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PERSPECTIVES

Diagnosis and Treatment of Bone Fragility in Childhood

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Abstract

What constitutes "bone fragility" in children and adolescents before the occurrence of fractures is still an unresolved question. In growing subjects, the clinical relevance of uncomplicated low bone mineral density (BMD) and its long-term consequences remain difficult to evaluate, and there is only preliminary evidence that a child's BMD is a predictor of fracture risk. There is no consensus on the threshold values of low BMD that define bone fragility and osteoporosis in the young.

Bone fragility should be suspected in all cases of fractures without evident trauma. In particular, recurrent and multiple fractures must be very carefully evaluated (considering also the possibility of child abuse).

There are primary causes of bone fragility in children and adolescents (*e.g.*, osteogenesis imperfecta) or bone fragility can be caused by many different chronic diseases (*e.g.*, all those treated with long-term glucocorticosteroids).

The increasing number of cases requires the highest attention. Height, weight, pubertal stage, calcium, sodium and protein intake, use and dose of glucocorticosteroids, mobility, pain, fractures (type, circumstances, outcome) are the key elements in the clinical evaluation of children with chronic diseases and possible bone complications.

The evaluation of BMD at this age is problematic, because of the continuous change of skeletal size and shape, and the great individual variability of the growth process, which makes it difficult to identify a meaningful reference population. The treatment of bone fragility is also problematic: bisphosphonates are now increasingly used in severe cases, but their long-term efficacy and safety has still not been demonstrated. *IBMS BoneKEy*. 2008 September;5(9):323-335.

Keywords: Children; Bone mass; Bone density; Bone fragility; Fractures; Calcium; Vitamin D; Bisphosphonates

Introduction

What constitutes "bone fragility" in children and adolescents before the occurrence of fractures is still an unresolved question. In adults, bone mineral density (BMD), usually measured by dual-energy X-ray absorptiometry (DXA), is a good predictor of fracture risk, which approximately doubles with each 1 SD decrease of BMD below the average value of gender-matched, healthy, young adults (1). According to the WHO, a diagnosis of osteoporosis is made when the BMD value falls 2.5 SD or more below this reference value (T-score ≤ -2.5) (2).

In growing subjects, there is no consensus on the meaning of the BMD value alone, and the clinical relevance of uncomplicated low bone density and its long-term consequences remain difficult to evaluate. There is only preliminary evidence that the BMD value is a predictor of fracture risk in the young (3-5). Even the BMD value that should be interpreted as "low bone density" in children and adolescents is a matter of discussion. In this case, the reference population is basically that of ethnicity-, gender- and age-matched healthy subjects, and the BMD difference (in SD units) between the studied subject and the reference population is called the Z-score. There are, however, specific difficulties in the calculation of the correct Z-score (briefly discussed below), and for this reason a diagnosis of low bone mass in children should be made only by experienced specialists. Z-score values below -2 are generally considered a serious warning of bone fragility, but most specialists would

speak of “osteoporosis” only in the presence of low BMD and at least one fragility fracture. A diagnosis of pediatric osteoporosis cannot be made on a BMD measurement alone (6;7).

Causes of Bone Fragility in Children

Low BMD and fragility fractures are increasingly recognized as serious manifestations or complications of many chronic diseases affecting children and adolescents. Among the primary causes (Table 1), the most frequent is osteogenesis imperfecta (OI), a heritable disease due to a defect in the collagen gene: several types of different severity have been identified (8;9). Another cause is idiopathic juvenile osteoporosis (IJO), an uncommon disease of unknown etiology, characterized by bone fragility and recurrent fractures, which generally resolves spontaneously after puberty (10).

The secondary causes are many and of a different nature (Table 1), ranging from chronic inflammatory diseases to endocrine diseases or inborn errors of metabolism. In particular, all the chronic diseases requiring long-term treatment with glucocorticosteroids (GCs), such as juvenile idiopathic arthritis (JIA), leukemia, cystic fibrosis (CF), Duchenne muscular dystrophy (DMD), etc., are associated with increased bone fragility and fractures.

