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REVIEW

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The role of bisphosphonates in diseases of childhood

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Abstract Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption by their action on osteoclasts. In recent years, bisphosphonates have been used in children for treatment of a growing number of disorders associated primarily with generalized or localized osteoporosis, metabolic bone diseases, heterotopic calcification in soft tissues, and for resistant hypercalcemia. In the present review we discuss the pharmacological aspects of bisphosphonates and related bone pathophysiology, review the pediatric literature on the role of bisphosphonates in childhood diseases and our experience with these drugs. The theoretical concerns of possible adverse effects of these drugs on the growing skeleton have not materialized in the limited pediatric clinical experience. Bisphosphonates provide the pediatrician with an opportunity to treat mineral and bone disorders of childhood which until recently did not have satisfactory therapy, at the same time, being aware of the theoretical concerns on microdamage accumulation in bone, bone quality and teratogenic potential of these drugs.

Keywords Bisphosphonates · Children · Osteoporosis

Introduction

Pyrophosphates are naturally occurring polyphosphates in the body that prevent calcification by binding to newly forming crystals of hydroxyapatite. Pyrophosphates are normally degraded by alkaline phosphatase. The significance of these compounds is appreciated in children with hypophosphatasia who develop a severe bone mineralization defect due to mutations in the tissue non-specific alkaline phosphatase enzyme causing elevated levels of pyrophosphate compounds [125]. Bisphosphonates, which are stable analogues of these naturally occurring pyrophosphates, were widely used as antiscaling additives in washing powder, water, and oil brines to prevent deposition of calcium carbonate scales in industry before their biological importance was appreciated. In 1968, Schibler et al. [102] showed that pyrophosphate and long-chain condensed phosphates could inhibit aortic calcification induced by vitamin D_3 in rats. In 1969, Bassett et al. [7] reported successfully treating two children with myositis ossificans, a disease characterized by progressive heterotopic ossification of the connective tissue, with etidronate. In addition to preventing heterotopic ossification, bisphosphonates also inhibit bone resorption. In 1971 Smith and colleagues [107] demonstrated that etidronate could inhibit bone resorption in patients with Paget's disease. Subsequent to these early clinical observations, bisphosphonates have been extensively used in adults with Paget's disease [23], hypercalcemia of malignancy [81] and postmenopausal osteoporosis [19,20], where they have been found to be effective and well tolerated. Until now the use of bisphosphonates in children has been limited due to concerns of possible adverse effects of these agents on the growing skeleton.

The morbidity from osteoporosis in children who now survive with chronic diseases, prolonged immobilization and steroid treatment is having significant impact on their quality of life, and in some cases the osteoporosis in adults may have its origin in childhood. In this review, we wish to introduce to the pediatricians, bisphosphonates as a drug class and its role in the management of both primary and secondary bone disorders of childhood. Bisphosphonates have been used in four broad categories of condition in children: generalized or localized osteoporosis, metabolic bone disease, soft tissue calcification and hypercalcemic states.

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Bone remodeling and modeling

The bone undergoes normal wear and tear with time. The remodeling cycle is a mechanism by which the skeleton replaces old bone and repairs microdamage that occurs in bone from physiological repetitive loading during daily activity. The remodeling process involves bone resorption by osteoclasts followed by bone formation by osteoblasts, which together form a temporary structure called the basic multicellular unit. At any time there are about one million active basic multicellular units, each measuring 1–2 mm in length and 0.2–0.4 mm in width and takes 6–9 months to complete one remodeling cycle. This allows for complete regeneration of the skeleton in about 10 years. Bone remodeling occurs with bone resorption always being followed by bone formation; a phenomenon referred to as coupling. At any time, some bone will have been resorbed and not yet replaced, which is referred to as the remodeling space. In addition, modeling is the process of shaping the skeleton during growth, which is responsive to mechanical forces that are placed on the skeleton. Bone formation exceeds bone resorption and the process results in a net increase in bone mass during childhood and adolescence. In modeling, osteoclast and osteoblasts are not regulated by a direct coupling process as in remodeling. Bisphosphonates, through their action on osteoclasts, decrease the rate of initiation of new remodeling cycles, resulting in fewer remodeling sites and a decrease in the remodeling space. The increase in bone mineral density observed with bisphosphonate treatment is due to the filling in of the remodeling space with new bone [17,40].

Biochemical markers of bone turnover

Biochemical assays for monitoring bone turnover rely on the measurement, in serum or urine, of enzymes, matrix proteins and collagen degradation products that spill over into the body fluids during bone modeling and remodeling. Markers of bone formation are all osteoblast products such as serum alkaline phosphatase, bone specific alkaline phosphatase, osteocalcin, and C-propeptide and N-propeptide of type I collagen while the markers for bone resorption are from osteoclast activity such as urinary hydroxyproline, hydroxylysine glycosides, pyridinoline, deoxypyridinoline, N- and C-telopeptide and serum tartrate resistant acid phosphatase. Serum osteocalcin and bone specific alkaline phosphatase are good indicators of bone formation activity though they do not always show parallel response as each may reflect the expression of these proteins at different stages of osteoblast development and synthetic activity [26]. Urinary cross-linked N-telopeptide is the most responsive bone resorption marker, followed by total pyridinoline and deoxypyridinoline [34]. The decrease in bone resorption markers is more marked than that of bone formation markers following therapy with bisphosphonates (Fig. 1). There are scant normative pediatric data for bone markers. Bone growth and modeling are responsible for higher breakdown products during childhood compared to adulthood. Mora et al. [73] found urinary N-telopeptides, pyridinolines and deoxypyridinolines to decrease with age, and the peak of excretion was observed at the onset of adolescence. Prepubertal levels of all markers were four- to five-fold higher than in adults, and they decreased towards adult levels in late puberty. Puberty has an independent effect on the bone markers independent of age and gender. The Ad Hoc Committee on Bone Turnover Markers of the National Osteoporosis Foundation on the current adult data concluded that more studies are needed to determine the optimal cut-off values, and to determine the predictive value of markers in combination with bone mineral density for osteoporotic fracture. Also, the relationship between baseline marker and magnitude of change in bone mineral density in response to therapy is weak [64].

Structure and mechanism of action

Bisphosphonates are analogues of endogenous pyrophosphate in which a carbon atom replaces the central atom of oxygen, which imparts resistance to hydrolysis by alkaline phosphatase to the drug (Fig. 2). The P-C-P motif of the bisphosphonates together with a hydroxyl group on the R^1side chain imparts high affinity to the drug for calcium hydroxyapatite crystal allowing rapid and efficient targeting of bisphosphonates to bone mineral surfaces. Once localized within bone, the structure and three dimensional conformation of the R^2 side chain become the critical determinant of antiresorptive potency and biological activity of the drug [113]. Bisphosphonates that contain a primary amino group on the R^2 domain are more potent than the non-amino containing bisphosphonates [113]. The decrease in bone resorption observed with bisphosphonates is mediated through suppression of osteoclast activity. At the *molecular level*, bisphosphonates that closely resemble the inorganic pyrophosphate e.g. clodronate or possibly etidronate, are incorporated into non-hydrolysable analogues of ATP that inhibit ATP-dependent intracellular enzymes [90,97]. The more potent nitrogen containing bisphosphonates, such as alendronate and risedronate, inhibit the mevalonate pathway needed for synthesis of farnesyl pyrophosphate and geranylgeranyl pyrophosphate for prenylation (post-translational modification) of small GTPases, such as Ras, Rho and Rac (an important group of signaling proteins), inhibit enzymes squalene synthase and protein tyrosine phosphatases [90,97]. The inhibition of these critical biochemical pathways at the molecular level of the osteoclasts leads to the significant *cellular effects* such as decreased osteoclast activity [15], inhibition of osteoclast recruitment [96], inhibition of osteoclast precursor [75], apoptosis of osteoclasts [48], osteoclast injury [30], alteration in the ruffled border [101] and loss of

