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Review Article

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Prevention and treatment of osteoporosis in chronically ill children

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Abstract

Osteoporosis secondary to chronic disease in children has emerged as a major health issue. As the severity of a child's illness increases, so too does the number of factors affecting their bone health. Determinants of bone health in children include level of mobility, exposure to osteotoxic medication, nutritional status, calcium and vitamin D intake, chronic inflammation and pubertal development.

Keywords: Osteoporosis, Children, Chronic Illness, Etiology, Prevention, Treatment

Introduction

Osteoporosis has emerged as a major health issue in pediatrics, with ramifications that extend into adult life. Childhood osteoporosis may arise from an intrinsic genetic bone abnormality (primary osteoporosis) or an underlying medical condition and/or its treatment (secondary osteoporosis). Bone and mineral physicians are seeing an increasing number of children with secondary osteoporosis. This reflects the increasingly complex nature of the medical conditions managed in pediatric health care facilities, the aggressive medical therapies available for chronic diseases and the improvement in long-term survival. It may also reflect an increased awareness of osteoporosis amongst pediatricians. Etiological factors responsible for osteoporosis secondary to chronic illness include immobility, pubertal delay and other hormonal disturbances, undernutrition and low body weight, inflammatory cytokines and glucocorticoid use[1].

Fractures cause not only pain and suffering for children with chronic illness but often a further reduction in mobility and independence, hospitalization, time out of school and considerable stress upon the family[2]. Osteopenia can also result in chronic bone pain, which too, impacts significantly on the child and family.

Clinicians are therefore facing new challenges; to ensure the maintenance of bone health throughout childhood and the provision of a strong skeletal foundation for adult life. There is however a paucity of data pertaining to the natural history and treatment of the bone disease associated with chronic illness in childhood, with the majority of our understanding of the skeletal complications of chronic illness coming from adult studies. Because it is not always possible to translate adult data into pediatrics, it is difficult to make evidence-based management decisions. To address this, a concerted effort needs to be made to perform prospective studies in children.

Given these caveats, this short review will outline the etiological factors of osteoporosis in children with chronic illness and provide a frame work for its prevention and treatment.

Diagnosis of osteoporosis

Osteopenia is defined as a decrease in the amount of bone tissue and osteoporosis is osteopenia with bone fragility. 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 etiology and management are very different. Details pertaining to the diagnosis of

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osteopenia and osteoporosis during childhood are covered in other sections of this issue. A number of points specific to children with chronic illness need to be highlighted however.

Dual energy X-ray absorptiometry (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 or improve the management of children with chronic illness.

Bone mineral density (BMD) as accessed 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 chronic illness 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. It is therefore important to correct for height when interpreting aBMD.

Pubertal delay is a common complication of chronic illness 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. Further confounders that need to be considered are movement artifact from an uncooperative child, positioning difficulties due to spine and limb deformities, and erroneous projection areas due to excessively osteopenic bones.

Assessment of bone health by DXA can be region specific, for example the hip or spine, or total body including bone mineral content and body composition variables, fat and lean tissue mass. Lean tissue mass (a surrogate measure of muscle strength) is an important determinant of total body and regional bone mineral content and its reduction in chronic disease may be the primary factor leading to osteoporosis[3,4]. Methods to adjust for height[4] and lean tissue mass[3] have been described[3] 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 immobility will have a major effect on bone strength of the lower limbs consisting predominantly of cortical bone, whereas chronic glucocorticoid therapy may preferentially affect the spine consisting predominantly of trabecular bone. Peripheral quantitative computed tomography (pQCT) is an emerging technique that is useful to assess cortical and trabecular bone in the limbs[5] and lateral spine X-ray remains an excellent modality to image vertebral morphology[6].

