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METABOLISMO MINERAL Y HUESO

How to take care of bone health in children and adolescents at risk

Cómo cuidar la salud ósea de los niños y adolescentes de riesgo

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Bone health encompasses bone growth, bone shape and bone quality. This minireview will focus on the optimization of bone mass and microarchitecture in children and adolescents at risk.

After childhood, bone mass increases until around the age of 25, at which time it reaches its maximum value, called peak bone mass. This peak bone mass correlates with the risk of developing osteoporosis in adulthood. Therefore, even in the absence of childhood fractures, any delay in the specific management of risk factors for bone fragility in children induces a reduction in peak bone mass in young adults and a risk of early osteoporosis, which worsens with age. Given the social and medico-economic impact of postmenopausal osteoporosis, this is a public health problem that goes far beyond the field of pediatrics.

Bone fragility, a term that is preferred to osteoporosis in children, is a generalized skeletal disease giving rise to a decrease in bone strength. The diagnosis is often delayed and manifests late by pain and fractures. This disorder still remains under-recognized, and there is much uncertainty about what is useful for its prevention, early detection, and treatment, which leads to different practices in different pediatric subspecialties.

Definition of bone health in children

As in adults, dual energy X-ray absorptiometry (DXA) is the measure most commonly used in routine clinical practice to study bone mass in children. Bone mineral content (BMC) of the whole body and bone mineral density (BMD) measured at the level of the whole body (without the head), and the lumbar spine or the femoral neck are the most reliable measures.

In adults, the risk of fracture correlates with bone mass regardless of clinical manifestations. Therefore, osteoporosis is defined mainly by low BMD values (≤ -2.5 T-scores). This is different in children, where the predictive value of fracture risk of an isolated low BMD value is uncertain. Bone fragility is thus defined mainly by its clinical consequences [1,2], i.e., more than one vertebral fracture without significant trauma and/or clinically significant long bone fractures associated with a CMO and/or BMD value < -2 Z-scores.

BMD assessed by bone densitometry (or DXA) is influenced by the child's height, bone maturation, and pubertal development. There is no consensus regarding methods proposed for adjusting BMD values for these parameters.

Which children and adolescents are at risk?

In the absence of primary bone fragility due to an intrinsic genetic bone defect, secondary bone fragility is often of multifactorial origin. The main mechanisms affecting bone health are musculoskeletal mobility, chronic inflammation, hormonal insufficiency, undernutrition, and genetic susceptibility factors (Table 2).

Undernutrition is a risk factor for bone fragility combining protein, fat, mineral, and vitamin deficiencies.

Undernutrition is associated with a decrease in bone mass. For instance, BMI is associated with lumbar BMD in children with multiple disabilities or in cystic fibrosis [3–5]. In young women with anorexia, weight is the most important predictor of BMD at all sites [6].

Moreover, risk factors are interconnected. Patients with multiple disabilities are often undernourished; the quality of the food is important as well.

Vitamin D deficiency is frequent in children of the general pediatric population and with chronic diseases or multiple disabilities [7]. Vitamin D deficiency is defined by the treshold of 25OHD that triggers an increase in PTH. Because this usually corresponds to 25(OH)D levels ≈ 20 ng/mL, in children, severe deficiency is defined by 25OHD levels below 10 ng/mL (<25 nmol/L), deficiency by 25OHD levels between 10 and 20 ng/mL (25 and 50 nmol/L), insufficiency by 25OHD levels between 20 and 29 ng/ mL (50–74 nmol/L), sufficiency by 25OHD levels between 30 and 60 ng/mL (75–150 nmol/L), excess by 25OHD levels above 60 ng/mL (>150 nmol/L), and risk of toxicity by 25OHD levels above 80 ng/mL (>200 nmol/L) [8,9]. According to the American Academy of Pediatrics and the Pediatric Endocrine Society, the target range of 30–60 ng/mL prevents rickets and urolithiasis [10,11].

Dairy products are the main source of calcium, which is absorbed in the intestine. Many dietary components affect calcium absorption, such as oxalate, phytate, and insoluble fibers. Dietary calcium deficiency induces an increase in PTH, phosphate leaks, cartilage and bone mineralization defects [12].