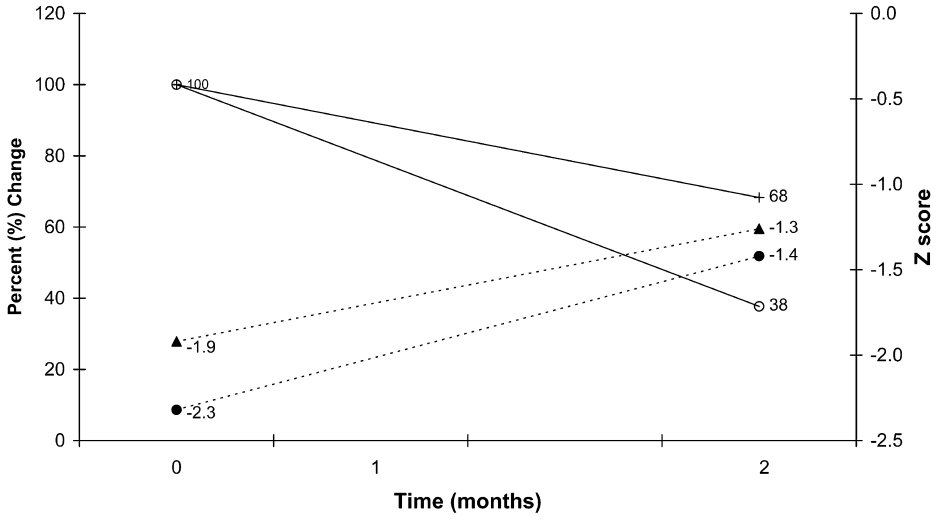

Fig. 1 Changes in bone markers, serum bone specific alkaline phosphatase (BSALP; *plus*) and urinary N-telopeptides (NTx; *open circles*), and bone mineral density Z scores for total body (*solid triangles*) and L_2-L_4 spine (*closed circles*) in five children treated with bisphosphonates over a period of 12 months for different osteoporotic conditions. Note that the reduction in bone resorption marker (NTx) is greater than that in bone formation marker (BSALP) as characteristically seen in patients successfully treated with bisphosphonates as reflected by the improvements in Z scores. The changes are expressed as means and all are statistically significant at $P < 0.05$

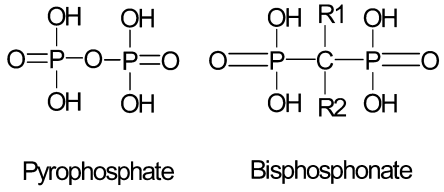

Fig. 2 Structure of pyrophosphate and germinal bisphosphonate

Na^+-independent acid extrusion [124]. In vitro studies have also suggested that bisphosphonates could inhibit osteoclast activity through its action on osteoblasts [75]. The net effect of these cellular changes at the *tissue level* is suppression of bone turnover as evident on histological examination and histomorphometric assessment. Bone biopsies following therapy with bisphosphonates show no gross qualitative bone abnormalities, normal bone mineralization (normal mineral apposition rate and minimal or no decrease in osteoid thickness) and decreased bone turnover (decrease in activation frequency, mineralizing surface, erosion depth, eroded volume/ bone volume) [17,40]. The increase in bone mineral density following therapy results from reduction in the remodeling space due to decreased activation frequency and a positive bone balance [17,40].

Pharmacokinetics

Bisphosphonates available for clinical use with their chemical structure, route of administration and relative potency compared to etidronate are shown in Table 1. Bioavailability of the oral preparations is very poor with less than 5% of an orally administered dose being absorbed. The absorption is further diminished by food, orange juice, coffee, milk, iron supplements, calcium and dairy products [27,97]. When administered, bisphosphonates are cleared rapidly from the circulation. The half-life in serum is short, a few hours or less, whereas the half-life in the bone may be several years depending on the rate of bone remodeling. Of the absorbed fraction, as much as 20%–80% is taken up by the skeleton and the remainder is excreted unchanged in the urine [27,97]. The drug is not enzymatically or chemically degraded. Bisphosphonates bind preferentially to bones that have high turnover rates and is influenced to some extent by vascular supply, species, age and gender [27]. Their distribution in bones is not homogeneous and is significantly higher in trabecular bone (i.e. joints of the tibia and femur) than in cortical bone (i.e. middle portions of these bones). Also the accumulation of bisphosphonates in the skeleton is not accompanied by a cumulative effect on bone resorption as only the bone surface bound bisphosphonates is biologically active while the compound which is buried in bone during the process of remodeling is biologically inert. Rapid or high intravenous dose can lead to bisphosphonate deposition in noncalcified tissues, mainly in the liver, spleen and kidney due to formation of complexes with metal or to aggregates [27]. In individuals with renal impairment, bisphosphonates should be used judiciously as the data are limited. Bisphosphonates have been used in small series of children with impaired renal function and on dialysis [91,104]. Saha et al. [98] showed that with declining renal function the cumulative urinary elimination of clodronate decreased and the total area under the serum concentration–time curves increased suggesting an increase retention of clodronate occurred with decreasing glomerular filtration rate, based on which the recommendation for dose adjustment for clodronate is: creatinine clearance from 50–80 ml/min, 75%–100% of normal dose; creatinine clearance from 12–50 ml/min,

Table 1 Bisphosphonates used in clinical trials, their chemical structure, route of administration and relative potency to etidronate

Name	R^1	R^2	Oral	Parenteral	Relative potency	USA
Etidronate	OH	CH_3	+	+	1	+
Clodronate	C	Cl	+	+	10	
Tiludronate	H	CH_2-S-phenyl-Cl	+		10	+
Pamidronate	OH	$CH_2CH_2NH_2$	+	+	100	+
Neridronate	OH	$(CH_2)_5NH_2$			100	
Olpadronate	OH	$CH_2CH_2N(CH_3)_2$	+		100–1000	
Alendronate	OH	$(CH_2)_3NH_2$	+		100–1000	+
Ibandronate	OH	$CH_2CH_2N(CH_3)$(pentyl)		+	1000–10000	
Risedronate	OH	CH_2-3-pyridine	+		1000–10000	+
Zolendronate	OH	CH_2-(imidazole)		+	> 10000	+

50%–75% of normal dose; and creatinine clearance < 12 ml/min, 50% of normal dose. Individuals with renal failure generally retain more drug even after correction for reduced clearance as the associated secondary hyperparathyroidism results in increased numbers of bone resorption pits, and more osteoclast activity, exposing more areas of bone remodeling for bisphosphonate binding [91].

Bisphosphonates in pediatric studies

Idiopathic juvenile osteoporosis

Osteoporosis is characterized by loss of bone mass and microarchitectural integrity, resulting in an increased bone fragility and risk of fractures with associated morbidity and mortality. Idiopathic osteoporosis in children and adolescents is uncommon and the vast majority of cases of pediatric osteoporosis are secondary to endocrine, neurological, hematological and gastroenterological disorders or to glucocorticoid treatment. Idiopathic juvenile osteoporosis occurs sporadically in prepubertal children with no family history of bone disease. It is characterized by four cardinal features: (1) onset before puberty, (2) fracture of vertebrae or long bones especially at the metaphyses, (3) formation of new osteoporotic bone without callus formation (neo-osseous osteoporosis) and (4) gradual remission after the onset of puberty [52]. It is manifested by recurrent fractures following minor trauma, bone pain and kyphosis and at times can lead to permanent skeletal damage. There are no distinct biochemical abnormalities characteristic of idiopathic osteoporosis although an increase in bone resorption has been implicated [12,52]. Brumsen et al. [12] treated six children with idiopathic osteoporosis with pamidronate (Table 2). The treatment resulted in suppression of bone resorption. There was a marked increase in bone mineral density, and the biochemical parameters of bone turnover (serum alkaline phosphatase and urinary hydroxyproline) decreased progressively in all patients. Patients who were immobilized due to their severe bone disease were able to walk normally within a few weeks of starting treatment. There was a marked increase in calcium balance in all patients, which was maintained in the following 3 years of therapy. Similar clinical and biochemical improvements were observed by other authors treating juvenile osteoporosis [45,52]. Due to the nature of spontaneous improvement in this entity after puberty, a judicious use of bisphosphonates should be carefully considered in these patients.