Children affected by these chronic diseases often fail to achieve their optimal peak bone mass and are at risk of osteoporosis in early adulthood. Moreover, adult men and women with a history of chronic diseases during childhood have increased bone turnover and reduced BMD in comparison with healthy control subjects matched for age, gender, height and weight (11-13).

Diagnosis

Bone fragility should be suspected in all cases of fractures without an efficient trauma (atraumatic fractures). In particular, recurrent and multiple fractures must be very carefully evaluated, keeping in mind also the possibility of child abuse. Persistent back pain in a child, especially if affected by a chronic disease, should always be evaluated radiologically to exclude the presence of vertebral fractures.

The primary causes of bone fragility, particularly the less severe forms of OI (not obviously characterized by recurrent atraumatic fractures since early childhood or other hallmarks of the disease), can be difficult to diagnose: fractures are relatively common in active children and adolescents, and the difference between a fragility fracture and a traumatic fracture can be very subtle.

On the other hand, most diseases that may cause bone fragility (secondary osteoporosis) at a young age are usually diagnosed well before the occurrence of fractures (a notable exception is leukemia, in which a vertebral fracture may be the presenting sign). In all of these cases, it is very important to consider the possible bone complications from the beginning, and to perform a baseline bone evaluation (including bone densitometry) as soon as possible. When long-term GCs are part of the standard treatment, the bone evaluation should be performed possibly before starting this therapy, so that meaningful comparisons can be made during follow-up. If low BMD, or a lower-than-normal rate of BMD gain, is observed during the course of the disease, appropriate measures should be taken to prevent fractures. For example, nutritional deficiencies (especially calcium and vitamin D) should be corrected and suitable physical activity recommended. In the case of GC treatment, reducing the dose or switching to a different GC might be considered.

Bone Evaluation in Children and Adolescents

Height, weight, pubertal stage, calcium intake (if possible, also sodium and protein intake), serum levels of 25-hydroxy vitamin D (25OHD), use and dose of GCs, mobility, pain, fractures (type, circumstances, outcome) are the key elements in the clinical evaluation of children with chronic diseases and possible bone complications.

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Table 1. Primary and secondary causes of low BMD and osteoporosis in children

A. PRIMARY CAUSES OF LOW BMD AND OSTEOPOROSIS IN CHILDREN

1. Idiopathic juvenile osteoporosis

2. Heritable disorders of connective tissue
Osteogenesis imperfecta
Ehler-Danlos syndrome
Bruck syndrome
Marfan syndrome
Osteoporosis pseudoglioma syndrome
Homocystinuria

B. SECONDARY CAUSES OF LOW BMD AND OSTEOPOROSIS IN CHILDREN

1. Neuromuscular disorders
Cerebral palsy
Duchenne muscular dystrophy
Prolonged immobilization

2. Chronic diseases
Leukemia
Diffuse connective tissue diseases
Cystic fibrosis
Inflammatory bowel diseases
Malabsorption syndromes (celiac disease)
Thalassemia
Primary biliary cirrhosis
Nephropathies (nephrotic syndrome)
Anorexia nervosa
Organ transplants
HIV infection

3. Endocrine diseases
Delayed puberty
Hypogonadism
Turner syndrome
Growth hormone deficiency
Hyperthyroidism
Juvenile diabetes mellitus
Hyperprolactinemia
Cushing syndrome

4. Inborn errors of metabolism
Protein intolerance
Glycogen storage diseases
Galactosaemia
Gaucher disease

5. Drugs
Glucocorticoids
Methotrexate
Cyclosporine
Heparin
Radiotherapy
Anticonvulsant drugs

Note: This table lists only the most frequent diseases according to the scientific literature.

The diagnosis of low bone mass and density can be made by several methods. DXA densitometry is most commonly used to obtain BMD measurements. The other methods include peripheral quantitative computed tomography (pQCT) and quantitative ultrasound (QUS) (14-21).

Bone densitometry

Bone densitometry in children is much more complex than in adults, and all densitometric techniques have some intrinsic difficulties. Rigorously standardized protocols must be followed, regarding in particular the positioning of the patient and the execution and analysis of the scans.

