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Bisphosphonate Treatment for Children With Disabling Conditions

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Abstract

Fractures are a frequent source of morbidity in children with disabling conditions. The assessment of bone density in this population is challenging, because densitometry is influenced by dynamic forces affecting the growing skeleton and may be further confounded by positioning difficulties and surgical hardware. First-line treatment for pediatric osteoporosis involves conservative measures, including optimizing the management of underlying conditions, maintaining appropriate calcium and vitamin D intake, encouraging weight-bearing physical activity, and monitoring measurements of bone mineral density. Bisphosphonates are a class of medications that increase bone mineral density by inhibiting bone resorption. Although bisphosphonates are commonly prescribed for treatment of adult osteoporosis, their use in pediatric patients is controversial because of the lack of long-term safety and efficacy data.

INTRODUCTION

Growing awareness of bone health in pediatric patients has increasingly led practitioners to evaluate and treat children for low bone mineral density (BMD), including children with either primary bone conditions or other disabling conditions that lead to secondary osteoporosis. Bisphosphonates are a staple of osteoporosis treatment and have been used extensively in adults for conditions associated with bone fragility [1]. The literature pertaining to adults supports improvement in clinical outcomes with the use of bisphosphonates [2,3]; however, because of differences in pediatric skeletal metabolism,

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caution is required when attempting to extrapolate adult data to children. This review will apprise practitioners of the current literature regarding bisphosphonate treatment in children with disabilities, address controversies regarding safety and efficacy, and discuss future directions for improving the knowledge gap in treatment of children with skeleton-related conditions.

BONE MODELING AND REMODELING

Bone remodeling is a continuous, lifelong process in which mature bone is broken down by osteoclasts and new bone is formed by osteoblasts. This process underlies BMD changes in adults, as well as fracture healing and repair of skeletal microdamage. Tight coupling of bone formation and resorption is required to maintain skeletal homeostasis. In childhood, skeletal growth occurs as the result of strictly regulated uncoupling of bone formation and resorption at specific sites, termed “bone modeling” [4]. On the outer periosteal surface, the formation of bone leads to an increase in bone size, driven by genetic factors and mechanical loading forces [5,6]. Bone resorption expands the marrow cavity on the inner periosteum and sculpts the bone on the outer surface, establishing the widened, funnel-like shape of the metaphyses [7,8]. The net result of bone modeling is an overall increase in bone size and mass.

In many skeletal disorders the bone remodeling cycle is disrupted, leading to a net loss of BMD. Treatment strategies include altering the cycle to either inhibit osteoclast activity or promote osteoblast activity, with the goal of shifting the balance in favor of bone formation.

BISPHOSPHONATES

Bisphosphonates are a class of drugs that increase BMD by inhibiting osteoclast activity. They are synthetic analogs of pyrophosphate, an endogenous regulator of bone metabolism. In bisphosphonates, the central oxygen atom in pyrophosphate is replaced with a carbon atom (Figure 1). All bisphosphonates share a common phosphorus-carbon-phosphorus motif with 2 side chains (R1 and R2 in Figure 1). The R2 side chain determines the chemical properties of the drug and distinguishes individual types of bisphosphonates. This chemical structure affords a high affinity for calcium hydroxyapatite, permitting rapid and specific targeting of the skeleton.

Bisphosphonates have 2 classes with distinct mechanisms of action [9]. The early compounds that do not contain nitrogen (ie, clodronate, tiludronate, and etidronate) are incorporated into the terminal pyrophosphate moiety of adenosine triphosphate, forming a nonfunctional molecule that disrupts osteoclast metabolism and apoptosis. Newer, more potent bisphosphonates that contain nitrogen (ie, pamidronate, alendronate, ibandronate, risedronate, and zoledronate) inhibit a key enzyme, farnesyl pyrophosphate synthase, in the mevalonic acid pathway. Inhibition of this enzyme blocks posttranslational modification of small guanosine triphosphatases such as Ras, Rho, and Rac, which act as signaling molecules for key components of osteoclast function. These effects disrupt osteoclast activity, reduce osteoclast recruitment, and induce apoptosis [10].

