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Review

Pediatric osteoporosis: An update

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ABSTRACT

The diagnosis of childhood osteoporosis is relatively straightforward in primary bone diseases. However, in chronic diseases that can cause osteoporosis, the focus is often on primary treatment, and the risk of osteoporosis is frequently overlooked. Primary bone disease typically presents in infancy or early childhood with multiple fractures of long bones, abnormalities of the sclera or teeth, and an associated family history. On the other hand, secondary osteoporosis is associated with underlying chronic disease and long-term use of medications for these conditions. It may present with vertebral fractures as the only sign. Clinicians must be vigilant in diagnosing it due to its more insidious course. Once diagnosed, diet and lifestyle changes should be made. Also, any vitamin and mineral deficiencies should be replaced. The next step will be the identification of patients who are suitable for medical treatment. In some cases, patients with multiple bone deformities may require corrective surgery. Children diagnosed with osteoporosis should be monitored by a pediatric bone specialist, and their treatment should be coordinated by a multidisciplinary team.

Keywords: osteoporosis, osteogenesis imperfecta, management, treatment, bisphosphonates

INTRODUCTION

Osteoporosis is typically distinguished by a decrease in bone mineral density and the deterioration of bone tissue, leading to an increased probability of fracture and bone deformities.[1] Osteoporosis is a significant health concern among the elderly; however, it is often overlooked in childhood. It is essential to understand how to promote and maintain optimal bone mass from infancy through adulthood.[2]

Bone Development and Pathophysiology of Osteoporosis

Bone mass is regulated through the coordination of osteoblasts, which form new bone tissue; osteoclasts, which cause bone resorption; and osteocytes, which regulate the activity of osteoblasts and osteoclasts in response to mechanical stimuli and aid in bone formation. Bone mineralization commences in the fetal period and attains its peak level during adolescence. Puberty plays a critical role in bone mass, as bone tissue is continuously renewed to achieve maximum size and density. The bone mass acquired during this period serves as a lifelong reserve and determines the risk of osteoporosis in later life. In healthy children, osteoblasts outnumber osteoclasts, resulting in a net increase in bone mass. However, this balance is disrupted in osteoporosis, leading to bone loss.[3–5]

Genetic factors are believed to contribute to 80% of bone mass acquisition, but adequate calcium intake, vitamin D levels, and physical activity are also crucial for bone development. [6] Genetic causes typically involve defects in intercellular signaling pathways, and pharmacotherapy often targets these pathways.

RANK (Receptor Activator of Nuclear Factor Kappa B) is expressed on the surface of osteoclast precursors, while RANK ligand (RANKL) is secreted by osteoblasts and osteocytes. The interaction between RANK and RANKL activates osteoclasts, leading to bone resorption. Osteoprotegerin (OPG), synthesized by osteoblasts, functions as a decoy receptor for RANKL, thereby

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inhibiting the RANK-RANKL interaction. The balance between RANKL and OPG is a critical determinant of osteoclast-mediated bone resorption (Figure 1).[7]

Inflammatory mediators, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), can disrupt this pathway and contribute to osteoporosis by promoting osteoclast activation.[8,9]

The Wnt signaling pathway is also involved in bone modeling and remodeling. It plays a crucial role in the differentiation of mesenchymal stem cells (MSC) into osteoblasts, with β-catenin serving as the core molecule responsible for signal transmission. β-catenin directly affects osteoblastic precursor cells and osteoblasts, enhancing their response to bone morphogenic protein (BMP)-2 and promoting their differentiation into osteoblasts. Several studies have also shown that β-catenin induces OPG activation in osteoblasts. Disruption of β-catenin significantly increases the number of osteoclasts and bone resorption, ultimately leading to osteoporosis. On the other hand, overexpression of β-catenin boosts the amount of osteoblast and bone mass, promoting bone formation. Thus, activating the Wnt/β-catenin signaling pathway might offer a new strategy for managing osteoporosis.[10,11] The Wnt pathway is activated by ligands, such as Wnt1 and Wnt3a, which bind to transmembrane Frizzled receptors and low-density lipoprotein receptor-related protein (LRP)-5 and LRP-6 complexes. Sclerostin, secreted by osteocytes, binds to LRP-5 and LRP-6 and inhibits Wnt signaling (Figure 2).[12]

