REVIEW ARTICLE

Childhood Osteoporosis

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Abstract

Osteoporosis has long been considered a health problem unique to postmenopausal women and elderly. It is being increasingly recognized that osteoporosis could affect children as a primary problem and as secondary to various diseases, and medications. The present review discusses the current definition of osteoporosis in children, its causes, types and risk factors for low bone mineral density, in addition to prevention and treatment strategies that can help optimize bone health in children.

Key words: Bone mineral density, Children, Fragility fractures, Osteopenia, Osteoporosis, Primary osteoporosis, Secondary osteoporosis.

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Introduction

Osteoporosis is a major public health problem worldwide and its prevalence is increasing. This morbidity burden has considerable medical, social and financial implications due to the fractures associated with the disease. Although osteoporotic fractures are an important cause of morbidity, disability and mortality, they are preventable. Osteoporosis is a well-established clinical worldwide problem for adults. On the other hand, osteoporosis in children and adolescents is rather new and increasingly recognized with certain unique diagnostic and clinical challenges[1-2]. In fact, some researchers suggested that osteoporosis seen later in life may originate during childhood or adolescence years[3-4].

Osteoporosis is a systemic disorder defined as "decreased bone strength that predisposes individuals to fragility fractures"[5]. Bone strength reflects the integration of two main features: bone density and bone quality[6]. In children, a somewhat different definition exists, requiring both a history of pathologic fractures and low bone mineral content or density[7]. These criteria are fulfilled by the diagnosis of a single significant fracture in a long bone of the lower extremity, two fractures in the long bone of an upper extremity, or one vertebral compression fracture[8-9]. The relationship between bone

density and fracture risk is currently unknown in children and therefore it is not possible to define thresholds below which there is an increased fracture risk; although there are now several studies that have examined the relationship between bone density in healthy children and fractures[10,11].

Osteopenia is a term that is often confused with osteoporosis. Osteopenia is defined as a decrease in the amount of bone tissue, and osteoporosis is osteopenia with bone fragility. On the other hand, osteopenia should not be confused with osteomalacia (reduction in bone mineral with the accumulation of unmineralized bone matrix). Both osteopenia and osteomalacia are associated with a reduction in bone density and may result in bone pain and fracture, but their causes and management are quite different[3].

Methods

An extensive literature search of English-language electronic databases in Medline, PubMed, and Cochrane database of evidence-based reviews was performed starting 2000 onwards. Further articles were obtained from the references of the initial search. Keywords osteoporosis, children, primary osteoporosis, secondary osteoporosis, osteopenia, bone mineral density and fragility fractures were used. Abstracts of the relevant articles were scrutinized, and the pertinent articles were reviewed in detail. This included narrowing down the search for osteoporosis in children in various regions of the world concerning its classification, presentation, pathophysiology, diagnostic modalities and prevention and treatment options, and inference was drawn.

Clinical Presentation

A common presentation of childhood osteoporosis is recurrent long bone fractures, particularly if associated with low impact trauma. Vertebral compression fractures often present with symptoms of back pain and potential spinal deformity. Occasionally, vertebral compression fractures may be asymptomatic and may only be identified when a spinal X-ray is performed in a child who is being investigated for a low bone density or any other reason. Symptomatic osteoporosis may be the first manifestation of an underlying chronic disease such as leukemia or Crohn's disease[12]. Idiopathic juvenile osteoporosis (IJO) which is a rare cause of primary osteoporosis will often present with progressive symptoms of back pain and difficulty in walking.

Causes and Classification

Race and ethnicity constitute non modifiable risk factors for osteoporosis. Genetic predisposition to other systemic illnesses and the treatments thus necessitated likewise play a role in bone health. Childhood osteoporosis may arise from an intrinsic genetic bone abnormality (primary osteoporosis) or more commonly secondary to an underlying medical condition and/or its treatment (secondary osteoporosis)[3,13].