Corticosteroid induced osteoporosis

Osteoporosis is a recognized complication of corticosteroid therapy. Long-term use of corticosteroids is associated with bone loss and an increased risk for fractures. Meta-analysis in adults with steroid induced osteoporosis showed that bisphosphonates were more effective than vitamin D, which with calcium was more beneficial than calcium supplementation or no therapy [2]. Another meta-analysis of 842 adults with steroid induced osteoporosis found bisphosphonates to be effective at preventing and treating bone loss in the lumbar spine (weighted mean difference of 4.0%; 95% CI 2.5, 5.5) and in the femoral neck (weighted mean difference of 2.1%; 95% CI 0.2, 4.0) between the treatment and placebo group and a 24% reduction in spinal fractures, which was not significant [46]. Bianchi et al. [10], in a prospective multicenter study of 38 children on steroids for diffuse connective tissue diseases were treated with oral alendronate showed an increase in vertebral bone mineral density of $14.9 \pm 9.8\%$ over baseline while it either decreased or remained unchanged in the control group. Similar findings were reported earlier by Lepore et al. [60] in seven children with juvenile chronic arthritis treated with clodronate for 1 year in which bone mineral density increased in the treated group (from 129 mg/cc to 134 mg/cc) while it decreased in the control group (from 123 mg/cc to 115 mg/cc). Falcini et al. [28] showed improvement in back pain and improvement in bone mineral density with intravenous alendronate given 3 months apart in four children who developed symptomatic steroid induced osteoporosis with veterbral fractures. Geusens et al. [35] showed remarkable improvement with pamidronate in an adolescent with severe steroid induced osteoporosis associated with multiple vertebral fractures and complete immobilization to complete ambulation (Table 2). Loss of bone is particularly rapid within the first 6–12 months of

Table 2 Bisphosphonates used in children to treat disorders associated with generalized osteoporosis

Reference	Cases (*n*)	Condition	Drug	Dose	Duration[a]
[12]	6	Idiopathic osteoporosis	Pamidronate	150–300 mg/day po	2.2–8.2 years
[45]	1	Idiopathic osteoporosis	Pamidronate	10 mg/day iv × 18 days; 300 mg/day po	1 year
[52]	1	Idiopathic osteoporosis	Residronate	5 mg/day po	4 month
[115]	9	Primary or secondary osteoporosis	Pamidronate Olpadronate	3–7 mg/kg per day po 0.5 mg/kg per day po	1.1–6.7 years
[10]	38	Corticosteroid induced osteoporosis	Alendronate	5–10 mg/day po	1 year
[60]	7	Corticosteroid induced osteoporosis	Clodronate	400 mg/day po	1 year
[28]	4	Corticosteroid induced osteoporosis	Alendronate	3.25 mg/day iv × 3 days, repeat 3 month	1 year
[35]	1	Corticosteroid induced osteoporosis	Pamidronate	300 mg iv over 9 months	1 year
[43]	6	Cerebral palsy	Pamidronate	1 mg/kg per day × 3 days q3 months	1 year
[105]	2	Cerebral palsy	Pamidronate	0.4 mg/kg iv q3 months	1 year
[105]	1	Cerebral palsy	Etidronate	7.5 mg/kg per day po × 2 weeks q3 months	18 months
[74]	17	Thalassemia	Alendronate Clodronate	10 mg/day po 100 mg q10 days im	2 years
[4]	16	Cystic fibrosis	Pamidronate	30 mg iv q3months	2 years
[42]	13	Cystic fibrosis	Pamidronate	30 mg iv q3months	6 month
[41]	12	Cystic fibrosis	Pamidronate	30 mg iv q3months	1 year
[78]	1	Congenital erythropoietic porphyria	Pamidronate	150–300 mg/day po	11 months
[85]	1	Congenital erythropoietic porphyria	Clodronate	1600 mg/day po	1 year
[11]	1	Severe congenital neutropenia	Etidronate	100 mg/day po	8 months

[a] The duration of therapy and/or follow-up reported in the manuscript

corticosteroid use [51]. Homik et al. [46], in their meta-analysis, found that clinical trials in which bisphosphonate therapy was provided for prevention of steroid induced osteoporosis showed greater bone loss in the placebo arm, with maintenance or small amounts in bone accrual in the treatment arm. Similarly, where bisphosphonate therapy was provided for treatment of steroid induced osteoporosis, it showed a greater degree of bone accrual in the treatment arm, with less dramatic bone loss in the placebo arm. However, overall response to bisphosphonate therapy appeared to be greater in the primary prevention trials. This supports the belief that bone loss is more prominent in the early stages of corticosteroid therapy, with a slower rate of loss as steroid therapy continues. Fig. 3 shows a child at our center who developed corticosteroid induced osteoporosis, which improved on weekly oral alendronate therapy as documented on a DEXA scan of the lumbar spine.

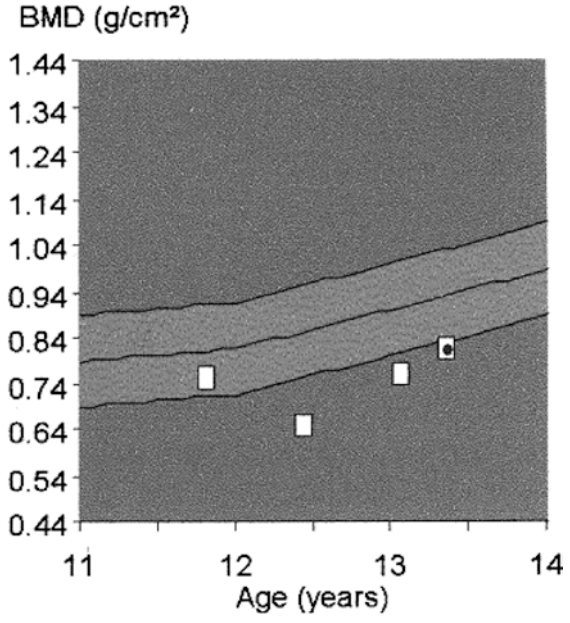

Fig. 3 The changes in bone mineral density (g/cm^2) observed on a DEXA scan of the lumbar spine in a child treated with corticosteroid for IgA nephropathy. Note the development of osteoporosis after treatment with corticosteroids was started. Following weekly oral alendronate started at 12.5 years of age while still receiving corticosteroids, gradual improvement in osteopenia is seen

Osteoporosis associated with cerebral palsy

The cause of osteoporosis in children with cerebral palsy is multifactorial; impaired weight-bearing ambulation, immobilization from multiple orthopedic surgery, diminished growth, poor nutrition, low calcium and vitamin D intake and/or anti-convulsant therapy are all implicated. Henderson et al. [43] in a double blind, placebo controlled clinical trial with six pairs of non-ambulatory children with cerebral palsy treated with pamidronate showed an increase in distal femur bone mineral density of $89 \pm 21\%$ compared to $9 \pm 6\%$ in the placebo group. The study did not report the impact of treatment on fracture or ambulation. In an earlier study, Shaw et al. [105] had treated three children with cerebral palsy with recurrent long bone fractures with

bisphosphonate. He found significant improvement in bone mineral density ranging from 20%–40% with only one fracture following initiation of therapy.