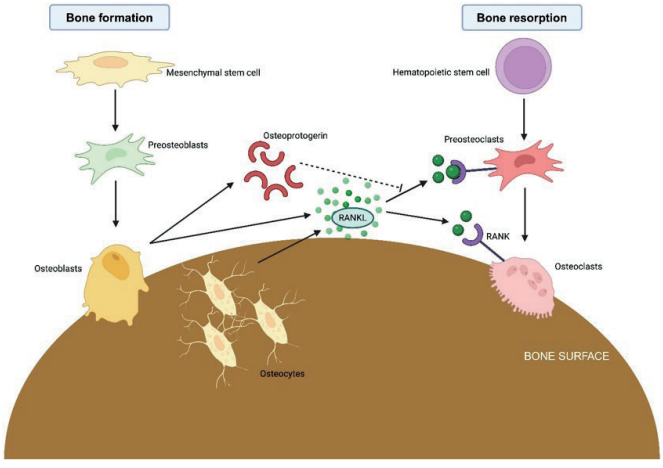

Figure 1. The RANK/RANKL/OPG System in Bone Resorption

RANK (Receptor Activator of Nuclear Factor Kappa B) and RANK ligand (RANKL) play a crucial role in bone resorption. The interaction of RANK, expressed on the surface of osteoclast precursors, with RANKL, which is secreted by osteoblasts and osteocytes, activates osteoclasts. Osteoprotegerin (OPG), synthesized by osteoblasts, functions as a decoy receptor for RANKL, thereby inhibiting the RANK-RANKL interaction.

Transforming growth factor-beta (TGF-β) and BMP signaling play significant roles in both embryonic skeletal development and postnatal bone homeostasis. TGF-β and BMPs transmit intracellular signals through the Smad complex or the mitogen-activated protein kinase (MAPK) cascade, resulting in cell proliferation, differentiation, and migration. Disruptions in TGF-β and BMP signaling can lead to bone disorders. Knockout or mutation of genes associated with TGF-β and BMP signaling in mice results in varying degrees of bone abnormalities.[13] Furthermore, the TGF-β pathway interacts with Wnt signaling by inhibiting sclerostin secretion and modulating different Wnt ligands.[14]

Diagnosis of osteoporosis

The diagnosis of osteoporosis is primarily based on bone mineral density (BMD) measurements using dual-energy X-ray absorptiometry (DXA) in adults. In pediatric patients, clinical

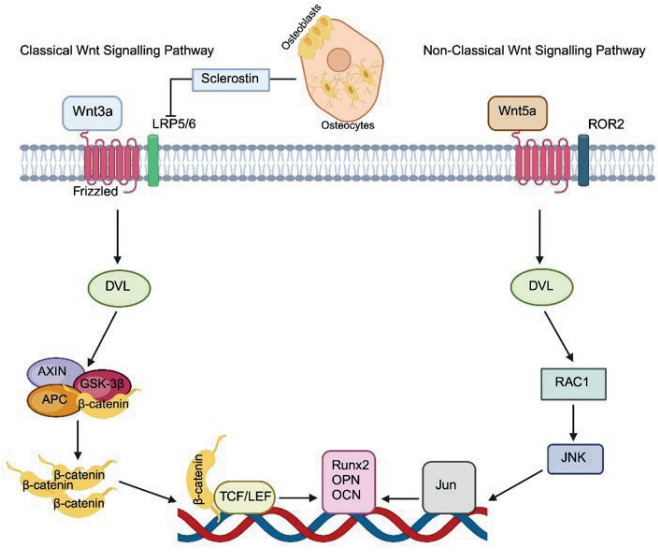

Figure 2. Classical and Non-classical Wnt Signalling Pathways in Bone Metabolism

In the classical pathway, binding of Wnt protein to Frizzled (FZD) and LRP5/6 receptor complex activates DVL. Activated DVL prevents the phosphorylation of β-catenin by inhibiting the AXIN-APC-GSK3β-β-catenin complex. This results in the accumulation of β-catenin, which translocates to the nucleus and binds to osteoblast marker molecules, leading to osteogenic differentiation. Osteocyte-derived sclerostin prevents the binding of Wnt to the receptor complex. In a non-classical pathway, binding of Wnt protein to Frizzled (FZD) and ROR2 receptor complex activates DVL, which in turn activates RAC1. RAC1 activates JNK, and JNK translocates to the nucleus, where it binds the transcription factor c-Jun. Jun binds to osteoblast marker molecules, terminating osteogenic differentiation.

