OSTEOPOROSIS AND BONE FRAGILITY IN CHILDREN

Rebecca J. Gordon, MD, Instructor in Pediatrics, Division of Endocrinology, Boston Children's Hospital, Harvard Medical School, Boston, MA. Rebecca.Gordon@childrens.harvard.edu

Madhusmita Misra, MD, MPH, Fritz Bradley Talbot and Nathan Bill Talbot Professor of Pediatrics, Division of Pediatric Endocrinology, Massachusetts General Hospital, Harvard Medical School, Boston, MA. Mmisra@mgh.harvard.edu

Deborah M. Mitchell, MD, Assistant Professor of Pediatrics, Division of Pediatric Endocrinology, Massachusetts General Hospital, Harvard Medical School, Boston, MA. Dmmitchell@mgh.harvard.edu

ABSTRACT

Childhood is a unique time during which individuals accrue bone rapidly, and peak bone mass is achieved early in the third decade of life. Several factors may adversely influence bone accrual, including primary skeletal disorders as well as secondary causes of low bone density such as specific endocrinopathies, altered weight-bearing, and certain medications. Pediatric osteoporosis is defined by both: 1) a clinically significant fracture history; and 2) a low bone mineral density (BMD). Pragmatically, the diagnosis of osteoporosis is indicated by a BMD Z-score $\leq$ -2.0 and a clinically significant fracture history, defined as two or more long bone fractures by age 10 years, or three or more long bone fractures at any age up to 19 years. Additionally, the finding of one or more vertebral non-traumatic compression fractures is diagnostic of osteoporosis independent of BMD. Notably, the diagnosis of pediatric osteoporosis should not be made based on densitometric criteria (i.e., DXA) alone. As childhood osteoporosis has several potential underlying etiologies, evaluation requires a careful assessment by a clinician with expertise in the possible mechanisms that may be contributing to the increased skeletal fragility. Both non-pharmacologic therapies as well as bone-active medications, such as bisphosphonates, increase bone mass and may lower the risk of fracture. The development of novel therapies that may restore physiologic anabolic bone activity in children with insufficient bone accrual from various causes has the potential to improve care for pediatric patients with osteoporosis. Prospective data acquisition to inform treatment strategies for primary prevention of fracture in children with osteoporosis, as is done in adult populations, is urgently needed to prevent the significant morbidity of fracture in this vulnerable population.

INTRODUCTION

Childhood and adolescence are unique time periods during which individuals accrue bone rapidly, and peak bone mass is only achieved early in the third decade of life. Several congenital or acquired factors may adversely influence bone accrual, including primary skeletal disorders, or secondary causes of low bone density such as delayed puberty, endocrinopathies, altered weight-bearing, and certain medications.

Pediatric osteoporosis is defined by both: 1) a clinically significant fracture history; and 2) a low bone mineral density (BMD). Pragmatically, the diagnosis of osteoporosis is indicated by a BMD Z-score $\leq$ -2.0 and a clinically significant fracture history, defined as two

or more long bone fractures by age 10 years, or three or more long bone fractures at any age up to 19 years. Additionally, the finding of one or more non-traumatic vertebral compression fractures is diagnostic of osteoporosis independent of BMD. Notably, the diagnosis of pediatric osteoporosis should not be made based only on densitometric criteria (i.e., DXA) (1).

ETIOLOGIES

Primary Causes of Low Bone Density or Osteoporosis

Genetic diversity overall accounts for 60-70% of the variability in bone mass, and numerous genes have been associated with bone density in genome-wide association studies and whole genome sequencing analyses (see Table 1). These include genes in the WNT signaling pathway (such as *LRP4, LRP5, SOST, WNT4, WNT16, WLS*), the osteoprotegerin-Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) pathway (such as *OPG, RANKL, RANK*), TGFβ signaling (*TGFBR3*), mesenchymal stem cell differentiation pathway, endochondral ossification pathway (such as *RUNX2*), the pathway of collagen synthesis (such as *COL1A1* and *COL1A2*) and other genes such as *ESR1, CCDC170 (*located adjacent to *ESR1), VDR,* and *CALCR (2, 3)*. Further, several bone density associated loci have been associated with fracture risk, including *FAM210A, SLC25A13, MEPE, SPTBN1, DKK1, LRP5, SOST,* and *EN1(2-4).*

In general, conditions that impair bone or connective tissue development can result in low bone density and increased fracture risk. Monogenic disorders leading to low bone density or osteoporosis include the various types of osteogenesis imperfecta, which are discussed in another chapter of Endotext (5) and will not be covered here. Marfan syndrome, caused by mutations in the gene coding for fibrillin-1 (*FBN1*), is a connective tissue disorder inherited in an autosomal dominant fashion. In addition to abnormalities in blood vessels, ligaments, muscles, and heart valves, the condition is associated with low bone density at multiple sites, particularly after adjusting for the taller height of these individuals, and with reduced bone accrual during adolescence, especially at the femoral neck (6-8). Similarly, certain forms of Ehlers-Danlos syndrome are associated with low bone density, such as those that result from mutations in *COL5A1, COL5A2* and *COL3A1* (8). One study of adults with classical or hypermobility Ehlers-Danlos syndrome reported lower bone density, altered bone quality (as assessed by the trabecular bone score), and increased prevalence of morphometric vertebral fractures compared with controls (32% vs. 8% in controls) (9). Another study has reported lower bone density and strength estimates in individuals with hypermobile Ehlers-Danlos syndrome and generalized joint hypermobility spectrum disorder compared to controls (10). Other studies have reported similar data (11, 12).

Low bone density is also observed in patients with homocystinuria with reported low bone density Z-scores in 38% of patients in one study (13) and lysinuric protein intolerance (14-16). High homocysteine levels have been demonstrated to have deleterious effects on osteoblasts and osteoclasts, to increase oxidative stress, disrupt cross-linking of collagen molecules, and increase levels of advanced glycation end products, all of which can reduce bone strength (17). Further, low lysine concentrations are related to growth failure and low bone density (18, 19).

Osteoporosis-pseudoglioma syndrome (OPPG) is a condition caused by homozygous or compound heterozygous inactivating mutations in the gene coding for low density lipoprotein related protein 5 (*LRP5*) (18-20). Wnt ligand binds to the Frizzled/LRP5 complex to activate the canonical Wnt signaling pathway and increase bone formation. Thus, inactivating mutations in LRP5 lead to severe juvenile osteoporosis. The condition is also associated with congenital vision loss that typically manifests in infancy and is a consequence of a spectrum of conditions ranging from phthisis bulbi to vitreoretinal dysplasia. Heterozygous carriers can have low bone

density for age and gender norms, but do not demonstrate the eye findings (20, 21).

Hypophosphatasia is a consequence of both recessive and dominant mutations in *ALPL*, the gene that codes for tissue nonspecific alkaline phosphatase (TNSALP), which is necessary for breaking down inorganic pyrophosphate in bone to enable bone mineralization (22). Reduced mineralization can lead to skeletal defects, altered growth plates resembling rickets, low bone density, and impaired cementum mineralization resulting in early loss of teeth. There are six major forms of hypophosphatasia ranging in severity from very severe (often associated with perinatal demise), to an infantile, juvenile, and adult form, to a very mild form that involves only the teeth (odontohypophosphatasia) and a rare form with normal ALP levels called pseudohypophosphatasia. The severity of the condition depends on the amount of ALP activity that results from the gene mutation.

Other primary conditions associated with fragility fractures but without low bone density include McCune-Albright syndrome, osteopetrosis, and pycnodysostosis (mutations in the gene coding for cathepsin-K). As these conditions are rarely associated with pediatric osteoporosis, they are not discussed further here.

Secondary Causes of Low Bone Density or Osteoporosis

NUTRITIONAL AND MALBSORPTIVE

Deficient Intake of Calcium and Vitamin D:

Insufficient intake of calcium and/or vitamin D can result in suboptimal bone mineralization, and the associated secondary hyperparathyroidism has the potential to cause deleterious effects on bone. However, data are conflicting regarding the impact of calcium or vitamin D deficiency and their replacement on bone mineral content (BMC) and BMD. One systematic review of dairy intake or calcium supplementation in children and adults 1-25 years old

concluded that these measures provide no beneficial effect on bone mineralization or fracture risk (23). A meta-analysis of 21 randomized controlled trials (RCTs) found no significant change in total body BMC in those randomized to supplemental dairy or calcium alone regardless of baseline intake; however, the study did find an increase in whole body BMC in children with low baseline calcium intake who received high doses of dietary calcium supplements or dairy products with or without vitamin D supplementation (24). Another meta-analysis of 19 RCTs reported a small favorable effect on total body BMC and upper limb BMD with calcium supplementation, but no effect at the lumbar spine or femoral neck (25). A more recent meta-analysis of 15 RCTs and three non-randomized studies did find a positive impact of calcium supplementation on femoral neck BMD in children (26). Calcium supplementation has also been reported to have a beneficial effect on bone strength estimates in prepubertal and early pubertal children (27). Of note, maternal calcium supplementation during pregnancy has not been demonstrated to benefit offspring BMD even when baseline intake was low (28). Overall, data suggest a possible small effect of dietary calcium or dairy supplementation on bone outcomes when baseline intake is low, with greatest effects at the whole body and femoral neck.

Similarly, data for the effects of vitamin D deficiency and supplementation are mixed, but overall suggest some effect on bone outcomes. One study reported that baseline 25-hydroxyvitamin D (25OHD) levels predict prospective changes in lumbar spine BMD over the next three years in peripubertal Finnish girls (29), and a case control study of 150 African American children 5-9 years old reported that those with forearm fractures were more likely to be vitamin D deficient (30). In Chinese adolescents, 25OHD levels 20-37 nmol/L (8-15 ng/mL) in girls and 33-39 nmol/L (13-16 ng/mL) in boys are reported to have positive effects on bone outcomes (31). The impact of race is interesting, with dark skinned children typically having lower 25OHD levels than light skinned children, but higher BMD measures. Further, data suggest that vitamin D supplementation in dark skinned (but not light skinned)

children living in northern latitudes positively impact femoral neck BMC (32). Some data (but not all) suggest that maternal vitamin D status may predict offspring BMD, with low maternal 25OHD levels being concerning for low peak bone mass in their children (33). However, a meta-analysis of vitamin D supplementation during pregnancy and infancy reported no impact on subsequent bone health (34).

Conditions of Low Energy Availability or Energy Deficit

Conditions such as anorexia nervosa and the female athlete triad (Triad)/relative energy deficiency in sports (RED-S) are known to be associated with low BMD, reduced bone strength, and increased prevalence of fractures (35, 36), even in adolescents. Anorexia nervosa in both male and female adolescents is associated with low BMD (35, 37-39), and reduced bone accrual in adolescent girls with anorexia nervosa (40) raises significant concerns regarding peak bone mass acquisition. Young oligo-amenorrheic athletes have lower BMD than eumenorrheic athletes at the femoral neck and hip and lower strength estimates at the distal tibia; they also have lower spine BMD and lower strength estimates at the radius than non-athletes (41-43). Factors contributing to impaired bone outcomes include lower lean mass, lower BMI, hypogonadism, low levels of insulin like growth factor-1 (IGF-1), relatively high cortisol levels, and alterations in levels of appetite regulating hormones that also have an impact on bone health, (such as insulin, leptin, peptide YY and oxytocin) (37, 44).

Conditions of Malabsorption

Conditions such as celiac disease, inflammatory bowel disease, cystic fibrosis, and biliary atresia are associated with malabsorption of essential nutrients, including vitamin D, that are important for optimizing bone health.

Celiac disease is associated with low BMD (45) and an increase in fracture risk (46). One meta-analysis reported that a lifetime history of bone fractures was twice as common in those with celiac disease versus controls, and that a baseline history of celiac disease is associated with a 30% increase in any fracture and 69% increase in spine fracture (46). The impact of celiac disease on bone health is related to a decrease in BMI and lean mass (in those who have poor weight gain or a decrease in body weight following diagnosis), malabsorption with reduced bioavailability of calcium and vitamin D, secondary hyperparathyroidism, an increase in intestinal production of inflammatory cytokines (IL-1β, IL-6 and TNF-α), and because of antibodies that may bind to bone tissue transglutaminase (47, 48). The institution of and adherence to a gluten free diet mitigates most of these factors.

Inflammatory bowel disease results in low bone mass in 30-50% of patients, who also demonstrate reduced rates of bone accrual during the adolescent years, resulting in compromised peak bone mass (49). Data for fractures are conflicting, with studies in children reporting modest to no increase in long bone fractures while studies in adults report a 32-40% increase in fracture risk (50-52); asymptomatic vertebral fractures are often missed in retrospective studies based on self-report. Some studies (but not all) report a higher risk of impaired bone health in children with Crohn's disease (53, 54) compared to those with ulcerative colitis, likely because the former more commonly affects areas of the intestine responsible for absorption of vital nutrients and is more likely to be associated with use of glucocorticoids, but data are conflicting in this regard (55-57). In general, children with Crohn's disease are most likely to present with growth and puberty delay. There are also conflicting data regarding whether or not bone compromise is more likely in boys (vs. girls) with inflammatory bowel disease (55, 57, 58).

In addition to malabsorption of vital nutrients, factors that contribute to low bone density and impaired bone accrual in inflammatory bowel disease include low BMI and reduced lean mass, associated pubertal delay and hypogonadism, poor nutritional intake, reduced physical activity, active inflammation (cytokine secretion by activated T-cells, and increased IFN-γ

and TNF-α, which may inhibit osteoblastic activity and active osteoclasts both directly and via RANK ligand), and chronic use of glucocorticoids, which have anti-inflammatory effects (which helps with the condition) but affect bone metabolism at multiple steps (52-55, 59, 60). In general, the severity of disease correlates with the extent of bone compromise.

Cystic fibrosis results in low bone density in 30-60% of individuals with the condition, associated with increased fracture risk in adults (61, 62). A 100-fold increase in vertebral fractures and a 10-fold increase in rib fractures has been reported in adults with cystic fibrosis (61), and this can be problematic, as poor bone health can result in non-eligibility for a lung transplant in certain centers (63). Many factors contribute to low bone density including reduced BMI and lean mass when associated with low body weight, low levels of IGF-1, pubertal delay and hypogonadism, malabsorption of fat-soluble vitamins (including vitamins D and K), insufficient protein intake in diet, fecal calcium losses, secondary hyperparathyroidism, physical inactivity, increased secretion of inflammatory cytokines (IL-1β, IL-6 and TNF-α), chronic use of glucocorticoids, and direct effects of chloride channel defects (64-66).

