Review Article

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Diagnosis and Management of Osteoporosis in Children and Adolescents

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Recent advances in medicine have led to an increase in the number of children and adolescents treated for various chronic diseases and cancer. Increasingly sophisticated genetic analysis techniques have also clarified some genetic factors that contribute to bone fragility. Osteoporosis, characterized by reduced bone mass and skeletal fragility, can result from primary or secondary causes that originate in childhood and adolescence, which are critical periods for bone mineral acquisition. It is essential to identify children and adolescents at risk of fractures due to osteoporosis, and early intervention is crucial. Conservative management strategies, such as treating underlying diseases, replacing deficient hormones, providing nutritional support to meet calcium and vitamin D requirements, and encouraging regular physical activity, should be prioritized. Pharmacological treatment should be initiated in a timely manner following a comprehensive bone health examination. Intravenous pamidronate therapy has been safely and effectively administered to children and adolescents, although long-term follow-up is necessary. Further investigation is needed regarding bone fragility fractures of unknown etiology and the application of new medications for pediatric use.

Introduction

Osteoporosis is a disorder characterized by a decrease in bone mass and changes in bone tissue micro-architecture, leading to skeletal fragility and an increased risk of fractures [1]. Historically, osteoporosis was considered an adult disease. However, it is now understood to have roots in childhood and adolescence, as these are the periods when bone mass and architecture are accumulated. The total bone mass reaches its peak a few years after the long bone epiphyses have fused. This maximum bone mass an individual can achieve is referred to as peak bone mass (PBM). A significant portion of PBM is determined by unmodifiable genetic factors [2]. However, other factors such as hormones, immobility, nutrition, pubertal timing, increased cytokines, and certain medications can also impact bone health. Therefore, chronic illnesses and specific osteotoxic treatments during childhood and adolescence can affect PBM accrual, leading to low bone mineral density (BMD). Low BMD during these formative years can increase the risk of fractures in youth, potentially leading to osteoporosis and fractures in adulthood. The incidence of fractures in children and adolescents is on the rise, with fractures resulting from a combination of intrinsic and extrinsic factors [3]. As such, it is crucial to assess bone health and adopt preventive measures early in children and adolescents at risk for low BMD. This article reviews the diagnosis,

causes, and management of osteoporosis in children and adolescents, with the aim of applying this knowledge to the clinical field for the evaluation and treatment of pediatric osteoporosis.

Definition and Diagnosis of Osteoporosis in Children and Adolescents

The World Health Organization defines osteopenia and osteoporosis based on T-scores, which are used to compare a patient's BMD with the maximum BMD of young adults. This comparison is only applicable to postmenopausal women. Some definitions categorize a Z-score of less than −1.0 as osteopenia and less than −2.5 as osteoporosis. The International Society for Clinical Densitometry (ISCD) recommends the term "low BMD for chronological age" when the BMD Z-score is lower than −2.0 [4]. The diagnosis of osteoporosis in children and adolescents should not be made solely based on bone densitometry (dual-energy X-ray absorptiometry [DXA]) [5]. The presence of one or more vertebral compression fractures without local disease or high-energy trauma indicates osteoporosis [6]. In the absence of a vertebral compression fracture, osteoporosis is defined by the presence of both a clinically significant fracture and a BMD Z-score of less than or equal to −2.0 [6]. Three or more long bone fractures are considered clinically significant (or two or more long bone fractures if the patient is under 10 years old) [6]. The ISCD definition aims to prevent the overdiagnosis and overtreatment of osteoporosis in young individuals who do not have skeletal fragility. However, waiting for a second or third fracture could unnecessarily delay treatment in children and adolescents with bone fragility, potentially leading to permanent disability [7]. In addition, a BMD Z-score>−2.0 does not preclude the possibility of skeletal fragility or increased fracture risk, as is also noted in the ISCD guidance [6]. Therefore, children and adolescents with risk factors for low BMD require a comprehensive bone health evaluation, which could lead to an accurate diagnosis of osteoporosis and identify the cause of bone fragility [7]. DXA is part of a comprehensive skeletal health examination in children and adolescents [6]. Although lumbar BMD and whole-body (total body minus head) BMD measurements are commonly performed in children, the 2019 ISCD guideline recommends using the proximal femur, lateral distal femur, and radius as skeletal sites for BMD measurement in children who need additional information, or in whom spine or whole-body DXA cannot be performed, if reference data are available [6]. Interpreting and reporting DXA results in children and adolescents should be done with caution. Appropriate reference data should be established, and BMD results should be adjusted in children with short stature or growth delay. The clinical utility of these measurements may be limited in very young children due to a lack of reference data for those under 5 years old. A few Korean pediatric reference BMD data sets have been published. BMD increases with age, reaching a plateau at 17–20 years in females and 20–23 years in males [8–10].