features should also be evaluated alongside densitometric criteria.[9]

Although most childhood fractures are benign, experiencing multiple fractures may suggest primary bone disease or reduced bone mineral density secondary to underlying conditions. Low-trauma fractures are particularly significant for diagnosis.

BMD should be assessed considering the patient's sex, age, and body proportions and is reported as a 'Z-score'. Z-scores below -2 standard deviations (SD) indicate low bone mineral density.[15,16]

The International Society for Clinical Densitometry has set criteria for pediatric osteoporosis:

1. One or more vertebral compression fractures (VCF), irrespective of BMD, in the absence of high-energy trauma* or local disease.

2. A clinically significant fracture history alongside a DXA BMD Z-score ≤ -2 SD (adjusted for age and sex). A significant fracture history is defined as ≥ 2 long bone fractures by age 10 or ≥ 3 by age 19. A BMD greater than -2 SD does not rule out an increased fracture risk.[17]

** High-energy trauma: Significant forces such as motor-vehicle accidents or falls from heights greater than 10 feet (approximately 3 meters). In chronic illness contexts, a more conservative definition is applied, referring to falls from a standing height or higher, occurring at more than walking speed*.[18]

These criteria help prevent overdiagnosis of osteoporosis in children but may not be fully applicable for primary (genetic) and secondary (acquired) bone diseases. If the number of fractures does not meet the existing criteria, diagnosis may be delayed. Diagnosis should consider underlying diseases, risk factors for fractures, characteristics of the fractures (such as location, mechanism, and radiological features), and family history without relying solely on BMD and the number of fractures.[18]

Primary osteoporosis

Primary osteoporosis results from intrinsic defects in bone tissue, leading to hereditary bone fragility. The most common cause of primary osteoporosis in children is osteogenesis imperfecta (OI).

• Osteogenesis imperfecta

OI is a rare skeletal dysplasia with a prevalence of 1:15-20,000, characterized by recurrent fractures, deformities, and growth retardation. The disease is primarily caused by defects in the production of type 1 collagen. Due to the expression of type 1 collagen in different tissues, patients may also exhibit brittle teeth (dentinogenesis imperfecta), blue sclerae, hearing loss, reduced respiratory capacity, and heart valve abnormalities. OI ranges from mild clinical presentations to severe forms with perinatal mortality.[19] The most common mutations are in the COL1A1 and COL1A2 genes, which are inherited in an autosomal dominant pattern. Recently, recessive and X-linked forms have been identified and are associated with several genes (Table 1).[20]

• Other causes of primary osteoporosis

Other rare causes of primary osteoporosis include connective tissue disorders such as Ehlers-Danlos and Marfan syndromes, as well as homocystinuria and osteoporosis-pseudoglioma syndrome (OPPG) which is caused by homozygous inactivating mutations in the LRP5 gene. Patients with OPPG may present with bone fragility, loss of vission due to exudative vitreoretinopathy type 4, learning difficulties, ligament laxity, and muscular hypotonia. Heterozygous LRP5 mutations can also lead to low bone density and increased fracture risk.

Additionally, mutations in WNT-1 and PLS3, along with the conditions such as Bruck syndrome (caused by mutations in the PLOD2 gene), Cole-Carpenter syndrome (associated with P4HB), Hajdu-Cheney syndrome (due to NOTCH2 mutations), geroderma osteodysplasticum (associated with GORAB), RAPADILINO syndrome (linked to RECQL4), gnathodiaphyseal dysplasia (caused by mutation in ANO5 gene), and spondylo-ocular syndrome (linked to XYLT2) are other rare causes of osteoporosis.[21]

