboratory used to assess bone mineral metabolism (F: female; M: male).

Free deoxypyridinoline values increase with age until the pubertal period where peak values are observed (attributable to the high turnover rate physiologically present at this time of development, as already said), and then begin to decrease until reaching adult reference values.

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