High-resolution peripheral quantitative computed tomography (pQCT) is a novel imaging method to evaluate BMD. pQCT at the radius and tibia can provide information about bone and muscle geometry, as well as volumetric cortical and trabecular BMD [11]. The potential diagnostic value and clinical applicability of pQCT for evaluating pediatric bone health warrant further investigation.

In cases of low BMD, a lateral thoracolumbar radiograph is recommended for detecting vertebral fractures. Lateral spine radiographs should be regularly performed in children and adolescents with persistent risk factors [12]. Asymptomatic vertebral fractures can sometimes be detected in patients with prolonged glucocorticoid (GC) treatment, progressive myopathy,

or immobility [12]. Specifically, children and adolescents with reduced mobility due to cerebral palsy or myopathy should receive a lateral spine X-ray examination at 6–8 years of age [13]. The bone condition of patients chronically treated with GCs requires careful follow-up, including a lateral spine X-ray before the initiation of GCs and regularly during treatment. Follow-up lateral spine X-rays are recommended according to the patient's risk factors, with a follow-up period ranging from 6 months to 2 years [14].

Physical examination and laboratory findings can provide us with clues to distinguish between various diseases that cause osteoporosis. The following clinical presentations may suggest congenital bone fragility: skin laxity, blue sclerae, abnormal dentition, easy bruising, a dysmorphic face, joint hypermobility, and wormian bones. In such instances, inheritable osteoporosis may be identified through molecular analysis. Genetic analysis has also revealed disease-causing variants of osteogenesis imperfecta (OI) associated genes in individuals who have a significant history of fractures but no extraskeletal symptoms [15]. Conversely, there have been instances of fragility fractures with unknown causes and mechanisms, despite negative genetic testing results. This highlights the need for further research into monogenic and polygenic determinants of skeletal strength. Hormonal studies should be conducted to diagnose or exclude hormone-deficient states. Bone turnover markers such as type 1 procollagen, carboxy-terminal telopeptides, alkaline phosphatase, and osteocalcin can be useful in monitoring medical therapy [16].

Causes of Osteoporosis in Children and Adolescents

Numerous factors can influence bone mineral deposition and the formation of bone mass. Certain genetic diseases can lead to inherent bone vulnerability and an increased risk of fractures, a condition known as primary osteoporosis. OI, Ehlers-Danlos syndrome, Marfan syndrome, cleidocranial dysplasia, osteoporosis-pseudoglioma syndrome, and fibrous dysplasia are all well-documented genetic diseases associated with bone fragility. Among these, OI is a rare inherited disorder characterized by bone fragility, which is caused by defects in the biosynthesis of type 1 collagen [17]. The clinical manifestations of OI can range from subclinical to lethal, and may include low bone mass, skeletal deformities, hypermobile joints, short stature, blue sclera, dentinogenesis imperfecta, and hearing loss. Consequently, OI is classified into several types based on these clinical features. The most common mutations associated with all types of OI are found in the *COL1A1* and *COL1A2* genes [18]. Apart from these genetic diseases, idiopathic juvenile osteoporosis can also present with symptoms such as bone pain, bone deformities, fractures, and low bone mass, all of which stem from an unknown cause. A diagnosis of idiopathic juvenile osteoporosis is made after other potential diseases have been ruled out.