The first problem in the evaluation of BMD at this age is the continuous change of the bones' size and shape, which makes follow-up of an individual patient a difficult task: is he or she really gaining bone mass or is there only an apparent gain, inadequate for growth and development? Moreover, there is great individual variability in the growth process, which makes the identification and the availability of a meaningful reference population (continuously changing with time) highly problematic.

Ideally, gender, age, ethnicity, body size, pubertal stage and skeletal maturation should all be considered in choosing the reference population; most often, however, the reference values are those of healthy controls matched only for ethnicity, gender and age. The evaluation is made using the Z-score, the only useful index for bone assessment in growing subjects. In recent years, several studies – mostly with DXA – allowed investigators to build large bone databases on healthy children and to publish reference values for different countries (*e.g.*, USA, Canada, UK, China, Taiwan, Korea, Finland, The Netherlands, Poland, Japan). In some cases, longitudinal follow-up was also performed (22-31).

In the study of young patients, the raw, uncorrected BMD and Z-score values are not always satisfactory, since important variables, like body size and pubertal stage, should also be taken into account. A smaller body size for age is frequently observed in children affected by chronic diseases, because of delayed or reduced growth, due to the disease itself or its treatment. In such cases, special precautions are needed to perform a correct bone assessment.

With DXA, the most widely used method, a specific technical problem must be considered to avoid the inaccurate evaluation of actual bone density or bone mass "loss". DXA calculates only an "areal" bone density (g/cm^2, *i.e.*, the ratio of the bone mineral content (BMC) to the projection area), instead of a true density (g/cm^3, BMC/bone volume), and this overestimates the BMD value for a greater bone size, and underestimates it for a smaller size. Some corrections have been proposed for the lumbar spine, hip, and total body BMD, to take body size into account (32-36). There is no consensus on the best correction (37), but for lumbar spine DXA scans many investigators use Carter's formula for "bone mineral apparent density" (BMAD), based on the assumption that the vertebral body is a cylinder (32). Many investigators prefer total body (TB) DXA scans in children, because they can evaluate not only bone mass and bone density, but also body composition, *i.e.*, fat mass and lean mass (38). A correction for height is often used for TB BMC (38;39).

Last but not least, many chronic diseases cause high variability, or even anomalies, in height, weight and pubertal development, may affect bone and bone development differently, or even may affect some skeletal regions more than others (*e.g.*, the lower limbs more than the trunk or vice versa). Long-term GCs affect trabecular bone most significantly, so lumbar spine scans should always be performed in subjects treated with GCs. Diseases affecting mobility, like cerebral palsy or DMD, require special attention in positioning, especially for follow-up measurements. In DMD, low bone density is earlier and more marked in the lower limbs, and the distal femur may be the only site available for DXA densitometry. This is not a usual site for DXA scans, but some investigators following children with DMD or cerebral palsy have obtained and published reference data for it (40;41). Of

course, such a non-standard scan requires special training.

Peripheral QCT is potentially very useful because it allows the measurement of a true (volumetric) bone density, not dependent on bone size, and thus not influenced by the patient's body size. It evaluates the trabecular and cortical volumetric bone density separately, and measures other parameters related to bone strength, like the axial moment of inertia. The sites of measurement are the radius, femur and tibia, the radius being most commonly used. However, this technique is still scarcely available in clinical practice and is used almost exclusively for research purposes.

The positions of the *International Society for Clinical Densitometry* (ISCD) on the evaluation of bone density and bone mass in the young were recently published (38).

Calcium and phosphate metabolism, calciotropic hormones and bone turnover

In all diseases potentially affecting bone health, the basic laboratory tests are serum and urinary calcium and phosphate, and serum 25OHD. They can reveal the presence of other problems like mild, asymptomatic rickets, or idiopathic hypercalciuria. These tests should be performed before starting treatment (even if only with calcium and vitamin D supplements), since knowing these baseline values will help to distinguish between a pre-existing condition and an adverse effect of therapy. It should be remembered that hypercalciuria and low levels of 25OHD are often present in children with chronic diseases, in particular those treated with long-term GCs; that hypercalciuria can be caused by immobilization; and that the normal level of serum 25OHD (the threshold value that effectively controls parathyroid hormone secretion) has recently been re-evaluated and established to be 30 ng/ml (42).

