CAUSES & RECENT MANAGEMENT OF OSTEOPOROSIS IN CHILDHOOD

Essay

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Abstract

As far as primary osteoporosis is concerned, spontaneous recovery is often seen in idiopathic juvenile osteoporosis. In severe osteogenesis imperfecta, cyclic administration of intravenous bisphosphonates reduces bone pain and fracture rate, and increases BMD. In secondary osteoporosis, bone mass acquisition can be optimized by treating the underlying disease.

For instance, treatment of Cushing's disease, hyperthyroidism and GHD resulted in a substantial increase or even normalization of BMD. When glucocorticoid therapy is inevitable, the dosage should be minimized to reduce detrimental side effects on bone.

Key words

MANAGEMENT OF OSTEOPOROSIS IN

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Definition

Osteoporosis is a reduction of bone mineral mass per volume unit of bone tissue in the absence of mineralization defects (osteomalacia). This concept is particularly important in infancy and childhood in order to avoid confusion with rickets, a form of osteomalacia still frequently encountered (1).

A consensus definition of osteoporosis before the appearance of fragility fractures in children is not yet available. The same definition used for adults is generally accepted: that is, ‘low bone mass and micro architectural deterioration of bone tissue, determining fragility fractures’(2) The difficulties arise in defining the degree of bone mass loss which should be considered as osteoporosis in children. Currently there are no widely accepted cut-off values for osteopenia and osteoporosis in children based on bone densitometry, such as those proposed by the WHO for adult women and now unanimously accepted.(3)

The lack of a definite cut-off value is due to two main reasons. The first is the intrinsic difficulties in the interpretation of densitometric data in the paediatric population. These difficulties are linked to the presence of a growing skeleton in which size, shape and mineral density are rapidly changing, and to the fact that different pathological conditions can affect these characteristis differently, or can affect some skeletal parts morethan others (e.g. the lower limbs more than trunk or vice versa). Moreover, the growing process itself, as well as the onset and stages of puberty, can be influenced by the primary disease, so that it may be difficult to identify an appropriate control group to define the normality of densitometric values. The usual comparison with sex- and age-matched controls can be inadequate in the presence of chronic diseases affecting

skeletal growth and maturation, and can give inaccurate results in terms of actual bone mass loss.

The second difficulty is that, on the basis of many important studies(4), regional bone mineral density (BMD) is a strong predictor of the fracture risk in adults, but there are not enough data to support a similar conclusion in the young, even if some recent findings seem to point in the same direction.(5)

On the basis of these problems, it can be safely stated that most researchers would consider a diagnosis of osteoporosis in the young only after at least one fracture with minimal trauma. (6)

Physiology of Bone

Bone modeling and remodeling:

Bone is an active tissue which is constantly regenerated throughout life. Bone remodeling occurs in small packets of cells called basic multicellular units (BMUs). First activation occurs, the bone surface is converted from resting lining cells to an activated bone surface on which circulating monocular cells of the hematopoietic lineage fuse and form differentiated osteoclasts. Subsequently, osteoclasts resorb bone, and in the following reversal phase pre-osteoblasts appear in the resorption cavity and formation is coupled to resorption. In this phase a cement line is formed, which marks the limit of resorption and acts as "glue" between the old and new bone. Finally, in the formation phase, osteoblasts fill the cavity with new bone (7). However, in addition to the remodeling, children grow, whereby bone modeling is achieved by appositional growth along periostal surfaces and by the calcification of cartilage adjacent to the growth plate (8).

Determinants of bone Health in Children

Despite the growing body of normative data in children, little agreement exists on the quantitative definition of osteopenia and osteoporosis in children. In addition, prospective data are insufficient to define the health risks associated with BMD levels in childhood. Pediatric research and acquisition of pediatric reference ranges have not kept pace with the technologic improvements in bone health assessment. Earlier studies of bone mineralization in healthy children were conducted using

single- or dual-photon absorptiometry or DXA in single-beam mode (9). Although these studies were instrumental in describing the determinants of PBM, they cannot be used as reference data for current research studies or clinical care because of the changes in bone density assessment technology. Changes in hardware and software technology, including fan-beam technology and low-density software analysis modes, result in significant alterations in the absolute levels of bone area, bone mass, and BMD

A further shortcoming of some previous studies of bone health is their small sample size and the lack of more detailed information for children across various maturational stages, ethnic groups, and gender groups. Most pediatric BMD reference data sets used to calculate z-scores contain small numbers of subjects within each age category and may not characterize normal variability in BMD accurately. The comparison of published pediatric DXA BMD normative tables reveals differences in the age-specific means and SDs for BMD. These differences have a significant impact on the diagnosis of osteopenia in children with chronic diseases (10).

Most BMD reference data sets in healthy children are based on chronologic age. Because considerable variability exists in bone mineralization because of body size and sexual maturation, especially during adolescence, reference data should allow for the assessment of bone mineralization in relation to body size and puberty stage, in addition to age.