• Idiopathic juvenile osteoporosis

In the absence of an underlying cause, the condition is termed idiopathic juvenile osteoporosis. This poorly understood disorder is characterized by widespread pain and difficulty in walking, often occurring during the pre-pubertal period. Vertebral compression fractures and long bone fractures in the metaphyseal regions are common, with the possibility of spontaneous remission after puberty or the development of persistent deformities.[22]

Secondary Osteoporosis

Secondary osteoporosis is more common and often caused by underlying chronic diseases and/or their treatment.[23] Frequent causes include chronic inflammatory diseases, endocrine disorders, immobilization, muscular diseases (especially Duchenne muscular dystrophy), malnutrition, and certain medications, particularly corticosteroids, anticonvulsants, and proton pump inhibitors (Table 2).[24]

Table 1. Types of OI*, Causing Genes, Inheritance Pattern and Mechanism			
OI Type	**Gene**	**Inheritance**	**Mechanism**
I-IV	COL1A1, COL1A2	AD	Defect in type 1 collagen synthesis
V	IFITM5	AD	Defect in mineralization
VI	SERPINF1	AR	Defect in mineralization
VII	CRTAP	AR	Defect in collagen modification
VIII	P3H1 (LEPRE1)	AR	Defect in collagen modification
IX	PPIB	AR	Defect in collagen modification
X	SERPINH1	AR	Defect in collagen folding
XI	FKBP10	AR	Defect in collagen folding
XII	SP7	AR	Defect in osteoblast differentiation and function
XIII	BMP1	AR	Defect in collagen processing
XIV	TMEM38B	AR	Defect in collagen modification
XV	WNT1	AR	Defect in WNT signaling
XVI	CREB3L1	AR	Defect in osteoblast differentiation and function
XVII	SPARC	AR	Defect in collagen processing
XVIII	TENT5A (FAM46A)	AR	Defect in osteoblast differentiation and function
XIX	MBTPS2	XLR	Defect in intramembrane proteolysis
XX	MESD	AR	Defect in WNT signaling
XXI	KDELR2	AR	Defect in retrograde Golgi to ER† transport
XXII	CDC134	AR	Defect in MAPK¥ signaling

*: Osteogenesis Imperfecta, †: Endoplasmic Reticulum, ¥: Mitogen-activated protein kinase

The mechanostat theory points out that bone development and strengthening occur in response to mechanical load. Genetic thresholds determine when osteoblast and osteoclast activities are activated to strengthen bone tissue. This mechanism provides functional adaptation to mechanical load, helping to maintain skeletal stability.[25] Chronic diseases, corticosteroid therapy, and muscle loss can impair the mechanostat, reducing its efficacy.

Proinflammatory cytokines such as TNF-α, IL-1, and IL-6 increase osteoclastogenesis and impair osteoblast function in chronic inflammatory diseases (e.g., Juvenile idiopathic arthritis, Crohn's disease), thereby negatively affecting bone formation. The use of corticosteroids for treatment in these conditions, along with reduced physical activity, delayed puberty, and decreased vitamin D levels, also contribute to the development of osteoporosis.[26,27]

Osteoporosis is a significant morbidity in cerebral palsy, with diagnosis often challenging due to patients' inability to express symptoms adequately. Anticonvulsants, immobility, and prolonged immobilization after surgeries exacerbate the risk of osteoporosis.[28]

The patients with Duchenne Muscular Dystrophy (DMD) are also at an increased risk of osteoporosis due to immobilization and long-term steroid use, which heigthen the risk of vertebral and lower extremity fractures.[29]

Corticosteroids suppress sex steroids and growth factors, increase PTH levels, reduce gastrointestinal calcium absorption, and promote muscle proteolysis, all of which contribute to osteoporosis and an increased risk of fractures.[27] Additionally, corticosteroids negatively impact linear growth, exert direct toxic effects on bone, accelerate osteoblast apoptosis, and prolong the lifespan of osteoclasts, thereby increasing bone resorption.[30]

Studies have shown that children with leukemia, the most common childhood malignancy, experience an increased risk of osteopenia at diagnosis and during treatment, particularly with chemotherapy.[31,32]