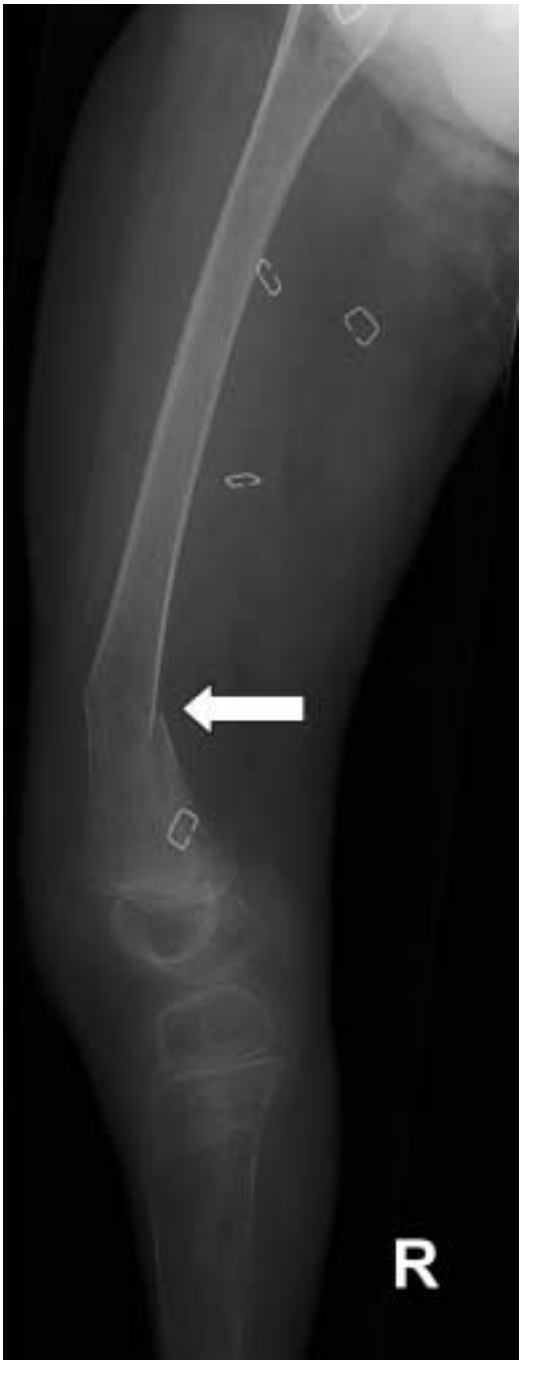

Figure 1. Lateral lower limb X-ray showing a right distal femoral fracture (arrow) in a 4-year-old female with immobility following a below knee amputation for severe burns.

Etiology and prevention of osteoporosis

A chronically ill child will usually have multiple factors influencing bone health and strength, with the number increasing as does the severity of the illness[7]. Bone strength relates to its mineral content and architectural design, the major determinant of which is genetic and therefore not amenable to intervention. There are however a number of modifiable factors that can influence the skeletal health of children with chronic illness, so as to help them reach their genetic potential.

	0 – 6 months	6 – 12 months	1 – 3 years	4 – 8 years	9 – 18 years
Adequate intake of calcium (mg/day)	210	270	500	800	1300

Table 1. Recommended daily intake of calcium for healthy children[86].

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[8]. In the normally ambulatory child, the major bone strains result from muscle pull and growth. These factors are of paramount importance to chronically ill children, in whom reduced mobility and thus muscle load is a major cause of reduced bone mass and strength[9]. This is most notable in children with neuromuscular disorders such as cerebral palsy, Duchenne muscular dystrophy and spinal muscular atrophy, and children with congenital or acquired spinal cord lesions. Transiliac bone biopsies from children with various neurological disorders and immobility have shown that the reduced mass results from small bone size, thin cortices and a reduced trabecular bone volume[10].

The most common site of fracture in children with immobility is the distal femur (Figure 1)[11-13]. This is because their long bones tend to be slender with thin cortices and reduced trabecular density, and the lower extremities are subject to trauma from accidents or handling. Vertebral crush fractures are less frequent, but can be complicated by the development of scoliosis.