Biliary atresia is also associated with malabsorption of fat-soluble vitamins, including vitamin D, and therefore, the condition can result in low bone density, which correlates with the severity of liver disease and jaundice (67, 68).

CONDITIONS OF REDUCED MECHANICAL BONE LOADING (INCLUDING DISUSE OR IMMOBILIZATION

Mechanical loading leads to a reduction in sclerostin secretion from osteocytes, the mechanosensors of bone, and increased signaling along the canonical Wnt pathway with an increase in bone formation (69). There are data to suggest that an optimal nutritional status and estrogen levels are permissive for these effects of mechanical loading on bone (70). Meta-analyses have demonstrated beneficial effects of bone loading activity on bone in children, particularly in the pre- and early pubertal years (71, 72). Therefore, conditions of reduced mechanical loading are associated with impaired bone accrual and low BMD. Similarly, the pull of muscle on bone is known to have bone anabolic effects. During periods of muscle disuse and prolonged immobilization, in addition to reduced osteoblastic activity (from increased production of sclerostin), there is an activation of osteoclastic bone resorption. Thus, conditions associated with hypotonia, spinal cord injury, spina bifida, muscular dystrophy, spinal muscular atrophy (SMA), and severe burns are associated with impaired bone accrual and low BMD in children and adolescents.

Patients with cerebral palsy (particularly those with limited ambulation) have low bone density and increased fracture risk associated with reduced mechanical loading of the skeleton, muscle wasting, suboptimal nutrition, and also vitamin D deficiency or impaired metabolism from concomitant use of certain anti-epileptic drugs (73-75). Studies have demonstrated that the severity of cerebral palsy predicts the severity of low BMD Z-scores in this condition (76, 77).

Duchenne and other muscular dystrophies are associated with reduced muscle mass, muscle strength, and muscle function resulting in low bone density and increased fracture risk (75, 78-82). Concomitant glucocorticoid therapy also impacts bone deleteriously, although amelioration of the underlying condition through glucocorticoid use may mitigate these effects to some extent (83). In one study, 53% of patients with Duchenne muscular dystrophy treated with deflazacort had vertebral fractures over a nine-year period (84). Another study has reported a 16-fold increased risk of fracture in patients taking daily deflazacort (85). Vamorolone, a dissociative steroidal anti-inflammatory drug, holds promise for use in this condition without significant bone effects (86). Studies have also reported impaired calcium metabolism and vitamin D status as well as high IL-6 levels in Duchenne muscular dystrophy, which could also

contribute to impaired bone health (75, 79, 80, 87). Similarly, spinal muscular atrophy (SMA) is associated with low bone density and increased fracture risk (88-91). Low bone density in patients recovering from burns (92) is consequent to immobilization, muscle wasting, increased release of inflammatory cytokines that active osteoclastic activity and increase bone turnover, and low 25OHD levels (93). In one study,

27% of children with severe burns had low bone density Z-scores (92).

ENDOCRINE CONDITIONS

Many hormones have a direct impact on osteoblast and osteoclast activity (Figure 1); thus, a disruption in these hormone systems can have deleterious effects on bone.
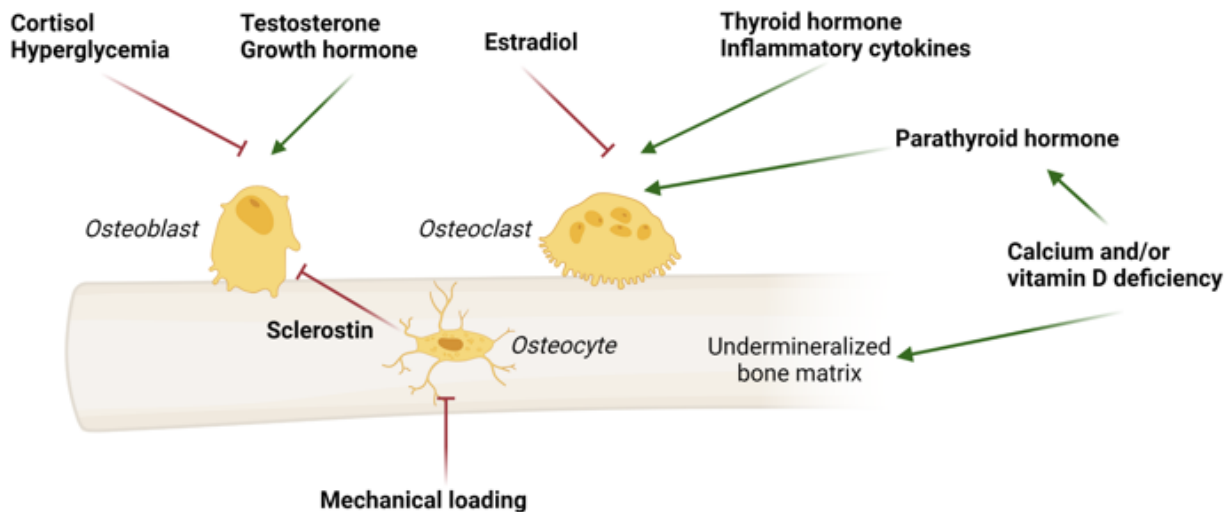

Figure 1. Regulation of Bone Formation and Resorption. Osteoblasts are the primary bone-forming cells. Osteoblast anabolic activity is stimulated by testosterone and growth hormone and inhibited by cortisol and hyperglycemia. Osteoclasts mediate bone resorption. Thyroid hormone, parathyroid hormone, and inflammatory cytokines increase bone resorption, while estradiol inhibits osteoclast function. Osteocytes embedded within the bone matrix secrete sclerostin which inhibits osteoblast function; mechanical loading decreases sclerostin production thereby "releasing the brake" on osteoblast activity. Calcium deficiency, often as a result of vitamin D deficiency, leads to poorly mineralized bone matrix as well as secondary hyperparathyroidism.

Hypogonadism

Conditions of hypogonadism (Table 1) are associated with low bone density and impaired bone accrual given the critical role of the gonadal hormones on bone (70). Estradiol has anti-resorptive effects through its effects on the RANK-RANK-ligand-osteoprotegerin system. Estradiol also inhibits secretion of sclerostin, which otherwise inhibits the canonical Wnt signaling pathway and therefore osteoblast action, and also inhibits osteoclastic action (94). Testosterone has both direct

bone anabolic and anti-resorptive effects, and also affects bone through its aromatization to estradiol. It increases periosteal bone apposition, while decreasing endosteal bone resorption, which collectively accounts for the larger size and thicker cortices of the male adult skeleton (70). During puberty, the rising levels of estradiol and testosterone are critical for adolescent bone accrual (95), and hypogonadism is therefore associated with reduced bone accrual, low bone density, and an increased risk of fracture (96, 97).

Hypercortisolemia

Chronic administration of glucocorticoids for underlying inflammatory or other conditions (such as inflammatory bowel disorders, chronic arthritis, Duchenne muscular dystrophy, renal conditions including post-transplant patients, and connective tissue disorders), and endogenous hypersecretion of cortisol (ACTH dependent or independent) can cause low bone density and increase the risk for fracture (98). Excessive exposure to glucocorticoids has multiple deleterious effects on bone. It inhibits osteoblastic activity (through direct effect on osteoblast precursors and stimulation of apoptosis of mature osteoblasts and osteocytes), reduces mechanosensing ability through its osteotoxic effects, increases osteoclast activity by decreasing osteoprotegerin and increasing RANK-ligand secretion from osteoblasts, impairs calcium absorption from the gut, impairs the renal handling of calcium, has an inhibitory effect on the growth hormone (GH)-IGF-1 axis, and leads to reduced muscle mass, impaired collagen formation, and suppression of the HPG axis (98, 99).

Importantly, hypercortisolemia is associated with increased fracture risk (particularly of the spine) independent of low BMD, related to the dose and duration of therapy (99). Low bone density can become evident within 3-6 months of therapy and improves in the first year after stopping glucocorticoids (particularly after the first six months). One study in children receiving glucocorticoids for three years for rheumatic disease reported an unadjusted vertebral fracture incidence rate of 4.4 per 100 person-years, and a 3-year incidence proportion of 12.4% (100). The highest annual incidence was in the first year, and every 0.5 mg/kg increase in glucocorticoid dose was associated with a doubling of fracture risk. Of concern, 50% of the fractures were asymptomatic and would have been missed without a lateral spine x-ray (100). Importantly, recovery of vertebral shape and height appears possible in children affected in the pre- or early pubertal years and is unlikely in those who are mid to late pubertal (99, 101).

Chronic, Untreated Hyperthyroidism

Chronically high thyroid hormone levels, including at initial diagnosis of Graves' disease, can lead to increased bone resorption and low BMD, particularly at cortical sites (102-104). An increase in IL-6 levels has been associated with this condition and contributes to increased bone resorption (105). Subclinical hyperthyroidism, as seen in survivors of pediatric differentiated thyroid carcinoma receiving levothyroxine at doses that suppress TSH (but with thyroid hormones levels still in the normal range), does not appear to have major negative effects on bone (106), indicating that high levels of thyroid hormones, but not suppressed TSH, account for the deleterious effects on bone in patients with hyperthyroidism.

Hyperparathyroidism

Primary hyperparathyroidism is rare in children and adolescents (and mostly associated with conditions such as MEN1 and MEN2), but secondary hyperparathyroidism occurs in conditions of hypocalcemia and vitamin D deficiency, and both secondary and tertiary hyperparathyroidism may be associated with chronic renal disease. The latter is discussed in a later section of this chapter. Chronic hyperparathyroidism causes increased bone resorption and results in low BMD, and the forearms (and primarily cortical sites) are involved to a greater extent that other parts of the body in this condition, with relative sparing of the spine (107).

Growth Hormone Deficiency and Resistance

Both GH and IGF-1 have multiple effects on bone. GH increases levels of osteoprotegerin, stabilizes the canonical Wnt signaling pathway, increases muscle mass and bone growth, while also stimulating local and hepatic IGF-1 secretion. The latter also stabilizes the canonical Wnt signaling pathway to activate osteoblasts, stimulate bone growth and an increase in

muscle mass, increases 1-α hydroxylase activity, thus increasing intestinal absorption of calcium and phosphorus, increases tubular reabsorption of phosphorus, and increases RANK ligand activity. Thus, conditions of GH deficiency and resistance are at risk for low BMD. Adults with GH deficiency in the KIMS database had a 2.7 times higher fracture risk than the general population (108), and other studies have also reported an increased fracture risk in this population (109). However, a higher risk of fractures has not been observed in children with GH deficiency who received GH replacement therapy (110). Further, areal BMD in children with GH deficiency is often no longer low after adjusting for body size (111). Quantitative computed tomography studies have reported normal volumetric BMD, lower cortical thickness, and no differences for trabecular structure in children with GH deficiency vs. controls (112). In conditions of undernutrition, an acquired state of GH resistance and low levels of IGF-1 contribute to low rates of bone accrual and low BMD (113).

Poorly Controlled Diabetes

While studies are still in the process of examining the effects of diabetes on bone in children, data seem quite clear that poorly controlled diabetes is associated with low BMD (114-117). This has been linked to low IGF-1 levels secondary to hypoinsulinemia resulting from poor diabetes control, increased markers of oxidative stress, and increased secretion of inflammatory cytokines (118).

CHRONIC MEDICAL CONDITIONS

Chronic inflammatory states such as inflammatory bowel disorders, connective tissue disorders, chronic arthritis and other inflammatory states are associated with low BMD for multiple reasons, including increased release of proinflammatory cytokines, which activate osteoclastic activity, chronic use of glucocorticoids and possibly some degree of undernutrition. Many of these conditions have been covered in previous sections.

Systemic Mastocytosis

Systemic mastocytosis is associated with low bone density in adults (119, 120), and BMD in these patients correlates with tryptase levels, mast cell proportion in bone marrow biopsies, and duration since diagnosis (119). Data are lacking in children.

Leukemia and Other Malignancies

Infiltrative conditions such as leukemia and other malignancies is associated with low bone density. Low bone density in patients with malignancy is a consequence of poor nutrition, malabsorption and diarrhea, vitamin D deficiency and associated hyperparathyroidism, release of inflammatory cytokines, chronic use of glucocorticoids, the effects of chemotherapy (gonadal failure, a direct suppressive effect of alkylating agents on bone marrow, and bone toxicity of high-dose methotrexate), as well as a direct effect of radiation therapy on osteoblasts. Pediatric acute lymphoblastic leukemia (ALL) is a known cause of low bone density and osteoporotic fractures (121-123). One study reported a cumulative fracture incidence of 32.5% for vertebral fractures and 23% for non-vertebral fractures in children with ALL over a six-year period, with 39% of children with vertebral fractures being asymptomatic (123). Vertebral reshaping occurred in younger children, but persistent vertebral deformity was noted in about 25%, particularly in older children and those with more severe vertebral collapse.

Beta-Thalassemia and Sickle Cell Disease

A large proportion of children with beta-thalassemia are reported to have low bone mass or bone density with reduced bone accrual compared to controls, regardless of transfusion and chelation regimens (124-126). One study reported BMC Z-scores of ≤ -2 in 61% of adolescents with beta-thalassemia (124). Another study reported that 82% and 52% of children and adolescents with transfusion dependent beta-thalassemia had low BMD Z-scores at the spine and the hip, respectively (125). Other studies, however,

have reported much lower rates of low BMD in these children. Overall, nutritional status is a major determinant of bone outcomes in this condition. Similarly, sickle cell disease in children and young adults has been associated with low bone density (127, 128), even after height adjustment (129), related to puberty, hip osteonecrosis, chronic pain, and hemoglobin values (129). Many of these children also have low calcium intake and low serum concentrations of 25OHD (127). Other predictors of low BMD include a low BMI, male sex, delayed puberty, and low serum zinc concentrations (128, 130).

Chronic Kidney Disease

Chronic kidney disease is a major risk factor for low BMD and fractures because of the associated secondary or tertiary hyperparathyroidism, hyperphosphatemia, reduced mineralization (reduced 1-α hydroxylase), increased cytokines such as TNF-α, and chronic use of glucocorticoids (131-133).

IATROGENIC CAUSES

Certain medications can also contribute to low bone density in children and adolescents. Antiepileptic medications such as phenytoin, primidone, phenobarbital, and carbamazepine impair vitamin D metabolism by stimulating hepatic microsomal cytochrome P450 enzymes, causing vitamin D deficiency, secondary hyperparathyroidism, and low BMD (134). Data also suggest that antiepileptic drugs may inhibit the cellular response to parathyroid hormone (PTH). Further, use of valproic acid has been associated with increased osteoclast activity and low BMD in some studies. In contrast, newer antiepileptic medications such as lamotrigine and topiramate have not been associated with impaired vitamin D metabolism or low bone density.