Table 2. Common Causes of Secondary Osteoporosis	
Endocrine Disorders	1. Hypercortisolism 2. Diabetes mellitus 3. Hyperthyroidism 4. Hyperparathyroidism 5. Hypogonadism 6. Vitamin D deficiency 7. Hypophosphatemia 8. Hypocalcemia
Haematologic Disorders	1. Leukemia 2. Thalassemia major 3. Bone-marrow transplantation
Medications	1. Anticonvulsants 2. Chemotherapy 3. Corticosteroids 4. Proton-pump inhibitors 5. GnRH analogues 6. Excess levothyroxine 7. Aromatase inhibitors
Chronic Inflammatory Disorders	1. Rheumatic diseases 2. Inflammatory bowel diseases 3. Kidney diseases
Neuromuscular Disorders	1. Duchenne muscular dystrophy 2. Spina bifida 3. Cerebral palsy
Malabsorption/Malnutrition	1. Anorexia nervosa 2. Celiac disease 3. Malnutrition

GnRH: Gonadotrophin-releasing hormone

Conditions that lead to estrogen deficiency, such as hypogonadism, anorexia nervosa, and gonadal failure due to chemotherapy, radiation, and autoimmune diseases, are also known to cause osteoporosis.[33,34]

APPROACH TO SUSPECTED OSTEOPOROSIS IN CHILDREN

The following steps should be considered in the evaluation of children presenting with suspected osteoporosis:

First step: Patient's medical history

1. **History and features of fractures:** Document the location, number, mechanism of injury (low or high energy trauma), the ages at which fractures occurred, and whether any surgical intervention or spontaneous recovery took place.

2. **Symptoms:** Assess for the presence of back pain indicative of vertebral fractures and any complaints related to underlying conditions (e.g., inflammatory bowel disease, leukemia).

3. **Family History:** Inquire about a history of osteoporosis, bone diseases, fractures, hearing loss, or kidney stones.

4. **Dietary Habits:** Evaluate dietary calcium, vitamin D, and protein intake.

5. **Medications:** Review any medications, particularly corticosteroids and anticonvulsants.

6. **Physical Activity:** Assess levels of physical activity.

Second step: Physical examination

1. **Anthropometric Measurements:** Record height, weight, head circumference, and upper-lower segment ratios.

2. **Systemic Examinations:** Conduct an examination of the cardiovascular, respiratory, and gastrointestinal systems, including an assessment of the thyroid gland.

3. **Bone and Joint Examination:** Evaluate for bone deformities, scoliosis, skin-joint laxity, and hypermobility

4. **Ocular Findings:** Note the presence of blue sclerae, myopia, vision defects.

5. **Dental Assessment:** Examine for signs of dentinogenesis imperfecta.

6. **Signs of Underlying Conditions:** Look for features suggestive of Cushing's syndrome, including acne, buffalo hump, moon face, hirsutism, striae, and any systemic diseases such as leukemia or inflammatory disorder.

7. **Pubertal Examination:** Assess for signs of hypogonadism.

Third step: Laboratory work-up

The parameters to be evaluated in the first step, as well as those for the second step, are listed in Table 3. Bone turnover markers should be assessed according to age and sex, as they can be physiologically high in young individuals due to rapid bone formation. Furthermore, it has been observed that BTMs increase during the process of fracture healing.[35,36]

Fourth step: Imaging

• ***Dual-energy X-ray Absorptiometry (DXA)***

DXA is the most commonly preferred method for evaluating bone mineral content (BMC) or BMD in children.[37] DXA measures BMC (in grams) and the projected bone area (in cm^2). These

Table 3. Laboratory work-up	
Key biochemical parameters	**Secondary assessments**
1. Complete blood count 2. BUN, creatinine 3. Transaminases (AST, ALT) 4. ESR* 5. Albumin, calcium, phosphate, ALP† (total and bone-specific), ionized calcium, blood gases 6. Urine calcium/creatinine ratio 7. TRP‡, TmP/GFR§ 8. 25-OH vitamin D 9. Parathormone	1. Bone turnover markers (osteocalcin, beta-crosslaps, P1NP‖) 2. TSH¶, free T4 3. IGFs (if required) 4. Celiac antibodies 5. Gonadotropic hormones, Prolactin 6. Urinary free cortisol/dexamethasone suppression test 7. Consider biochemical testing for inborn error of metabolism