To prevent immobilization bone loss in children with chronic illness, weight-bearing activity should be maximized, which in healthy children and adolescents has been shown to increase bone mineral accrual and bone size[14-16]. For children with extreme bone fragility, swimming and hydrotherapy may be beneficial. In ambulant and non-ambulant children with spastic cerebral palsy, weight-bearing activity has been shown to significantly improve femoral neck bone mineral content and volumetric BMD compared to controls[17]. In non-ambulant children with cerebral palsy, 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[2]. A recent pilot study in non-ambulant children, demonstrated that high frequency low-magnitude strain, applied through a vibration platform, increases volumetric BMD in the proximal tibia and possibly also the spine[18]. These data support larger studies into the use of biomechanically based therapies to prevent and treat disuse osteoporosis in children.

2. Pubertal delay

Delayed or arrested pubertal development may occur as a result of an underlying chronic illness and/or its treatment, and unless assessed prospectively may be easily overlooked in the care of the chronically ill child[7]. Pubertal hormones, oestradiol 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[19-21]. Pubertal hormones may also help provide children with the emotional maturity required to cope with chronic illness[7].

It is unclear if the induction of puberty in otherwise normal children with constitutional delay (CD) positively influences bone mass at final height. The situation is even less clear for children with a chronic illness, where osteoporosis is associated with low bone turnover and small bone size. Males at final height with a history of CD have a normal lumbar spine and femoral neck volumetric BMD, but reduced long bone mass and size[21]. The reduction in long bone mass and size, which may put them at an increased risk of long bone fracture, may be secondary to impaired periosteal expansion during puberty[21]. Short-term (6 month) androgen therapy, either monthly injections of 50 mg testosterone propionate-enanthate or 0.1 mg/kg/day oral oxandrolone, has been demonstrated to progress puberty without adversely affecting final height in males with CD[22]. Another therapeutic option is 40 mg/day testosterone undecanoate. Androgen therapy does not however positively affect bone mass[21].

No data on sex steroid 'priming' is available in females. Here, if there is no pubertal development by age 13.5 years, it is recommended to introduce low dose estrogen either orally or transdermally, with a gradual increase in dose over 2-3 years. Once pubertal development has been achieved, it may be possible to withdraw therapy to see if puberty can be maintained spontaneously. The beneficial skeletal effects of pubertal induction in females stems from data in Turner syndrome that showed a height-independent prepubertal decrease in bone mass accrual that ceased with the induction of puberty[20]. In males, if sex steroid priming is not followed by spontaneous pubertal development, low dose androgens should be instituted by age 14.5 years. In the chronically ill or disabled child, pubertal induction may exacerbate behavioural difficulties and raise concerns about hygiene. These are important issues and need to be addressed appropriately.

3. Nutrition and low body weight

Adequate nutrition is essential for normal growth and development. It is not surprising, therefore, that osteoporosis is associated with nutritional and low body weight disorders such as anorexia nervosa, inflammatory bowel disease, malignancy and cystic fibrosis[8,23]. The etiology 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[1].

An adequate intake of calcium and vitamin D is essential for skeletal mineralization. In adolescents, a dietary intake of approximately 1,100 mg/day is associated with peak calcium accretion rates of 350 mg/day in boys and 300 mg/day in girls[24]. In healthy adolescents, short-term gains in BMD have been achieved through calcium supplementation[8]. It is unclear, however, whether such gains are sustainable, improve peak bone mass or most importantly, increase bone strength. Given this, the recommended daily intake of calcium for healthy children is summarised in Table 1. Further studies are required to assess if the calcium needs are similar for children with a chronic illness. Until then, children during both health and illness should receive the recommended daily requirement of calcium.

Without adequate sun exposure, as is often the case in the chronically ill, even children living in sunny climates can become vitamin D deficient[25]. Because of this, the vitamin D status of chronically ill children should be evaluated on an annual basis and if necessary, vitamin D supplementation commenced at 400 IU/day.