This allowance is particularly important for the clinical care of children with chronic disease who frequently experience growth failure, malnutrition, and delayed sexual and skeletal maturation. Therefore,

despite the widespread availability of data on normal children, the prevalence of osteopenia in many childhood diseases is not known.

Biochemical markers of bone metabolism

Biochemical markers include those specific for bone formation and for bone resorption. The assessment of bone markers in the study of adult osteoporosis is an evolving science. No single marker has been found to be ideal. Additionally, biochemical markers may vary widely within a subject when assayed at different time points. When used with BMD measures, bone markers are important tools for the diagnosis, and especially the evaluation of treatment of metabolic bone diseases (11)**.** One needs to be aware that markers may be difficult to interpret, especially in growing children. Pediatric normative data do not exist for most markers and markers may mostly reflect normal growth, necessitating correction for age and gender (12)**.**

Bone formation markers include serum bone-specific alkaline phosphatase (BAP), an enzyme produced uniquely by osteoblasts and essential for mineralization (13). Osteocalcin (OC), also called bone Gla protein, is a small noncollagenous protein of uncertain function that is synthesized by osteoblasts for incorporation into the bone matrix; a fraction of the newly synthesized osteocalcin is released into the circulation where it can be measured by radioimmunoassay (14). Osteocalcin has been shown to follow a circadian pattern (15) and to reflect bone formation. Carboxy-terminal propeptide of type I procollagen and amino-terminal propeptide of type I procollagen are extension peptides cleaved from type I procollagen as part of the extracellular processing of type I collagen (16).

Although they are measured in the serum by immunoassay, they also reflect collagen metabolism from other sites, such as skin (17). The

noncollagenous proteins produced by osteoblasts (OC and BAP) are the more clinically useful bone formation markers (18).

Useful bone resorption markers are generally collagen-degradation products. Collagen type I cross-linked N-telopeptide (NTx) and collagen type I cross-linked C-telopeptide (CTx) are breakdown products of type I collagen that are measured by immunoassay in the urine, with development of serum markers for NTx and CTx underway (19). Pyridinoline and deoxypyridinoline (Dpd) are covalent cross links found in type I collagen; they are released during bone resorption, metabolized, and found in the urine in both the free and peptide-bound forms (20).

They are more sensitive markers of bone resorption than hydroxyproline, the classical urinary resorption marker (21). Serum tartate-resistant acid phosphatase (TRAP) is an enzyme released by osteoclasts, but also is derived from erythrocytes. Its use has been limited because it is not stable in serum even when frozen. Recent immunoassays have been developed that may increase its utility (22). The best markers for characterizing bone resorption are Dpd and either NTx or CTx (18).

Factors affecting bone growth during childhood:

Peak bone mass is achieved during the late teens and is a result of continued bone growth throughout the childhood years (23). Bone mass is accrued during the childhood years and parallels linear growth. There is a continual increase in bone density with age, mirroring changes in bone size, with a rapid increase of bone mass during the pubertal growth spurt. If there is a perturbation of this process, with a resultant decrease in peak bone mass, the resultant fracture risk may be increased for life (24).

There are many factors that influence childhood skeletal maturation including nutritional, hormonal, mechanical, environmental, and genetic factors;.

A)Nutritional factor:

Nutrition, most importantly calcium intake and those factors that influence calcium homeostasis, play a key role in bone metabolism. Although calcium supplementation has been shown to increase bone density, especially in prepubertal children, the positive effects are seen only while supplementation is ongoing (25).

Once supplementation is stopped, the positive effect on bone density disappears. Dietary calcium intake is preferable to calcium supplementation in terms of increased gastrointestinal absorption and decreased renal excretion. Vitamin D serum levels fluctuate seasonally in countries where milk is not supplemented with Vitamin D.

B)Hormonal factor:

Hormonal influences during childhood have tremendous effects on bone growth. This is illustrated in populations of sex steroid deficient children, such as those with Turners Syndrome, and amenorrheic teenage girls (eg, anorexics or those engaged in vigorous physical activity) where bone mass is found to be low (26). Aditionally 40% to 60% of peak bone mass is accrued during puberty .

C) Mechanical factor:

Mechanical loading is important for bone development; the amount of physical activity is a significant predictor of bone mass in children (27). The mechanostat theory proposes that bone expands in response to the magnitude and direction of the biomechanical forces to which it is subjected (28). Mechanical forces on the skeleton arise from

muscle contraction, and these forces generate signals that determine bone architecture. Consistent with this paradigm is the report that exercise - induced increases in bone mass and bone strength are caused by an enlargement of cortical bone size without changes in cortical or trabecular density (28).

This capacity of bone to respond to mechanical loading with increased bone size and strength is greatest during growth, especially during adolescence (29).