Primary osteoporosis

Primary osteoporosis as defined by decreased bone strength that predisposes individuals to fragility fractures, is most commonly caused in children by one or other of the forms of osteogenesis imperfecta (OI)[14]. In OI there is an underlying abnormality in bone matrix composition, usually due to defective synthesis of type I collagen. The original classification by Sillence D, based on phenotypic features, consisted of four types which are varying in severity. Type II OI is lethal in the perinatal period. Type III is a severe form of the disease with obvious bony deformities and reduced bone mineral density (BMD). Although types I and IV are milder and less easily recognized, they should be considered in the differential diagnosis of children with multiple fractures[4,8]. Collagen can often be demonstrated with either a reduction in amount (type I) or quality (types II, III and IV). It is recognized that some children with OI do not clearly fall into one of these four types.

In recent years, three additional forms of OI have been identified (types V, VI, and VII) based on a combination of phenotypic and bone histological features[15].

Another example of primary osteoporosis is IJO which is a rare condition with an estimated incidence of 1 in 100,000 that is characteristically presents with back pain, difficulty walking and vertebral compression fractures usually in early puberty **(Figure 1)**. Its precise cause is unclear although on bone histology, there is an evidence of reduced bone formation. Spontaneous resolution has been reported in some IJO patients while others go on to have a severe disability with a potential loss of walking ability.

Osteoporosis pseudoglioma syndrome is a third very rare example in which there is a combination of osteoporosis, and congenital blindness due to failure of peripheral retina vascularization[8].

Figure 1: *Vertebral compression fractures in the lumbar spine with osteopenia in a child with idiopathic juvenile osteoporosis.*

Secondary Osteoporosis

Chronic systemic diseases can be detrimental to the growing skeleton in children. Chronic renal insufficiency leads to abnormal bone metabolism via disturbances in calcium and phosphate handling, altered vitamin D and parathyroid hormone (PTH) levels and function, and altered renal clearance of aluminum and other metabolites. Additional factors include malnutrition, metabolic acidosis, and anemia[16]. Gastrointestinal disorders such as celiac disease and inflammatory bowel disease interfere with calcium absorption from the gut and cause vitamin D insufficiency or deficiency. Liver dysfunction can affect children and may impair bone health through calcium and vitamin malabsorption, failure of vitamin D activation, bile salt deficiency, and chronic malnutrition[12,17].

Endocrine system disorders that result in inadequate or excessive levels of systemic hormones can negatively impact bone health in the growing skeleton in children. For example, growth hormone deficiency, diabetes mellitus (DM), and hyperthyroiddism are all risk factors for osteoporosis[18,19]. Bone turnover is altered in type 1 DM children, whereas BMD remains normal during growth. Physical activity and optimal calcium intakes may improve bone metabolism and delay osteoporosis[20]. Pubertal hormones, especially estrogen, play a critical role in bone mass acquisition. Because the majority of BMD is accrued during the peripubertal years, recognition and timely treatment of hypogonadism are key. Decreased muscle development and impaired ambulation in children with cerebral palsy (CP) and muscular dystrophy contribute to increased risk of osteoporosis **(Table 1)**[21-22].

Causes of secondary osteoporosis

1. Reduced mobility

Bones develop to withstand the mechanical forces applied to them in everyday life. The magnitude of these forces and the skeleton's ability to sense and respond to them have a major influence on the mineral content and architectural design of bone, and therefore its strength[22]. In a normal ambulatory child, the major bone strains result from muscle pull and growth. These factors are of paramount importance to chronically diseased children, in whom reduced mobility and thus muscle load is a major

cause of reduced bone mass and strength. This is most notable in children with neuromuscular disorders **(Table 1)**. The most common site of fracture in children with reduced mobility is the distal femur **(Figure 2)**. This is because their long bones tend to be slender with thin cortices and reduced trabecular density, and the lower limbs are usually more subjected to trauma from accidents or handling[23-24]. Vertebral compression fractures are less frequent, but if they occur they can be complicated by the development of scoliosis.

Figure 2: *Plain radiograph of the lower limb showing osteopenia and fracture in lower third of femur in a child with cerebral palsy.*

2. Disordered puberty

Delayed or arrested pubertal development may occur as a result of an underlying chronic disease and/or its treatment, and unless assessed prospectively may be easily overlooked in the care of the affected child[25]. Pubertal hormones, estradiol in females and testosterone in males, influence longitudinal bone growth and bone mineral accrual, with their appropriate timing being important for normal skeletal development and the attainment of peak bone mass[3,26-27]. It is unclear if the induction of puberty in otherwise normal child with constitutional delay positively influences bone mass at final height. Androgen therapy does not however positively affect bone mass[26].