4. Iatrogenic

Glucocorticoids. Glucocorticoids are commonly prescribed to children with chronic inflammatory and autoimmune disorders. Even at low doses, glucocorticoids may result in osteopenia by decreasing bone formation and increasing bone resorption[25,27]. The high frequency of their use has led to glucocorticoid-induced osteoporosis being the most common form of secondary osteoporosis in adults[28]. In the majority of situations there will be multiple factors responsible for the deterioration in bone health of children receiving glucocorticoid therapy including the medication itself, inflammatory cytokines, decreased mobility, poor nutrition and hormonal disturbance.

Vertebral crush fractures are the most prevalent fractures associated with glucocorticoid use in children (Figure 2). A prednisolone dose of 0.62 mg/kg/day in children with juvenile idiopathic arthritis is associated with a mean time to vertebral collapse of 2.6 years[29,30]. Intermittent steroid use may also predispose to fracture, with a recent study reporting an increased fracture incidence in children who received over four courses of glucocorticoids[31]. It is however difficult to differentiate between glucocorticoid-induced bone loss and that associated with the primary disorder and its associated increase in inflammatory cytokines, malnutrition and decrease in weight bearing[32]. To address this, Leonard et al. evaluated the effect of glucocorticoids on the skeletal integrity in a cohort of children with glucocorticoid-sensitive nephrotic syndrome[32]. Their results highlight the importance of correcting for the confounders of DXA results and the subtle effects of glucocorticoids on pediatric bone health.

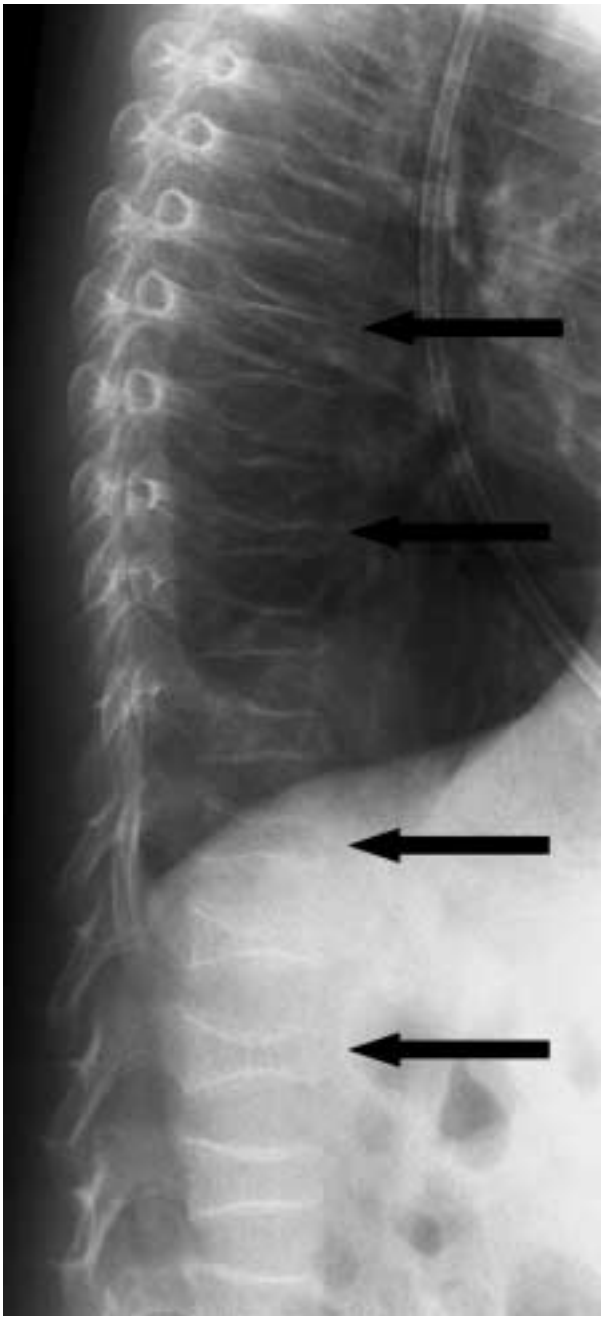

Figure 2. Lateral spine X-ray showing multiple vertebral crush fractures (arrows) in an 8-year-old male post-bone marrow transplant for aplastic anemia, complicated by chronic graft versus host disease requiring chronic glucocorticoid therapy.