The bioavailability of oral bisphosphonates is low, with an estimated absorption rate of 0.6%–2.5% [11]. Approximately 40%–60% of each dose is incorporated into bone, and the remainder is excreted unchanged in the urine [11]. The terminal half-life of bisphosphonates in bone is estimated to exceed 10 years, reflecting release from the skeleton with bone remodeling [12]. Bisphosphonates have been detected in the urine of children up to 8 years after use of the drug is discontinued, consistent with prolonged skeletal release after the completion of treatment [13].

LOW BMD IN CHILDREN

Assessment of BMD in Children

As in adults, the most commonly used method to asses BMD in children is dual x-ray absorptiometry (DXA). This modality offers practical advantages, including wide availability, rapid scanning time, and low use of radiation. In children the posteroanterior spine and total body minus the head are the most accurate and reproducible sites and should be used preferentially [14]. DXA results are expressed as *z* scores calculated from age, gender, and ethnicity-adjusted norms, and should be derived from normative databases specific to the brand of densitometer used [15].

Children with disabilities present unique challenges with regard to evaluation by DXA [16,17]. Contractures may prevent patients from lying in the proper fully supine position. Lumbar spine evaluation may be hindered by scoliosis and the placement of surgical hardware. Proximal femoral anatomy may likewise be disrupted as a result of hip dysplasia, subluxation, or dislocation, which may require placement of surgical hardware. The lateral distal femur is frequently used as an alternate imaging site in these patients, offering the advantages of easier positioning and rare interruption by surgical hardware. This area also offers the potential for subregional analysis, where bone may be separated into primarily cortical and trabecular compartments based on its location [16].

A number of limitations inherent in DXA technology complicate its application to children. Because BMD is greatly influenced by sex steroids, children with early or delayed puberty may be compared with children at a different pubertal stage. A primary limitation is the inability of DXA to account for bone depth. DXA approximates BMD by quantifying the bone mineral content of a 2-dimensional area of interest. Areal BMD is thus expressed in grams of mineral per centimeters squared, as opposed to true volumetric BMD (defined by mineral mass in three dimensions, ie, grams per centimeters cubed). Because areal BMD is dependent on bone size, DXA *z* scores will be inaccurate in children with heights significantly greater or less than the mean for age. This factor is particularly relevant in children with chronic diseases, who frequently have impairments in growth and sexual maturation. A number of approaches have been proposed to address the impact of skeleton size on DXA results, including mathematical models and adjustment for height [18,19]. Longitudinal data are limited, and no consensus exists with regard to the preferred method. Practitioners thus must use a patient-specific approach when interpreting DXA results, taking into account height, bone age, and pubertal status.

Several emerging densitometry methodologies offer significant technical advantages compared with DXA. Quantitative computed tomography of the spine has the capability of assessing BMD in 3 dimensions, thus providing measurements of true volumetric bone density. This technique also assesses bone microarchitecture, distinguishing between trabecular and cortical bone [20]. Unfortunately, its applicability to routine clinical use has been hindered by high radiation exposure, expense, and availability. Quantitative computed tomography may be performed on the peripheral skeleton with use of only minimal radiation; however, interpretation of longitudinal measurements is confounded by growth effects on the size and shape of the skeleton [21]. Quantitative ultrasound is an emerging method in which BMD is determined by quantifying attenuation of ultrasound waves through bone [22]. This technique offers multiple advantages, including information about bone structure and biomechanical properties, relatively low cost, lack of radiation, and portability. However, because of a lack of standardization of technique and reference data, routine clinical use is currently limited.

Definition of Osteoporosis in Childhood

The overlying objective in identifying and treating low BMD is prevention of fractures. BMD in adults is highly predictive of fracture risk, and osteoporosis typically is diagnosed on the basis of a DXA T score less than −2.5. The implications of low BMD in childhood are less clear. Data for healthy children suggest a 1- to 2-fold increased fracture risk for every −1 decrease in *z* score [23,24]; however, few studies have correlated fractures and BMD in children with chronic illnesses. Given the lack of a defined relationship between DXA results and the risk of fracture, the criteria for diagnosis of pediatric osteoporosis has been an area of controversy. In 2007, an expert panel recommended that pediatric osteoporosis be diagnosed on the basis of a DXA *z* score less than −2 in conjunction with a clinically significant fracture history, defined as a lower extremity long-bone fracture, vertebral compression fracture, or 2 or more upper extremity long-bone fractures [14]. The current definition of osteoporosis in children is thus based on a combination of clinical and radiographic features, marking a major departure from adult practice.