Osteoporosis associated with beta-thalassemia

As beta-thalassemia children survive, bone disease becomes a serious cause of morbidity from rickets, scoliosis, spinal deformities, nerve compression, fracture and severe osteoporosis in young and adult thalassemia subjects. The etiology is multifactorial; hormonal deficiency (gonadal failure), bone marrow expansion, nutritional deficiency, calcium and vitamin D deficiency, and desferal toxicity [117]. In a randomized placebo controlled trial over 2 years, Morabito et al. [74] observed a significant increase in lumbar spine and femoral neck bone mineral density with nine subjects treated with alendronate, while it decreased or remained unchanged with clodronate and placebo. The impact of treatment on bone pain or fracture was not reported. In our experience there was an improvement in bone mineral density in our patient treated with intravenous pamidronate 30 mg monthly and subsequently with zolendronate 0.5 mg monthly for 2 years, receiving the medication while in the hospital each time for blood transfusion. No complaint of bone pain and no fractures have occurred during this period.

Osteoporosis associated with cystic fibrosis

Children with cystic fibrosis are living longer with a mean survival now of more than 30 years. Premature osteoporosis has been documented in these children for some time but the rapid deterioration following lung transplantation has highlighted this problem. Poor bone health in children with cystic fibrosis is multifactorial; hormonal failure (hypogonadism), malabsorption, inadequate bone mineral accretion in childhood, pancreatic deficiency, calcium and vitamin D deficiency, reduced weight bearing exercises, corticosteroid use, presence of pro-inflammatory cytokines and disease severity [18]. Haworth et al. [42] in a placebo controlled trial of 6 months showed that although the bone mineral density increased with pamidronate over the lumbar spine and hip compared to placebo, it was associated with significant bone pain in subjects not receiving steroids. Of these patients, 75% developed severe bone pain, starting about 12 h after the infusion and lasting up to 3 days [41]. The bone pain typically started in the spine, then migrated to the ribs, and finally to the lower limbs. Bone pain has been attributed to further increase in proinflammatory cytokines, especially TNF-α, by pamidronate, to an already elevated baseline value of proinflammatory cytokines in patients with cystic fibrosis [41,111]. In subjects following lung transplantation, Aris et al. [4] found a significant increase in bone mineral density over the spine and femur with pamidronate compared to placebo but it did not have any impact on fracture rate between the two groups. It has been our experience (unpublished) that children with cystic fibrosis complain more often than others treated with bisphosphonates of generalized bone pain. Treatment with lower doses of bisphosphonates advanced slowly over time may be better tolerated.

Bone diseases associated with hematological disorders

Congenital erythropoietic porphyria is a rare genetic disorder of heme synthesis in which patients may develop osteodystrophy characterized by sclerotic lesions and osteopenia due to accelerated bone turnover in areas of active bone marrow. Oliveri et al. [78] treated a woman with congenital erythropoietic porphyria with oral pamidronate 150–300 mg/day for 11 months, which resulted in an increase in bone mineral density and decrease in bone turnover markers, while Pullon et al. [85] used oral clodronate, which decreased serum alkaline phosphatase and urinary hydroxyproline but did not affect the bone mineral density. Severe congenital neutropenia can be associated with bone loss due to enhanced production of phagocytic mononuclear cells, and an increase in IL-1 and other cytokines from neutrophils following treatment with G-CSF, which leads to increased osteoclast mediated bone resorption. Bishop et al. [11] treated a 5-year-old girl with severe congenital neutropenia with etidronate and stanozolol for 8 months for osteoporosis. They showed a significant increase in bone mineral density. At our center we have treated children with other hematological disorders such as Diamond-Blackfan syndrome and Job syndrome with beneficial effects on both the clinical and bone density findings.

Osteogenesis imperfecta

Osteogenesis imperfecta, or brittle bone disease, represents a phenotypically heterogeneous group of conditions that result from over 200 genetic mutations in qualitative and/or quantitative defects in type I collagen synthesis [3]. The clinical expression is primarily that of bone fragility, but other tissues can also be involved, including teeth, ligaments, and joints. In children with osteogenesis imperfecta when compared to normal, Rauch et al. [86] observed a decrease in biopsy core width, cortical width, and cancellous bone volume reflecting a defect in modeling of external bone size and shape, a reduction in trabecular number, trabecular thickness and either absent or decreased annual increase in trabecular thickness, and a decreased amount of bone formed during a remodeling cycle, although the recruitment of remodeling units was increased. No matrix mineralization defect was observed. Thus children with osteogenesis imperfecta have small, thin bones with few trabeculae, thin cortices, and high remodeling rates,

Table 3 Bisphosphonates used in children to treat bone disorders. (*FIH* familial idiopathic hyperphosphatasia, *MAS* McCune-Albright syndrome, *OPS* osteoporosis pseudoglioma syndrome)

Reference	Cases (*n*)	Condition	Drug	Dose	Duration[a]
[37]	30	Osteogenesis imperfecta	Pamidronate	0.5–1 mg/kg per day iv × 3 days q4–6 months	1.3–5.0 years
[123]	18	Osteogenesis imperfecta	Pamidronate	1 mg/kg per day iv × 3 days q4 months	2 years
[83]	9	Osteogenesis imperfecta	Pamidronate	0.5 mg/kg per day iv × 3 days q6–8 weeks	1 year
[36]	7	Osteogenesis imperfecta	Pamidronate	0.83–3.77 mg/kg per cycle iv q3–12 months	1–7 years
[58]	6	Osteogenesis imperfecta	Pamidronate	1.5 mg/kg iv q 2month	1–2 years
[29]	6	Osteogenesis imperfecta	Pamidronate	1 mg/kg per day iv × 3 days q2–5 months	2 years
[33]	5	Osteogenesis imperfecta	Pamidronate	0.6–1.2 mg/kg iv q1 month	6–17 months
[12]	4	Osteogenesis imperfecta	Pamidronate Olpadronate	150–300 mg/day po 10–20 mg/day po	5.1–7.8 years
[56]	3	Osteogenesis imperfecta	Olpadronate	5–10 mg/day po	5–7 years
[39]	3	Osteogenesis imperfecta	Pamidronate	30–60 mg iv q6 months	4 years
[5]	3	Osteogenesis imperfecta	Pamidronate	10–30 mg/m^{2}iv q1 month	2–5 years
[9]	3	Osteogenesis imperfecta	Pamidronate	15–30 mg iv q10–20 days	22–29 months
[47]	1	Osteogenesis imperfecta	Pamidronate	100 mg/day po	6 months
[69]	13	MAS/fibrous dysplasia	Pamidronate	0.5–1 mg/kg per day iv × 2–3 days q4–12 months	2–6 years
[61]	9	MAS/fibrous dysplasia	Pamidronate	180 mg iv over 3 days q6 months	1.5–4 years
[82]	8	MAS/fibrous dysplasia	Pamidronate	45–90 mg iv over 3–6 days q6 months or 200 mg/day po	0.5–10.5 years
[79]	5	MAS/fibrous dysplasia	Pamidronate	1 mg/kg per day iv × 3 days q6 months	2 years
[16]	1	FIH	Pamidronate	0.75 mg/kg iv × 5 days; 8 mg/kg per day po	1 year
[22]	1	FIH	Alendronate	10 mg/day po	10 weeks
[100]	5	Gaucher disease	Pamidronate	50–300 mg/day po	14–83 months
[8]	1	Gaucher disease	Pamidronate	10 mg iv q3 weeks	20 months
[23]	2	Hadju-Cheney syndrome	Alendronate	10 mg/day po	6–48 months
[122]	3	OPS	Pamidronate Clodronate	1 mg/kg iv × 3 days q6 months 300–900 mg iv q2 month	2 years