Therapeutic Agent	Proposed mechanism for osteoporosis
Glucocorticoids	Multifactorial. Initial rapid bone loss followed by low bone turnover state with decreased bone formation[28]. Apoptosis of osteoblasts and osteoclasts, decreased osteoclast gene expression, decreased osteoblastogenesis, impaired intestinal calcium absorption and renal reabsorption.
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[28].
Heparin	Uncertain. a) Decreased 1-α-hydroxylase activity with reduced 1,25-dihydroxyvitamin 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, avascular necrosis, 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[7]. Decreased trabecular bone and increased cortical bone: absolute bone mass normal.

Table 2. Therapeutic agents associated with osteoporosis in children. Modified from Ward et al.[8].

While glucocorticoids may have adversely affected the bones of the children in their study, it also increased body weight. The increase in weight placed added strain upon the bones of these otherwise normal and ambulant children, which countered any deleterious effect of the glucocorticoid therapy on bone health. This resulted in normalization of the bone mineral content. Their data suggest that a major cause of the poor bone health seen in children treated with glucocorticoids may not be the medication, but the underlying disease.

Gafni et al. elegantly showed that following the cessation of glucocorticoid therapy in young rabbits, growth and modelling 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. These data also suggest that early in life, temporary insults to the pediatric skeleton may not decrease peak bone mass. However, insults towards the end of the growing period may have more long lasting affects on bone integrity[33]. Further studies are required to establish the extent and etiology of the osteoporosis in children receiving glucocorticoid therapy.

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 these drugs and commenced on steroid sparing medication as rapidly as possible. Alternate day dosing may prevent bone loss secondary to glucocorticoid use while maintaining the therapeutic benefits[34,35].

The "bone sparing" effect of deflazacort may provide a means of minimizing the skeletal complications of glucocorticoid therapy. Histomorphometric studies in adults demonstrated that therapeutically effective doses of deflazacort led to significantly less trabecular bone loss than did prednisolone[36]. In children with juvenile chronic arthritis, short-term studies have shown that deflazacort gives similar therapeutic benefits as prednisolone, while preserving vertebral bone mass[29]. Deflazacort did not however reduce vertebral fracture rate[29]. Both deflazacort and prednisolone are used widely in children with Duchenne muscular dystrophy[13,37]. This cohort of children may therefore provide the means by which the potential bone sparing effects of deflazacort can be effectively evaluated.

The role of calcium and vitamin D supplementation in the prevention of glucocorticoid-induced osteoporosis remains controversial. A meta-analysis of randomized trials with calcium and either vitamin D or dihydroxyvitamin D versus calcium alone or placebo, concluded that treatment improved lumbar spine and radial BMD, but did not reduce non-traumatic fracture incidence[38]. Pediatric data are lacking, with conflicting results on the effectiveness of calcium and vitamin D supplementation on improving BMD[39,40]. There is no data on the use of calcium and vitamin D supplementation and fracture incidence in children on glucocorticoid therapy.

Until further data are available, children on glucocorticoid therapy should receive the recommended daily intake of calcium (Table 1) and vitamin D supplementation, 400 IU/day, if their serum vitamin D concentrations are low.

Other medication. Table 2, adapted from Ward et al., outlines other agents associated with pediatric osteoporosis[8]. The underlying mechanism responsible for the osteoporosis caused by these agents is unclear, and like glucocorticoids, much prospective study is required.