3. Malnutrition and abnormal body weight

Adequate nutrition is essential for normal growth and development. It is not surprise-ing; therefore, that osteoporosis is associated with malnutrition and low body weight disorders **(Table 1)**[22]. The cause of the osteoporosis in such disorders is multifactorial with interplay between low body weight, low calcium, vitamin D and protein intake, gonadal deficiency, growth hormone resistance and malabsorption[28]. Children during both health and disease should receive the recommended daily requirement of calcium. Without adequate sun exposure, even children living in sunny climates can become vitamin D deficient[29]. Because of this, the vitamin D status of chronically diseased children should be evaluated on an annual basis and if necessary, vitamin D supplementation commenced.

Conversely, the obesity epidemic among youth is staggering. The overweight or obese children are undernourished in the sense that their diets are generally poor and lack many important nutrients. In addition, obesity itself is a risk factor for fractures in children[30]. Although it seems counterin-tuitive, the data are convincing. Obese children are generally sedentary, causing poor musculoskeletal coordination and in-adequate lean muscle mass to control their body mass. Because their bone development does not keep pace with their weight gain, their relatively immature skeletons must bear a disproportionate amount of weight when they fall and can result in fragility fractures[30].

4. Inflammatory cytokines and growth factors

Systemic inflammatory disorders are frequently associated with osteopenia and osteoporosis. The cause of the bone loss is multifactorial, but increased circulating and focal concentrations of inflammatory cyto-kines [interleukin-1 (IL-1), IL-6, IL-7, tumor necrosis factor-α, and receptor activator of

nuclear factor-κB ligand (RANKL)] and growth factors are likely to play an important role[28]. Cytokines have been shown to stimulate osteoclastogenesis, suppress osteoblast recruitment and induce resistance to vitamin D, thus increasing bone resorption and decreasing bone formation[28].

Table 1: Classification of childhood osteoporosis. Modified from Shaw[8].

Primary osteoporosis	• Osteogenesis imperfecta • Idiopathic juvenile osteoporosis • Osteoporosis pseudoglioma syndrome • Others like Homocystinuria, Ehlers-Danlos Syndrome (type1)…	
Secondary osteoporosis	**Can be discussed under the following subheadings:**	
	Reduced mobility	• Cerebral palsy • Spinal cord injury and spina bifida • Duchenne muscular dystrophy • Spinal muscle atrophy • Head injury • Unknown neurodisability
	Disordered puberty	• Thalassemia major • Anorexia nervosa • Gonadal damage due to radiotherapy/ chemotherapy • Klinefelter's syndrome • Galactosemia
	Malnutrition / abnormal body weight	• Anorexia nervosa • Chronic systemic disease • Inflammatory bowel disease • Cystic fibrosis
	Inflammatory cytokines	• Juvenile idiopathic arthritis • Systemic lupus erythematosis • Dermatomyositis • Inflammatory bowel disease
	Systemic glucocorticoids and other medications	• Rheumatological conditions • Nephrotic syndrome • Leukemia • Organ and bone marrow transplantation

5. Systemic glucocorticoids

Glucocorticoids are commonly prescribed to children with chronic inflammatory and autoimmune disorders. Glucocorticoids are well known for their potent anti-inflammatory effects in patients with chronic

inflammatory disorders. One adverse effect of glucocorticoid use is its detrimental impact on BMD. At pharmacologic doses, glucocorticoids impair the function and reduce the life of osteoblasts[31]. Simultaneously, glucocorticoids accelerate the maturation and activity of osteoclasts while exerting antiapoptotic effects on these cells[32]. In addition, glucocorticoids reduce intestinal calcium absorption and promote renal calcium excretion. Thus, chronic glucocorticoid therapy results in an increase in PTH secretion which promotes bone resorption[29]. Therefore, the combination of impaired bone formation and accelerated bone resorption increases risk of osteopenia and osteoporosis **(Figure 3)**.