[a] The duration of therapy and/or follow-up reported in the manuscript

which put them at risk for bone deformities and fractures. Rauch et al. [87] found on iliac bone biopsy that in children with osteogenesis imperfecta treated with cyclical pamidronate for 2.4 ± 0.6 years, in areas of bone remodeling (bone resorption and bone formation are coupled), both processes were inhibited, while in areas of bone modeling (bone resorption and bone formation are not coupled), bone resorption was selectively targeted which allowed for continuing bone formation. Thus an increase in cortical width, increase in cancellous bone volume from increased numbers of trabeculae, decreased osteoclast number and eroded surface was observed. In two large case series of severe osteogenesis imperfecta, Glorieux et al. [37] treated 30 children with pamidronate (0.5–1.0 mg/kg per day) for 3 days (one cycle) given at 4–6 monthly interval for 1.3–5.0 years, receiving a cumulative dose of 6.8 ± 1.1 mg/kg per year, and Zacharin et al. [123] treated 18 children with pamidronate (1 mg/kg per day) for 3 days every 4 months for 2 years. The treatment of these children with pamidronate led to a sustained reduction in serum alkaline phosphatase and urinary cross linked N-telopeptide with an increase in bone mineral density. There was a decrease in the number of fractures without adverse effect on fracture healing or fracture non-union. The treatment did not effect linear growth. The increase in bone mineral density and decrease in fractures led to an improvement in mobility and a substantial relief from chronic pain and fatigue. Thus bisphosphonates decrease bone turnover markers, increase bone mineral density, decrease fracture rate, increase vertebral size and ameliorate vertebral shape at the skeletal level and clinically improve quality of life by improving ambulation. Provision of relief from chronic pain and fatigue without affecting linear growth has been consistently observed in other small series and case reports of osteogenesis imperfecta treated with either intravenous or oral pamidronate (Table 3). There was no correlation between phenotype severity, age at start of treatment and treatment response [123]. Gonzalez et al. [39] reported that similar clinical response can be achieved with a lower dose (cumulative dose 2–4 mg/kg per year) pamidronate in children with osteogenesis imperfecta. There is limited experience in very young children. Pamidronate has been used in treatment of children younger than 3 years of age with severe osteogenesis imperfecta, where the observations were similar as in older children, with increase in bone mineral density, increase in vertebral coronal area and decrease in fracture rate [83]. An interesting observation made in these young children was an increased frequency of treatment (every 6–8 weeks) needed for decreasing the child's discomfort. This increased need for pamidronate in such young children has been attributed to rapid bone turnover and growth at this age. It must be emphasized, however, that all the reports published so far concern uncontrolled

observational studies. Pamidronate does not alter the genetic defect underlying osteogenesis imperfecta and therefore is a symptomatic, not a curative, treatment. Roldan et al. [94] have raised the concern that although pamidronate therapy improves bone mineral density, the bone strength as analyzed by peripheral quantitative computerized tomography suggests that the bones are still fragile with poor resistance to torque or bending forces. Similar observations were made in oim/oim mice (osteogenesis imperfecta mouse model) treated with alendronate which showed significant reduction in fractures, increase in bone density, increase in metaphyseal tibial bone and increase in bone stiffness, although other bone parameters such as bone geometry, breaking strength and modulus were not changed [70]. It is unclear at present how long this treatment should be continued, optimal treatment schedule and whether other bisphosphonates have a similar or better effect on the clinical course of the disease. At our center we have treated our patients with osteogenesis imperfecta predominantly with intravenous pamidronate, although we have obtained a similar outcome in children treated orally with weekly alendronate or daily risedronate. This could be done only after weekly alendronate became available and is favored by the families as it avoids intravenous access and hospitalization.

Fibrous dysplasia of bone and McCune-Albright syndrome

Fibrous dysplasia of bone is a rare congenital disease leading to osteolytic lesions. Bone biopsy of pathological tissue shows a combination of bone, fibrous tissue and cartilage. McCune-Albright syndrome, a form of fibrous dysplasia, consists of osteolytic lesions in the long bones and cranium and sclerosis of the skull base caused by hyperproliferation of pre-osteoblastic cells and multiple endocrinopathies that occur due to an activating mutation of the $G_s\alpha$ proteins [69]. McCune-Albright syndrome and fibrous dysplasia are associated with a high bone turnover reflected by raised serum alkaline phosphatase and urinary hydroxyproline, and is associated with bone pain, bone fractures and bone deformity (Table 3). Matarazzo et al. [69] have treated 13 children with fibrous dysplasia of bone and McCune-Albright syndrome since 1994. The initial pamidronate protocol of 0.5 mg/kg per day for 3 days every 12 months has been progressively increased to the current protocol of 1 mg/kg per day for 3 days every 4 months with clinical experience [69]. They observed that the bone pain and gait abnormalities due to pain disappeared after 2–3 therapeutic cycles. Elevated serum alkaline phosphatase and urine hydroxyproline values were reduced by the treatment, demonstrating drug activity at the lesional level. The effectiveness of pamidronate was also seen at the non-lesional level through an increase in bone density and decrease fracture rate. Cranial asymmetry and limb length discrepancy remained unchanged. The therapy did not have significant impact on healing of lesions on radiographic and scintigraphic evaluation [69]. Similar clinical experience was reported in earlier series by Liens et al. [61] with continuous pamidronate infusion of 180 mg over 3 days every 6 months and Pfeilschifter et al. [82] with intravenous pamidronate given every 6 months (cumulative dose of 60–660 mg) and/or daily oral pamidronate (cumulative dose of 0–380 mg) for a total period of 37 patient years. Unlike Matarazzo et al. [69] they observed radiologically a progressive reduction in osteolytic lesions and increase in cortical thickening. Pfeilschifter et al. [82] also observed that patients when given pamidronate intermittently whenever their serum alkaline phosphatase returned to its high baseline level, there was an improvement in bone pain and decline in serum alkaline phosphatase, which indicates that therapy must be titrated to clinical response and that the bone effects of pamidronate might be reversible. O'Sullivan et al. [79] made a subjective observation that during surgery the diaphyseal bone is of better quality after bisphosphonate therapy.

Familial idiopathic hyperphosphatasia

Familial idiopathic hyperphosphatasia (juvenile Paget's disease) is characterized by progressive skeletal deformity due to increased bone turnover with elevated levels of serum alkaline phosphatase and high urinary excretion of hydroxyproline. Clinical presentation may be variable ranging from severe forms starting in infancy to milder forms that present in early adulthood. There are two case reports of children treated with bisphosphonates for familial idiopathic hyperphosphatasia. Cassinelli et al. [16] treated a child with familial idiopathic hyperphosphatasia with intravenous pamidronate (0.75 mg/kg per day for 5 days) followed by oral pamidronate (8 mg/kg per day) for 1 year and Demir et al. [22] treated their patient with oral alendronate for 10 weeks. Both treatments resulted in clinical improvement and a decrease in serum alkaline phosphatase and urinary hydroxyproline. The serum calcium and phosphorous levels remained normal throughout the reported treatment course.

Gaucher disease

Episodes of bone crisis occur in patients with Gaucher disease due to localized osteonecrosis, which can lead to significant morbidity from osteoarthritis of major joints, pathological fractures and bone deformities. The bone lesions are probably caused by toxic processes occurring around the Gaucher cells (glucosylceramide laden histiocytes and macrophages) scattered throughout the bone tissue and bone marrow. Samuel et al. [100] treated five adolescents with significant bone crisis with oral pamidronate ranging from 50–300 mg/day. In the subsequent 14 to 83 months of follow-up, three children

Table 4 Bisphosphonates used in children to treat heterotopic ossifications

Reference	Cases (*n*)	Condition	Drug	Dose	Duration[a]
[7]	3	Fibrodysplasia ossificans progressiva	Etidronate	10 mg/kg per day po	1–18 month
[62]	1	Fibrodysplasia ossificans progressiva	Etidronate	20 mg/kg per day po	6 years
[93]	1	Fibrodysplasia ossificans progressiva	Etidronate	20–40 mg/kg per day po	3 years
[71]	1	Infantile arterial calcification	Etidronate	Not available	3 years
[116]	1	Infantile arterial calcification	Etidronate	Not available	14 months
[112]	1	Infantile arterial calcification	Etidronate	5–30 mg/kg per day po	1 year
[114]	1	Infantile arterial calcification	Etidronate	15–35 mg/kg per day po	18 months
[49]	11	Heterotopic ossification	Etidronate	10–20 mg/kg per day po	3–12 months
[106]	1	Heterotopic ossification	Etidronate	20 mg/kg per day po	7 months

[a] The duration of therapy and/or follow-up reported in the manuscript

remained free of bone crisis and the numbers of episodes were dramatically reduced in the other two children. The average frequency of bone crisis episodes decreased from 1.6 episodes per patient year prior to pamidronate treatment to 0.2 episodes per patient year. The average fracture rate decreased from 0.33 fracture per patient year to 0.06 fracture per patient year on pamidronate therapy and no further progression of bone disease was noted on repeat radiographs. Bembi et al. [8] treated a child with Gaucher disease with periodic intravenous infusion of pamidronate (10 mg) every 3 weeks for 20 months prior to therapy with alglucerase. They observed normalization of bone mineral density, formation of bone callus in areas of the femoral heads and a positive calcium balance (Table 3).