Disorders Associated With Osteoporosis in Children

Conditions leading to low BMD in childhood are numerous and diverse in presentation (Table 1). In general, they may be divided into 2 broad categories: primary osteoporosis, resulting from intrinsic skeleton abnormalities, and secondary osteoporosis, where factors external to the skeleton impair mineralization. Primary osteoporosis arises from genetic disorders, whereas secondary osteoporosis results from a diversity of processes, including endocrinopathies, disuse, malnutrition, and other processes. A representative selection is included in Table 1.

Given the broad range of possible conditions, the evaluation for pediatric osteoporosis must be directed by history (including fracture history) and physical examination (with special attention to both axial and appendicular appearance and alignment). In general, a basic laboratory workup includes assessment of mineral metabolism (including calcium, phosphorus, parathyroid hormone, and vitamin D levels) and screening for chronic disease (including blood count, chemistry panel, inflammatory markers, and celiac screening).

Additional testing should be guided by clinical suspicion. Measurement of bone turnover markers such as alkaline phosphatase, osteocalcin, and N-terminal telopeptides may suggest a state of high or low turnover. Levels must be interpreted cautiously, however, because (1) bone turnover varies depending on maturation of the skeleton; (2) normal pediatric ranges have not been well established; and (3) markers are increased during fracture healing.

General Measures for Treatment of Pediatric Osteoporosis

The initial steps in treatment of low BMD are largely conservative. Studies have shown that secondary osteoporosis in childhood is largely reversible with remission or optimization of the primary causative condition [25,26]; therefore, primary management involves the identification and treatment of underlying disorders. Maintaining appropriate vitamin D and calcium intake is essential. Target serum 25-hydroxyvitamin D levels have been an area of debate, with the Institute of Medicine recommending levels greater than 20 ng/mL for healthy children [27], and the Endocrine Society recommending 40–60 ng/mL [28]. Nutritional intake should also be addressed, because malnutrition is associated with BMD impairment. Correction of nutrition is supported by studies of patients with anorexia nervosa; these studies have shown improvement in BMD with weight gain and improved nutritional status [29].

Physical activity is essential for bone health and should be assessed in all children with low BMD. An analysis of 22 controlled trials regarding the effects of weight-bearing exercise on BMD in healthy children reported overall positive effects, particularly during early puberty [30]. Weight-bearing physical activity programs in children with impaired mobility have been shown to lead to improvements in BMD [31]. Some reports have indicated improved BMD as a result of standing on vibrating platforms [32], although data are mixed [33]. Families of children with severely compromised bone health should be counseled about the need for the child to avoid physical activities associated with high risk of fracture, including contact sports, activities involving high impact to the neck and spine (such as horseback riding and riding roller coasters), and forward flexion exercises.

Selected Disabling Conditions Associated With Osteoporosis

Osteogenesis Imperfecta—Osteogenesis imperfecta (OI) is a group of heritable disorders that constitutes the most common cause of primary osteoporosis in children and adults. Persons with OI have bone fragility as a result of defects in collagen I synthesis, which is a critical component of bone matrix. More than 90% of persons with OI can be identified by mutations in *COL1A1* or *COL1A2,* the genes encoding type I collagen alpha chains [34]. A wide spectrum of clinical severity exists, with relatively poor genotype-phenotype correlation. Clinical features vary depending on the level of severity. In patients with moderate to severe disease, fractures develop in infancy and early childhood, leading to kyphoscoliosis, long bone deformities, short stature, and loss of mobility. Persons with mild disease present with a variable number of fractures in childhood, and their condition generally improves after puberty.