5. Inflammatory cytokines and growth factors

Systemic inflammatory disorders are frequently associated with osteopenia and osteoporosis[1]. The etiology of the bone loss is multifactorial, but increased circulating and focal concentrations of inflammatory cytokines (IL-1, IL-6, IL-7, TNF-α and β and RANKL) and growth factors (PDGF) are likely to play an important role[1,41,42]. Cytokines have been shown to stimulate osteoclastogenesis, suppress osteoblast recruitment and induce resistance to 1,25-dihydroxyvitamin D_3, thus increasing bone resorption and decreasing bone formation[1,41,42].

Treatment of osteoporosis

The measures outlined above are frequently inadequate in preventing the development of osteoporosis with chronic bone pain or fragility fractures. In these situations, specific anti-osteoporosis therapy should be considered.

Bisphosphonates are the most widely used medications for the treatment of pediatric osteoporosis[43]. They are potent anti-resorptive agents that disrupt osteoclastic activity by interfering with the mevalonate pathway of cholesterol biosynthesis[32,33,44,45]. Although bisphosphonates have been used for many years in adults, their systematic use in children has been limited to the last 10 years. 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 osteogenesis imperfecta (OI)[13,46]. 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[46]. In long bones, pamidronate has been shown to increase cortical thickness and improve bone strength[46]. Histomorphometric studies in OI have shown that pamidronate increases bone mass by increasing cortical thickness and trabecular number[47].

Similar clinical and densitometric results have been demonstrated in small numbers of children with osteoporosis associated with various chronic illnesses including glucocorticoid-induced osteoporosis, cystic fibrosis, cerebral palsy, Duchenne muscular dystrophy, spina bifida and Gaucher disease[48-52]. Oral bisphosphonates have been shown to be well tolerated and increase BMD in children with diffuse connective tissue diseases[53]. These data support the establishment of large controlled studies into the use of bisphosphonates in children with chronic illness and symptomatic osteoporosis.

The safety of bisphosphonate therapy continues to be of concern to many clinicians[54]. 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[46]. In vitamin D replete individuals receiving the recommended calcium intake, the hypocalcaemia is self remitting[46]. The majority of children have an acute phase reaction (fever, muscle pain, headache and vomiting) 12-36 hours following initial exposure to bisphosphonates[55]. It is unusual for this to recur with subsequent doses, and can be limited by pre-treatment with paracetamol, acetaminophen or ibuprofen[55]. Oral bisphosphonates may result in chemical esophagitis[56].

Animal studies have shown that high-dose bisphosphonates can suppress growth[57,58] and concerns have been raised of this possibility in children[59]. Zeitlin et al. showed, however, that pamidronate significantly improved the growth of children and adolescents with moderate to severe OI compared to historical controls over a 4-year treatment period[60]. Transient uveitis occurs in approximately 1% of children who receive pamidronate[46].

Pamidronate suppresses bone turnover in children with OI to well below that of normal age-matched controls[47]. As highlighted recently, at high doses, this can interfere with bone modeling and result in undertubularization of long-bones[61]. In the growing skeleton, a reduction in bone remodeling results in the accumulation of mineralized cartilage within the bone[47]. The mineralized cartilage has a high density which contributes to the increase in bone density seen with pamidronate treatment[46]. Further, acute reductions in remodeling and persistence in calcified cartilage accounts for the characteristic sclerotic metaphyseal lines seen on long bone radiographs of children receiving pamidronate therapy[62]. Suppressed bone remodeling can also interfere with the repair of microdamage[63] and may account for the delay in osteotomy and possibly fracture repair seen in children with OI who receive pamidronate[64].