As already discussed, chronic glucocorticoid use has several deleterious effects on calcium absorption,

retention, and osteoblast and osteoclast function. Methotrexate and certain antiviral drugs have also been demonstrated to contribute to impaired bone health. Further, medications that suppress the hypothalamic-pituitary-gonadal axis such as GnRH analogs and depo medroxyprogesterone acetate are associated with low BMD. Lastly, radiation therapy is known to have direct deleterious effects on osteoblasts.

LIFESTYLE FACTORS

Cigarette smoking is believed to be a risk factor for low bone density (135), although it is difficult to sort out the effects of smoking on bone versus the contribution of risk factors common among smokers, which include a low BMI, greater intake of alcohol, lower levels of physical activity, and poor diet. The longer the duration of smoking and the greater the number of cigarettes consumed, the greater the risk of fracture. Further, healing following a fracture is slower in smokers than non-smokers, and complications during the healing process are more common in smokers. Even exposure to secondhand smoke has been related to suboptimal bone outcomes. Women who smoke often produce less estrogen and tend to enter menopause earlier, which would also contribute to increased bone loss. Further, levels of cortisol and free radicals are higher in smokers, which may also contribute, and nicotine and free radicals are toxic to osteoblasts. Importantly, quitting smoking does reduce the risk of low bone density and fractures. However, it may take several years to lower a former smoker's risk.

Additionally, alcohol is deleterious to bone when consumed in excess (136); more than two alcoholic drinks per day are associated with low bone density, and may be related to decreased absorption of calcium, increased concentrations of cortisol and PTH, lower levels of estrogen, and alcohol *per se* is toxic to osteoblasts. Reduced bone density and impaired bone quality contribute to increased fracture risk (137).

Table 1. Causes of Low Bone Density or Osteoporosis
PRIMARY CAUSES OF LOW BONE DENSITY OR OSTEOPOROSIS
Osteogenesis imperfecta (COL1A1, COL1A2, IFITMF5, SERPINF1, CRTAP, LEPRE1 and other genes) Marfan syndrome (FBN1) Ehlers Danlos syndrome (COL5A, COL3A, non-monogenic forms) Homocystinuria (CBS, MTHFR, MTR, MTRR, and MMADHC genes) Lysinuric protein intolerance (SLC7A7) Osteoporosis pseudoglioma syndrome (LRP5) Idiopathic juvenile osteoporosis Hypophosphatasia (ALPL) Others
Other Primary Conditions Associated with Fragility Fractures but Without Low Bone Density Polyostotic fibrous dysplasia (GNAS1) Osteopetrosis (LRP5, CLCN6, CA2, others) Pycnodysostosis (CTSK)
SECONDARY CAUSES OF LOW BONE DENSITY OR OSTEOPOROSIS
Nutritional and Malabsorptive Conditions • Deficient intake of calcium and vitamin D • Conditions of low energy availability or energy deficit (e.g., anorexia nervosa, Female Athlete Triad/Relative Energy Deficiency in Sports (RED-S)) • Conditions of malabsorption (e.g., celiac disease, inflammatory bowel disease, cystic fibrosis, biliary atresia)
Conditions of Reduced Mechanical Bone Loading (Including Disuse or Immobilization) • Cerebral palsy • Spinal cord injury • Spina bifida • Muscular dystrophy • Spinal muscular atrophy • Severe burns • Conditions of prolonged immobilization
Endocrine Conditions • Hypergonadotropic hypogonadism: O   Primary ovarian insufficiency O   Primary testicular insufficiency • Hypogonadotropic hypogonadism: O   Isolated or combined pituitary hormone deficiencies (genetic and acquired causes) O   Hyperprolactinemia O   Functional hypothalamic amenorrhea (conditions of energy deficit, chronic stress) O   Medications (e.g., depot medroxyprogesterone acetate, GnRH analog therapy) • Hypercortisolemia: O   Iatrogenic from prolonged use of glucocorticoids for underlying chronic conditions* O   Endogenous: adrenal, pituitary and ectopic tumors

• Hyperthyroidism (chronic untreated)
• Hyperparathyroidism
• Growth hormone deficiency and resistance
• Diabetes (particularly when poorly controlled)
Chronic Medical Conditions
• Chronic inflammatory states**
• Mastocytosis
• Infiltrative conditions (e.g., leukemia and other malignancies)
• Thalassemia and sickle cell disease
• Chronic kidney disease
Iatrogenic
• Antiepileptic medications
• Glucocorticoids
• Methotrexate
• Antiretroviral drugs
• Depot medroxyprogesterone acetate
• GnRH analogs
• Radiation therapy
Lifestyle factors
smoking and chronic alcohol use

*Examples: Duchenne muscular dystrophy, inflammatory bowel disorders, chronic arthritis, renal conditions including post-transplant patients, connective tissue disorders, leukemia and other malignancies

**Examples: Inflammatory bowel disease, chronic arthritis, connective tissue disorders, nephrotic syndrome

EVALUATION

History and Physical Exam

Initial evaluation includes a thorough medical history, with special attention to aspects that may adversely affect bone health such as chronic immobility or oncology treatments; medication history, with a focus on past and current medications that may adversely influence bone health, such as glucocorticoids, anti-epileptic drugs, and hormonal contraception; pubertal history, dependent upon age; and family history of recurrent fractures, pre-menopausal osteoporosis, and bone disorders.

Additionally, a bone health assessment should include the following: 1) fracture history, including mechanism of injury (e.g., traumatic, fall from a standing height, etc.), treatment (e.g., cast, surgery, and if any complications such as prolonged healing); 2) dietary intake of calcium-rich foods, with quantification of the typical servings per day of dairy, and any supplementation of calcium and vitamin D, including type of supplementation (e.g., calcium carbonate, cholecalciferol, etc.) and dosages; 3) physical activity including sports, dance, gym class, physical therapy, and time in stander, as applicable.

The physical exam should be comprehensive and include a thyroid and pubertal exam, palpation of the spine, and assessment for hyper flexibility and any physical restrictions (i.e., contractures).

Laboratory Studies

Dependent upon the degree of clinical concern for osteoporosis or increased bone fragility, determined by the history, next steps could include assessment of bone mineral density by DXA, laboratory studies, and additional testing. If the bone fragility history is

equivocal, it is reasonable to start with a DXA and perform additional evaluation if there is demonstrated low BMD. However, if the history is strongly suggestive of osteoporosis or increased bone fragility, the next steps are typically DXA and laboratory evaluation (see Table 2). It is helpful to assess calcium, magnesium, phosphorus, alkaline phosphatase, 25OHD, PTH, screening for celiac disease, and creatinine. Urinary calcium and creatinine ratio (spot) can be helpful to assess calcium status and there is an increased risk of hypercalciuria in non-ambulatory patients. Rarely, bone turnover markers, such as bone formation markers osteocalcin and bone specific alkaline phosphatase and the bone resorption marker c-telopeptide, may be helpful, if there is a clinical concern for a low bone turnover state. Also, 1,25-dihydroxyvitamin D (1-25OHD) is not routinely assessed, but is helpful if there is a clinical concern for a disorder of vitamin D metabolism. Additional biochemical assessments should be considered on a case-by-case basis. Notably, for all laboratory assessments, it is important to have pediatric reference ranges, and pubertal specific (i.e., Tanner stage) reference ranges when applicable, in order to properly interpret values.

Imaging Studies

EVALUATION OF BONE MINERAL DENSITY

DXA is the clinical gold standard for measuring BMD (138). The current International Society for Clinical Densitometry (ISCD) pediatric guidelines for optimal bone densitometry assessments include: for 4-15 years old total body less head and lumbar spine; 16 years and older lumbar spine and hip (1). By age 15 years, the skeletal landmarks at the hip that guide positioning are well-developed and enable the replication of positioning. In adolescent patients, it may be useful to perform a transition scan around 16 years old, including total body less head, lumbar spine, and hip, as this will enable assessment of interval change at two skeletal sites. The current ISCD pediatric guidelines suggest measurement of hip BMD in the school-age child if lack of weight-bearing and

skeletal fragility are concerns. In certain clinical scenarios, it may be useful to obtain a distal lateral femur or forearm scans, such as in patients with neuromuscular disorder with impaired mobility (139). Distal lateral femur scans can be very informative in non-ambulatory patients. Forearm scans can be useful in patients who are unable to hold still, those with significant contractures, and in patients with orthopedic hardware that precludes scans of other skeletal sites.

It is helpful to assess interval change enabling evaluation of bone accrual and comparison of Z-scores over time (i.e., did they increase, remain the same, or decrease). The shortest interval usually assessed is one year, and dependent upon the clinical situation, it may be prudent to reassess after two years or longer, especially if it would not change clinical management. From a practical standpoint, insurance typically requires DXA scans to be performed at least one year apart (> 365 days from last DXA scan), but all scanning sites should be covered and are determined by medical necessity.

DXA is interpreted via areal BMD (g/cm^2) calculated Z-scores which are age, sex, and ancestry matched and based on pediatric normative data (140). A Z-score less than -2.0 SD is low, and between -1.0 to -2.0 SD is considered borderline low and may be of clinical significance in patients with risk factors for increased bone fragility. Notably, in pediatrics, the diagnosis of osteoporosis requires both: 1) a clinically significant fracture history, which is defined as at least two long bone fractures in children less than 10 years old, at least three long bone fractures by 19 years old, or any vertebral fractures; and 2) low bone density, with BMD Z-scores $\leq$ -2.0, assessed by DXA.

However, as a two-dimensional projected area of a three-dimensional structure, DXA is affected by bone size. For this reason, pediatric DXA derived areal BMD is affected by bone size and smaller bones may have an artifactually lower BMD Z-score. To take this into account, the BMD Z-score can be adjusted for height (i.e., height for age Z-score) in those with short stature

(https://zscore.research.chop.edu/calcpedbonedens.php) or, in certain scenarios, adjusted for bone age if a patient has delayed puberty but is not short (141).

DXA only assesses bone mass and density and does not fully capture all factors contributing to bone fragility, such as volumetric BMD (g/cm^3), bone microarchitecture (e.g., trabecular vs. cortical bone), bone quality, or bone strength. Additional research modalities allow for the assessment of bone microarchitecture, quality, and strength, such as peripheral quantitative computed tomography (pQCT), high resolution pQCT, and trabecular bone score (TBS), a measure of bone quality of the lumbar spine which correlates to bone microarchitecture. There are recently published pediatric TBS reference ranges (142). However, there are few pediatric normative data for these alternative modalities, currently limiting their use to primarily the research setting.

ASSESSING FOR COMPRESSION FRACTURES

It is important to evaluate the patient for compression fractures in patients with low bone density and clinical concern, such as back pain or unexplained decrease in physical activity. If there is acute concern for compression fractures, initial evaluation should include spine x-rays, typically two-view anteroposterior and lateral radiographs. If imaging is consistent with compression fracture(s), there should be prompt evaluation by orthopedics and endocrinology, as the disease course can be positively affected with appropriate treatment.

Vertebral fracture assessment (VFA) is an additional spine assessment that can be performed concurrently with DXA to assess for spine vertebral fractures. It is commonly used in adults but has only recently been utilized in children (143). Advantages of VFA over spine radiographs include lower radiation dose, logistics (done at the same visit as DXA), and lower cost. There is emerging evidence that it is useful to screen for vertebral fractures with VFA in high-risk pediatric populations, such as those with Duchenne muscular dystrophy and osteogenesis imperfecta.

RADIOGRAPHY

Radiographs (i.e., x-rays) do not quantify bone mass and are not a good screening tool for low bone mass. However, if radiographs are performed for other indications, such as a clinical concern for fracture or related to another medical evaluation, when there is at least 30-40% bone loss, there are typical findings, such as bone demineralization, gracile bones, and thin cortex. If there is radiographic concern for low bone mass, with concurrent risk factors for suboptimal bone accrual, this should be further evaluated with a DXA to quantify BMD. Radiographs can be useful to assess for specific findings in several bone disorders including rickets, which is a consequence of under-mineralization of bone in growing children; skeletal dysplasias, which are often diagnosed based on radiographs; osteopetrosis, with over-mineralization of bone; and osteogenesis imperfecta, of which several types have a substantial number of wormian bones on skull radiograph.

Consultative Services

Additional consultations may be required, depending upon the specific underlying etiology of the patient's low bone density. For many patients, especially those who are underweight, intolerant of cow milk-based foods (i.e., milk protein allergy), or have an eating disorder, working closely with a nutritionist to ensure adequate caloric intake and calcium-rich foods is very useful. Patients with mobility challenges, such as hypermobility and non-ambulatory patients, often benefit from working with physical therapy. Dependent upon the suspected underlying disease, additional evaluation by other subspecialists, such as a geneticist or gastroenterologist, may be helpful.

Table 2. Laboratory and Imaging Evaluation for Increased Bone Fragility and Osteoporosis	
Laboratory Studies	
Standard Evaluation	calcium with albumin, magnesium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D, parathyroid hormone, tissue transglutaminase with IgA, creatinine
Consider*	genetic testing for osteogenesis imperfecta and possibly other genetic disorders (dependent upon family history), TSH/fT4, pubertal assessment (FSH, LH, estradiol, testosterone), bone turnover markers (osteocalcin, bone specific alkaline phosphatase, c-telopeptide), 1,25-dihydroxyvitamin D, erythrocyte sedimentation rate and c-reactive protein (if known or suspected chronic inflammatory disease), urine calcium and creatinine ratio (spot)
Imaging Assessments	
Standard Evaluation	DXA – sites dependent upon age and logistics[**]
Consider*	Screening lateral spine x-rays in high-risk patients, VFA in high-risk patients, skull x-ray if concern for osteogenesis imperfecta, skeletal survey if concerned for skeletal dysplasia

* Consider additional assessment on a case-by-case basis
** See text for details regarding recommended sites

TREATMENT

Non-Pharmacologic Interventions to Optimize Bone Mineral Density and Bone Strength

CALCIUM AND VITAMIN D

Calcium is a critical component of bone, necessary for the formation of hydroxyapatite which confers strength to the bone matrix (144). Calcium is a threshold nutrient, meaning that once adequate intake is achieved to maximize calcium retention, further intake does not provide additional benefit to bone health (145). The optimal calcium intake for any individual depends on several factors: these include vitamin D status, given that vitamin D stimulates gut absorption of calcium, as well as other dietary factors such as sodium and protein intake which can alter renal calcium excretion (146). In addition to impairing skeletal mineralization, dietary calcium insufficiency may cause a secondary hyperparathyroidism, promoting bone resorption and phosphate excretion, further decreasing bone density. The United States National Academy of Sciences guidelines provide a Recommended Dietary Allowance (RDA) of calcium which is anticipated to meet the needs of 97.5% of the healthy population (Table 3) (147).