Studies relating to OI represent the largest body of literature of bisphosphonate use in children. The first study of cyclic pamidronate in children with OI was published in 1998,

and since then multiple studies have reported improvements in BMD, pain, vertebral body morphology, histomorphometric analyses, and fractures [35–42]. Beneficial effects have been reported with multiple formulations, including neridronate [43], zoledronic acid [44–46], alendronate [47–49], and olpadronate [50], with studies of risedronate yielding conflicting results [51,52].

Two meta-analyses that examined the efficacy of bisphosphonate treatment for OI reported inconsistent results. In 2009 a Cochrane review of 8 randomized trials found a significant difference in fractures in only one trial, with no effect in 3 trials [53]. Two trials reported an increase in spinal BMD. In a separate analysis using different methodology, Castillo and Samson-Fang [54] also identified 8 trials for review and reported consistent effects on BMD and evidence for fracture reduction in 3 of 4 small controlled trials. The benefits of bisphosphonate treatment on the skeleton in children with OI have thus not been conclusively determined. Data suggest short-term improvements in BMD, whereas effects on fracture risk remain an area of debate.

The optimal bisphosphonate regimen in children with OI has not been standardized. Intravenous formulations are most commonly used, because oral bisphosphonates appear to have less pronounced pain effects [49]. Data are insufficient to definitively identify which children with OI will benefit from treatment with bisphosphonates. The literature disproportionately reports on patients with moderate to severe disease, and extrapolation of this data to children with mild OI is inappropriate. Currently, routine treatment of mildly affected children is not recommended [55]. Similarly, the optimal time to initiate treatment has not been determined. Most children included in controlled trials were older than 2 years; however, 2 studies in infants have shown positive effects with pamidronate treatment, including improvement in BMD [36,56], vertebral body morphology [56], bone histomorphometric measures [56], and the incidence of fracture [36].

Fibrous Dysplasia—Fibrous dysplasia (FD) is a rare disorder in which normal bone and marrow are replaced by fibro-osseous tissue [57]. FD may occur in isolation or in association with cutaneous hyperpigmentation and hyper-functioning endocrinopathies, termed McCune-Albright syndrome [58]. FD/McCune-Albright syndrome arises from somatic activating *GNAS* mutations, leading to bone marrow stromal cell proliferation and production of abnormal matrix prone to fracture, deformity, functional impairment, and pain.

Currently no effective medical treatments exist for persons with FD. Use of bisphosphonates has been advocated because of the prominent osteoclastogenesis present in FD tissue. Early studies of pamidronate showed positive preliminary results, with reported improvement in pain, bone turnover markers, and the radiographic appearance of FD lesions [59–61]. The authors of larger studies have been unable to replicate the radiographic effects, although they have demonstrated consistent benefits regarding pain and turnover markers [62–64]. Defining the role of bisphosphonates in the management of FD has been limited by a lack of placebo-controlled trials, and at present, their indication is limited to treatment of bone pain.

Conditions Associated With Impaired Mobility

Bone loss is a known complication of acute and chronically impaired mobility [65,66]. Many children with impaired mobility have additional risk factors for poor bone health, including anticonvulsant use, spasticity, poor nutrition, and impaired coordination leading to increased risk of falls and fractures. Antiresorptive therapy is not an intuitive choice for treatment of osteoporosis resulting from impaired bone formation. However, in part because of a lack of available anabolic medications, practitioners increasingly are using bisphosphonates for treatment of low BMD in children with these conditions.

Cerebral Palsy—Cerebral palsy (CP) is a heterogeneous group of nonprogressive disorders impairing movement and posture that arise from abnormalities in the motor center of the brain. CP has many causes, including perinatal infections, asphyxiation, and stroke, among others [67]. Osteoporosis is common in children with CP. Approximately 80% of patients with severe CP have low BMD, with an annual fracture incidence of 4% [68,69]. Three controlled trials of bisphosphonates for children with CP have been conducted, with pamidronate used in 1 trial [70] and risedronate used in 2 trials [71,72]. All studies demonstrated beneficial effects on BMD but were insufficiently powered to detect an effect on fracture incidence. A recent meta-analysis of 5 studies concluded that the data support probable efficacy for increasing BMD and possible efficacy in reducing fractures in children with CP [73]. Because of the relatively small numbers and lack of long-term safety and efficacy data, the authors recommended that the use of bisphosphonates be limited to children with a history of at least one fragility fracture. Oromotor dysfunction and/or gastrointestinal reflux are often associated with CP and other neuromuscular disorders, and thus important safety considerations may preclude the use of oral bisphosphonates [74].