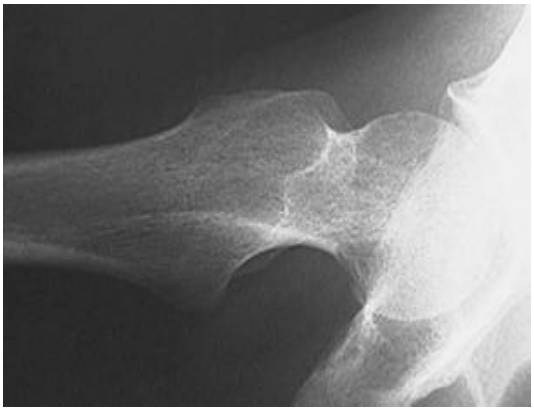

Figure 3: *Left femur demonstrates severe osteoporosis with marked loss of bone density in an older child on long standing steroid therapy.*

Vertebral compression fractures are the most prevalent fractures associated with glucocorticoid use in children. Gafni et al, showed that following the cessation of glucocorticoid therapy in young rabbits, growth and modeling allowed for steroid-induced osteoporotic bone to be completely replaced by normal healthy bone[33]. This may provide another mechanism by which the bone health of the children studied by Leonard et al, improved between steroid doses[34]. These data also suggest that early in life, temporary insults to the child skeleton may not decrease peak bone mass. However, insults towards the end of the growing period may have more long lasting effects on bone integrity[33]. It is unclear if there is a safe, yet therapeutic, dose below which glucocorticoids do not adversely influence bone in children. Until this data is available, it is essential that children be prescribed the smallest effective dose of glucocorticoid and be withdrawn from it and commenced on steroid sparing medication as rapidly as possible. Alternate day dosing may prevent bone loss secondary to glucocorticoid use while maintaining therapeutic benefits, together with optimizing the intake of calcium and vitamin D[3].

6. Other medication

Table 2 outlines other agents associated with childhood osteoporosis. The underlying mechanism responsible for the osteoporosis caused by these agents is unclear, and like glucocorticoids, much prospective research is required.

As the number of survivors of childhood cancer increases, the toxic effects of chemotherapy and radiation on the skeleton are becoming more apparent. Osteoporosis is one of many health issues in a long list of potential "late effects" caused by these therapies[35]. Therefore, pediatrician must provide appropriate surveillance. Patients with disorders that require combination therapy and taking more than one agent at a time that may cause osteoporosis are at an even greater risk.

Diagnosis

The most obvious clinical manifestation of weak bones is a fracture after low-impact trauma. Chronic back pain in predisposed children may indicate vertebral compression fractures, but it is important to note that such fractures may also be asymptomatic, especially in those with increased risk for low BMD[38]. Conversely they may not be reported and remain under-diagnosed radiologically with false negative rates up to 45%[39]. When a child with one or more risk factors for low BMD is identified, it is particularly important to measure BMD. Most Pediatric subspecialists are aware of the risks to skeletal health posed by various chronic diseases in their given fields of practice and routinely screen such patients

for evidence of low BMD using dual-energy x-ray absorptiometry (DXA) scans **(Table 3)**. DXA is the most widely used technique to assess bone mass in children. Although great importance is often given to DXA, it should be remembered that there is no evidence that densitometric data can predict the likelihood of fracture in children **(Figure 4).**

Table 2: Therapeutic agents associated with childhood osteoporosis. Modified from Munns and Cowell[3].

Therapeutic agent	Proposed mechanism for osteoporosis
Methotrexate	Uncertain. Impaired osteoblastic protein synthesis, abnormal vitamin C metabolism.
Cyclosporine	Uncertain. Possible dysregulation of the osteoprotegerin (OPG)-OPG ligand system with a resultant high turnover state[36].
Heparin	Uncertain. a) Decreased 1-α-hydroxylase activity with reduced vitamin D and elevated PTH. b) direct effect on cancellous bone with an increase in bone resorption and decrease in bone formation.
Radiotherapy	Growth hormone deficiency, hypogonadism, AVN, muscle atrophy.
Depot medroxyprogesterone acetate	Central hypogonadism.
Gonadotropin releasing hormone (GnRH) analogues	Central hypogonadism.
L-thyroxine suppressive therapy	Increased bone resorption secondary to osteoblast mediated T3 osteoclast activation.
Anti-convulsants	Altered liver metabolism of 25-OH vitamin D[25]. Low BMD is also induced by the direct effects of anti-convulsant drugs on bone cells, resistance to PTH, inhibition of calcitonin secretion, and impaired calcium absorption[37].