Table 3. Recommended Daily Intake of Calcium and Vitamin D by Age		
Age	Calcium intake (mg)	Vitamin D intake (IU)
0-6 months	200	400
7-12 months	260	400
1-3 years	700	600
4-8 years	1000	600
9-18 years	1300	600
19-50 years	1000	600

1-25OHD, the active metabolite of vitamin D, is critical for optimal gastrointestinal absorption of calcium. Vitamin D sufficiency is assessed by circulating concentrations of 25OHD, though there is some controversy regarding the 25OHD threshold which reflects sufficiency. The Institute of Medicine (IOM) has defined sufficiency as 25OHD ≥ 20 ng/mL (147), based largely on bone biopsy evaluation of unmineralized osteoid accumulation (148), while other guidelines recommend a target of 30 ng/ml (149). To achieve these serum concentrations, the IOM recommends daily intake of 400 IU in the first year of life, and 600 IU from ages 1-70 years (Table 3). However, individual patients may require higher intakes to achieve vitamin D sufficiency, including those with malabsorptive conditions such as cystic fibrosis and inflammatory bowel disease (150, 151). In addition, individuals with obesity have a smaller incremental increase in 25OHD concentration with supplemental vitamin D and may require 2000 IU daily or more to achieve target serum concentrations (152).

For children on high-dose glucocorticoid therapy for underlying inflammatory or oncologic disease, several specific effects on calcium and vitamin D metabolism must be considered. Glucocorticoids can directly inhibit the gut absorption of calcium via decreased expression of epithelial calcium channels (153). In addition, glucocorticoids can inhibit the synthesis of 1-25OHD and accelerate the catabolism of vitamin D metabolites (154). Therefore, these patients may require higher than typical intake of calcium and vitamin D, which should be guided by monitoring circulating concentrations of 25OHD and PTH.

Studies of calcium supplementation in healthy children suggest that increases in BMD may be limited to prepubertal children and in those with low baseline calcium intake, again supporting the model of calcium as a threshold nutrient (155, 156). Long-term follow-up studies indicate that the effect of calcium supplementation wanes after discontinuation of the intervention (25, 157-160). Similarly, a meta-analysis of pediatric vitamin D supplementation studies indicated only modest effects on BMD which were limited to those with a baseline 25OHD <14 ng/mL (161). One follow-up study showed a loss of effect on BMD three years after completion of the supplementation intervention (162). These data suggest that, for children at risk for low calcium intake or low circulating vitamin D metabolites, optimization of these factors should be an ongoing process.

PHYSICAL ACTIVITY

Mechanical loading of the skeleton via high-impact physical activity promotes bone acquisition in growing children (71). Several observational studies have shown an association of childhood physical activity with increased BMD (163-167), with effects that persist into young adulthood (168, 169). A meta-analysis of RCTs confirmed a significant though small effect of physical activity on measures of bone mass, with increased responsiveness in pre-pubertal participants (170). Interestingly, this analysis also revealed a positive association of calcium intake with bone mineral content and density, suggesting that calcium enables or synergizes with the effects of weight-bearing (171, 172). Among healthy children, a threshold force of approximately 3 times the force of

gravity, such as experienced during running or jumping, seems to be required to stimulate bone formation (173). Importantly, physical activity is beneficial even in healthy children with a high genetic risk for low BMD (174).

The role of weight-bearing activity in children with underlying musculoskeletal disease is less well-studied. Small studies of children with cerebral palsy have shown efficacy of increasing time of use in a stander (175) and a physical therapy program (176) to improve BMD. Whole-body vibration (WBV) has been studied in children with several conditions (177) including cerebral palsy (178-182), Duchenne muscular dystrophy (183-185), osteogenesis imperfecta (186, 187), and Down syndrome(188). Synthesis of the results of these studies is challenging due to methodological variation in the magnitude and frequency of vibration as well as the length of treatment sessions. In general, among children with cerebral palsy, WBV appears to have positive effects on bone density and bone strength estimates, while data are conflicting or limited in other conditions.

Pharmacologic Intervention

WHOM TO TREAT WITH BONE ACTIVE MEDICATIONS

Selection of appropriate pediatric patients for pharmacological intervention is not straightforward (189). Unlike in adults, for whom low BMD alone suffices to confer a diagnosis of osteoporosis, the diagnosis of osteoporosis in children requires evidence of skeletal fragility, defined as multiple long-bone fractures or a vertebral compression fracture (190). Current evidence-based guidelines for the use of pharmacotherapy do not recommend prophylactic use of pharmacotherapy given the absence of robust prospective data enabling estimation of fracture risk in vulnerable children (191). This differs from guidelines for osteoporosis management in adults, in whom primary prevention of fracture is a goal (192). Given that, particularly in children with progressive neuromuscular disease, a single fracture can lead to

permanent loss of ambulation (193, 194), further research to better define which pediatric patients may benefit from prophylactic therapy is urgently needed. Indeed, in certain particularly high-risk patients, such as those with spinal muscular atrophy (SMA), clinicians may choose to treat in advance of a patient meeting pediatric osteoporosis criteria (195).

Conversely, some children who fulfill criteria for osteoporosis may not warrant pharmacotherapy. Children with secondary causes of osteoporosis which may be transient, such as an inflammatory disease that responds to treatment, or glucocorticoids that are discontinued, have the potential to repair BMD losses as well as to spontaneously heal vertebral fractures. As an example, in a cohort of children with Crohn's disease, initiation of anti-TNF-alpha therapy led to significant increases in BMC and BMD Z-scores over 12 months, indicating "catch-up" bone accrual (196). A study of fractures among children with acute lymphocytic leukemia (ALL) demonstrated that, while the cumulative incidence of vertebral compression fracture over 6 years was 33%, complete healing with restoration of normal vertebral shape was observed in 77% of those with fractures. Predictors of healing included younger age (mean 4.8 vs 8.0 years) and number and severity of fractures (123). Lower cumulative glucocorticoid doses may also correlate with greater chance of spontaneous healing in children with inflammatory disease (101). The decision whether or not to initiate pharmacotherapy thus depends on a careful weighing of each child's individual clinical history and anticipated course of disease (189).

BISPHOSPHONATE TREATMENT

For children at high risk of fracture, bisphosphonates are the best-studied and most widely used pharmacologic treatment. Bisphosphonates are non-hydrolysable analogs of pyrophosphate that bind tightly to hydroxyapatite crystals and inhibit osteoclast-mediated bone resorption (197). Once embedded in bone, bisphosphonates are retained in the pediatric skeleton for several years, as evidenced by detectable

urinary concentrations up to eight years after administration (198). Bisphosphonates are available in both oral and intravenous formulations. The bioavailability of oral bisphosphonates is extremely low, and there is significant intraindividual skeletal retention of bisphosphonates, which depends in part on endogenous bone turnover and renal function (199).

Table 4. Selected Bisphosphonates: Dosing and Examples of Pediatric Uses			
Bisphosphonate	**Administration**	**Typical Dosing Regimen**	**Use in Pediatrics**
Alendronate	PO	5-10 mg daily(200) or 35 mg weekly(201)	Osteogenesis imperfecta(200, 202-204) Glucocorticoid induced osteoporosis(205, 206) Duchenne muscular dystrophy(207, 208) Cerebral palsy(209) Cystic Fibrosis(210) Acute lymphoblastic leukemia(211) Spinal cord injury(212) Transplant(213)
Risedronate	PO	2.5-5 mg daily(214) or 15-30 mg once weekly(215)	Osteogenesis imperfecta(214-216) Duchenne muscular dystrophy(217) Cerebral palsy(218) Non-ambulatory children(219)
Pamidronate	IV	9 mg/kg year, given as 0.25-1 mg/kg daily for 3 days every 2-4 months(220)	Osteogenesis imperfecta(204, 221, 222) Glucocorticoid induced osteoporosis (223) Cerebral palsy(224-226) Acute lymphoblastic leukemia(227) Idiopathic juvenile osteoporosis(228) Burns(229)
Zoledronic acid	IV	0.05-0.1 mg/kg year, every 3-12 months(230, 231)	Osteogenesis imperfecta(230, 232-235) Glucocorticoid induced osteoporosis(236)

			Duchenne muscular dystrophy(237) Cerebral palsy(238, 239) Rett syndrome(239)
Neridronate	IV	2 mg/kg every 3-6 months(240)	Osteogenesis imperfecta(240, 241) Osteoporosis pseudoglioma syndrome(242)

Early studies of bisphosphonate therapy in children focused on those with osteogenesis imperfecta. Treatment with both oral and intravenous formulations leads to significant increases in BMD at both the hip and spine (200, 214, 215, 243-245). Subsequent studies in other conditions including cystic fibrosis and glucocorticoid induced osteoporosis showed similar increases in BMD with bisphosphonate use (205, 210). This is a non-trivial result, given that skeletal fragility in osteogenesis imperfecta, as in most pediatric conditions, is not mediated by accelerated bone resorption. A primarily anti-resorptive medication thus does not address the underlying cause of low BMD. However, trans-iliac biopsy data demonstrate that bisphosphonate therapy in children leads to increases in cortical width, via modeling-based bone formation at the periosteal and endocortical surfaces (246). In addition, trabecular BMD increases via an increase in trabecular number but not in thickness. This effect is hypothesized to be due to a greater retention of primary trabeculae after new bone formation and subsequent incorporation into secondary spongiosa (246).

While the beneficial effects of bisphosphonates on bone density are well-documented, effects on the more critical outcomes of fracture and associated morbidities are less clear and almost exclusively limited to the osteogenesis imperfecta population (see Endotext chapter on osteogenesis imperfecta for details). In adults, data from a recent individual patient data meta-regression of osteoporosis trials revealed significant and strong correlations between increases in BMD and fracture risk reduction (247). Whether this

result generalizes to growing children is uncertain. Small observational studies and randomized controlled trials suggest that bisphosphonates may reduce the incidence of vertebral fracture in glucocorticoid-treated children (101, 237, 248). Data regarding anti-fracture efficacy in other conditions including cerebral palsy is lacking (238).

The choice of which bisphosphonate to use, as well as the optimal dosing regimen and length of treatment, is challenging due to a limited number of trials as well as their relatively small size. Some studies suggest that intravenous (IV) agents may be more effective at promoting vertebral fracture healing (249), though a head-to-head study of alendronate vs. pamidronate in children with osteogenesis imperfecta showed no difference in BMD accrual, suppression of bone turnover markers, or fracture incidence (250). A major consideration is the risk of pill esophagitis with oral bisphosphonates, which is exacerbated by the presence of gastrointestinal reflux, leading to the recommendation that patients should swallow pills only with water and remain upright for at least 30 minutes after administration. Given the significant challenge this poses to many children with osteoporosis due to an underlying neuromuscular or other chronic disease, IV bisphosphonate therapy is often the most practical choice. Dosing regimens vary both by underlying condition and between institutions; typical dosing regimens are noted in Table 4.

How long to continue therapy once initiated is also not well-defined. Because growing children accrue new bone via modeling-based growth, intermittent dosing

regimens result in new bone not being exposed to bisphosphonates. This leads to the classic "zebra-lines" seen on x-rays of children treated with IV bisphosphonates (251). Concern has arisen that the junction between regions of treated and non-treated bone may be at particularly high risk of fracture (252, 253). For children with primary osteoporosis, continuation of therapy until the completion of growth is thus typically recommended. Monitoring of BMD, via DXA, as well as careful assessment of fracture incidence both by history and spine imaging can guide the maintenance phase of therapy which may require decreases in the dose or frequency of administration (252, 253). In children with secondary osteoporosis in which the underlying condition has resolved or is well-controlled, discontinuation of treatment with close monitoring may be appropriate (191).

Short-term Adverse Effects of Bisphosphonates

Because the skeleton functions as a reservoir for calcium as well as phosphate, anti-resorptive therapy can lead to short-term hypocalcemia and hypophosphatemia, which typically presents in the first 1-3 days after infusion though may have a more delayed onset (234, 254, 255). While often asymptomatic, due to the possibility of symptomatic hypocalcemia requiring IV calcium infusion, it is critical to mitigate this risk by ensuring vitamin D sufficiency (i.e., 25OHD $\geq$ 30 ng/mL) and optimization of oral calcium intake via diet or supplementation starting the night prior to infusion and continuing for the following 5-10 days. Due to the higher risk of electrolyte abnormalities with the first dose, a 50% reduction is commonly employed (256). Acute phase reaction characterized by myalgia, bone pain, fever, nausea, and headache is seen in 20-80% of patients following the first IV infusion (255-258) and can typically be managed with anti-pyretic, analgesic, and anti-nausea medication as needed.

Particular care must be taken with patients on glucocorticoid therapy who may have iatrogenic central adrenal insufficiency and may thus require stress-dose glucocorticoid treatment to provide 24-hour glucocorticoid coverage as well as careful anticipatory guidance about the risk of adrenal crisis in this setting. As bisphosphonates are renally cleared, it is critical to assess renal function in children prior to administration to prevent nephrotoxicity. For children with underlying musculoskeletal disease, serum creatinine may not be an accurate reflection of renal function, and measurement of cystatin C as an alternative assessment of renal function should be performed (259). While concerns about bisphosphonates interfering with fracture healing have been raised, this has not been borne out by evidence except in the special case of iatrogenic injury via osteotomy (260).

Other Adverse Effects of Bisphosphonates

In adults, particularly at the high doses used in malignancy, bisphosphonates have been reported to cause several rare but serious adverse events including atypical femoral fracture (AFF) and osteonecrosis of the jaw (ONJ). An AFF is a low-trauma, transverse fracture of the subtrochanteric femur, typically preceded by prodromal pain (261). While such fractures have been seen in children with osteogenesis imperfecta, this may reflect the natural history of the disease and not be related to bisphosphonate use (262, 263). Case reports of AFFs in bisphosphonate-treated children with other conditions including idiopathic juvenile osteoporosis (264) and SMA (195), suggest that anticipatory guidance regarding the possibility of AFF and early symptoms should be offered to patients. Several case-finding series have not identified bisphosphonate associated ONJ in children (265, 266). Several cases of an osteopetrosis-like phenomenon have been reported in children exposed to bisphosphonates; in all cases, these were at substantially higher bisphosphonate doses than are typically prescribed to children (267, 268). Finally, possible teratogenicity of bisphosphonates, particularly given their prolonged retention in and release from the skeleton has been raised as a potential concern. However, a case series of twenty one women exposed to bisphosphonates just prior to conception or during pregnancy did not

demonstrate any concerning signal of fetal harm (269).