Bisphosphonates are contraindicated during pregnancy and all females of reproductive age should have a negative pregnancy test before each treatment cycle or before commencing oral bisphosphonates. Because bisphosphonates persist in mineralized bone for many years, concern has also been expressed that bisphosphonates administered before conception could be released from the maternal skeleton during the pregnancy and effect the fetus[54,65]. A recent report described two women with OI who became pregnant after 5 years of pamidronate therapy[66]. No pamidronate was administered following conception. Both pregnancies went to term and there were no maternal complications noted. It could not be excluded, however, that the adverse events of hypocalcaemia and talipes equinovarus, observed in the two babies, were related to maternal pamidronate therapy[66]. Clearly, further systematic

Figure 3. Lateral lower limb X-ray showing a mid-femoral shaft fracture (arrow) in a 5-year-old female with quadriparetic spastic cerebral palsy. Note the thin femoral corticies.

follow-up of pregnancy outcome in this cohort is required and females should be counselled about the uncertainty surrounding this aspect of bisphosphonate therapy.

Intermittent recombinant human parathyroid hormone (rhPTH) is a potent bone anabolic agent that increases BMD and reduces vertebral fractures in postmenopausal and glucocorticoid-induced osteoporosis[67]. By increasing bone formation, rhPTH may be useful in children either alone or as an adjunct to bisphosphonate therapy. However, the occurrence of osteosarcomas in a significant proportion of young rats treated with rhPTH[68], and the possibility of this occurring in humans[69], has meant the risks of rhPTH use in children outweighs any potential benefit.

In children with juvenile idiopathic arthritis requiring glucocorticoid treatment, recombinant human growth hormone (rhGH) has been shown to increase muscle mass with a resultant increase in bone mineral content[70].

Specific disorders

Cerebral palsy. Cerebral palsy (CP) is a non-progressive encephalopathy with disordered posture and movement, and a prevalence of between 2-4/1,000[71]. It results from an abnormality in brain development, although the precise etiology remains unclear in the majority of cases[71].

Orthopedic complications of CP include scoliosis, joint subluxation and dislocation and fracture of long bones and vertebrae[8,72]. Fracture incidence in children with CP is variously reported between 5 and 30%[8,73], with the majority of fractures occurring in the femoral shaft and supracondylar region[72,74] (Figure 3).

Reduced mobility is the major etiological factor 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 seizure or unusual weight bearing or transfer[8]. Other factors include vitamin D deficiency from reduced sunlight exposure and possibly anti-convulsant therapy[75], disorders of puberty and nutritional disorders.

Lumbar spine BMD is often normal in children with CP who sustain a pathological fracture[76]. This, in association with the observations that children with CP prefer to lay on their side and that the majority of fractures occur in the distal femur, led Henderson et al. to produce normative data for bone density of the distal femur[76]. In children with CP, distal femur DXA was found to correlate well with level of function[73], as would be predicted by the mechanostat theory of bone development. Distal femoral DXA also gave a greater association than spinal DXA between a measure of bone density and a history of previous long bone fracture[73]. Distal femoral DXA may therefore prove an important tool in evaluating the bone health of children with CP, but further studies are required.

To prevent osteoporosis in children with CP a concerted effort must be made to maintain ambulation and weight bearing. To this end, a multidisciplinary team consisting of rehabilitation specialists, physiotherapists, orthopedic surgeons and bone and mineral physicians provides the optimal treatment approach. 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. Because the majority of children with CP have difficulty swallowing, intravenous therapy is preferable. One randomized trial of intravenous pamidronate has been completed[49]. Compared to controls, children with CP who received intravenous pamidronate experienced a significant increase in distal femoral and lumbar spine BMD. Further trials are required to investigate if bisphosphonates reduce fracture incidence in this cohort of children.

Leukemia. The leukemias are the most common form of childhood malignancy, with acute lymphoblastic leukemia (ALL) accounting for approximately 75% of cases[77]. With an overall survival rate approaching 80%, children with ALL