* Eritrocyte sedimentation rate, †Alcaline phosphatase, ‡Tubular reabsorption of phosphate, §The ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate, ‖Serum type 1 procollagen, ¶Thyroid-stimulating hormone

values are subsequently used to calculate areal BMD (aBMD, expressed in g/cm²). The measurements are then converted to age- and sex-specific Z-scores for comparison with normal population. However, DXA is considered unreliable in children under 5 years of age due to motion artifacts and a lack of age-specific reference data.[9]

BMD measurement typically focuses on the posterior-anterior lumbar spine and total body minus head in children. In specific cases, other regions, such as the proximal femur, distal radius, and lateral distal femur, may be utilized for BMD measurement.[35] For instance, imaging may be suboptimal due to spinal rods and plates resulting from scoliosis surgery, evaluating these additional regions valuable for assessment.

In children and young adults, BMD scanning is usually recommended after two or more fractures, fractures occurring in unusual locations (such as the spine or hip), or the presence of chronic diseases or medications that predispose individuals to osteoporosis.[38]

The advantages of DXA include low radiation exposure and rapid application. However, as a two-dimensional measurement, it may yield lower-than-normal results in shorter children or higher-than-normal results in taller children; therefore, height adjustments are necessary.[39] Additionally, vertebral compression fractures and mineral deposits may lead to falsely elevated DXA values.[35]

- ***Radiography***

Radiography is commonly used to detect VCFs and scoliosis. Children with VCFs may not exhibit obvious symptoms, such as back pain, as often seen in adults; therefore, lateral vertebral radiographs should be obtained for all children suspected of having osteoporosis.[14] Standard evaluation typically involves lateral views from the T4 to L4 vertebrae. It is important to distinguish physiological wedging in the mid-thoracic vertebrae (T5-T7) from actual fractures.[40]

- ***Vertebral Fracture Assessment (VFA)***

VFA has been recognized as a suitable alternative for detecting lateral vertebral fractures, particularly due to the potential side effects associated with frequent radiographs in children. VFA utilizes DXA to obtain lateral vertebral images, delivering significantly less radiation than traditional radiography.[41,42]

- ***Bone Biopsy***

Bone biopsies provide valuable information on bone microarchitecture, and dynamic parameters can be assessed through tetracycline labeling. Bone biopsy is especially useful when the diagnosis is unclear, as it aids in distinguishing different types of osteoporosis by analyzing histological features and bone metabolic activity.[9,24]

Fifth step: Genetic investigations

Genetic diagnosis helps confirm clinical suspicion and facilitates the management of osteoporosis. It enables screening for family members of diagnosed individuals, promotes early detection of existing conditions in these individuals, and contributes to preventive treatment and genetic counseling.[43]

Numerous skeletal disorders leading to low and high BMD have been identified, forming an expanding group.[44]

MANAGEMENT OF CHILDHOOD OSTEOPOROSIS

General Advice

Childhood osteoporosis should be managed by a multidisciplinary team comprising pediatric endocrinologists specializing in bone health, orthopedic surgeons, neurosurgeons, physiotherapists, geneticists, dentists, audiologists, and child psychiatrists.

Effective management of osteoporosis requires lifestyle changes, including increased physical activity and improved nutrition quality. The diet should be rich in calcium and protein. It is recommended that 25-OH vitamin D levels be maintained at or above 50 nmol/L (20 ng/dL). Additionally, zinc, magnesium, copper, and vitamins C and K are also essential for sustaining bone health.[45]

Medication

Pharmacological treatment is not always immediately necessary following the diagnosis of childhood osteoporosis, as children's skeletal systems rapidly repair decreased BMD and remodel vertebral deformities. This capacity for recovery depends on the temporary nature of the risk factor and the remaining growth potential.[18] For instance, approximately 80% of childhood leukemia patients with VFs are able to reshape their vertebral bodies within six years of diagnosis without any treatment.[46] Conversely, in conditions such as corticosteroid-treated DMD, the high incidence of long bone fractures and vertebral fractures, coupled with persistent risk factors, makes spontaneous improvement in BMD and vertebral body reshaping less likely without treatment.[47] Therefore, when deciding to initiate pharmacological treatment, it is essential to consider both the reversibility of risk factors for osteoporosis and the remaining growth potential. Adolescents have more limited bone repair capacity compared to younger children and may require earlier intervention. Early treatment is also recommended for children with primary osteoporosis due to the permanent nature of the underlying issue.[9,18]