Multiple disabilities or diseases associated with decreased mobility such as Duchenne muscular dystrophy are independent risk factors for fractures, mainly in the long bones [9]. Lumbar BMD is associated with the level of activity [13].

Some medications are deleterious for bone health, such as high-dose glucocorticoid exposure acting predominantly on the trabecular bone. This explains the high incidence of vertebral fractures in chronic rheumatism and leukemia, more rarely nephrotic syndrome, which is asymptomatic in half of the cases [14]. Several thresholds that have consequences on BMD have been identified, see Table 1 [15,16].

Table 1. Thresholds of glucocorticoids exposure.

	Bone consequences	Lack of bone consequences
Cumulative dose	3 months	
Daily dose	Prednisone > 1 mg/kg/day	Prednisone < 0.2 mg/kg/day
Route of administration	Oral Inhaled > 800 ug/day	Inhaled (less than 6 months, after 6 yrs of age)

Anticonvulsive therapies e.g., hydantoin, sodium valproate, are independently associated with fracture occurrence in disabled children. Anti-vitamin K (AVK) and low molecular weight heparin treatments also limit bone mass accruals [9].

Deficits in hormone synthesis or production, which may be congenital, secondary to diseases, tumors or treatments, have major consequences on bone development for stature and quality. This will also affect muscle mass development and, in turn, major bone deficiency. Growth hormone deficiency during childhood or adolescence alters bone and muscle mass, although it is reversible with replacement therapy. Sex steroids, especially estrogens, are required for peak bone mass; as pubertal delay is very common in patients with chronic diseases, undernutrition or cerebral palsy, this is an additional risk factor for bone fragility and fractures in these children [15].

Table 2. Short overview of risk factors of bone fragility in children.

Risk factor	Details	Mode of evaluation
Disease	Neuromuscular Undernutrition Inflammation	Medical record Disease activity scores
Medication	Glucocorticoids Anticonvulsants Anticalcineurins, LMW heparin, AVK	Medical record, evaluation of exposure
Mobility		Walking distance GMFCS level 6MWT
Calcium and vitamin D		Questionnaire on dietary calcium intake Calcium, phosphate, ALP, creatinine, PTH, 25OHD Urinary calcium and creatinine
Nutrition		Weight, BMI, growth chart Blood count, iron status, albumin, creatinine If digestive disease, vitamin A and E, folate and vitamin B12
Hormone deficiencies		Pubertal stage T4, TSH

Evaluation of bone quality and density in children

Many bone markers exist to evaluate the formation and resorption of bones, and provide information that is complementary to the bone mineral density more rapidly. Among these markers, some are very reliable and can be used in clinical practice, yet their limits should be highlighted. In children, the evaluation of bone resorption through crosslaps and bone formation through osteocalcin and bone alkaline phosphatase markers has been described.

In neuromuscular diseases, we usually observe an increase in bone resorption markers. It is less clear in other diseases such as inflammatory rheumatism, where markers are not correlated with BMD and are highly variable, making them of little use in the diagnosis of bone fragility. In children, bone markers are mostly used for the follow-up of disease and treatment [16,17].

Dual X-ray absorptiometry (or DXA) is the most widely used examination for bone density because of radiation exposure, and the existence of age- and sex-specific standards.

Current recommendations are to measure total bone mineral density (BMD) at the whole body level without the head, or at the lumbar spine level [18,19]. However, in neuromuscular diseases, it is interesting to measure bone density at the distal femur where fractures predominate, although in practice it is rarely feasible [20].

Children's BMD values should be expressed as Z-scores according to age and gender. Standards are available from the age of 5 years. BMD values are influenced by the child's height, bone maturation i.e., pubertal stage, and body composition. Careful and expert analysis is recommended.

Vertebral fractures are present in many diseases that induce bone fragility in children, such as inflammation and glucocorticoid therapy. These fractures may be present at the time of diagnosis; in addition, the presence of a vertebral fracture at the time of diagnosis or immediately thereafter is a predictive factor for the development of other fractures. It is therefore recommended to search for vertebral fractures in children considered 'at risk' even in the absence of painful symptomatology. However, there is no consensus as to the technique to be used to screen for vertebral fractures or for the repetition of this screening. The most widely used technique is to perform front and side thoracolumbar spine radiographs, if possible with a less radiating EOS system [19].