OTHER AGENTS

Denosumab is a humanized monoclonal antibody against RANKL, a critical factor for osteoclast differentiation and activation. As such, similar to bisphosphonates, denosumab is a potent anti-resorptive medication. The effective half-life of denosumab is much shorter than bisphosphonates, and a major clinical challenge in its use is the "rebound effect," specifically an increase in bone turnover markers above pre-treatment baseline levels and a significant increase in vertebral fractures after discontinuation in adults (270, 271). In several case reports of denosumab use in children, this rebound can present as severe hypercalcemia within just several weeks following the previous dose (272-276). Given these considerations, denosumab is currently used only sparingly in pediatric populations with specific indications including osteogenesis imperfecta type 6 (277, 278) and giant cell tumors (279-281).

Given that most pediatric osteoporosis stems from insufficient bone accrual (i.e., decreased bone formation), the use of anabolic rather than anti-resorptive agents may offer better efficacy (282, 283). Sclerostin is an endogenous inhibitor of the canonical wnt-β-catenin signaling pathway, and romosozumab, an anti-sclerostin antibody, has been approved for women with post-menopausal osteoporosis (284, 285). An alternative sclerostin antibody, setrusumab, has been investigated in a phase 2 trial of adults with osteogenesis imperfecta (286), and pediatric studies of both antibodies in osteogenesis imperfecta are ongoing (Clinicaltrials.gov: NCT05768854, NCT05125809, and NCT04545554).

Teriparatide, the c-terminal portion of PTH, is also approved for post-menopausal osteoporosis and has potent osteoblast-stimulating activity. Until recently, the United States FDA included a black box warning about increased risk of osteosarcoma in patients treated with teriparatide based on pre-clinical models. While phase 4 data have not confirmed an excess risk in clinical patients and this black box warning was removed in 2020, persistent FDA guidance to avoid teriparatide in patients with open epiphyses has limited its use. A recent small study of adolescent boys with Duchenne muscular dystrophy suggested decreased fracture incidence with teriparatide and no significant adverse events (287). Most patients in this study were treated for two years and then transitioned to an anti-resorptive therapy to prevent the loss of BMD observed after discontinuation of teriparatide in adults (288, 289).

CONCLUSIONS

Childhood osteoporosis has several potential underlying etiologies, requiring a careful assessment by clinicians with expertise in the numerous mechanisms which can contribute to skeletal fragility. Both non-pharmacologic therapies as well as bone-active medications such as bisphosphonates increase bone mass and may lower the risk of fracture. The development of novel therapies that can restore physiologic anabolic bone activity in children with insufficient bone accrual of various causes has the potential to improve care for pediatric patients with osteoporosis. Prospective data acquisition to inform treatment strategies for primary prevention of fracture in children with osteoporosis, as is done in adult populations, is urgently needed to prevent the significant morbidity of fracture in this vulnerable population.

REFERENCES

1.

Shuhart, C.R., et al., Executive Summary of the 2019 ISCD Position Development Conference on Monitoring Treatment, DXA Cross-calibration and Least Significant Change, Spinal Cord Injury, Peri-prosthetic and Orthopedic Bone Health, Transgender Medicine, and Pediatrics. J Clin Densitom, 2019. 22(4): p. 453-471.

2.   Estrada, K., et al., Genome-wide meta-analysis identifies 56 bone mineral density loci and reveals 14 loci associated with risk of fracture. Nat Genet, 2012. 44(5): p. 491-501.

3.   Mullin, B.H., et al., Genome-wide association study using family-based cohorts identifies the WLS and CCDC170/ESR1 loci as associated with bone mineral density. BMC Genomics, 2016. 17: p. 136.

4.   Zheng, H.F., et al., Whole-genome sequencing identifies EN1 as a determinant of bone density and fracture. Nature, 2015. 526(7571): p. 112-7.

5.   Marini, J.C. and A.N. Dang Do, Osteogenesis Imperfecta. 2000.

6.   Folkestad, L., et al., Bone Geometry, Density, and Microarchitecture in the Distal Radius and Tibia in Adults With Marfan Syndrome Assessed by HR-pQCT. J Bone Miner Res, 2020. 35(12): p. 2335-2344.

7.   Trifiro, G., et al., Areal bone mineral density in children and adolescents with Marfan syndrome: evidence of an evolving problem. Bone, 2015. 73: p. 176-80.

8.   Grover, M., et al., Assessment of bone mineral status in children with Marfan syndrome. Am J Med Genet A, 2012. 158A(9): p. 2221-4.

9.   Eller-Vainicher, C., et al., Bone involvement in adult patients affected with Ehlers-Danlos syndrome. Osteoporos Int, 2016. 27(8): p. 2525-31.

10.   Coussens, M., et al., Bone parameters in hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorder: A comparative cross-sectional study. Bone, 2023. 166: p. 116583.

11.   Mazziotti, G., et al., High prevalence of radiological vertebral fractures in adult patients with Ehlers-Danlos syndrome. Bone, 2016. 84: p. 88-92.

12.   Banica, T., et al., Higher fracture prevalence and smaller bone size in patients with hEDS/HSD-a prospective cohort study. Osteoporos Int, 2020. 31(5): p. 849-856.

13.   Weber, D.R., et al., Low bone mineral density is a common finding in patients with homocystinuria. Mol Genet Metab, 2016. 117(3): p. 351-4.

14.   Al-Qattan, S., C. Malcolmson, and S. Mercimek-Andrews, Lysinuric protein intolerance mimicking N-acetylglutamate synthase deficiency in a nine-year-old boy. Mol Genet Metab Rep, 2021. 27: p. 100741.

15.   Lukkarinen, M., et al., Effect of lysine infusion on urea cycle in lysinuric protein intolerance. Metabolism, 2000. 49(5): p. 621-5.

16.   Gomez, L., et al., Treatment of severe osteoporosis with alendronate in a patient with lysinuric protein intolerance. J Inherit Metab Dis, 2006. 29(5): p. 687.

17.   Saito, M. and K. Marumo, The Effects of Homocysteine on the Skeleton. Curr Osteoporos Rep, 2018. 16(5): p. 554-560.

18.   Abdel-Hamid, M.S., et al., Osteoporosis-pseudoglioma syndrome in four new patients: identification of two novel LRP5 variants and insights on patients' management using bisphosphonates therapy. Osteoporos Int, 2022. 33(7): p. 1501-1510.

19.   Tuysuz, B., et al., Osteoporosis-pseudoglioma syndrome: three novel mutations in the LRP5 gene and response to bisphosphonate treatment. Horm Res Paediatr, 2012. 77(2): p. 115-20.

20.   Balemans, W. and W. Van Hul, The genetics of low-density lipoprotein receptor-related protein 5 in bone: a story of extremes. Endocrinology, 2007. 148(6): p. 2622-9.

21.   Hartikka, H., et al., Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children. J Bone Miner Res, 2005. 20(5): p. 783-9.

22.   NORD, https://rarediseases.org/rare-diseases/hypophosphatasia/.

23.   Lanou, A.J., S.E. Berkow, and N.D. Barnard, Calcium, dairy products, and bone health in children and young adults: a reevaluation of the evidence. Pediatrics, 2005. 115(3): p. 736-43.

24.   Huncharek, M., J. Muscat, and B. Kupelnick, Impact of dairy products and dietary calcium on bone-mineral content in children: results of a meta-analysis. Bone, 2008. 43(2): p. 312-321.

25.   Winzenberg, T., et al., Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ, 2006. 333(7572): p. 775.

26.   Cormick, G., et al., Effect of Calcium Fortified Foods on Health Outcomes: A Systematic Review and Meta-Analysis. Nutrients, 2021. 13(2).

27.   Macdonald, H., et al., Bone strength and its determinants in pre- and early pubertal boys and girls. Bone, 2006. 39(3): p. 598-608.

28.   Tihtonen, K., et al., Calcium supplementation during pregnancy and maternal and offspring bone health: a systematic review and meta-analysis. Ann N Y Acad Sci, 2022. 1509(1): p. 23-36.

29.   Lehtonen-Veromaa, M.K., et al., Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. Am J Clin Nutr, 2002. 76(6): p. 1446-53.

30. Ryan, L.M., et al., Bone mineral density and vitamin D status among African American children with forearm fractures. Pediatrics, 2012. 130(3): p. e553-60.

31. Wu, F., L.L. Laslett, and Q. Zhang, Threshold Effects of Vitamin D Status on Bone Health in Chinese Adolescents With Low Calcium Intake. J Clin Endocrinol Metab, 2015. 100(12): p. 4481-9.

32. Karlsland Akeson, P., et al., Vitamin D Intervention and Bone: A Randomized Clinical Trial in Fair- and Dark-skinned Children at Northern Latitudes. J Pediatr Gastroenterol Nutr, 2018. 67(3): p. 388-394.

33. Zhu, K., et al., Maternal vitamin D status during pregnancy and bone mass in offspring at 20 years of age: a prospective cohort study. J Bone Miner Res, 2014. 29(5): p. 1088-95.

34. Ma, K., et al., Effect of Vitamin D Supplementation in Early Life on Children's Growth and Body Composition: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients, 2021. 13(2).

35. Faje, A.T., et al., Fracture risk and areal bone mineral density in adolescent females with anorexia nervosa. Int J Eat Disord, 2014. 47(5): p. 458-66.

36. Ackerman, K.E., et al., Fractures in Relation to Menstrual Status and Bone Parameters in Young Athletes. Med Sci Sports Exerc, 2015. 47(8): p. 1577-86.

37. Misra, M. and A. Klibanski, Endocrine consequences of anorexia nervosa. Lancet Diabetes Endocrinol, 2014. 2(7): p. 581-92.

38. Misra, M., et al., Bone metabolism in adolescent boys with anorexia nervosa. J Clin Endocrinol Metab, 2008. 93(8): p. 3029-36.

39. Misra, M., et al., Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls. Pediatrics, 2004. 114(6): p. 1574-83.

40. Misra, M., et al., Weight gain and restoration of menses as predictors of bone mineral density change in adolescent girls with anorexia nervosa-1. J Clin Endocrinol Metab, 2008. 93(4): p. 1231-7.

41. Christo, K., et al., Bone metabolism in adolescent athletes with amenorrhea, athletes with eumenorrhea, and control subjects. Pediatrics, 2008. 121(6): p. 1127-36.

42. Ackerman, K.E., et al., Bone microarchitecture is impaired in adolescent amenorrheic athletes compared with eumenorrheic athletes and nonathletic controls. J Clin Endocrinol Metab, 2011. 96(10): p. 3123-33.

43. Ackerman, K.E., et al., Cortical microstructure and estimated bone strength in young amenorrheic athletes, eumenorrheic athletes and non-athletes. Bone, 2012. 51(4): p. 680-7.

44. Pedreira, C.C., J. Maya, and M. Misra, Functional hypothalamic amenorrhea: Impact on bone and neuropsychiatric outcomes. Front Endocrinol (Lausanne), 2022. 13: p. 953180.

45. Fedewa, M.V., et al., Celiac Disease and Bone Health in Children and Adolescents: A Systematic Review and Meta-Analysis. J Clin Densitom, 2020. 23(2): p. 200-211.

46. Heikkila, K., et al., Celiac disease and bone fractures: a systematic review and meta-analysis. J Clin Endocrinol Metab, 2015. 100(1): p. 25-34.

47. Webster, J., et al., Prevalence of and Risk Factors for Low Bone Mineral Density in Children With Celiac Disease. Clin Gastroenterol Hepatol, 2019. 17(8): p. 1509-1514.

48. Fouda, M.A., et al., Evaluation and management of skeletal health in celiac disease: position statement. Can J Gastroenterol, 2012. 26(11): p. 819-29.

49. Laakso, S., et al., Compromised peak bone mass in patients with inflammatory bowel disease--a prospective study. J Pediatr, 2014. 164(6): p. 1436-43 e1.

50. Hidalgo, D.F., et al., Inflammatory Bowel Disease and Risk of Osteoporotic Fractures: A Meta-Analysis. Cureus, 2019. 11(9): p. e5810.

51. Bernstein, C.N., et al., The Impact of Inflammatory Bowel Disease in Canada 2018: Extra-intestinal Diseases in IBD. J Can Assoc Gastroenterol, 2019. 2(Suppl 1): p. S73-S80.

52. Laakso, S., et al., Impaired bone health in inflammatory bowel disease: a case-control study in 80 pediatric patients. Calcif Tissue Int, 2012. 91(2): p. 121-30.

53. Dubner, S.E., et al., Longitudinal assessment of bone density and structure in an incident cohort of children with Crohn's disease. Gastroenterology, 2009. 136(1): p. 123-30.

54. Semeao, E.J., et al., Bone mineral density in children and young adults with Crohn's disease. Inflamm Bowel Dis, 1999. 5(3): p. 161-6.

55. Gordon, R.J. and C.M. Gordon, Bone Health in Pediatric Patients with IBD: What Is New? Curr Osteoporos Rep, 2021. 19(4): p. 429-435.

56. Jin, H.Y., et al., Growth, puberty, and bone health in children and adolescents with inflammatory bowel disease. BMC Pediatr, 2021. 21(1): p. 35.

57. Schmidt, S., et al., Longitudinal assessment of bone mineral density in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr, 2012. 55(5): p. 511-8.

58. Sigurdsson, G.V., et al., Bone Mass Development from Childhood into Young Adulthood in Patients with Childhood-onset Inflammatory Bowel Disease. Inflamm Bowel Dis, 2017. 23(12): p. 2215-2226.

59. Semeao, E.J., et al., Risk factors for low bone mineral density in children and young adults with Crohn's disease. J Pediatr, 1999. 135(5): p. 593-600.

60. Lopes, L.H., et al., Risk factors for low bone mineral density in children and adolescents with inflammatory bowel disease. Dig Dis Sci, 2008. 53(10): p. 2746-53.

61. Aris, R.M., et al., Increased rate of fractures and severe kyphosis: sequelae of living into adulthood with cystic fibrosis. Ann Intern Med, 1998. 128(3): p. 186-93.