Hadju-Cheney syndrome

Hadju-Cheney syndrome (hereditary osteodysplasia with acro-osteolysis) is a rare disorder, the prominent features of which include dissolution of the terminal phalanges of the hands and feet, dolichocephaly with multiple wormian bones, delayed closure of cranial sutures, absence of frontal sinuses, a prominent occipital ridge, and skeletal demineralization with vertebral and extremity fractures. Drake et al. [24] treated a mother and son with oral alendronate for 48 and 6 months respectively, which was associated with decrease in bone markers, increase in bone mineral density and a fracture free period. We have been treating a 20-year-old girl for the past 3 years, initially with intravenous pamidronate and subsequently changed to weekly oral alendronate, after it became available, with marked improvement in quality of life, and prevention of further bone resorption.

Osteoporosis pseudoglioma syndrome

Osteoporosis pseudoglioma syndrome is a rare autosomal recessive disorder characterized by visual loss that presents at birth or in infancy and by fracturing bone diseases that presents in childhood. Zacharin et al. [122] observed in three children treated with either intravenous pamidronate or clodronate, a reduction in bone pain, no new fracture, increased mobility with normal growth and pubertal development. X-ray films showed dense new bone in the vertebral end plates and remodeling of the vertebral bodies with an increase in bone mineral density in the lumbar spine after 2 years.

Heterotopic calcifications

Fibrodysplasia ossificans progressiva, alternatively called myositis ossificans, is a rare autosomal dominant disorder, which is characterized by symmetrical congenital skeletal abnormalities and progressive heterotopic ossification of the connective tissue. Fibrodysplasia ossificans progressiva is a better term than myositis ossificans as the fibrodysplastic process occurs not only in the muscle but also in other soft connective tissues. It is believed to be a gain in function mutation in the genetic regulation of bone morphogenetic proteins [14]. Etidronate (10–40 mg/kg per day) therapy has shown improvement in ambulation, and a significant reduction of previously existing calcifications and the disappearance of some new ectopic ossifications (Table 4). There are more single case reports with similar outcomes but with shorter duration of follow-up available in the literature. Rogers et al. [92] in a survey evaluation of 42 patients, predominantly children, with fibrodysplasia ossificans progressiva treated with etidronate (10–20 mg/kg per day) for at least 1 year found that ten patients considered the drug helpful, five patients did not know if the drug had helped, and the remainder felt that the drug was of no help. There is a single report of development of significant osteopenia following intermittent use of etidronate over a period of 6 years in a child with fibrodysplasia ossificans progressiva [76].

Idiopathic infantile arterial calcification is a rare disease of unknown etiology, which is characterized by deposition of calcium salts (calcium apatite) in the internal elastic lamina of numerous arteries throughout the body. Four cases of idiopathic infantile arterial calcification have been treated with etidronate, which caused the calcification to resolve on follow-up [71, 112, 114,116].

Heterotopic ossification occurs in 14.4% of children who develop traumatic brain injury, frequently around the hips and knees, followed by the shoulder and elbow

[49]. The mineralization in heterotopic ossification involves an amorphous calcium phosphate phase, which is gradually replaced by enlarging hydroxyapatite crystals. This leads to the formation of lamellar cortico-spongiosal bone with a thin cortex, tightly latticed spongiosa, and occasional Haversian systems at the heterotopic site. Stover et al. [109], in prospective placebo controlled study, treated adult patients with spinal cord injury with either etidronate 20 mg/kg for 2 weeks followed by 10 mg/kg for 10 weeks or placebo. The treated group had significantly less heterotopic ossification compared to the placebo group. Hurvitz et al. [49] in a retrospective analysis of children who developed heterotopic ossification following traumatic brain injury found 11 of the 13 children who were treated with etidronate. Only one child needed surgical release and three developed ankylosis, which was better than historical controls. Silverman et al. [106] treated a 12-year-old child with etidronate (20 mg/kg per day) for 7 months for heterotopic ossification following severe traumatic brain injury which led to widened growth plates with periarticular pain, similar to rickets but with normal calcium, phosphorous and vitamin D, and slipped femoral capital epiphyses. The growth plate changes resolved 5 months after discontinuation of etidronate. In heterotopic ossification, as in idiopathic infantile arterial calcification, fibrodysplasia ossificans progressiva or following traumatic brain or spinal injury, the need is to dissolve the pathological calcification. The choice is limited to etidronate as it is the only bisphosphonate that leads to bone demineralization at a clinical dose, which is used to the patients' advantage in heterotopic ossification.

Hypercalcemia of malignancy

Hypercalcemia in pediatric malignancies is a rare event, occurring in about 0.2%–0.7% children with cancer [54]. It occurs either from direct invasion of the skeleton by malignant cells that release bone resorbing cytokines directly into the skeletal site, or from production of parathyroid hormone related protein which when secreted into the circulation leads to osteoclastic bone resorption. The effect of bisphosphonates is incomplete in parathyroid hormone related protein related hypercalcemia as the drug cannot counteract the calcium reabsorption stimulated by parathyroid hormone related protein in the kidneys. Bisphosphonates are used in patients with tumor-induced hypercalcemia because of their anti-resorptive properties. They are used in the treatment of hypercalcemia only after the hypercalcemia remains resistant to furosemide and saline hydration, calcitonin, and restriction of calcium and vitamin D. The experience with bisphosphonates in pediatric malignancies is limited to occasional case series and case reports (Table 5). There are more single case reports with similar outcomes available in the literature. The limited experience suggests that pamidronate can be given as a single 0.5–1.0 mg/kg per dose intravenously. This should normalize serum calcium concentration within 2–5 days during which period the conservative management should continue with fluids, diuretics, and calcitonin. If the child's clinical condition so demands, a repeat dose can be given preferably after a week, however, in several instances it was given within shorter intervals.

Hypercalcemia associated with subcutaneous fat necrosis

The dermatological changes in subcutaneous fat necrosis appear to be the result of hypoxic injury to subcutaneous adipose tissue, causing fat to crystallize. There is a granulomatous inflammatory reaction to this fat necrosis. It has been postulated that hypercalcemia is due to unregulated 1,25-dihydroxyvitamin D production by these granulomatous cells. Hypercalcemia following subcutaneous fat necrosis has been successfully treated in a 7-week-old child with intravenous pamidronate, and two 4- and 7-week-olds with oral etidronate (Table 5).

Other conditions associated with hypercalcemia

Occasionally hypercalcemia can be difficult to control with conventional treatment. Hypercalcemia which was resistant to saline hydration, loop diuretics and calcitonin in children awaiting liver transplantation [6], renal disease [104], following liver transplantation [84], children with primary oxalosis with combined kidney and liver transplant [120], bone marrow transplantation for osteopetrosis [88], due to immobilization [38,119], or hypercalcemia of unknown etiology [65] were treated with intravenous pamidronate or oral etidronate which resulted in normalization of serum calcium concentrations (Table 5). There are more single case reports with similar outcomes available in the literature. Bisphosphonates are effective in normalizing the serum calcium level within 2–5 days. Treatment with bisphosphonates has been repeated successfully following recurrence of hypercalcemia due to the primary disease [6, 84 ,88,120]. So far, only intravenous pamidronate, except for one case treated with etidronate, has been used in children to treat hypercalcemia in acute clinical situations although oral alendronate and clodronate have been used for maintenance after initial therapy with intravenous pamidronate [65,119].

