Diagnosis and Management of Osteoporosis in Pediatric Patients

Abstract
In recent years, there has been a growing awareness of pediatric osteoporosis, a condition that can lead to weakened bones and a higher risk of fractures in children. It is essential for pediatricians to be knowledgeable about this issue so that they can identify and treat patients with osteoporosis or those at risk for it. Genetic factors and various disorders play a role in bone formation and quality. Osteogenesis imperfecta is the most common genetic condition linked to primary osteoporosis. Secondary osteoporosis can occur in children with chronic illnesses. X-rays can help diagnose the condition. Prevention is key in managing pediatric osteoporosis, as understanding normal bone development allows for early detection and treatment. Medications can help prevent bone loss in pediatric patients. The definition of pediatric osteoporosis involves low bone mass and significant fractures. Factors such as genes, medications, lack of movement, and corticosteroid use can contribute to osteoporosis in children. Treatment options for pediatric osteoporosis are limited, but anabolic agents and bisphosphonates may be used. Close monitoring and follow-up are crucial to prevent further fractures. It is important for pediatricians to understand the diagnosis and treatment of pediatric osteoporosis, as well as lifestyle factors and the effectiveness of treatment approaches.
Keywords : Osteoporosis , Pediatrics , Osteogenesis imperfecta, Bone Fractures , Vitamin D
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Introduction to Pediatric Osteoporosis

In recent years, there has been a growing awareness of osteoporosis in children. Both genetic and acquired bone disorders in children can weaken bones, making them more susceptible to fractures. If not addressed, these conditions can lead to decreased bone mass, deformities, and overall impact on the child's quality of life, with potential long-term effects. It is crucial for pediatricians to be aware of these issues in order to identify and treat patients with or at risk of developing osteoporosis.[1, 2]

Before reaching the age of 18, around 95% of the body's skeletal size, bone, and muscle mass are already determined. This highlights the importance of childhood in the development of a robust musculoskeletal system. Factors such as genetic background, organ function, chronic systemic illnesses, medications, muscular disorders, and metabolic disorders all contribute to the formation and quality of bones. The main cause of primary osteoporosis is often an underlying genetic defect, with osteogenesis imperfecta (OI) being the most prevalent condition at least 24 genes have been related to OI[1, 3-5].

Secondary, or acquired, osteoporosis can occur in individuals with chronic systemic illnesses as a result of the disease or its treatment. Children and teens with osteoporosis may experience frequent fractures, deformities, and back pain. Furthermore, the discovery of vertebral fractures on lateral spine x-rays can also help in diagnosing osteoporosis.[6, 7]

Often confused with fragile bone disease, pediatric osteoporosis can be quickly identified using simple X-ray techniques, preventing it from causing further issues. Prevention is key for managing osteoporosis in mobile and non-functional children, as many skeletal issues in pediatric patients are overlooked due to a lack of understanding of normal bone and joint physiology. By understanding the normal bone development process, physicians can identify and address abnormalities before they progress. This early recognition allows for prompt treatment to prevent complications. This article discusses the diagnosis and treatment of pediatric osteoporosis, focusing on the use of pharmacologic

treatment strategies for bone loss. As survival rates for systemic conditions improve, the incidence of osteoporosis is increasing, emphasizing the importance of monitoring bone health in follow-up care.[8]

Definition

The first International Consensus Conference on Osteoporosis in 1992 suggested that osteoporosis be defined as a state in which the bone mass and structural changes within the bone, and the resistance of the bone to stress are of such nature that the risk of bone fractures increases. Osteopenia is a term used to describe a total bone mass below the normal peak bone mass of young adult women.Osteopenia is considered a precursor of osteoporosis. Pediatric osteoporosis refers to reduced bone mass in the skeletally immature patient.[9]