The study of bone turnover is useful in evaluating the changes induced by drug therapy, but is difficult in children, because of the high variability of bone turnover markers in relation to age and pubertal stage, and the lack of reference data for many markers. Recently, some authors evaluated the changes in bone markers in relation to the physiological growth and development of healthy children. Other investigators studied bone markers to monitor the bone effects of the primary disease or the response to treatment (43-47).

Treatment

Depending on the nature of the primary disease, the aims of treating low bone density and osteoporosis in children are to prevent fractures and disability, relieve pain, maintain locomotor function and sustain satisfactory growth and development. However, no guidelines are available and controlled studies are still lacking. Only a few studies have evaluated sufficient numbers of patients and reached reliable conclusions. Treating bone problems in children and adolescents cannot be reduced to the prescription of a bone-active drug on the basis of the effects observed in adults. To treat a growing skeleton is much more difficult, because at this age many variables interfere with the delicate physiological equilibrium of bone, and the possible consequences in adult life must also be considered (48;49).

In many chronic diseases, some specific factors (*e.g.*, undernutrition or malnutrition, reduced physical activity, hypogonadism, vitamin D deficiency) may increase the risk of bone loss. They should first be identified and then, whenever possible, reduced or eliminated prior to starting a specific therapy. Pubertal stage and disease activity must always be taken into account.

The primary forms of low bone density and osteoporosis should be approached in a very different way than the secondary forms. In the former, the severity of bone problems is the main element in treatment decisions. In the latter, effective control of the underlying disease is the rational approach. For example, a strict gluten-free diet can often restore bone health in celiac disease (50) and the control of inflammation reduces both the periarticular and the systemic bone loss in JIA (51). Growth retardation, pubertal

delay, or hypogonadism should be corrected with hormonal therapy.

One of the most important environmental factors for bone health is the availability of calcium, phosphate, proteins and vitamin D. The correct daily intake of these nutrients according to the patient's age, sex, and physical characteristics should be assured. Some diseases require special attention: for example, many adolescents with JIA have protein-energy malnutrition (52) and CF patients need a greater caloric intake. Dietary habits, for example, soft drink intake or fruit and vegetable consumption, can influence bone mineral accrual (53;54). Physical activity and weight-bearing exercises have been shown to increase BMD both in health and disease (55-57). However, excess physical activity, as is often observed in anorexia nervosa, can negatively affect bone (58). Long-term GC therapy must be reserved for carefully selected cases of absolute necessity: the minimum effective dose must be accurately determined, and the drug should be discontinued as soon as possible (59).

Calcium

The adjustment of calcium intake to the RDA is the first treatment step for low bone mass in children. The effect of calcium intake on bone mass increase during growth has been widely studied, and many consistent observations show that calcium supplementation determines an increase in bone mass (60-62). However, the persistence of the positive effect on BMD has not been proven yet, and further investigations are required.

Calcium-rich foods should be preferred because the calcium within dairy products is more highly absorbed than calcium salts (61) and, in addition, it is very difficult to obtain long-term compliance with the latter in children. Gastrointestinal symptoms (constipation, abdominal pain, meteorism) are common and are a serious limiting factor.

Vitamin D

The availability of vitamin D is mainly dependent on the cutaneous synthesis of cholecalciferol induced by UV rays. Thus, chronically ill young patients with reduced outdoor activities may be at high risk of deficiency. In some diseases, like systemic lupus erythematosus, exposure to sunlight is forbidden. Moreover, hepatic, renal and intestinal diseases, as well as many drugs (*e.g.*, corticosteroids, anticonvulsants, heparin, cyclosporin, tacrolimus), can affect the metabolism and function of vitamin D (63-67). Low vitamin D can induce an increase in parathyroid hormone secretion (secondary hyperparathyroidism) with further negative effects on bone (68;69).