Some studies have demonstrated a strong correlation between muscle strength and cortical bone thickness in healthy children (30). This relationship is consistent with the theory that adaptation to changes in biomechanical usage during childhood results in changes in bone geometry, not density. This relationship has important implications for the assessment of skeletal disorders in children (31). Some agents long thought to exert bone effects by acting directly on bone cells also affect muscle strength. In that way, they could affect bone strength indirectly. Such agents include growth hormone, glucocorticoids, androgens, calcium, and vitamin D and its metabolites. Because bone and muscle form an operational unit, the evaluation of muscle strength should play a significant role in the assessment of skeletal disorders in childhood; For example, bone-active medications may be ineffective in the absence of mechanical stimulation of bone formation. At present, no published reference data relate cortical thickness to muscle strength in healthy children (32).

D)Physical Activity

Physical activity plays an important role in tissue anabolism, yet little is known about the mechanisms that link patterns of exercise with tissue anabolism.

Considerable anabolic stimuli arise even from relatively modest physical activity of daily living. Therefore, anabolic effects of exercise training are not limited to individuals participating in competitive sports who focus particularly on improvements of muscle strength and endurance. For example, complete limb immobilization1 or lack of gravitational mechanical loading (e.g. space flight)(33) lead to destructive bone loss, while bone formation dramatically increases when immobilized subjects resume exercise.(34) This has led to the popular conclusion that physical activity enhances bone formation and, consequently, bone mineral density (BMD).

The exercise-associated anabolic effects are age and maturity dependent. It is remarkable that spontaneous levels of physical activity, energy expenditure, and muscle strength and bone turnover exhibit some of their most rapid increases during childhood and adolescence. The combination of rapid growth and bone development, high levels of physical activity, and spontaneous puberty- related increases in anabolic hormones (growth hormone, insulin-like growth factor-I, sex steroids and bone turnover markers) suggest the possibility of integrated mechanisms linking exercise with anabolic bone responses during this important life period.

Moreover, the potential contribution of physical activity to increase bone mass is particularly important in children and adolescents since BMD reaches about 90% of its peak by the end of the second decade, (35) and because about one quarter of adult bone is accumulated during the two years that surround the peak bone velocity. (36) This supports the

idea that patterns of physical activity during childhood and adolescence can act to prevent bone disorders (like osteoporosis) later in life.

Despite strong indirect evidence in highly trained athletes or immobilized subjects linking physical activity with increased bone formation, direct evidence for this relationship in an otherwise healthy, mobile population, is lacking. A variety of investigators have been unable to find a consistent relationship between *habitual* physical activity levels and bone mass in moderately active adults.(37) In contrast, the majority of cross-sectional studies in normally active children and adolescents suggest that higher levels of physical activity are indeed associated with increased bone mass.(38) Interestingly, similar to adults, there have been few controlled, prospective, longitudinal studies designed to examine the effect of a quantified training intervention on bone turnover and bone mineral density(39).

Pathophysiology of Osteoporosis

If the definition of osteoporosis is as per WHO, it has two components: low bone mass and microarchitectural deterioration. Hence alteration in remodelling, balance does not of itself result in osteoporosis: alteration or deterioration in structure is also required. Classical post-menopausal osteoporosis involves both principles.

Childhood osteoporosis may occur as a result of a change in any of the components that contribute to bone mass either singly or in combination. Thus low bone mass for body size could be due to:

1- Reduced bone width (thin or gracile bones)

2- Reduced cortical thickness

3- Increased cortical porosity

4- Reduced trabecular number

5- Reduced trabecular thickness

6- Increased trabecular perforation

7- Increased remodelling space (40)

Additional risk factors for bone loss in chronic diseases.

- Low body mass
- Malnutrition or undernutrition (calcium!)
- Inactivity
- Reduced mechanical load
- Hyposecretion of sexual hormones
- Reduced exposure to sunlight
- Lifestyle factors (e.g. excessive soft drinks intake, passive smoking)(41).

Disorders at Risk for Osteopenia/Osteoporosis

Many disorders, by various mechanisms, may be associated with osteopenia/osteoporosis. A primary genetic defect in the structure and/or assembly of bone collagen causing a defect in bone matrix, or secondary bone damage as a consequence of endocrine, nutritional, and chronic disorders, or induced by some treatments or disuse represent the cause for osteopenia / osteoporosis in children and adolescents (42).

A)Genetic and Chromosomal diseases

Many genetic defects can be associated with osteopenia/osteoporosis; however, the list is far from complete and likely many disorders will be added, or will be newly classified according to their pathogenesis:

a) Primary defects of bone structure as a main determinant

1) Osteogenesis Imperfecta:

- Autosomal dominant or Autosomal recessive
- Mutations in the genes encoding chains of type procollagen (43). Osteogenesis Imperfecta (OI) "brittle bone disease" may be considered the prototype of a genetic disease with osteoporosis associated with fragility fractures caused by abnormal collagen structure. Histomorphometric data provide evidence that patients with OI have defects in all three mechanisms that normally lead to an increase in bone mass during childhood:
  - modeling of external bone size and shape.
  - production of trabeculae by endochondral ossification.
  - thickening of secondary trabeculae by remodeling.

No defect in matrix mineralization has been found in