Table 3: Indications for considering a dual-energy x-ray absorptiometry scan for children. Modified from Henwood and Binkovitz[4].

Risk factor for low bone mass density	
Chronic disease	• Chronic renal insufficiency • Gastrointestinal diseases • Cystic fibrosis • Endocrine system disorders
Medications or treatments	• Glucocorticoids, anti-convulsant drugs, chemotherapy and radiotherapy
Primary bone disease (i.e., osteogenesis imperfecta)	
Malnutrition	
Lifestyle habits	• Lack of physical activity
History of multiple fractures or a single fracture following low impact trauma	

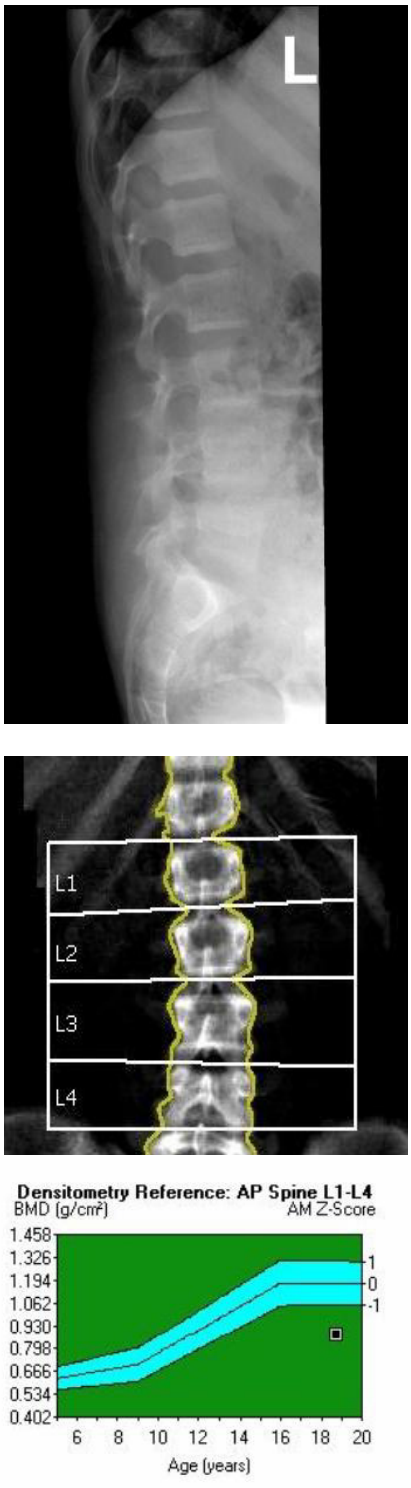

Figure 4: *Lateral radiograph lumbar spine showing increased radiolucency of vertebra L1 – L4 with slightly radiodense endplates. DXA scan AP view lumbar spine showing BMD of 0.877 g/cm2 with estimated Z-Score of -2.5 indicating established osteoporosis.*

The Z-score is the number of standard deviations (SD) of the patient's bone density above or below the values expected for the patient's age. By comparing the patient's BMD with the expected BMD for his or her age, the Z-score can help diagnose and classify osteoporosis, but it is by no means diagnostic by itself. Other patient factors should be taken into account, including height, weight, and physiological maturity[40,41].

- Normal is a BMD that is within 1 SD of the young adult reference mean.
- Osteopenia is a BMD between 1.0 and 2.5 SD below the young adult reference mean.
- Osteoporosis is a BMD more than 2.5 SD below the young adult reference mean[42].

BMD as assessed by DXA is not a true volumetric density, but rather, it is the mass of bone mineral per projection area (grams/cm^2) and is given the term 'areal BMD' (aBMD). Areal BMD is a size-dependent measure. Shorter children therefore have a reduced aBMD compared to age-matched controls. Children with secondary osteoporosis to chronic disease frequently have short stature resulting from their primary disease or its treatment, and may have a reduction in aBMD, not because there is anything abnormal with the composition or structure of their bones, but simply because the bones are small. Pubertal disturbance is another common problem associated with secondary osteoporosis and can result in an erroneous reduction in aBMD when comparing results to that of normally developed age-matched controls. This has led some authors to suggest that DXA results should be corrected for bone age and height when interpreting aBMD[3].