62. Anabtawi, A., et al., Cystic fibrosis bone disease: Pathophysiology, assessment and prognostic implications. J Cyst Fibros, 2019. 18 Suppl 2: p. S48-S55.

63. O'Reilly, R., et al., Severe bone demineralisation is associated with higher mortality in children with cystic fibrosis. Ir Med J, 2009. 102(2): p. 47-9.

64. Putman, M.S., et al., Cystic fibrosis bone disease treatment: Current knowledge and future directions. J Cyst Fibros, 2019. 18 Suppl 2: p. S56-S65.

65. Javier, R.M. and J. Jacquot, Bone disease in cystic fibrosis: what's new? Joint Bone Spine, 2011. 78(5): p. 445-50.

66. Sermet-Gaudelus, I., et al., Update on cystic fibrosis-related bone disease: a special focus on children. Paediatr Respir Rev, 2009. 10(3): p. 134-42.

67. Homchan, K., et al., Low bone mineral density and the severity of cholestasis in biliary atresia. World J Hepatol, 2017. 9(16): p. 746-751.

68. Honsawek, S., et al., Relationships between OPG, RANKL, bone metabolism, and bone mineral density in biliary atresia. Pediatr Surg Int, 2009. 25(3): p. 261-7.

69. Omran, A., et al., Sclerostin: From Molecule to Clinical Biomarker. Int J Mol Sci, 2022. 23(9).

70. Riggs, B.L., S. Khosla, and L.J. Melton, 3rd, Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev, 2002. 23(3): p. 279-302.

71. Tan, V.P., et al., Influence of physical activity on bone strength in children and adolescents: a systematic review and narrative synthesis. J Bone Miner Res, 2014. 29(10): p. 2161-81.

72. Mello, J.B., et al., Exercise in school Physical Education increase bone mineral content and density: Systematic review and meta-analysis. Eur J Sport Sci, 2022. 22(10): p. 1618-1629.

73. Mergler, S., et al., Epidemiology of low bone mineral density and fractures in children with severe cerebral palsy: a systematic review. Dev Med Child Neurol, 2009. 51(10): p. 773-8.

74. King, W., et al., Prevalence of reduced bone mass in children and adults with spastic quadriplegia. Dev Med Child Neurol, 2003. 45(1): p. 12-6.

75. Bianchi, M.L., et al., Bone mineral density and bone metabolism in Duchenne muscular dystrophy. Osteoporos Int, 2003. 14(9): p. 761-7.

76. Henderson, R.C., et al., Predicting low bone density in children and young adults with quadriplegic cerebral palsy. Dev Med Child Neurol, 2004. 46(6): p. 416-9.

77. Nazif, H., et al., Bone mineral density and insulin-like growth factor-1 in children with spastic cerebral palsy. Childs Nerv Syst, 2017. 33(4): p. 625-630.

78. Bothwell, J.E., et al., Vertebral fractures in boys with Duchenne muscular dystrophy. Clin Pediatr (Phila), 2003. 42(4): p. 353-6.

79. Soderpalm, A.C., et al., Low bone mineral density and decreased bone turnover in Duchenne muscular dystrophy. Neuromuscul Disord, 2007. 17(11-12): p. 919-28.

80. Perera, N., et al., Fracture in Duchenne Muscular Dystrophy: Natural History and Vitamin D Deficiency. J Child Neurol, 2016. 31(9): p. 1181-7.

81. Tian, C., et al., Bone health measures in glucocorticoid-treated ambulatory boys with Duchenne muscular dystrophy. Neuromuscul Disord, 2016. 26(11): p. 760-767.

82. Del Rocio Cruz-Guzman, O., et al., Muscle function and age are associated with loss of bone mineral density in Duchenne muscular dystrophy. Muscle Nerve, 2019. 59(4): p. 417-421.

83. Crabtree, N.J., et al., Regional changes in bone area and bone mineral content in boys with duchenne muscular dystrophy receiving corticosteroid therapy. J Pediatr, 2010. 156(3): p. 450-5.

84. Singh, A., E.K. Schaeffer, and C.W. Reilly, Vertebral Fractures in Duchenne Muscular Dystrophy Patients Managed With Deflazacort. J Pediatr Orthop, 2018. 38(6): p. 320-324.

85. Joseph, S., et al., Fractures and Linear Growth in a Nationwide Cohort of Boys With Duchenne Muscular Dystrophy With and Without Glucocorticoid Treatment: Results From the UK NorthStar Database. JAMA Neurol, 2019. 76(6): p. 701-709.

86. Guglieri, M., et al., Efficacy and Safety of Vamorolone vs Placebo and Prednisone Among Boys With Duchenne Muscular Dystrophy: A Randomized Clinical Trial. JAMA Neurol, 2022. 79(10): p. 1005-1014.

87. Rufo, A., et al., Mechanisms inducing low bone density in Duchenne muscular dystrophy in mice and humans. J Bone Miner Res, 2011. 26(8): p. 1891-903.

88. Wasserman, H.M., et al., Low bone mineral density and fractures are highly prevalent in pediatric patients with spinal muscular atrophy regardless of disease severity. Neuromuscul Disord, 2017. 27(4): p. 331-337.

89. Khatri, I.A., et al., Low bone mineral density in spinal muscular atrophy. J Clin Neuromuscul Dis, 2008. 10(1): p. 11-7.

90. Baranello, G., et al., Evolution of bone mineral density, bone metabolism and fragility fractures in Spinal Muscular Atrophy (SMA) types 2 and 3. Neuromuscul Disord, 2019. 29(7): p. 525-532.

91. Vai, S., et al., Bone and Spinal Muscular Atrophy. Bone, 2015. 79: p. 116-20.

92. Klein, G.L., et al., Long-term reduction in bone mass after severe burn injury in children. J Pediatr, 1995. 126(2): p. 252-6.

93. Klein, G.L., C.B. Langman, and D.N. Herndon, Vitamin D depletion following burn injury in children: a possible factor in post-burn osteopenia. J Trauma, 2002. 52(2): p. 346-50.

94. Drake, M.T. and S. Khosla, Hormonal and systemic regulation of sclerostin. Bone, 2017. 96: p. 8-17.

95. Soyka, L.A., W.P. Fairfield, and A. Klibanski, Clinical review 117: Hormonal determinants and disorders of peak bone mass in children. J Clin Endocrinol Metab, 2000. 85(11): p. 3951-63.

96. Gordon, C.M., et al., Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, 2017. 102(5): p. 1413-1439.

97. Misra, M., Effects of hypogonadism on bone metabolism in female adolescents and young adults. Nat Rev Endocrinol, 2012. 8(7): p. 395-404.

98. Tack, L.J., et al., Effects of Glucocorticoids on Bone: What we can Learn from Pediatric Endogenous Cushing's Syndrome. Horm Metab Res, 2016. 48(11): p. 764-770.

99. Ward, L.M., Glucocorticoid-Induced Osteoporosis: Why Kids Are Different. Front Endocrinol (Lausanne), 2020. 11: p. 576.

100. LeBlanc, C.M., et al., Incident Vertebral Fractures and Risk Factors in the First Three Years Following Glucocorticoid Initiation Among Pediatric Patients With Rheumatic Disorders. J Bone Miner Res, 2015. 30(9): p. 1667-75.

101. Ward, L.M., et al., Osteoporotic Fractures and Vertebral Body Reshaping in Children With Glucocorticoid-treated Rheumatic Disorders. J Clin Endocrinol Metab, 2021. 106(12): p. e5195-e5207.

102. Lee, H.S., et al., Low Bone Mineral Density at Initial Diagnosis in Children and Adolescents with Graves' Disease. J Clin Densitom, 2021. 24(2): p. 275-280.

103. Numbenjapon, N., et al., Low cortical bone density measured by computed tomography in children and adolescents with untreated hyperthyroidism. J Pediatr, 2007. 150(5): p. 527-30.

104. Mora, S., et al., Longitudinal changes of bone density and bone resorption in hyperthyroid girls during treatment. J Bone Miner Res, 1999. 14(11): p. 1971-7.

105. Lakatos, P., et al., Serum interleukin-6 and bone metabolism in patients with thyroid function disorders. J Clin Endocrinol Metab, 1997. 82(1): p. 78-81.

106. Dekker, B.L., et al., Bone Mineral Density in Adult Survivors of Pediatric Differentiated Thyroid Carcinoma: A Longitudinal Follow-Up Study. Thyroid, 2021. 31(11): p. 1707-1714.

107. Lewiecki, E.M. and P.D. Miller, Skeletal effects of primary hyperparathyroidism: bone mineral density and fracture risk. J Clin Densitom, 2013. 16(1): p. 28-32.

108. Wuster, C., Fracture rates in patients with growth hormone deficiency. Horm Res, 2000. 54 Suppl 1: p. 31-5.

109. Vestergaard, P., et al., Fracture risk is increased in patients with GH deficiency or untreated prolactinomas--a case-control study. Clin Endocrinol (Oxf), 2002. 56(2): p. 159-67.

110. Hogler, W. and N. Shaw, Childhood growth hormone deficiency, bone density, structures and fractures: scrutinizing the evidence. Clin Endocrinol (Oxf), 2010. 72(3): p. 281-9.

111. Gahlot, M., et al., The effect of growth hormone deficiency on size-corrected bone mineral measures in pre-pubertal children. Osteoporos Int, 2012. 23(8): p. 2211-7.

112. Baer, T.G., et al., Deficits in Bone Geometry in Growth Hormone-Deficient Prepubertal Boys Revealed by High-Resolution Peripheral Quantitative Computed Tomography. Horm Res Paediatr, 2019. 92(5): p. 293-301.

113. Misra, M., et al., Alterations in growth hormone secretory dynamics in adolescent girls with anorexia nervosa and effects on bone metabolism. J Clin Endocrinol Metab, 2003. 88(12): p. 5615-23.

114. Dongare-Bhor, S., et al., Muscle and bone parameters in underprivileged Indian children and adolescents with T1DM. Bone, 2020. 130: p. 115074.

115. Wierzbicka, E., et al., Skeletal Status, Body Composition, and Glycaemic Control in Adolescents with Type 1 Diabetes Mellitus. J Diabetes Res, 2018. 2018: p. 8121634.

116. Mitchell, D.M., et al., Elevated HbA1c Is Associated with Altered Cortical and Trabecular Microarchitecture in Girls with Type 1 Diabetes. J Clin Endocrinol Metab, 2020. 105(4): p. e1648-56.

117. Weber, D.R., et al., Poor Glycemic Control Is Associated With Impaired Bone Accrual in the Year Following a Diagnosis of Type 1 Diabetes. J Clin Endocrinol Metab, 2019. 104(10): p. 4511-4520.

118. Napoli, N., et al., Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol, 2017. 13(4): p. 208-219.

119. Meyer, H.J., et al., Bone mineral density in patients with systemic mastocytosis: correlations with clinical and histopathological features. Clin Exp Rheumatol, 2021. 39(1): p. 52-57.

120. Rossini, M., et al., Bone mineral density, bone turnover markers and fractures in patients with indolent systemic mastocytosis. Bone, 2011. 49(4): p. 880-5.

121. Inaba, H., et al., Bone mineral density in children with acute lymphoblastic leukemia. Cancer, 2018. 124(5): p. 1025-1035.

122. Ghassemi, A., et al., Evaluation of Bone Mineral Density in Children with Acute Lymphoblastic Leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL): Chemotherapy with/without Radiotherapy. Int J Hematol Oncol Stem Cell Res, 2016. 10(3): p. 153-60.

123. Ward, L.M., et al., Bone Morbidity and Recovery in Children With Acute Lymphoblastic Leukemia: Results of a Six-Year Prospective Cohort Study. J Bone Miner Res, 2018. 33(8): p. 1435-1443.

124. Vogiatzi, M.G., et al., Low bone mineral density in adolescents with beta-thalassemia. Ann N Y Acad Sci, 2005. 1054: p. 462-6.

125. Mirhosseini, N.Z., et al., Bone-related complications of transfusion-dependent beta thalassemia among children and adolescents. J Bone Miner Metab, 2013. 31(4): p. 468-76.

126. Karimi, M., et al., Bone mineral density in beta-thalassemia major and intermedia. Indian Pediatr, 2007. 44(1): p. 29-32.

127. Lal, A., et al., Bone mineral density in children with sickle cell anemia. Pediatr Blood Cancer, 2006. 47(7): p. 901-6.

128. Miller, R.G., et al., High prevalence and correlates of low bone mineral density in young adults with sickle cell disease. Am J Hematol, 2006. 81(4): p. 236-41.

129. Adesina, O.O., et al., Height-corrected low bone density associates with severe outcomes in sickle cell disease: SCCRIP cohort study results. Blood Adv, 2019. 3(9): p. 1476-1488.

130. Giordano, P., et al., Mechanisms of Bone Impairment in Sickle Bone Disease. Int J Environ Res Public Health, 2021. 18(4).

131. Wesseling-Perry, K. and I.B. Salusky, Chronic kidney disease: mineral and bone disorder in children. Semin Nephrol, 2013. 33(2): p. 169-79.

132. Meza, K., et al., Tumor necrosis factor-alpha is associated with mineral bone disorder and growth impairment in children with chronic kidney disease. Pediatr Nephrol, 2021. 36(6): p. 1579-1587.

133. Santos, F., et al., Bone Disease in CKD in Children. Calcif Tissue Int, 2021. 108(4): p. 423-438.

134. Valsamis, H.A., et al., Antiepileptic drugs and bone metabolism. Nutr Metab (Lond), 2006. 3: p. 36.

135. Weng, W., H. Li, and S. Zhu, An Overlooked Bone Metabolic Disorder: Cigarette Smoking-Induced Osteoporosis. Genes (Basel), 2022. 13(5).

136. Cheraghi, Z., et al., The effect of alcohol on osteoporosis: A systematic review and meta-analysis. Drug Alcohol Depend, 2019. 197: p. 197-202.

137. Gaddini, G.W., et al., Alcohol: A Simple Nutrient with Complex Actions on Bone in the Adult Skeleton. Alcohol Clin Exp Res, 2016. 40(4): p. 657-71.

138. Binkovitz, L.A. and M.J. Henwood, Pediatric DXA: technique and interpretation. Pediatr Radiol, 2007. 37(1): p. 21-31.

139. Weber, D.R., et al., The Utility of DXA Assessment at the Forearm, Proximal Femur, and Lateral Distal Femur, and Vertebral Fracture Assessment in the Pediatric Population: 2019 ISCD Official Position. J Clin Densitom, 2019. 22(4): p. 567-589.