Secondary osteoporosis develops due to chronic illness or treatments affecting bone formation, resorption, or bone matrix mineralization. The incidence of pediatric secondary osteoporosis is increasing as a consequence of improvements in the survival rates of chronic diseases, including cancer. Low BMD could be caused by hormone deficiencies or excess, malnutrition, immobilization, chronic inflammation, and medication associated with underlying diseases.

Table 1 summarizes various causes of secondary osteoporosis. Sex hormones influence the growth and maintenance of bone, consequently impacting PBM [19]. Therefore, the risk of fractures increases in several clinical conditions associated with hypogonadism, including delayed puberty, premature ovarian failure, hyperprolactinemia, Turner syndrome, Klinefelter syndrome, and hypogonadism induced by cancer treatment. Bone formation and resorption

Table 1. Causes of secondary osteoporosis

Neuromuscular disorders	Cerebral palsy
	Duchenne muscular dystrophy
	Progressive myopathy
Endocrine disorders	Delayed puberty
	Hypogonadism
	Growth hormone deficiency
	Hyperthyroidism
	Hyperparathyroidism
	Cushing disease
	Vitamin D metabolism disorder
Hematologic disorders	Leukemia/Lymphoma
	Hemoglobinopathy
Gastrointestinal disorders	Inflammatory bowel disease
	Celiac disease
	Malabsorption
	Chronic liver disease
	Milk intolerance
Renal disorders	Chronic renal failure
	Nephrotic syndrome
Connective tissue disorders	Systemic lupus erythematosus
	Juvenile idiopathic arthritis
	Juvenile dermatomyositis
Inborn errors of metabolism	Glycogen storage disease
	Galactosemia
	Gaucher disease
Others	Immobilization
	Anorexia nervosa
	Glucocorticoids
	Chemotherapeutic agents
	Immune suppressants
	Anticonvulsants
	Anticoagulant
	Radiation therapy

Adapted from Galindo-Zavala et al. [14] with CC-BY.

are also affected by growth hormone deficiency and thyroid disorders, leading to secondary osteoporosis. Hyperparathyroidism, which can result from parathyroid adenoma, chronic renal failure, disorders related to vitamin D metabolism, and multiple endocrine neoplasms, can enhance bone resorption by stimulating the receptor activator of nuclear factor kappa B ligand (RANKL) and reducing osteoprotegerin (OPG) levels due to an excess of parathyroid hormone [20]. In addition to endocrinologic disorders, neuromuscular, gastrointestinal, and renal disorders can also contribute to the development of secondary osteoporosis (Table 1). Childhood

cancer survivors often have low BMD due to the cancer itself, the effects of chemotherapy and radiotherapy, accompanying hormonal deficiencies, and poor nutritional status [21]. GC treatment is necessary for children and adolescents with certain chronic diseases, including cancer. Excessive GCs, whether iatrogenic or not, can directly or indirectly inhibit bone formation while increasing bone resorption [22]. Direct effects include upregulation of PPAR-γR2, increased sclerostin expression, and an increased RANKL/OPG ratio. Secondary hypogonadism, reduced calcium resorption, and decreased insulin-like growth factor-1 production can indirectly affect bone remodeling [22]. Therefore, patients receiving GC treatment for more than three months require special attention. A higher cumulative dose and longer duration of GC treatment are risk factors for low lumbar BMD in pediatric patients with chronic diseases [23].

Management of Osteoporosis in Children and Adolescents

It is essential to identify children or adolescents who are at risk for osteoporosis based on the abovementioned causes. Early diagnosis and management are critical for preventing recurrent fractures and permanent bone deformities. A developing skeleton has more potential for recovery and reshaping because growing bones continuously elongate, widen, and strengthen. Thus, the diagnosis of osteoporosis in children and adolescents does not automatically necessitate pharmacologic therapy. A comprehensive bone health examination should assess whether risk factors are transient and whether there remains growth potential. In cases of secondary osteoporosis, treatment of the underlying disease and cessation of osteotoxic medication are prioritized. Hormonal deficiencies should be diagnosed as early as possible and adequately managed [24,25]. Although conservative management is preferred in children and adolescents, pharmacological therapy should be considered in patients with recurrent lone bone fractures or vertebral fractures [7].