Preventing bone fragility in children at risk

The correction of underlying factors is the priority in children considered at risk. This includes the control of the causative disease, the measure to ensure an adequate nutritional status, the correction of calcium and vitamin D deficiencies according to the recommended intakes for age and disease status, the promotion of muscle mass and physical activity, and the correction of hormonal deficiencies, including pubertal delay in children with disabilities.

In some diseases, e.g., Duchenne muscular dystrophy, nephrotic syndrome, and juvenile idiopathic arthritis, calcium and vitamin D supplementation improves bone mineral density and decreases bone resorption. To optimize calcium absorption, prevent the prolonged "vitamin D winter" effect, and limit the risk of increased PTH and thus bone resorption, not only regular vitamin D supplementation of children is recommended (Table 3), but also annual determination of 25OHD status in patients identified as being at risk of secondary bone fragility [9,19,21].

Table 3. Recommended calcium and vitamin D intake in children 'at risk'.

Recommended intakes	Vitamin D French society of pediatrics, 2022 [9]	Vitamin D ESPGHAN [22]	Calcium [12]
Toddler 0-6 months	400 to 800 IU per day	400 IU per day	200 mg/day
Toddler 6 months – 2 years	400 to 800 IU per day	400 IU per day	> 300 mg/day
Child 4-6 years	800 to 1600 IU per day If daily intake is not possible, 50,000 IU every 6 weeks or 80,000–100,000 IU quarterly	400 IU per day	700 mg/day
Child 7-9 years			900 mg/day
Adolescent 10-18 years			1200 mg/day
Objectives	25(OH) vitamin D level Minimal > 20 ng/ml Optimal > 30 ng/ml Maximal < 60 ng/ml		Urinary calcium/creatinine > 0.2 (mmol/l / mmol/l) *

**In malnourished children with low creatinine levels, the urinary calcium/creatinine ratio may be distorted.*

From the age of 1 to 18 years, three or four dairy products are needed daily to meet calcium requirements. Consumption of mineral waters rich in calcium should be encouraged, especially when the daily dairy product intake is insufficient (Table 3) [9].

It is now well accepted that physical activity has a beneficial effect on bone health, especially weight-bearing activities in children with chronic diseases or physical disabilities, as it acts on muscle mass, bone mineral content, and BMD of the femoral neck. It is extremely important to highlight that for most of these children physical activity is not contraindicated and should therefore be encouraged.

Treating bone fragility in children at risk

The decision to initiate active curative treatment in children with bone fragility relies on different criteria. Some are solid, like children suffering from symptomatic bone fragility i.e., presence of long bone and/or vertebral fractures, and others require discussion among physicians or referral to an expert center (see Table 4).

Pharmacological options for children are limited to IV bisphosphonates. They inhibit osteoclast-mediated bone resorption and unfortunately have been poorly evaluated in secondary osteoporosis in children. Nevertheless, most studies show an improvement in the lumbar spine and femoral BMD, and a decrease in bone resorption markers. We do not have strong data on the incidence of long bone and/or vertebral fractures. Pamidronate has been the most frequently studied treatment at a dosage of 1 mg/kg three days in a row every 3 months; however, in children with cerebral palsy, the option of using the lowest efficient dose has often been preferred. The efficacy and safety of zoledronate seem similar using an infusion of 0.025 to 0.05 mg/kg every 6 months. The duration of treatment is highly debated in the pediatric literature, and each center almost appears to have its own opinion! It depends on the underlying disease and the persistence of the risk factors. Treatment is recommended if they are present, and this may include the whole growth period. After the improvement in BMD that occurs in the first 2-3 years of treatment, the dose is usually halved to maintain this effect. It is imperative that optimal calcium and vitamin D intakes are combined with bisphosphonate therapy [23–25].

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Table 4. Indication for bisphosphonates treatment in children with bone fragility, experience of the Bicêtre Paris Saclay Hospital.

	Indication to initiate treatment	Requires consensus among treating physicians and family
International recommendations	Fractures e.g., vertebral or long bones	Exposure to glucocorticoids (see Table 1)
Bicêtre Paris Saclay expertise	Spine surgery planned Hip surgery planned Urothiasis secondary to hypercalciuria and hypersorption	Bone pain Progressive decline of BMD well below -2SD despite adequate preventive measures

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