140. Zemel, B.S., et al., Revised reference curves for bone mineral content and areal bone mineral density according to age and sex for black and non-black children: results of the bone mineral density in childhood study. J Clin Endocrinol Metab, 2011. 96(10): p. 3160-9.

141. Zemel, B.S., et al., Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. J Clin Endocrinol Metab, 2010. 95(3): p. 1265-73.

142. Kalkwarf, H.J., et al., Trabecular Bone Score Reference Values for Children and Adolescents According to Age, Sex, and Ancestry. J Bone Miner Res, 2022. 37(4): p. 776-785.

143. Crabtree, N.J., et al., Vertebral fractures assessment in children: Evaluation of DXA imaging versus conventional spine radiography. Bone, 2017. 97: p. 168-174.

144. Boskey, A.L., Bone composition: relationship to bone fragility and antiosteoporotic drug effects. Bonekey Rep, 2013. 2: p. 447.

145. Matkovic, V. and R.P. Heaney, Calcium balance during human growth: evidence for threshold behavior. Am J Clin Nutr, 1992. 55(5): p. 992-6.

146. Greer, F.R., N.F. Krebs, and N. American Academy of Pediatrics Committee on, Optimizing bone health and calcium intakes of infants, children, and adolescents. Pediatrics, 2006. 117(2): p. 578-85.

147. Ross, A.C. and Institute of Medicine (U. S.). Committee to Review Dietary Reference Intakes for Vitamin D and Calcium., Dietary reference intakes : calcium, vitamin D. 2011, Washington, DC: National Academies Press. xv, 536, 1075-1115 p.

148. Priemel, M., et al., Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res, 2010. 25(2): p. 305-12.

149. Holick, M.F., et al., Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, 2011. 96(7): p. 1911-30.

150. Pappa, H.M., R.J. Grand, and C.M. Gordon, Report on the vitamin D status of adult and pediatric patients with inflammatory bowel disease and its significance for bone health and disease. Inflamm Bowel Dis, 2006. 12(12): p. 1162-74.

151. Tangpricha, V., et al., An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab, 2012. 97(4): p. 1082-93.

152. Sacheck, J.M., et al., Impact of Three Doses of Vitamin D3 on Serum 25(OH)D Deficiency and Insufficiency in At-Risk Schoolchildren. J Clin Endocrinol Metab, 2017. 102(12): p. 4496-4505.

153. Huybers, S., et al., Prednisolone-induced Ca2+ malabsorption is caused by diminished expression of the epithelial Ca2+ channel TRPV6. Am J Physiol Gastrointest Liver Physiol, 2007. 292(1): p. G92-7.

154. Roizen, J.D., et al., CYP3A4 mutation causes vitamin D-dependent rickets type 3. J Clin Invest, 2018. 128(5): p. 1913-1918.

155. Johnston, C.C., Jr., et al., Calcium supplementation and increases in bone mineral density in children. N Engl J Med, 1992. 327(2): p. 82-7.

156. Bonjour, J.P., et al., Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. J Clin Invest, 1997. 99(6): p. 1287-94.

157. Slemenda, C.W., et al., Reduced rates of skeletal remodeling are associated with increased bone mineral density during the development of peak skeletal mass. J Bone Miner Res, 1997. 12(4): p. 676-82.

158. Bonjour, J.P., et al., Gain in bone mineral mass in prepubertal girls 3.5 years after discontinuation of calcium supplementation: a follow-up study. Lancet, 2001. 358(9289): p. 1208-12.

159. Chevalley, T., et al., Skeletal site selectivity in the effects of calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys. J Clin Endocrinol Metab, 2005. 90(6): p. 3342-9.

160. Matkovic, V., et al., Calcium supplementation and bone mineral density in females from childhood to young adulthood: a randomized controlled trial. Am J Clin Nutr, 2005. 81(1): p. 175-88.

161. Winzenberg, T., et al., Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. BMJ, 2011. 342: p. c7254.

162. Zhu, K., et al., Growth, bone mass, and vitamin D status of Chinese adolescent girls 3 y after withdrawal of milk supplementation. Am J Clin Nutr, 2006. 83(3): p. 714-21.

163. Bailey, D.A., et al., A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study. J Bone Miner Res, 1999. 14(10): p. 1672-9.

164. Janz, K.F., et al., Everyday activity predicts bone geometry in children: the iowa bone development study. Med Sci Sports Exerc, 2004. 36(7): p. 1124-31.

165. Farr, J.N., et al., Associations of physical activity duration, frequency, and load with volumetric BMD, geometry, and bone strength in young girls. Osteoporos Int, 2011. 22(5): p. 1419-30.

166. McKay, H., et al., Physical activity positively predicts bone architecture and bone strength in adolescent males and females. Acta Paediatr, 2011. 100(1): p. 97-101.

167. Gabel, L., et al., Physical Activity, Sedentary Time, and Bone Strength From Childhood to Early Adulthood: A Mixed Longitudinal HR-pQCT study. J Bone Miner Res, 2017. 32(7): p. 1525-1536.

168. Baxter-Jones, A.D., et al., A longitudinal study of the relationship of physical activity to bone mineral accrual from adolescence to young adulthood. Bone, 2008. 43(6): p. 1101-7.

169. Erlandson, M.C., et al., Higher premenarcheal bone mass in elite gymnasts is maintained into young adulthood after long-term retirement from sport: a 14-year follow-up. J Bone Miner Res, 2012. 27(1): p. 104-10.

170. Behringer, M., et al., Effects of weight-bearing activities on bone mineral content and density in children and adolescents: a meta-analysis. J Bone Miner Res, 2014. 29(2): p. 467-78.

171. Courteix, D., et al., Cumulative effects of calcium supplementation and physical activity on bone accretion in premenarchal children: a double-blind randomised placebo-controlled trial. Int J Sports Med, 2005. 26(5): p. 332-8.

172. Bass, S.L., et al., Exercise and calcium combined results in a greater osteogenic effect than either factor alone: a blinded randomized placebo-controlled trial in boys. J Bone Miner Res, 2007. 22(3): p. 458-64.

173. Deere, K., et al., A cross-sectional study of the relationship between cortical bone and high-impact activity in young adult males and females. J Clin Endocrinol Metab, 2012. 97(10): p. 3734-43.

174. Mitchell, J.A., et al., Physical Activity Benefits the Skeleton of Children Genetically Predisposed to Lower Bone Density in Adulthood. J Bone Miner Res, 2016. 31(8): p. 1504-12.

175. Caulton, J.M., et al., A randomised controlled trial of standing programme on bone mineral density in non-ambulant children with cerebral palsy. Arch Dis Child, 2004. 89(2): p. 131-5.

176. Chad, K.E., et al., The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. J Pediatr, 1999. 135(1): p. 115-7.

177. Swolin-Eide, D. and P. Magnusson, Does Whole-Body Vibration Treatment Make Children's Bones Stronger? Curr Osteoporos Rep, 2020. 18(5): p. 471-479.

178. Ward, K., et al., Low magnitude mechanical loading is osteogenic in children with disabling conditions. J Bone Miner Res, 2004. 19(3): p. 360-9.

179. Ruck, J., G. Chabot, and F. Rauch, Vibration treatment in cerebral palsy: A randomized controlled pilot study. J Musculoskelet Neuronal Interact, 2010. 10(1): p. 77-83.

180. Wren, T.A., et al., Effect of high-frequency, low-magnitude vibration on bone and muscle in children with cerebral palsy. J Pediatr Orthop, 2010. 30(7): p. 732-8.

181. El-Shamy, S.M., Effect of whole-body vibration on muscle strength and balance in diplegic cerebral palsy: a randomized controlled trial. Am J Phys Med Rehabil, 2014. 93(2): p. 114-21.

182. Saquetto, M., et al., The effects of whole body vibration on mobility and balance in children with cerebral palsy: a systematic review with meta-analysis. J Musculoskelet Neuronal Interact, 2015. 15(2): p. 137-44.

183. Bianchi, M.L., et al., Low-Intensity Vibration Protects the Weight-Bearing Skeleton and Suppresses Fracture Incidence in Boys With Duchenne Muscular Dystrophy: A Prospective, Randomized, Double-Blind, Placebo-Controlled Clinical Trial. JBMR Plus, 2022. 6(11): p. e10685.

184. Soderpalm, A.C., et al., Whole body vibration therapy in patients with Duchenne muscular dystrophy--a prospective observational study. J Musculoskelet Neuronal Interact, 2013. 13(1): p. 13-8.

185. Petryk, A., et al., Feasibility and tolerability of whole-body, low-intensity vibration and its effects on muscle function and bone in patients with dystrophinopathies: a pilot study. Muscle Nerve, 2017. 55(6): p. 875-883.

186. Hoyer-Kuhn, H., et al., A specialized rehabilitation approach improves mobility in children with osteogenesis imperfecta. J Musculoskelet Neuronal Interact, 2014. 14(4): p. 445-53.

187. Hogler, W., et al., The Effect of Whole Body Vibration Training on Bone and Muscle Function in Children With Osteogenesis Imperfecta. J Clin Endocrinol Metab, 2017. 102(8): p. 2734-2743.

188. Matute-Llorente, A., et al., Effect of whole-body vibration training on bone mass in adolescents with and without Down syndrome: a randomized controlled trial. Osteoporos Int, 2016. 27(1): p. 181-91.

189. Ward, L.M., Part 2: When Should Bisphosphonates Be Used in Children with Chronic Illness Osteoporosis? Curr Osteoporos Rep, 2021. 19(3): p. 289-297.

190. Bishop, N., et al., Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2013 Pediatric Official Positions. J Clin Densitom, 2014. 17(2): p. 275-80.

191. Simm, P.J., et al., Consensus guidelines on the use of bisphosphonate therapy in children and adolescents. J Paediatr Child Health, 2018. 54(3): p. 223-233.

192. LeBoff, M.S., et al., The clinician's guide to prevention and treatment of osteoporosis. Osteoporos Int, 2022. 33(10): p. 2049-2102.

193. Larson, C.M. and R.C. Henderson, Bone mineral density and fractures in boys with Duchenne muscular dystrophy. J Pediatr Orthop, 2000. 20(1): p. 71-4.

194. Yildiz, S., et al., Retrospective Analysis of Fractures and Factors Causing Ambulation Loss After Lower Limb Fractures in Duchenne Muscular Dystrophy. Am J Phys Med Rehabil, 2020. 99(9): p. 789-794.

195. Nasomyont, N., L.N. Hornung, and H. Wasserman, Intravenous bisphosphonate therapy in children with spinal muscular atrophy. Osteoporos Int, 2020. 31(5): p. 995-1000.

196. DeBoer, M.D., et al., Increases in IGF-1 After Anti-TNF-alpha Therapy Are Associated With Bone and Muscle Accrual in Pediatric Crohn Disease. J Clin Endocrinol Metab, 2018. 103(3): p. 936-945.

197. Drake, M.T., B.L. Clarke, and S. Khosla, Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc, 2008. 83(9): p. 1032-45.

198. Papapoulos, S.E. and S.C. Cremers, Prolonged bisphosphonate release after treatment in children. N Engl J Med, 2007. 356(10): p. 1075-6.

199. Cremers, S.C., G. Pillai, and S.E. Papapoulos, Pharmacokinetics/pharmacodynamics of bisphosphonates: use for optimisation of intermittent therapy for osteoporosis. Clin Pharmacokinet, 2005. 44(6): p. 551-70.

200. Ward, L.M., et al., Alendronate for the treatment of pediatric osteogenesis imperfecta: a randomized placebo-controlled study. J Clin Endocrinol Metab, 2011. 96(2): p. 355-64.

201. Houston, C., K. Mathews, and A. Shibli-Rahhal, Bone density and alendronate effects in Duchenne muscular dystrophy patients. Muscle Nerve, 2014. 49(4): p. 506-11.

202. Ward, L.M., et al., Single-dose pharmacokinetics and tolerability of alendronate 35- and 70-milligram tablets in children and adolescents with osteogenesis imperfecta type I. J Clin Endocrinol Metab, 2005. 90(7): p. 4051-6.

203. Seikaly, M.G., et al., Impact of alendronate on quality of life in children with osteogenesis imperfecta. J Pediatr Orthop, 2005. 25(6): p. 786-91.

204. Dimeglio, L.A., et al., A comparison of oral and intravenous bisphosphonate therapy for children with osteogenesis imperfecta. J Pediatr Endocrinol Metab, 2005. 18(1): p. 43-53.

205. Rudge, S., et al., Effects of once-weekly oral alendronate on bone in children on glucocorticoid treatment. Rheumatology (Oxford), 2005. 44(6): p. 813-8.

206. Bianchi, M.L., et al., Efficacy and safety of alendronate for the treatment of osteoporosis in diffuse connective tissue diseases in children: a prospective multicenter study. Arthritis Rheum, 2000. 43(9): p. 1960-6.

207. Hawker, G.A., et al., Alendronate in the treatment of low bone mass in steroid-treated boys with Duchennes muscular dystrophy. Arch Phys Med Rehabil, 2005. 86(2): p. 284-8.

208. Tian, C., et al., Oral bisphosphonate treatment in patients with Duchenne muscular dystrophy on long term glucocorticoid therapy. Neuromuscul Disord, 2020. 30(7): p. 599-610.

209. Paksu, M.S., et al., Osteopenia in children with cerebral palsy can be treated with oral alendronate. Childs Nerv Syst, 2012. 28(2): p. 283-6.

210. Bianchi, M.L., et al., Treatment of low bone density in young people with cystic fibrosis: a multicentre, prospective, open-label observational study of calcium and calcifediol followed by a randomised placebo-controlled trial of alendronate. Lancet Respir Med, 2013. 1(5): p. 377-85.

211. MacDonald, P., et al., Safety and Efficacy of Alendronate to Treat Osteopenia in Children During Therapy for Acute Lymphoblastic Leukemia: A Retrospective Cohort Study of Sequential Outcomes. J Pediatr Hematol Oncol, 2023. 45(4): p. 200-206.

212. Gilchrist, N.L., et al., Alendronate prevents bone loss in patients with acute spinal cord injury: a randomized,

double-blind, placebo-controlled study. J Clin Endocrinol Metab, 2007. 92(4): p. 1385-90.

213. El-Husseini, A.A., et al., Treatment of osteopenia and osteoporosis in renal transplant children and adolescents. Pediatr Transplant, 2004. 8(4): p. 357-61.