1. Conservative measures

The Committee on Pediatric Bone Health of the Korean Society of Pediatric Endocrinology has published clinical practice guidelines for optimizing bone health [26]. These guidelines recommend calcium and vitamin D supplementation, lifestyle changes, and regular physical activity for children and adolescents with chronic diseases to help prevent osteoporosis. Additionally, maintaining a healthy body composition and ensuring adequate hormonal status are also advised for optimal bone health.

Calcium and vitamin D supplementation improves BMD, particularly in children and adolescents with a low-calcium diet or decreased vitamin D concentration [27,28]. Calcium-rich foods are preferred over calcium tablets or powder. The recommended daily calcium requirements range from 500 mg to 1,000 mg according to age [26]. The 25-OH-vitamin D level should be maintained above 20 ng/mL (50 nmol/L) [29]. Vitamin D must be prescribed for patients with chronic diseases with vitamin D levels below 20 ng/mL. In individuals with low BMD (Z-score≤–2.0), vitamin D supplementation should be considered when vitamin D levels are below 30 ng/mL (75 nmol/L) [14]. However, meta-analyses of vitamin D supplementation have shown no effects on BMD or fracture risk when the baseline 25-OH-vitamin D level is >16 ng/mL (40 nmol/L) [30]. The maintenance dose of vitamin D is 400 IU for children below 1 year old and 600 IU for children over 1 year old. Calcium and vitamin D should be provided to all children and adolescents taking GCs, particularly when treatment lasts over 3 months. Healthy dietary supplements that contain appropriate calories, proteins, and vegetables or fruits containing

vitamins and minerals are also helpful for maintaining bone health [26].

Regular physical activity may enhance bone quality and strength, as the mechanical forces exerted on the bone aid in bone remodeling [31,32]. Weight-bearing exercises, including running, jogging, jumping, and resistance training, can boost bone mineral acquisition in children, especially during early puberty [31]. However, excessive exercise may also heighten the risk of fractures, underscoring the need for careful monitoring and control of activity intensity. For optimal bone health maintenance, a sedentary lifestyle should be avoided. Furthermore, an extremely lean physique can impact PBM accrual in adolescents, indicating the importance of maintaining an appropriate body weight [33].

2. Drug therapy

Bisphosphonates are the most frequently used medications for treating osteoporosis. These are synthetic analogs of pyrophosphate that inhibit osteoclastic function and decrease bone remodeling. Bisphosphonates are commonly prescribed to individuals with primary osteoporosis, such as OI. Current research indicates that oral or intravenous bisphosphonates can enhance BMD and decrease the frequency of fractures in both children and adults with OI [34,35]. Bisphosphonate therapy has proven to be effective and safe for both secondary and primary pediatric osteoporosis [36]. Bisphosphonates can significantly improve BMD in conditions of bone fragility related to disuse, such as cerebral palsy [37]. Intravenous bisphosphonate therapy can alleviate back pain and improve the vertebral height ratio when used to treat painful vertebral fractures in Duchenne muscular dystrophy [38]. Furthermore, bisphosphonates are well tolerated in childhood cancer survivors with low BMD [21].