Duchenne Muscular Dystrophy—Duchenne muscular dystrophy (DMD) is an X-linked disorder arising from mutations in the dystrophin gene, which encodes a protein critical for structural integrity of muscle fibers. Patients present with progressive muscular weakness, loss of ambulation, and death within the third to fourth decade from respiratory and/or cardiac dysfunction [75]. Treatment with corticosteroids attenuates loss of muscle function, leading to prolonged ambulation and preservation of cardiac and respiratory function [76]. The combination of chronic glucocorticoid use, severe muscle weakness, and impaired ambulation places patients at high risk for fractures, especially vertebral compression fractures which affect the majority of patients [77,78]. Few retrospective studies and no controlled studies of bisphosphonates in persons with DMD have been conducted; however, preliminary results are supportive. In a small uncontrolled study of alendronate treatment, spinal BMD was preserved despite disease progression [79]. A retrospective analysis of patients with DMD who were given pamidronate or zoledronic acid after sustaining vertebral compression fractures demonstrated improvements in pain, spinal BMD, and vertebral height ratios [80]. A recent retrospective survival analysis associated bisphosphonate use with improved life expectancy, although lack of data regarding skeleton-related outcomes and other clinical outcomes raises questions regarding the clinical applicability of these findings [81]. Regardless, a critical need exists to define bone-preserving therapies in persons with DMD, given its severe and progressive skeletal morbidity.

Spinal Cord Injury—Patients with spinal cord injuries (SCIs) experience rapid loss of bone density, particularly in the long bones of the lower limbs, resulting in a high incidence of fractures [82]. Bone loss results primarily from prolonged immobilization and muscle atrophy; however, neurologic and hormonal effects after neural injury likely play contributory roles [83]. Bisphosphonates have been used frequently in adults with SCI, but study findings are conflicting. The majority show a mild reduction in bone loss that is variably maintained, and results are insufficient to support routine use in patients without a history of fractures [84]. Data for bisphosphonate use in children with SCIs are limited to a single case report, in which a child treated with zoledronic acid for 18 months demonstrated significant gains in BMD [85]. Although use of bisphosphonates to prevent bone loss in adults with SCIs is not well supported, the potential for added benefits during bone modeling and skeletal growth justify additional investigation into the use of these medications in children.

Traumatic Brain Injury—Traumatic brain injury is another form of neurologic injury that may lead to static encephalopathy and impaired mobility in children [86]. No trials of bisphosphonate use for low BMD in this population have been conducted, and it not known whether extrapolation from studies in persons with SCI or other forms of neurologic injury, such as CP, are relevant.

Spina Bifida—Spina bifida (also known as myelomeningocele) is a congenital disorder resulting from incomplete closure of the embryonic neural tube. Clinical sequelae arise primarily from abnormal neurologic function, including paralysis, impaired sensation, and bladder and bowel incontinence. Patients with spina bifida, particularly children who are nonambulatory, have severe impairment in bone modeling because of a congenital lack of muscular forces on the skeleton [87]. Fractures are common, with a reported prevalence of around 30% [88]. Fractures frequently occur in the metaphyses and diaphyses of the affected lower extremities and are more common in patients with higher level spinal defects [88]. At present, no trials or case series dedicated to bisphosphonate treatment for persons with spina bifida have been reported, although 2 series of nonambulatory children included a patient with spina bifida [89,90]. Bisphosphonate treatment of children with spina bifida thus must be guided by literature relating to other disorders of disuse osteoporosis.