Antiresorptive treatment

• Bisphosphonates (BPs)

Bisphosphonates are pyrophosphate analogs that inhibit bone resorption and are considered the first-line treatment for childhood osteoporosis.[6] BP therapy should be considered in children with a history of low-trauma fractures and persistent risk factors that compromise bone health. Common indications for treatment include low-trauma long bone fractures, symptomatic VFs, or moderate-to-severe asymptomatic VFs.[48]

Before initiating BPs, the patient's suitability must be thoroughly assessed. Patients should have normal pre-treatment calcium, phosphate, and 25-OH vitamin D levels, with no evidence of renal insufficiency. Intravenous (IV) zoledronic acid is contraindicated in patients with acute renal insufficiency, and dose adjustments are necessary for those with a glomerular filtration rate of less than 60 ml/min/1.73m².[49]

Pamidronate was first shown to benefit bone health in children with osteoporosis. It is administered at intervals of 2-4 months, with a total annual dose of 6-12 mg/kg.[50] Zoledronic acid is typically administered every 6 to 12 months at doses ranging from 0.0125-0.5 mg/kg, with a maximum annual dose of 4 mg (Figure 3).[51–53] Zoledronic acid is 100 times more potent than pamidronate.[49] Various studies have demonstrated similar long-term effects on BMD for both zoledronate and pamidronate.[54,55]

• Side effects of BPs

The most common side effects of BPs include acute-phase reactions, such as low-grade fever, headache, myalgia, nausea, vomiting, rash, and decreased lymphocyte count.[56] Hypocalcemia and hypophosphatemia have been reported following the first dose of zoledronic acid, although serious cases requiring calcium infusion are rare.[57] Zolendronic acid is more likely to cause hypocalcemia than pamidronate.[56]

Chronic corticosteroid users should receive stress coverage or be closely monitored for signs of adrenal crisis during the first dose of BPs.[49] Osteonecrosis of the jaw is a potential long-term side effect, although it has not been reported in any studies involving children.[51,58] Atypical femur fractures represent another long-term side effect.[59]

Children with moderate to severe OI often require bone correction surgery, and BP treatment has been reported to prolong bone healing at osteotomy sites. Therefore, it is

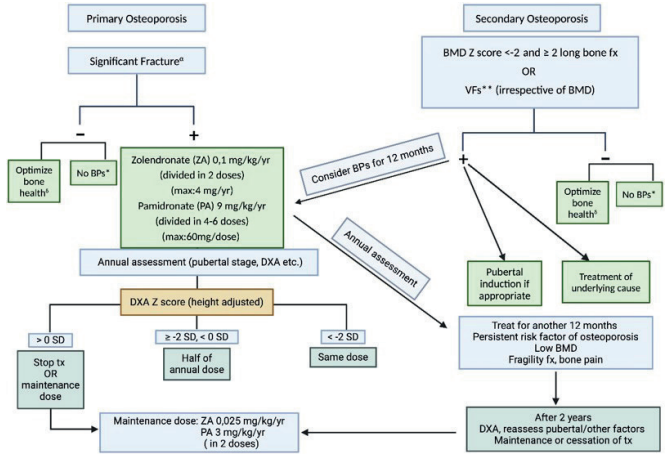

Figure 3. Treatment Algorithm in Primary and Secondary Osteoporosis

[α] Vertebral compression fractures or ≥ 2 long bone fractures caused by low trauma, * Bisphosphonates, ** Vertebral fractures, [δ] Dietary calcium intake, adequate Vitamin D levels, weight-bearing exercises

recommended to withhold BP treatment for at least 4 months post-osteotomy. This issue has not been reported following fractures;[60] thus, the dose of BP treatment should not be omitted due to the presence of fractures.