Several bisphosphonates exist, each with varying potency and dosage (Table 2). Oral bisphosphonates are typically considered for mild cases or those without vertebral fractures [39]. However, the efficacy and safety of oral bisphosphonates in children have not been well studied. If oral bisphosphonates are contraindicated or vertebral fractures are present, an intravenous bisphosphonate should be used [14]. Intravenous pamidronate (3-amino-1-hydroxypropylidene-bisphosphonate) is primarily used in children and adolescents, and can be administered to children under 2 years of age. The dosage, interval, and duration of pamidronate may vary based on the center's or clinician's experience (Table 2). Zoledronic acid (ZA), a highly potent third-generation intravenous bisphosphonate, is increasingly being used in children and adolescents [40]. Recent studies have shown that ZA significantly improved BMD in children and adolescents

Table 2. Bisphosphonates used in pediatric patients

Drug	Administration	Dose	Potency
Pamidronate (second generation)	Intravenous (in 200–250 mL saline in 3–4 hours)	0.5–1 mg/kg/day, 2–3 consecutive days every 2–4 months 9–11.5 mg/kg/year Maximum: 60 mg/dose	100
Alendronate (second generation)	Oral	1–2 mg/kg/week <40 kg: 5 mg/day or 35 mg/week >40 kg: 10 mg/day or 70 mg/week Maximum: 70 mg/week	100–1,000
Neridronate (third generation)	Intravenous (in 200–250 mL saline in 3 hours)	1–2 mg/kg/day every 3–4 months Maximum: 100 mg/dose	100
Zoledronate (third generation)	Intravenous (in 50 mL saline in 30–45 minutes)	0.025–0.5 mg/kg every 6–12 months Maximum: 4 mg/dose	>10,000

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[38,41]. Compared to pamidronate, ZA treatment has a beneficial effect as it is generally infused over a shorter duration (30 minutes) with a longer interval (6–12 months) [42]. During bisphosphonate therapy, regular clinical monitoring using DXA and risk factor assessments should be conducted to determine whether to cease, reduce, or continue the same dose of bisphosphonate treatment [39].

Intravenous bisphosphonates may trigger acute phase reactions within 24–48 hours following the initial administration. These reactions can include symptoms such as fever, nausea, and malaise, which are typically self-limiting or can be managed with antipyretics. Iritis, characterized by red or painful eyes, is a rare side effect, particularly in patients with preexisting rheumatological conditions. Oral bisphosphonates, on the other hand, may cause esophagitis, dysphagia, and retrosternal pain. Transient hypocalcemia is a side effect common to both forms of bisphosphonates, necessitating the intake of calcium and vitamin D both before and after infusion. Bisphosphonates are retained in the bone, and as such, patients on long-term bisphosphonate therapy should be monitored due to an increased risk of atypical proximal fractures and jaw osteonecrosis. The use of bisphosphonates is contraindicated in children and adolescents with renal impairment, as the kidneys are responsible for the excretion of these drugs.

Denosumab received approval for the treatment of postmenopausal osteoporosis in 2010. Since then, it has emerged as a promising new therapy for skeletal diseases in pediatrics, although it has not yet received approval for pediatric use [43,44]. RANKL, expressed by osteoblasts, interacts with RANK on the surface of osteoclasts, thereby promoting osteoclast activity. Soluble OPG, also produced by osteoblasts, inhibits the interaction between RANKL and RANK. Denosumab, a monoclonal antibody, inhibits the binding between RANKL and its receptor RANK, effectively mimicking the effects of OPG [45]. To date, denosumab has been administered to a limited number of patients with various diseases such as OI, juvenile Paget disease, fibrous dysplasia, central giant-cell granuloma, metastatic giant cell tumor, and aneurysmal bone cyst in children. However, limited data are available regarding the dosage, duration, and response to denosumab therapy in children and adolescents. Furthermore, its efficacy and safety for pediatric use still need to be thoroughly investigated.

Conclusion

Personalized therapy, guided by a comprehensive risk factor assessment, is necessary for treating osteoporosis in children and adolescents. It is crucial to identify those at risk of osteoporotic fractures for early intervention. Conservative management can enhance BMD in this population, given the potential for spontaneous recovery of bone health. However, it is also essential to initiate an optimal pharmacological approach to prevent significant morbidity, such as irreversible bone deformity. Unkown etiology and mechanism of bone fragility need to be clarified. Additional research is needed to determine the efficacy, safety, dosage, and treatment duration of medical interventions, including new drugs.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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