ADVERSE EFFECTS AND MONITORING WITH BISPHOSPHONATE TREATMENT

Bisphosphonate treatment has largely been well tolerated in children and adolescents. The most common adverse effect is an acute phase reaction after the initial dose, which may include flu-like symptoms such as fever, myalgia, and gastrointestinal upset. Symptoms generally begin within 24 hours and may last several days. Premedicating with nonsteroidal anti-inflammatory drugs or steroids may attenuate this reaction. Inhibition of osteoclast activity places patients at risk for hypocalcemia. For this reason, it is important to ensure that the patient has adequate vitamin D stores before treatment and to maintain appropriate dietary calcium intake during the treatment course. Practitioners may consider a short course

of calcium and/or calcitriol supplementation for several days after the infusion in children at high risk for hypocalcemia.

Osteonecrosis of the jaw is a rare but potentially serious adverse effect of bisphosphonate use that is typically seen in patients with cancer who are treated with repeated high-dose intravenous infusions [91]. Although this complication has not been reported in children, it is prudent for the patient to undergo a dental examination and complete required dental work before bisphosphonates are administered. The use of bisphosphonates has been variably associated with additional adverse effects in adults, including esophagitis, atrial fibrillation, and severe arthralgias [92]. Because of the association with esophageal ulcerations, we do not recommend use of oral bisphosphonates in children with gastrointestinal disease, neuromuscular disorders carrying a high risk of gastrointestinal reflux and/or oromotor dysfunction, or an inability to report gastrointestinal pain. Children who are treated with oral formulations should be monitored for gastrointestinal symptoms at each evaluation.

Pregnant women treated with bisphosphonates during childhood risk fetal exposure to bisphosphonates, because these medications easily cross the placenta. Administration of high-dose bisphosphonates to pregnant rats resulted in fetal skeleton abnormalities [93]; however, bisphosphonate toxicity has not been reported in human infants, despite numerous reports of women treated before and during pregnancy [94].

Treatment duration is an important consideration, but little evidence is available to guide practitioners. Because the uncoupling of bone formation and resorption in the growing skeleton allows selective inhibition of resorption with relative sparing of bone formation, bisphosphonates are expected to benefit growing children and adolescents more than persons who have obtained their final height [42,95]. This uncoupling is evidenced by the formation of sclerotic bands at the epiphyses, metaphyses, and vertebral bodies when bisphosphonates are given to children with open growth plates (Figure 2) [96]. These bands eventually resolve within continued bone modeling. However, long-term bone turnover suppression may have consequences for the growing skeleton. Abnormalities at the distal radius were demonstrated in children with OI even after discontinuation of bisphosphonates [95]. After the discontinuation of bisphosphonates in growing children, new bone will be formed at the growth plate and intersect with bisphosphonate-treated bone, and concern has been expressed that this bone may have an increased susceptibility to fracture [95]. Treatment with excessively high doses of bisphosphonates has led to osteopetrosis and persistent remodeling defects [97,98], which have persisted for more than 6 years after discontinuation [99].

Long-term effects of bisphosphonates on healing of the skeleton have not been well studied in children. In one report of OI, investigators found no effect on spontaneous fracture healing but delayed healing after osteotomy procedures [100]. For this reason, practitioners frequently discontinue use of bisphosphonates several months after planned orthopedic procedures. The development of rare atypical femoral fractures in adults treated with bisphosphonates on a long-term basis raises additional concerns regarding the safety of continuous bone turnover suppression [101].

FUTURE DIRECTIONS

In recent years, insights into bone remodeling pathways have spurred the development of multiple novel bone-altering therapies. Intact parathyroid hormone and teriparatide are anabolic agents typically used in combination with bisphosphonates in adults; however, their use in pediatric patients is limited by a black box warning concerning an increased risk of osteosarcoma in treated juvenile rats [102]. Denosumab, a potent antiresorptive agent recently approved to treat osteoporosis in adults, acts through inhibition of receptor activator of nuclear kappa-B ligand [103]. Additional therapies under investigation include anabolic antisclerostin monoclonal antibodies and the antiresorptive cathepsin K inhibitor odanacatib [104,105]. These therapies offer multiple theoretical advantages compared with bisphosphonates, including high selectivity, improved promotion of bone formation, and a shorter half-life.