Adverse effects

Bisphosphonates as a group of drugs are well tolerated both orally and intravenously. Commonly reported adverse effects are headache, diarrhea, dyspepsia and constipation. Although the incidence of corrosive

Table 5 Bisphosphonates used in children to treat resistant hypercalcemia

Reference	Cases (*n*)	Condition	Drug	Dose
[121]	5	Malignancy	Pamidronate	1–2 mg/kg iv × single dose
[13]	2	Embryonal tumor	Pamidronate	0.5 mg/kg × 2 doses
[21]	1	Leukemia	Pamidronate	30 mg iv × single dose
[9]	1	Leukemia	Pamidronate	30 mg iv × single dose
[54]	1	Lymphoma	Pamidronate	75 mg iv x single dose
[103]	1	Lymphoma	Pamidronate	1 mg/kg iv × single dose
[1]	1	Medulloblastoma	Pamidronate	1.7 mg/kg iv × single dose
[63]	1	Paraganglioma	Pamidronate	90 mg iv q1–2 weeks × 4 doses
[77]	1	Rhabdomyosarcoma	Etidronate	10 mg/kg po × single dose
[53]	1	Subcutaneous fat necrosis	Pamidronate	1 mg/kg per day iv × 3 days
[118]	1	Subcutaneous fat necrosis	Etidronate	10 mg/kg per day po × 8 days
[89]	1	Subcutaneous fat necrosis	Etidronate	5–10 mg/kg per day po × 16 days
[6]	4	Pre liver transplant	Pamidronate	35–50 mg/m^2 iv × 1–2 doses
[104]	3	Renal disease	Pamidronate	0.4–0.5 mg/kg iv × 1–3 doses
[84]	1	Post liver transplant	Pamidronate	60 mg/1.73 m^2 iv × 3 doses
[120]	1	Post renal-liver transplant	Pamidronate	7.5–30 mg iv × 3 doses
[88]	1	Bone marrow transplant	Pamidronate	5 mg iv × 3 doses
[38]	1	Immobilization	Etidronate	3.7 mg/kg per day po × 2 weeks
[119]	1	Osteogenesis imperfecta	Pamidronate	15 mg iv × 2 doses

esophagitis is quite low with bisphosphonate therapy, nevertheless when it does occur, it can be quite severe, hence the presence of achalasia or esophageal stricture is an absolute contraindication to the use of oral bisphosphonates [57]. Taggart et al. [110], in a meta-analysis of 5020 adults treated with risedronate which included patients with past history and active gastroenterological diseases, showed no increase in adverse gastroenterological side-effects (RR 1.01; 95%CI: 0.94–1.09) compared to placebo, even in patients with active gastroenterological diseases. On intravenous therapy, common adverse effects observed have been a transient rise in temperature by $>1°C$ and an influenza-like illness [12]. The metabolic changes seen with bisphosphonates are transient hypocalcemia and hypophosphatemia, which in turn result in secondary hyperparathyroidism and increased $1,25(OH)_2$ D formation. These biochemical changes are rarely of any clinical significance. Anterior uveitis, scleritis, episcleritis, iritis and transient conjunctivitis have been reported following pamidronate treatment [32]. A transient decrease in lymphocyte counts occurs following bisphosphonate therapy. Collapsing focal segmental glomerulosclerosis has been reported in seven adults treated with high doses of pamidronate treatment (90–360 mg/month) for multiple myeloma and breast cancer [66].

There have been some theoretical concerns to the use of bisphosphonates both in the adult and especially in a child with growing skeleton due to the medications' antiresorptive effect. The suppression of bone turnover induced by long-term treatment with bisphosphonates has been found to be reversible on discontinuing treatment in adults [55]. Hoekman et al. [45] observed in a child with juvenile osteoporosis that 1 month following pamidronate withdrawal, all the biochemical parameters reverted to pretreatment levels requiring reinstitution of therapy suggesting that pamidronate does not induce permanent inhibition of bone activity. Although the bone turnover markers return to baseline within 6–9 months, the beneficial effect of bisphosphonate treatment on the skeletal bone mineral density appears to be maintained for at least 2 years [55,95]. There is no increase in fracture frequency after withdrawal of therapy [55]. Fracture healing was not delayed and there was no instance of fracture nonunion even in children with osteogenesis imperfecta during bisphosphonate therapy [37,47]. In animal models of fractures treated with bisphosphonates, one observes that the size of the callus is either increased or is unchanged but never decreased and the slowing of callus turnover is accompanied by a higher mechanical strength [31].

In children, there is an additional and crucial concern of the effect of bisphosphonates on physical growth and the possibility of damage to the growth plate. In the available pediatric literature, the linear growth was found to proceed normally or even better during treatment [9, 12, 37, 45, 58, 100,123]. A cohort of 12 children treated before or during early puberty demonstrated catch up growth whereas children treated in late puberty continued to grow on the same percentile [12]. In children with osteogenesis imperfecta, Glorieux et al. [37] found the appearance of the growth plate to be unchanged and the bone ages of children corresponded with their chronological age. Although studies have not shown alterations in the growth plate, there is a single report of widened growth plates, suggestive of a rachitic syndrome, in a child treated with etidronate for 7 months for heterotopic ossifications that resolved after 5 months of discontinuation of therapy [106]. However, etidronate treatment is now not used routinely for osteopenic conditions but rather for the less common causes of extraskeletal calcifications (vide supra). A characteristic sclerosis has been consistently observed at the metaphyses of long bones (around the knees and the distal forearm) and in the vertebrae when the treatment

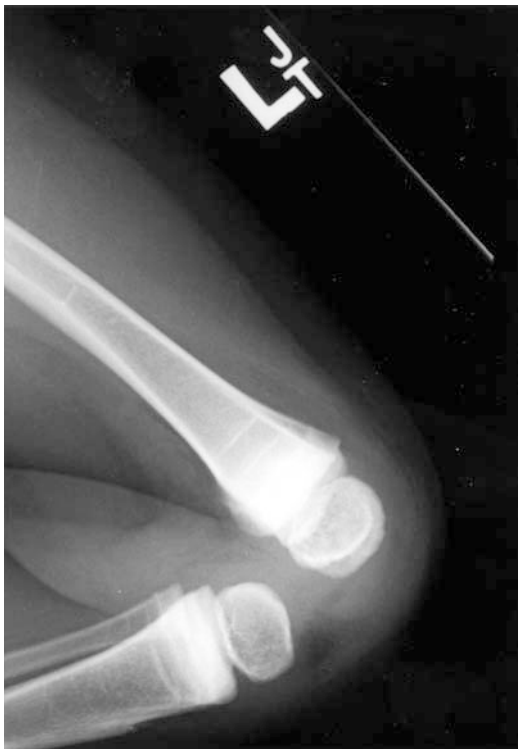

Fig. 4 An X-ray film of the knee showing transverse sclerotic lines at the metaphyses in child with Lowe syndrome treated with one cycle of 3 days intravenous pamidronate followed by two cycles of 3 days intravenous zolendronate

was given before closure of the epiphyses was completed [37, 61, 93,100]. The relative increase in bone formation in addition to the already high level of osteoblastic activity near the growth plates result in the development of sclerosis in the growing child [115]. A gradual decrease or complete disappearance of the sclerosis was observed after withdrawal of therapy before the closure of the growth plates and in patients who continued to receive therapy after closure [115]. In children who receive repetitive doses of intravenous pamidronate or zolendronate, a typical picture of transverse sclerotic lines representing individual treatment cycles are seen at the end of long bones (Fig. 4).