According to the International Society for Clinical Densitometry (ISCD), pediatric osteoporosis is diagnosed when an individual has a bone mineral density (BMD) Z-score of -2 or lower and has suffered from clinically significant fractures. These fractures can include either two or more long bone fractures before the age of 10, or three or more long bone fractures before the age of 19. Additionally, pediatric osteoporosis can occur with one or more vertebral compression fractures that have occurred without high energy trauma or local disease, regardless of the BMD Z-score.[10-15]

The purpose of this definition is to differentiate between children with a preexisting medical condition and those with fractured bones due to typical childhood activities or intentional injury. However, there are various difficulties associated with this definition. For instance, the requirement for a BMD Z-score cut-off of ≤ –2 as a component of the osteoporosis definition. The score could vary by up to 2 standard deviations based on the reference data utilized to calculate the BMD Z-score. [[15-17]

Another issue to consider is the potential for not properly diagnosing conditions that make individuals more likely to develop osteoporosis. For instance, this could occur when children have low bone mineral density (BMD) but have not yet experienced a second or third fracture, or when the BMD Z-score is above -2 despite having recurrent fractures. As a result, it is important to follow current guidelines and not rely solely on BMD when diagnosing osteoporosis, but instead take into consideration the overall clinical context, including the seriousness and expected outcome of the underlying disease or treatment. .[18]

Etiology and Risk Factors

Primary osteoporosis (PO) is an idiopathic bone disorder prevalent in the adult population. However, adult PO is often considered as a continuum of a bone mass failure to develop in childhood.

PO refers to conditions of heritable bone fragility caused by intrinsic skeletal defects with abnormal composition of bone tissue. Causative genes affect different pathways such as collagen type I synthesis, bone mineralization, osteoblasts, or osteocyte dysfunction.[19,20] Children with primary osteoporosis are a diverse group with a wide range of skeletal and extraskeletal features, which can vary from mild to severe forms. These conditions lead to serious bone disease and low bone mass accumulation. It is crucial to identify these conditions early in order to begin treatment and seek specialized care.[20-22]

OI, or osteogenesis imperfecta, is the most frequently occurring primary form of osteoporosis. Common symptoms include recurring fractures, skeletal abnormalities, short stature, blue sclera, dentinogenesis imperfecta, hearing impairment, and loose ligaments. However, the specific symptoms experienced can differ from patient to patient based on the type of OI.[23]

Many diseases and medications can cause secondary osteoporosis (SO). Although the terminology for the etiology and pathophysiology of pediatric osteoporosis is sometimes unclear, there are many conditions that can lead to alterations in pediatric bone mass, strength, and/or microarchitecture, which may predispose patients to fractures during growth or later in life. These pediatric "symptomatic" bone disorders should not be viewed as causes of pediatric osteoporosis but rather as forms of secondary pediatric SO.[24]

Children and adolescents can present with fractures. It is important to note that fractures, although not specific to abnormal bone health, can often be associated with low bone mass or quality packed fracture (i.e., impaction-dependent fracture of a healthy bone). Some examples of fractures that fall into this category include vertebral compression, sacral insufficiency, and scapular fractures. Additionally, there are also other types of fractures such as pubic rami stress reaction, proximal femoral corner fractures, fibular fractures, pilon fractures (triplane), and talar neck fracture subtypes. These

various fracture subtypes highlight the complexity and diversity of fractures seen in children and adolescents. Understanding the different types of fractures is crucial for accurate diagnosis, appropriate management, and optimal outcomes for these young patients.

Lack of movement often leads to osteoporosis. The mechanostat theory suggests that bone strength is controlled by muscle force. When a person is immobile, their muscles do not provide enough tension to put pressure on the bones, which is detected by osteocytes and causes them to send signals that result in thinner and less dense bones.[6,25,26]

So, children who have conditions like cerebral palsy experience decreased periosteal apposition in the bones of their lower extremities, leading to decreased cortical thickness. As a result, fractures most frequently happen in the distal femur and tibia. [27,28] Children with Duchenne Muscular Dystrophy need to be closely monitored by a pediatric bone specialist due to their immobility, extended use of steroids, and the development of hypogonadism.[29] The harmful impact of glucocorticosteroids (GCs) on bone occurs because of an initial period of heightened bone breakdown followed by a period of reduced bone growth. [30-33]