Oral BPs (e.g., alendronate, risedronate) have been shown to increase BMD in osteopenic children, with studies highlighting their ease of use and tolerability.[61–63] However, some studies suggest that IV BPs may be superior to oral therapy for reducing VF risk, increasing vertebral height and trabecular volumetric BMD. Therefore, intravenous therapy is preferred, while oral BPs may be considered in mild cases or when IV access is unavailable.[49,64]

For children at high risk of osteoporosis, it is recommended that BP therapy continue until the epiphyseal plates are fully closed and the children reach their final height. This is due to the fact that newly formed bone around the growth plate is less dense and may predispose the child to new fractures.[65] The current approach involves administering a high-dose regimen until the patient is clinically stable (at least 2 years from the beginning of treatment), after which treatment may continue at a maintenance dose (half dose or lower) until final height is achieved to avoid over-treatment.[66]

If the risk factor is eliminated in children at temporary risk, treatment discontinuation can be considered after a fracture-free period of 6-12 months (both VF and non-VF), resolution of previous VFs, and normalization of the BMD Z-score.[49]

- ***Denosumab***

Denosumab is a monoclonal antibody developed against RANKL, which regulates osteoclast differentiation and function. It inhibits bone resorption by preventing the binding of RANKL to RANK.[67] Its use has been explored in pediatric patients with conditions such as giant cell bone tumors, aneurysmal bone cysts, fibrous dysplasia, and OI.[68]

In a study comparing the efficacy of denosumab with zoledronic acid in patients with OI, denosumab significantly increased BMD and improved spinal morphometry, demonstrating effects similar to zoledronate. However, denosumab is associated with a risk of severe hypercalcemia following discontinuation or interruption of the treatment, with some cases of hypercalcemic crisis reported. This side effect can be managed by BPs. Therefore, denosumab is not yet recommended as a first-line treatment for OI.[69]

In children with the SERPINF1 mutations (OI Type VI), where the osteomalacic nature of the bone was assumed to reduce the effectiveness of BPs, alternating treatments with denosumab and zoledronate were implemented. This approach mitigated rebound hypercalcemia and utilized the anti-resorptive effect of denosumab.[70]

Anabolic treatments

- ***Testosterone***

Pubertal induction may be recommended if the patient's age is appropriate, particularly in cases of chronic disease associated with delayed puberty, such as prolonged corticosteroid use. In patients with DMD and delayed puberty, testosterone treatment has been administered, resulting in increased BMD.[71]

- ***Teriparatide***

Teriparatide is a recombinant analog of parathyroid hormone that promotes osteoblastogenesis and prevents osteoblast apoptosis.[9] Studies in adults, particularly in postmenopausal women, have demonstrated its ability to reduce the risk of VF and increase BMD.[72] Animal studies have identified a potential risk of osteosarcoma, and until recently, its use in children was not approved.[73] In late 2020, the FDA determined that this side effect is limited to animal studies.[9,49] Clinical trials are needed to evaluate the use of teriparatide in pediatric osteoporosis.

- ***Growth Hormone (GH)***

Growth hormone increases cortical bone thickness and muscle mass.[74] A study in patients with OI type III and IV indicated that GH treatment moderately increased BMD and reduced fracture rates.[75] However, there is insufficient evidence to support the use of GH treatment for osteoporosis.

Anti-Sclerostin Treatment

Sclerostin inhibits bone formation by blocking the Wnt signaling pathway. Anti-sclerostin monoclonal antibody treatments (e.g., setrusumab, romosozumab, blosozumab) counteract this effect. Animal studies have demonstrated increases in BMD and bone formation markers, as well as positive changes in bone geometry.[76] Romosozumab is FDA-approved for the treatment of postmenopausal osteoporosis in women.[77] International clinical phase trials for anti-sclerostin treatment in pediatric patients with OI are currently ongoing.

CONCLUSION

Osteoporosis, caused by both primary and secondary factors, is associated with significant morbidity. In addition to primary

osteoporosis, it is crucial to understand the predisposing conditions that may lead to osteoporosis in patients presenting with features of primary osteoporosis. It is also essential to screen for secondary causes in these patients. Furthermore, early diagnosis and treatment are vital to improve quality of life. While BPs, which inhibit bone resorption, are the preferred agents for treatment, new drugs, and clinical phase trials focusing on reducing bone resorption and promoting bone formation show promise.

Author contribution

Review conception and design: ST, AG; literature review: AG; draft manuscript preparation: AG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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