Methods to adjust for height and lean tissue mass have been described and can help determine if the osteopenia/osteoporosis is in part secondary to reduction in lean tissue or a primary disorder of bone. Chronic disease may have differential effects on cortical and trabecular bone dimensions and density. For example reduced mobility will have a major effect on bone strength of the lower limbs consisting predominantly of cortical bone, whereas chronic glucocor-

ticoid therapy may preferentially affect the spine consisting predominantly of trabecular bone[3,43-44].

Another mode of assessing osteoporosis is ultrasound; by measuring the bone speed of sound at the tibial, radial, or calcaneal bones reflecting both cortical density and thickness[9]. In a recent study Alwis et al[45], reported the use of broadband ultrasound attenuation in children and it seemed to be the quantitative ultrasound parameter that best resembled the changes in bone mineral content during growth. While ultrasound is being used more frequently in pediatrics especially for screening, DXA remains the gold standard as a diagnostic tool for osteoporosis. Comparison between both modalities in children is needed to see if ultrasound can be used for diagnosis as well.

Role of biochemical markers of bone turnover

Remodeling is a normal, natural process that maintains skeletal strength, enables repair of microfractures and is essential for calcium homeostasis. During the remodeling process, osteoblasts synthesize a number of cytokines, peptides and growth factors that are released into the circulation. Their concentration thus reflects the rate of bone formation. Bone formation markers include serum osteocalcin, bone-specific alkaline phosphatase and procollagen-I carboxy-terminal propeptide[46]. Osteoclasts produce bone degradation products that are also released into the circulation and are eventually cleared via the kidney. These include collagen cross-linking peptides and pyridinolines, which can be measured in the blood or urine and enable estimation of bone resorption rate. Bone resorption markers include urinary hydroxyproline, urinary pyridinoline, urinary deoxy-pyridinoline as well as collagen Type I cross-linked N telopeptide and collagen Type I cross-linked C telopeptide[47-49]. Markers of bone formation and resorption are of value in estimating bone turnover rates. These biochemical markers may be used to identify fast bone losers[50]. The utility of bone markers to identify fast bone losers was prospectively evaluated in a large cohort of healthy postmenopausal women over four years[50]. It was not used to evaluate fast bone losers in children yet and this needs to be evaluated further.

Higher levels of bone formation and resorption markers were significantly associated with faster and possibly greater BMD loss. In population studies, it appears that markers of bone resorption may be useful predictors of fracture risk and bone loss. Elevated bone resorption markers may be associated with an increased fracture risk in elderly women although the data are not uniform[51]. The association of markers of bone resorption with hip fracture risk in adults is independent of BMD, but a low BMD combined with high bone resorption biomarker doubled the risk associated with either of these factors alone[51]. However, the predictive value of biomarkers in assessing an individual child has not yet been confirmed. Biomarkers may be of value in predicting and monitoring response to potent antiresorptive therapy in clinical trials. Bone turnover markers may have a future role in the clinical management of osteoporosis. In population studies, the combination of low BMD and high bone turnover markers may provide a superior indication of fracture risk to either BMD or bone turnover markers alone[51-52].

Prevention

Adult bone health is predominantly governed by two factors: (a) maximum attainment of peak bone mass; and (b) rate of bone loss which occurs with ageing. Both aspects are determined by a combination of endogenous and exogenous factors and, although genetic influences are believed to account for up to three-quarters of the variation in bone mass, there is still room for the modifiable factors (including nutrition) to play an important role[53]. The data support that both high physical activity —especially weight bearing exercise— and intake of adequate amounts of calcium and vitamin D are associated with a higher BMD, and attaining maximum bone mass particularly in adolescence because puberty is a critical time for accruing bone mass (peak adult bone

mass). Recent studies found that jumping-based activities resulted in substantial improvements in bone mass in prepubertal and pubertal children[54]. The recommended dietary allowances of calcium have been fixed to 800 mg/d for prepubertal children (ages 4-8 years) and for adolescents (ages 9-18 years) 1300 mg/d[52]. On the other hand, overweight showed the opposite effect. Diet habits and exercise must be considered as the main strategies to prevent adult osteoporosis during childhood[55-56].