CONCLUSIONS

Pediatric osteoporosis arises from a broad range of genetic, neurologic, and metabolic disorders and is common in children with physical disabilities. Assessment of BMD in children is challenging because of the limitations of DXA in evaluating the growing skeleton. Initial management steps include optimizing treatment of underlying conditions and initiation of conservative measures such as weight-bearing physical activity and ensuring adequate nutrition. Bisphosphonates increase BMD through inhibition of bone resorption and are commonly used to treat osteoporosis in adults. Increasing evidence suggests that bisphosphonates may be beneficial for pediatric disorders of the skeleton; however, their routine use is limited by a lack of long-term safety and efficacy data. Practical considerations include significant knowledge gaps regarding optimal dosing, formulation, and the target population for bisphosphonate use in children.

The decision to initiate treatment with bisphosphonates in children must be made using clinical judgment, with the clinician weighing the potential risks and benefits for each individual patient. Based on the current literature, treatment with bisphosphonates is justified in children with significantly low BMD who have a history of fragility fractures, a high risk of morbidity from fractures, and disabling bone pain that is not responsive to conservative measures, and in the context of clinical trials.

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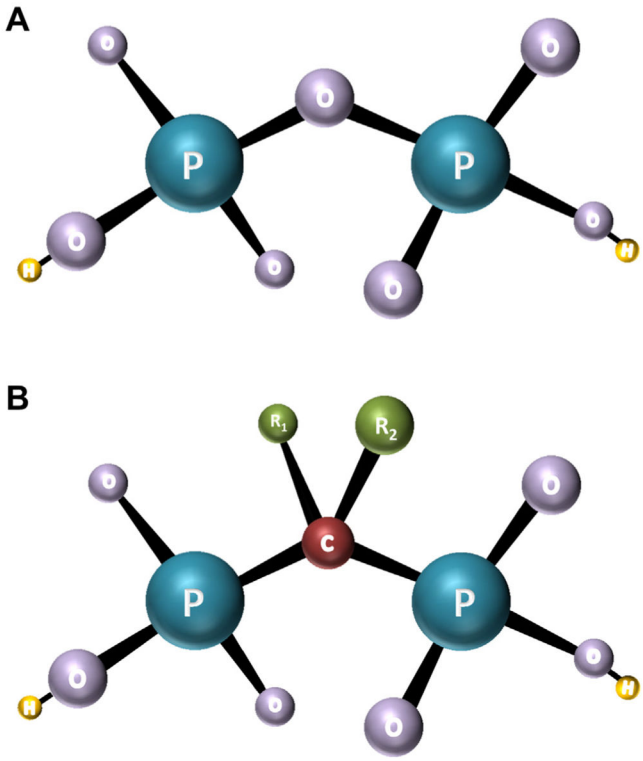

Figure 1.
Chemical structure of pyrophosphate (A) and bisphosphonates (B). P = phosphorus, O = oxygen, H = hydrogen, C = carbon, R = side chain.