214. Bishop, N., et al., Risedronate in children with osteogenesis imperfecta: a randomised, double-blind, placebo-controlled trial. Lancet, 2013. 382(9902): p. 1424-32.

215. Rauch, F., et al., Risedronate in the treatment of mild pediatric osteogenesis imperfecta: a randomized placebo-controlled study. J Bone Miner Res, 2009. 24(7): p. 1282-9.

216. Bishop, N., et al., A randomized, controlled dose-ranging study of risedronate in children with moderate and severe osteogenesis imperfecta. J Bone Miner Res, 2010. 25(1): p. 32-40.

217. Srinivasan, R., et al., Prophylactic oral bisphosphonate therapy in duchenne muscular dystrophy. Muscle Nerve, 2016. 54(1): p. 79-85.

218. Iwasaki, T., et al., Secondary osteoporosis in long-term bedridden patients with cerebral palsy. Pediatr Int, 2008. 50(3): p. 269-75.

219. Cohran, V., et al., Oral risedronate sodium improves bone mineral density in non-ambulatory patients: a randomized, double-blind, placebo controlled trial. J Pediatr Rehabil Med, 2013. 6(2): p. 85-93.

220. Rauch, F., et al., Osteogenesis imperfecta types I, III, and IV: effect of pamidronate therapy on bone and mineral metabolism. J Clin Endocrinol Metab, 2003. 88(3): p. 986-92.

221. Glorieux, F.H., et al., Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. N Engl J Med, 1998. 339(14): p. 947-52.

222. Plotkin, H., et al., Pamidronate treatment of severe osteogenesis imperfecta in children under 3 years of age. J Clin Endocrinol Metab, 2000. 85(5): p. 1846-50.

223. Acott, P.D., et al., Pamidronate treatment of pediatric fracture patients on chronic steroid therapy. Pediatr Nephrol, 2005. 20(3): p. 368-73.

224. Bachrach, S.J., et al., Decreased fracture incidence after 1 year of pamidronate treatment in children with spastic quadriplegic cerebral palsy. Dev Med Child Neurol, 2010. 52(9): p. 837-42.

225. Henderson, R.C., et al., Bisphosphonates to treat osteopenia in children with quadriplegic cerebral palsy: a randomized, placebo-controlled clinical trial. J Pediatr, 2002. 141(5): p. 644-51.

226. Plotkin, H., et al., Low doses of pamidronate to treat osteopenia in children with severe cerebral palsy: a pilot study. Dev Med Child Neurol, 2006. 48(9): p. 709-12.

227. Goldbloom, E.B., E.A. Cummings, and M. Yhap, Osteoporosis at presentation of childhood ALL: management with pamidronate. Pediatr Hematol Oncol, 2005. 22(7): p. 543-50.

228. Baroncelli, G.I., et al., Pamidronate treatment stimulates the onset of recovery phase reducing fracture rate and skeletal deformities in patients with idiopathic juvenile osteoporosis: comparison with untreated patients. J Bone Miner Metab, 2013. 31(5): p. 533-43.

229. Klein, G.L., et al., The efficacy of acute administration of pamidronate on the conservation of bone mass following severe burn injury in children: a double-blind, randomized, controlled study. Osteoporos Int, 2005. 16(6): p. 631-5.

230. Barros, E.R., et al., Safety and efficacy of a 1-year treatment with zoledronic acid compared with pamidronate in children with osteogenesis imperfecta. J Pediatr Endocrinol Metab, 2012. 25(5-6): p. 485-91.

231. Ooi, H.L., et al., Zoledronic acid improves bone mineral density in pediatric spinal cord injury. J Bone Miner Res, 2012. 27(7): p. 1536-40.

232. Li, L.J., et al., Effects of zoledronic acid on vertebral shape of children and adolescents with osteogenesis imperfecta. Bone, 2019. 127: p. 164-171.

233. Saraff, V., et al., Efficacy and treatment costs of zoledronate versus pamidronate in paediatric osteoporosis. Arch Dis Child, 2018. 103(1): p. 92-94.

234. Vuorimies, I., et al., Zoledronic acid treatment in children with osteogenesis imperfecta. Horm Res Paediatr, 2011. 75(5): p. 346-53.

235. Brown, J.J. and M.R. Zacharin, Safety and efficacy of intravenous zoledronic acid in paediatric osteoporosis. J Pediatr Endocrinol Metab, 2009. 22(1): p. 55-63.

236. Ward, L.M., et al., Zoledronic Acid vs Placebo in Pediatric Glucocorticoid-induced Osteoporosis: A Randomized, Double-blind, Phase 3 Trial. J Clin Endocrinol Metab, 2021. 106(12): p. e5222-e5235.

237. Zacharin, M., et al., Randomized Controlled Trial Evaluating the Use of Zoledronic Acid in Duchenne Muscular Dystrophy. J Clin Endocrinol Metab, 2021. 106(8): p. 2328-2342.

238. Granild-Jensen, J.B., et al., Cerebral palsy and bisphosphonates - and what can be learned from other types of secondary osteoporosis in children: A scoping review. Acta Paediatr, 2023. 112(4): p. 617-629.

239. Wiedemann, A., et al., Annual Injection of Zoledronic Acid Improves Bone Status in Children with Cerebral Palsy and Rett Syndrome. Calcif Tissue Int, 2019. 104(4): p. 355-363.

240. Gatti, D., et al., Intravenous neridrate in children with osteogenesis imperfecta: a randomized controlled study. J Bone Miner Res, 2005. 20(5): p. 758-63.

241. Maines, E., et al., Children and adolescents treated with neridrate for osteogenesis imperfecta show no evidence of any osteonecrosis of the jaw. J Bone Miner Metab, 2012. 30(4): p. 434-8.

242. Celli, M., et al., Clinical and biochemical response to neridrate treatment in a patient with osteoporosis-pseudoglioma syndrome (OPPG). Osteoporos Int, 2017. 28(11): p. 3277-3280.

243. Adami, S., et al., Intravenous neridronate in adults with osteogenesis imperfecta. J Bone Miner Res, 2003. 18(1): p. 126-30.

244. Gatti, D., et al., Intravenous bisphosphonate therapy increases radial width in adults with osteogenesis imperfecta. J Bone Miner Res, 2005. 20(8): p. 1323-6.

245. Dwan, K., et al., Bisphosphonate therapy for osteogenesis imperfecta. Cochrane Database Syst Rev, 2016. 10(10): p. CD005088.

246. Rauch, F., et al., The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. J Clin Invest, 2002. 110(9): p. 1293-9.

247. Black, D.M., et al., Bone mineral density as a surrogate biomarker for fracture risk reduction - Authors' reply. Lancet Diabetes Endocrinol, 2020. 8(11): p. 876.

248. Nasomyont, N., et al., The effect of oral bisphosphonate therapy on vertebral morphometry and fractures in patients with Duchenne muscular dystrophy and glucocorticoid-induced osteoporosis. Muscle Nerve, 2021. 64(6): p. 710-716.

249. Ward, L.M., V.N. Konji, and J. Ma, The management of osteoporosis in children. Osteoporos Int, 2016. 27(7): p. 2147-2179.

250. DiMeglio, L.A. and M. Peacock, Two-year clinical trial of oral alendronate versus intravenous pamidronate in children with osteogenesis imperfecta. J Bone Miner Res, 2006. 21(1): p. 132-40.

251. Loizidou, A., S. Andronikou, and C.P. Burren, Pamidronate "zebra lines": A treatment timeline. Radiol Case Rep, 2017. 12(4): p. 850-853.

252. Rauch, F., et al., Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta. Bone, 2007. 40(4): p. 821-7.

253. Biggin, A., et al., Fracture during intravenous bisphosphonate treatment in a child with osteogenesis imperfecta: an argument for a more frequent, low-dose treatment regimen. Horm Res Paediatr, 2014. 81(3): p. 204-10.

254. Sbrocchi, A.M., et al., The use of intravenous bisphosphonate therapy to treat vertebral fractures due to osteoporosis among boys with Duchenne muscular dystrophy. Osteoporos Int, 2012. 23(11): p. 2703-11.

255. George, S., et al., Short-Term Safety of Zoledronic Acid in Young Patients With Bone Disorders: An Extensive Institutional Experience. J Clin Endocrinol Metab, 2015. 100(11): p. 4163-71.

256. Munns, C.F., et al., Acute phase response and mineral status following low dose intravenous zoledronic acid in children. Bone, 2007. 41(3): p. 366-70.

257. Srivastava, T., et al., Serum 25-hydroxyvitamin D level and acute-phase reaction following initial intravenous bisphosphonate. J Bone Miner Res, 2011. 26(2): p. 437-8.

258. Nasomyont, N., et al., Outcomes following intravenous bisphosphonate infusion in pediatric patients: A 7-year retrospective chart review. Bone, 2019. 121: p. 60-67.

259. Viollet, L., et al., Utility of cystatin C to monitor renal function in Duchenne muscular dystrophy. Muscle Nerve, 2009. 40(3): p. 438-42.

260. Munns, C.F., et al., Delayed osteotomy but not fracture healing in pediatric osteogenesis imperfecta patients receiving pamidronate. J Bone Miner Res, 2004. 19(11): p. 1779-86.

261. Starr, J., Y.K.D. Tay, and E. Shane, Current Understanding of Epidemiology, Pathophysiology, and Management of Atypical Femur Fractures. Curr Osteoporos Rep, 2018. 16(4): p. 519-529.

262. Vuorimies, I., et al., Bisphosphonate Treatment and the Characteristics of Femoral Fractures in Children With Osteogenesis Imperfecta. J Clin Endocrinol Metab, 2017. 102(4): p. 1333-1339.

263. Trejo, P., et al., Diaphyseal Femur Fractures in Osteogenesis Imperfecta: Characteristics and Relationship With Bisphosphonate Treatment. J Bone Miner Res, 2017. 32(5): p. 1034-1039.

264. Boyce, A.M., et al., A Subtrochanteric Femoral Stress Fracture following Bisphosphonate Treatment in an Adolescent Girl. Horm Res Paediatr, 2017. 87(1): p. 69-72.

265. Neal, T.W. and T. Schlieve, Medication-Related Osteonecrosis of the Jaws in the Pediatric Population. J Oral Maxillofac Surg, 2022. 80(10): p. 1686-1690.

266. Brown, J.J., L. Ramalingam, and M.R. Zacharin, Bisphosphonate-associated osteonecrosis of the jaw: does it occur in children? Clin Endocrinol (Oxf), 2008. 68(6): p. 863-7.

267. Whyte, M.P., et al., Bisphosphonate-induced osteopetrosis. N Engl J Med, 2003. 349(5): p. 457-63.

268. Whyte, M.P., et al., Drug-induced osteopetrosis. Bone, 2023. 173: p. 116788.

269. Levy, S., et al., Pregnancy outcome following in utero exposure to bisphosphonates. Bone, 2009. 44(3): p. 428-30.

270. Tsourdi, E., et al., Fracture risk and management of discontinuation of denosumab therapy: a systematic review and position statement by ECTS. J Clin Endocrinol Metab, 2020.

271. Kim, A.S., C.M. Girgis, and M.M. McDonald, Osteoclast Recycling and the Rebound Phenomenon Following Denosumab Discontinuation. Curr Osteoporos Rep, 2022. 20(6): p. 505-515.

272. Gossai, N., et al., Critical hypercalcemia following discontinuation of denosumab therapy for metastatic giant cell tumor of bone. Pediatr Blood Cancer, 2015. 62(6): p. 1078-80.

273. Setsu, N., et al., Severe hypercalcemia following denosumab treatment in a juvenile patient. J Bone Miner Metab, 2016. 34(1): p. 118-22.

274. Trejo, P., F. Rauch, and L. Ward, Hypercalcemia and hypercalciuria during denosumab treatment in children with osteogenesis imperfecta type VI. J Musculoskelet Neuronal Interact, 2018. 18(1): p. 76-80.

275. Uday, S., et al., Osteonecrosis of the Jaw and Rebound Hypercalcemia in Young People Treated With Denosumab for Giant Cell Tumor of Bone. J Clin Endocrinol Metab, 2018. 103(2): p. 596-603.

276. Seale, E., et al., Mitigating the Denosumab-Induced Rebound Phenomenon with Alternating Short- and Long-Acting Anti-resorptive Therapy in a Young Boy with Severe OI Type VI. Calcif Tissue Int, 2023. 112(5): p. 613-620.

277. Semler, O., et al., First use of the RANKL antibody denosumab in osteogenesis imperfecta type VI. J Musculoskelet Neuronal Interact, 2012. 12(3): p. 183-8.

278. Ward, L., et al., Osteogenesis Imperfecta Type VI in Individuals from Northern Canada. Calcif Tissue Int, 2016. 98(6): p. 566-72.

279. Chawla, S., et al., Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. Lancet Oncol, 2013. 14(9): p. 901-8.

280. Ferriero, K., et al., Case Report: Safety and Efficacy of Denosumab in Four Children With Noonan Syndrome With Multiple Giant Cell Lesions of the Jaw. Front Pediatr, 2020. 8: p. 515.

281. Vanderniet, J.A., et al., Denosumab for central giant cell granuloma in an Australian tertiary paediatric centre. Bone, 2022. 159: p. 116395.

282. Jacobsen, C.M., Application of anti-Sclerostin therapy in non-osteoporosis disease models. Bone, 2017. 96: p. 18-23.

283. Ward, L.M. and F. Rauch, Anabolic Therapy for the Treatment of Osteoporosis in Childhood. Curr Osteoporos Rep, 2018. 16(3): p. 269-276.

284. McClung, M.R. and A. Grauer, Romosozumab in postmenopausal women with osteopenia. N Engl J Med, 2014. 370(17): p. 1664-5.

285. Cosman, F., et al., Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med, 2016. 375(16): p. 1532-1543.

286. Glorieux, F.H., et al., BPS804 Anti-Sclerostin Antibody in Adults With Moderate Osteogenesis Imperfecta: Results of a Randomized Phase 2a Trial. J Bone Miner Res, 2017. 32(7): p. 1496-1504.

287. Nasomyont, N., et al., Safety and efficacy of teriparatide treatment for severe osteoporosis in patients with Duchenne muscular dystrophy. Osteoporos Int, 2020. 31(12): p. 2449-2459.

288. Black, D.M., et al., One year of alendronate after one year of parathyroid hormone (1-84) for osteoporosis. N Engl J Med, 2005. 353(6): p. 555-65.

289. Leder, B.Z., et al., Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab, 2009. 94(8): p. 2915-21.