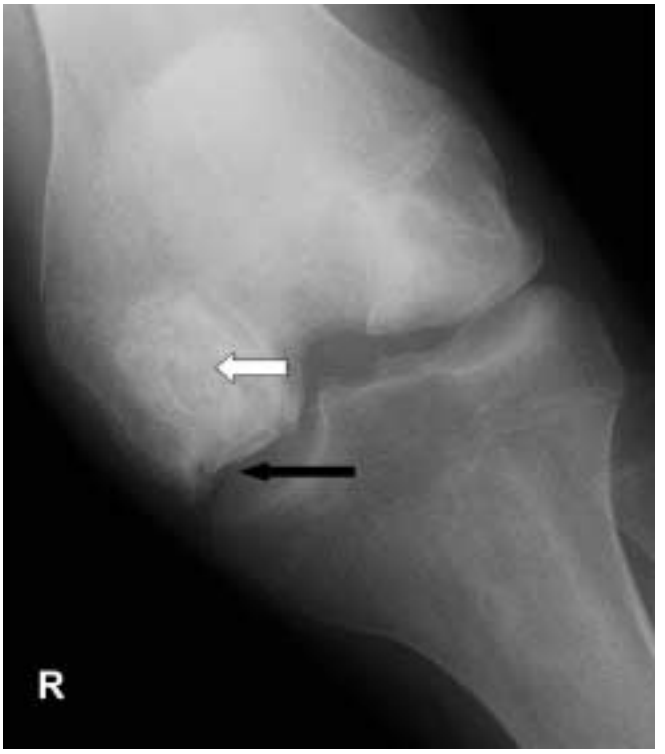

Figure 4. Avascular necrosis of the right knee in a 15-year-old male diagnosed with ALL aged 12-years-old and treated with high dose glucocorticoid therapy. The black arrows indicate areas of irregularity at the distal femur and the white arrow indicates an area of sclerosis.

have an excellent prognosis[77]. The two major skeletal complications of leukemia are osteoporosis and avascular necrosis[78].

Strauss et al. reported a 5-year cumulative fracture incidence in children with ALL of 28%[78]. An increased fracture frequency was also reported by van der Sluis et al., who found a fracture rate in children with ALL six times that of healthy controls, up to 12 months following chemotherapy[79]. Bone mass is often reduced at diagnosis in ALL[79] and falls significantly during the first 6 months of chemotherapy[79,80]. Risk factors for the development of skeletal complications in ALL include glucocorticoid administration, poor nutrition, reduced mobility, methotrexate, cranial irradiation, impaired bone mineralization, older age at diagnosis and male sex[8,78]. Despite this initial skeleton insult, the long-term follow-up of children with ALL, who had not received cranial irradiation, indicates that bone health tends to fully recover[81,82].

The development of hypothyroidism, growth hormone deficiency and hypogonadism, may influence the bone health of children with leukemia and requires close monitoring[8]. Other general measures to maximize the bone health of children with leukemia include minimizing glucocorticoid exposure, maintaining adequate nutrition; especially calcium and vitamin D, and encouraging weight-bearing activity[8,78]. The use of bisphosphonate therapy to prevent bone loss has not been systematically studied in children with leukemia. Once a fragility fracture has occurred, a stronger case can be made for the use of bisphosphonate therapy, although again, no studies have been performed in this cohort of children.

Approximately 15% of children with leukemia and lymphoma have magnetic resonance image changes consistent with avascular necrosis (AVN)[83]. Clinically, 1% - 4% of children develop significant AVN, with the frequency increasing to approximately 10% in children with high-risk ALL[83,84]. Risk factors for the development of AVN include glucocorticoid exposure, older age at diagnosis and male sex[78,83]. On average, greater than 3 joints are affected per child[84]. Joint pain is the most common symptom, with progressive joint destruction requiring surgical replacement reported in <10% of patients with AVN[83] (Figure 4). Little et al. recently demonstrated that intravenous zoledronic acid preserves bone architecture in an animal model of AVN[85]. If this approach proves effective, it provides an exciting therapeutic avenue, not only for children with AVN secondary to leukemia, but also for children with Perthes disease of the hip and AVN secondary to slipped capital femoral epiphysis.

Summary

Osteoporosis secondary to chronic disease is a major pediatric health concern. With many factors influencing the bone health of the chronically ill child, 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 this group of children, but also their general well-being and quality of life.

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