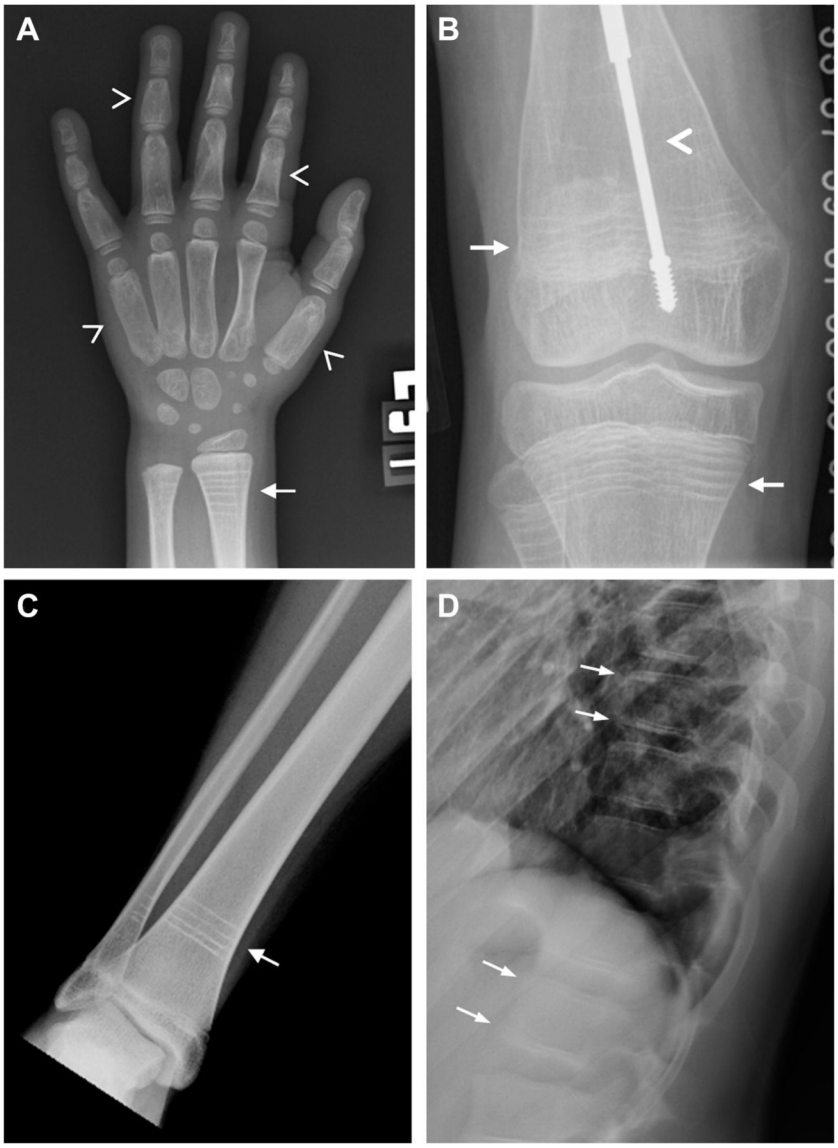

Figure 2.

Images depicting sclerotic bands associated with bisphosphonate treatment. (A) A 10-year-old girl with fibrous dysplasia who was treated with a 3-year course of pamidronate was found to have transverse sclerotic bands at the radial epiphysis and metaphysis (arrow). Note the expansile, ground glass appearance of the fibrous dysplasia in her metacarpals and phalanges (arrowheads). (B) Radiographs from a 13-year-old boy with osteogenesis imperfecta who was treated with pamidronate for 2 years demonstrate metaphyseal bands in the distal femur and proximal tibia (arrows). An intramedullary rod has been placed for fixation of a femoral fracture (arrowhead). (C) A 13-year-old girl with fibrous dysplasia underwent a 1-year course of pamidronate at age 7 years, which caused residual sclerotic bands that appear to have migrated toward the tibial diaphysis with continued skeletal

growth (arrow). (D) Spine films from the patient in (C) demonstrate sclerosis at the superior and inferior end plates of the vertebral bodies (arrows).

Table 1

A representative sample of disorders associated with low bone mineral density in children

Primary bone disorders
Osteogenesis imperfecta
Fibrous dysplasia
Hypophosphatasia
Osteoporosis pseudoglioma syndrome
Ehlers-Danlos syndrome
Idiopathic juvenile osteoporosis
Secondary bone disorders
Impaired mobility
Cerebral palsy
Spina bifida
Spinal cord injury
Traumatic brain injury
Duchenne muscular dystrophy
Chronic inflammatory conditions
Juvenile idiopathic arthritis
Inflammatory bowel disease
Systemic lupus erythematosus
Nutritional deficiencies and malabsorption
Vitamin D deficiency
Calcium deficiency
Celiac disease
Anorexia nervosa
Liver failure
Cystic fibrosis
Infiltrative disorders
Leukemia
Inborn errors of metabolism
Endocrinopathies
Hypogonadism
Hyperparathyroidism
Hyperthyroidism
Growth hormone deficiency
Medication-induced and iatrogenic effects
Antiepileptics
Chemotherapeutics
Glucocorticoids
Radiotherapy