To prevent vitamin D deficiency in children and adolescents, supplementation with 200-400 IU/day of vitamin D_3 is usually recommended and is safe, although the recommended requirements may be higher (42). Calcium carbonate supplements (1,000 mg/day) plus vitamin D (400 IU/day) or calcifediol (0.5 mcg/kg/day) have been studied in pediatric patients with rheumatic diseases or CF, treated with GCs or not. Therapeutic dosages of calcifediol can ameliorate BMD, but the long-term effects are still uncertain. The side effects of calcium and vitamin D treatment (hypercalcemia, hypercalciuria) seem negligible (70-73). The use of calcitriol (1,25-dihydroxy vitamin D) or alfacalcidol (1-alpha-hydroxy vitamin D) has not been tested systematically in children. According to a recent prospective study on 10 children with cerebral palsy, alfacalcidol was effective in increasing BMD (74).

Bisphosphonates

Bisphosphonates (BPs) are the most widely used anti-resorptive drugs, and the only ones clinically used in children and adolescents. They reduce osteoclast-mediated bone resorption, and shift the balance of bone remodeling towards an increase in bone mass. In carefully selected pediatric cases, they are considered useful and effective. Adverse effects are similar to those observed in adults, and generally mild and reversible. Intravenous pamidronate and oral alendronate have been used in most cases (75;76). Newer, more potent

forms, such as zoledronate, have been and are being studied in international multicenter trials and are beginning to replace pamidronate in some centers.

There is no doubt about using these potent drugs in the presence of severe bone loss and repeated fractures, as occur in the severe forms of OI or in cerebral palsy. On the contrary, there is still much doubt about using these drugs in mild primary diseases like OI with a low fracture rate, or in spontaneously resolving diseases like most cases of IJO, or in the presence of low bone mass without fractures. This uncertainty derives from the lack of long-term efficacy and safety data, even if the major concerns about the risks of bisphosphonate use in children have not been confirmed after more than ten years of clinical, radiographic and histological evaluation. Height gain, growth, skeletal maturation, fracture repair, and growth plates seem not to be impaired (77-79). Osteonecrosis of the jaw – a possible adverse effect of BP use – has not been reported in children until now, also during long-term BP treatment (80). BP treatment has recently been associated with a delay (1.67 yr) in tooth eruption in children with OI (81). Cyclical intravenous pamidronate, in combination with orthopedic, physiotherapy and rehabilitation programs, is now the standard of care for children affected by moderate to severe OI. It reduces bone pain and increases bone mass and density. There is an increase in size of vertebral bodies and thickening of cortical bone, with decreased fracture incidence and improved ambulation. No negative effects on growth or fracture repair have been observed, but the long-term consequences of low bone turnover in these children are still unknown (82;83). BPs have been used on a significant number of patients in many cases of secondary osteoporosis, mainly corticosteroid-induced osteoporosis in connective tissue diseases, such as JIA (78), cerebral palsy (84;85), CF (86), and leukemia (87).

In conclusion, considering the difficulties in establishing the correct dose, monitoring the effects, and deciding the duration of therapy and the criteria for suspension, the use of BPs in children and adolescents should be reserved to specialists experienced in pediatric bone diseases, and BPs should be used only after all the alternative measures have been tried and failed to ameliorate bone mass.

Conclusions

There are still no guidelines or consensus statements for the diagnosis and treatment of bone fragility and osteoporosis in children. The basis for a correct approach is a deep knowledge of the physiology and pathology of bone growth and development.

Therapeutic interventions must be prudent, beginning with the simplest and safest ones, such as calcium and vitamin D supplementation. Physical activity is an essential stimulus for bone remodeling, and is particularly important during growth and development (55-57;88). Special programs may be required for patients with low mobility. BPs can be used after careful risk-benefit analysis, when all the other measures have failed, considering the patient's condition and quality of life. Organ transplants and the use of GCs have dramatically changed the outcome of many severe chronic diseases, but longer survival has often led to the development of bone problems. Secondary osteoporosis, particularly during long-term GC therapy, is increasingly encountered in clinical practice. Finally, considering that the pediatric bone field is still relatively new, further and deeper research on bone fragility and osteoporosis, specifically focused on the young, is required and should be actively supported. More international collaboration and multi-center studies are needed to assemble large study samples, particularly in the rarer diseases.

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