To prevent bone loss secondary to reduced mobilization in children with chronic disease, weight-bearing activity should be maximized, which in healthy children and adolescents has been shown to increase bone mineral accrual and bone size[57]. For children with extreme bone fragility, swimming and hydrotherapy may be beneficial. In ambulant and non-ambulant children with spastic CP, weight-bearing activity has been shown to significantly improve femoral neck bone mineral content and volumetric BMD compared to controls[58]. In non-ambulant children with CP, a standing frame to facilitate an upright position has been shown to improve BMD, with the gains in BMD being proportional to the duration of standing[3,59].

Treatment

The underlying principles of treatment of secondary osteoporosis in both children and adults is, where possible, to remove the underlying cause. Where this is not possible, minimizing the effects of treatment with drugs that adversely affect bone may be sufficient to eliminate any deterioration in bone quality. If this is not possible, the use of bone sparing drugs such as the bisphosphonates may be necessary whilst ensuring that attention is paid to optimizing calcium and vitamin D intake and encouraging mobility and exercise[13].

The measures outlined in the prevention section are frequently inadequate in preventing the development of osteoporosis. In these situations, specific anti-osteoporosis therapy should be considered. While the guidelines for the treatment of osteoporosis in adults are widely accepted, the much less abundant data for children and adolescents with osteoporosis makes it harder to set clear guidelines for the pediatric population. Bisphosphonates are the most widely used medications for the treatment of childhood osteoporosis[60]. They are potent anti-resorptive agents that disrupt osteoclastic activity[33,61]. Although bisphosphonates have been used for many years in adults, their systematic use in children has been limited. The majority of data pertaining to the clinical utility and mechanism of action of bisphosphonates in children comes from studies of cyclical intravenous pamidronate therapy in moderate to severe OI. The treatment of osteoporosis with bisphosphonates, specifically alendronate and pamidronate in pediatric cancer patients is described. Results showed that these medications were efficacious in reducing BMD loss during cancer therapy and were well tolerated in this special population[62]. In children and adolescents with OI, pamidronate therapy has been associated with improvements in muscle force, vertebral bone mass and size, bone pain, fracture rate and growth. In long bones, pamidronate has been shown to increase cortical thickness and improve bone strength[15,63].

Minodronate is a new nitrogen-containing bisphosphonate[64]. It was the first drug to demonstrate significant prevention of vertebral fractures in patients with osteoporosis in a phase III doubleblind comparative study. In vitro studies demonstrated that minodronate is one of the most potent inhibitors of bone resorption among currently available bisphosphonates. These data suggest that minodronate is a promising new potent bisphosphonate for the treatment of osteoporosis[64]. The use in children is not yet approved.

The safety of bisphosphonate therapy continues to be of concern to many clinicians[65]. To allow for this issue to be systematically evaluated, it is of paramount importance that children and adolescents only receive bisphosphonates as part of well-run clinical trials. Pamidronate lowers serum calcium concentrations that is most marked following the first infusion cycle[15]. In vitamin

D replete individuals receiving the recommended calcium intake, the hypocalcaemia is self-remitting[15]. The majority of children have an acute phase reaction "flu-like" (fever, muscle pain, headache and vomiting) 12-36 hours following initial exposure to bisphosphonates which is self-limiting[66]. It is unusual for this to recur with subsequent doses, and can be limited by pre-treatment with paracetamol or ibuprofen[66]. Oral bisphosphonates may result in chemical esophagitis. Transient uveitis occurs in approximately 1% of children who receive pamidronate[15]. Bisphosphonates are also used for other diseases involving bone remodeling, such as IJO or familial hyperphosphatemia. The question of longterm side effects cannot be answered with the currently available data[67]. Because bisphosphonates accumulate in bone, they create a reservoir leading to continued release from bone for months or years after treatment is stopped. Studies with risedronate and alendronate suggest that if treatment is stopped after 3-5 year, there is persisting antifracture efficacy, at least for 1-2 year. It is recommended to take a drug holiday after 5-10 year of bisphosphonate treatment. The duration of treatment and length of the holiday are based on fracture risk and pharmacokinetics of the bisphosphonate used. Patients at mild risk might stop treatment after 5 year and remain off as long as BMD is stable and no fractures occur. Higher risk patients should be treated for 10 year, have a holiday of no more than a year or two, and perhaps be on a non-bisphosphonate treatment during that time[68]. In general, as a substance group bisphosphonates are well tolerated and, when applied correctly, the toxicity is low.