Issues in bone health analysis and bisphosphonates in children

Measurement of bone mineral density in children

Bone mineral density is measured by either linear absorption methods (single photon absorptiometry, dual photon absorptiometry or dual energy X-ray absorptiometry), computed tomographic procedures (peripheral quantitative computed tomography, quantitative computed tomography), or sonographic procedures. The limitation of linear absorption methods in children is that the geometry of all bones continually changes during growth, which is in turn responsible for an increase in absorption, which was not well accounted for during the original development of the method. Thus the bone thickness used in calculation for bone area and density is an estimate of the actual bone thickness. The computed tomographic methods, although more accurate, are influenced by bone size, bone thickness and the partial volume effect. The ultrasonic methods based on speed of sound and broadband ultrasound attenuation are subject to constantly changing bone with growth. Bone is not a homogenous substance, it is composed of cortical and spongious components. A low bone mineral density can result from either insufficient mineralization or a reduced structural density (decreased number of trabeculae or trabecular thickness). The bone mineral density calculated as bone mineral content/ bone area may not be optimal in children as it is significantly influenced by bone size [72]. Molgaard et al. [72] suggest that the bone mineral content should be corrected for height for age ('short bones'), bone area for height ('narrow bones'), and bone mineral content for bone area ('light bones'). In addition to the methodological limitations in children, the problem is further compounded by lack of good normative data. This latter problem was highlighted by Leonard et al. [59] who found a wide variability from 11% to 30% children being classified as osteopenic (z score <-2) using the same bone mineral density data subjected to five different available reference data sets. This raises the concern of the analysis of bone mineral density reported in the pediatric literature of children treated with bisphosphonates, although in most cases the subject acted as his/her own control, but the impact of normal growth needs to be addressed when the therapy has extended over the years and across puberty. Practically at this point it is important to note that most normative data incorporated into the software of the device used to measure bone health are based on age and gender. These data might be invalid in the too small or too large children and correction for body size needs to be made during data interpretation.

Microdamage accumulation

Bone turnover remodels the skeleton every 10 years and it is believed that remodeling serves to repair microfractures. Microdamage are microscopic cracks (30–80 μm long in cross-section) that occur in bone subsequent to physiological repetitive loading during daily activity. Bone remodeling allows for selective removal of damaged bone and replacing it with a new bone. Beagle dogs when treated with risedronate and alendronate showed an increase in microdamage accumulation with a significant nonlinear relationship with intracortical bone remodeling suppression and a significant linear relationship with reduced bone toughness [67]. Beagle dogs treated with high doses of etidronate developed fractures of ribs and/or thoracic spinal

processes compared to controls and beagle dogs treated with lower doses of etidronate, in whom the microdamage accumulation was significantly higher compared to those treated with high doses [44,68]. This is believed to result from suppression of bone remodeling by etidronate allowing for microdamage accumulation at low dose, but the increased accumulation of osteoid with high doses reduces the production of microdamage, but the inhibition of mineralization by etidronate at high doses of this excessive amount of unmineralized bone leads to occurrence of fractures [44,68]. The above data come from experimental animals who were subjected to much higher doses than used in clinical practice. Although currently there is no evidence that microdamage accumulation occurs during treatment with clinical doses of bisphosphonates, one should always keep that in consideration while planning therapy in children.

Teratogenic effects

Bisphosphonates remain embedded in dormant bone and are released months after the cessation of treatment at the time of bone remodeling. The molecular weight of most bisphosphonates is relatively low enabling them to easily pass through the placenta to the embryo or fetus. This could lead to exposure to bisphosphonates in the fetus where the bone turnover is high. Patlas et al. [80] have shown accumulation in rat fetuses of radioactive ^{14}C-alendronate following treatment of pregnant rats, which demonstrates that alendronate can pass through the rat placenta. Offspring of female rats treated with subcutaneous alendronate during days 11–20 of pregnancy, the period of active development of bone from mesenchyme, showed shortening of diaphysis, increase in diaphyseal bone trabeculae with a concomitant decrease in bone marrow volume but no change in cartilage volume [80]. On the other hand, two pregnant women were given intravenous pamidronate in the third trimester for metastatic breast cancer with beneficial effect to the mother and no serious adverse effects on the fetus [25,50]. Although the theoretical risk of bisphosphonates administered to a woman of child bearing age to her future fetuses has not been substantiated, it is our practice to discuss this matter with our female patients and their families.

Conclusions and recommendations

Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption through their action on osteoclasts. They have been used in four broad categories of conditions in children: generalized osteoporosis, localized bone disease, soft tissue calcification and hypercalcemic states. They are well tolerated and safe in the doses used in clinical trials. The theoretical concerns of growth impairment and fracture healing from bisphosphonates have not materialized in the reported pediatric literature. Mineralization defects observed with the first bisphosphonate (etidronate) have not been observed with more recent bisphosphonates. Although not observed in clinical trials, the potential adverse effects of accumulation of microdamage in bone, alteration in bone architecture and bone quality, and teratogenic effects reported from animal experiments using many fold higher doses of bisphosphonate than that used in clinical trials should be considered when planning therapeutic strategies with these drugs in children.

Bisphosphonates thus offer the pediatrician a new tool to treat children with primary and secondary metabolic bone diseases associated with increased bone resorption. Unfortunately there seems to be a great lack of consistency in modes of drug administration and even more so in dosing of bisphosphonates in children. In long-term therapy for primary and secondary metabolic bone diseases, the earlier experience in children was mostly with intravenous pamidronate, which was given either as cycles of 0.5–1.0 mg/kg per dose for 3 days every 2 to 6 months or 0.5–1.0 mg/kg per dose once every 3 to 4 weeks. Intravenous pamidronate is administered in a calcium free solution, such as saline or 5% dextrose, by a slow infusion over a 4 h period with optional pre-medication with acetaminophen. Since elimination of the drug is via the kidneys, dose adjustment is required in cases with renal failure, halving the dose in those with end stage kidney disease. The experience with long-term daily oral bisphosphonate is limited and requires several precautions and a detailed education of the child and his/her family as we have previously detailed [108].

The recent formulation of weekly alendronate at seven times the conventional daily dose allows a school-age child the convenience to take the medicine during the weekend and thus better adhere to the instructions. We have seen good compliance and almost complete disappearance of heartburn complaint in our 50 children treated with oral weekly alendronate. Interestingly, the drug is available in two concentrations 35 and 70 mg and the treatment is not adjusted per kg body weight as done with the intravenous medications. The other recent development is availability of intravenous zolendronate, which can be given rapidly over 15 min with clinical and bone effect similar to pamidronate (Fig. 4). Although no pediatric data are available for dosing, the suggested equivalent dose is 2 to 4 mg zolendronate for 90 mg pamidronate (The Medical Letter 2001 43: 110). In long-term therapy for metabolic bone diseases with bisphosphonates, the child should also receive 800–1000 mg/day of calcium and 400 IU/day of vitamin D supplementation. Once the therapy is initiated with bisphosphonates, the issue of discontinuation of therapy remains uncertain and is further compounded by lack of available data. We currently discontinue treatment once bone density on DEXA normalizes, and follow the child clinically and by DEXA ready to resume treatment in case of deterioration. In general, therapy should be

tailored for each individual based on the nature and severity of the disease and the intended clinical and radiological end points.

Bisphosphonates also contribute to the arsenal of medications used to treat resistant hypercalcemia and heterotopic ossifications. Our review of the literature would suggest that the choice for treatment of acute resistant hypercalcemia should be pamidronate given as a single 0.5–1.0 mg/kg dose intravenously and if the child's clinical condition so demands, a repeat dose can be given preferably after a week. In clinical situations of heterotopic ossification, the choice is limited to etidronate as it is the only bisphosphonate that leads to bone demineralization, which is used to the patients' advantage.

There is a need to perform more placebo controlled clinical trials with bisphosphonates in children as they have a great potential for treatment in common conditions like corticosteroid induced osteoporosis and osteogenesis imperfecta, as well as several rare disorders which might be alleviated partially or completely with the use of bisphosphonates.

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