It was noticed that vitamin D insufficiency was remarkably common in children with primary and secondary osteopenia or osteoporosis. The inverse relationship between vitamin D and parathyroid hormone levels suggests a physiologic impact of insufficient vitamin D levels that may contribute to low bone mass or worsen the primary bone disease. It is suggested that monitoring and supplementation of vitamin D should be a priority in the management of children with osteopenia or osteoporosis[69].

It has been suggested that vitamin K2 (which is found in meat, cheese and fermented products) may not only stimulate bone formation but also suppress bone resorption in vivo[70]. Clinically, vitamin K2 sustains the lumbar BMD and prevents osteoporotic fractures in patients with age-related osteoporosis and prevents vertebral fractures in patients with glucocorticoid-induced osteoporosis. Even though the effect of vitamin K2 on the BMD is quite modest, this vitamin may have the potential to regulate bone metabolism and play a role in reducing the risk of osteoporotic fractures. Prabhoo et al[53], reported vitamin K2 safety in children and suggested that it can be considered for prevention and treatment in those conditions known to contribute to osteoporosis.

Specific disorders resulting in osteoporosis in children

1. Cerebral palsy

CP is a non-progressive encephalopathy with disordered posture and movement. Fracture incidence in children with CP is variously reported between 5 to 30%, with the majority of fractures occurring in the femoral shaft and supracondylar region[21-22].

Reduced mobility is the major cause for bone fragility in children with CP. Reduced mobility results in bone with a low bone mass and abnormal architectural design, which is unable to withstand the occasional mechanical challenges placed upon it, such as forceful muscle contractures associated with a convulsion or unusual weight bearing or transfer[22]. Other factors include vitamin D deficiency from reduced sunlight exposure and possibly anti-convulsant therapy, disorders of puberty and nutritional disorders. Lumbar spine BMD is often normal in children with CP who sustain a pathological fracture except in more involved children when spine is affected as well[71].

To prevent osteoporosis in children with CP a concerted effort must be made to maintain ambulation and weight bearing. As outlined above, biomechanical stimulation of bone requires further investigation as it holds great promise. Other general measures such

as ensuring adequate calcium and vitamin D intake and general nutrition, minimizing iatrogenic causes of bone loss and ensuring timely pubertal development are also important to the child with CP. Once osteoporosis is established, the use of bisphosphonate therapy is justified[3].

2. Leukemia

The leukemias are the most common form of childhood malignancy. The two major skeletal complications of leukemia are osteoporosis and AVN[72]. Strauss et al, reported a 5-year cumulative fracture incidence in children with acute lymphoblastic leukemia of 28%[72]. Risk factors for the development of skeletal complications in acute lymphoblastic leukemia include glucocorticoid administration, malnutrition, reduced mobility, methotrexate, cranial irradiation, impaired bone mineralization, older age at diagnosis and male sex[22,72]. The development of hypothyroidism, growth hormone deficiency and hypogonadism, may influence the bone health of children with leukemia and requires close monitoring[22].

3. Children with intellectual disabilities

have increased risk factors associated with osteoporosis. It has been identified that this population has an increased prevalence of low BMD, osteoporosis and osteopenia[73]. The main contributory factors for low BMD are age, use of anti-convulsants, reduced mobilety and diagnosis of Down's syndrome. In most studies individuals with intellectual disabilities presented with more than two risk factors. It was identified in a survey that an increased prevalence of risk factors associated with osteoporosis, namely use of anti-convulsants (64%), reduced mobility (23%), history of falls (20%) and fractures (11%). Screening for the risk factors associated with low BMD in individuals with intellectual disabilities is important. If these are present further investigations should take place and those found to have osteopenia and osteoporosis should have treatment at an early stage to prevent morbidity and improve their quality of life[73].

Conclusion

Osteoporosis as primary disorder or secondary to chronic disease is increasingly recognized major childhood health problem. With many factors influencing the bone health of children, the physician must take a broad approach to the prevention and treatment of bone disease. It is necessary to utilize nutritional, hormonal and biomechanical therapeutic regimes, as well as bisphosphonate therapy. With this approach and continued research, it may be possible to improve, not only the bone health of children, but also their general wellbeing and quality of their future life as adults and into old age. Osteoporosis in children is still a wide open area for research.

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