In children, the administration of high doses of corticosteroids via intravenous or oral routes, as well as repeated pulse therapy treatments, has been associated with the development of osteoporosis.[34]

Insufficient data exists regarding the impact of low and moderate steroid doses. Nevertheless, based on adult population data, the continual use of systemic corticosteroids at medium to low doses is also believed to hinder growth and impact bone development.[35, 36] Additionally, prolonged use of inhaled corticosteroids (ICS) in kids may have an adverse impact on bone mineral density. This was observed in children who were prescribed high doses of ICS, but not in those who received low or moderate doses.[37-39] When taking into account the severity of asthma, there is no observed increase in the rate of fractures among children using ICS.[40]

Comprehensive Assessment of Clinical Presentation and Manifestation of Symptoms

Skeletal fragility is significantly influenced by bone mass, as well as disease, age, and genetic factors for children and adolescents. Skeletal irregularities or deformity can lead to pain and other problems of the spine, including asymmetry, kyphosis, or scoliosis. Bone pain and malformations are frequent reasons for pediatric patients to present to medical and subspecialized healthcare providers, with levels of care encompassing the spectrum from emergency medicine, urgent care, and primary care practices, to musculoskeletal, orthopedic, developmental, and endocrinology subspecialists, as well as to pediatric rheumatology, neurology, and rehabilitation services. Treatment should be aimed at relieving pain, providing injury care, and preventing further musculoskeletal damage.

When evaluating a child for osteoporosis, it is important to gather a comprehensive medical history. This includes investigating any previous fractures, such as the number, location, cause, and findings from X-rays. Inquiring about back pain is also crucial, as it could indicate vertebral fractures. Additionally, obtaining a detailed history of any other health conditions, physical activity, diet, medications, growth and development, and family medical history (including fractures and hearing loss) is necessary. The physical examination should encompass measurements such as head circumference and body proportions, as well as assessments of teeth, eyes, joint flexibility, spine, skin, and puberty status.[41]

Diagnosis

It is highly recommended to obtain laboratory tests for osteopenia, particularly in individuals who present with differing clinical picture and radiologic findings. These tests should include a thorough analysis of 25-hydroxyvitamin D, calcium, phosphate, alkaline phosphatase, and PTH levels. In cases where severe liver disease is present, it is crucial to also conduct a serum protein electrophoresis and a comprehensive metabolic panel as these can provide valuable insights. Furthermore, for other specific conditions, it may be prudent to consider tests for gluten sensitivity, celiac disease, copper levels, stool calprotectin levels, and TSH. Maintaining serum 25OHD levels above 30 ng/mL is of utmost importance, especially in colder climates and throughout the winter months, where achieving optimal levels can pose a challenge. This can be accomplished through a combination of dietary sources, exposure to sunlight, and the use of recommended supplements. Additionally, tests focusing on conditions like gluten sensitivity, celiac

disease, copper levels, and stool calprotectin can offer additional benefits. Incorporating an evaluation of thyroid function when assessing individuals with osteopenia is also strongly advised. By conducting comprehensive laboratory tests, healthcare professionals can gather essential information that enables them to make accurate diagnoses and develop effective treatment plans specifically tailored to patients with osteopenia.[42]

In some instances, fractures or bone pain may be the initial symptoms of an underlying condition. Therefore, it is recommended to also undergo an erythrocyte sedimentation rate, a full blood count with leucocyte differentiation, serum TSH, free T4, and celiac screening. If hypogonadism is suspected, it is advised to check levels of LH, FSH, testosterone (for males) or estradiol (for females). If Cushing's disease is suspected, it is recommended to check 24-hour urinary cortisol levels. The tests should be based on the symptoms presented and pediatric reference data appropriate for the population should be used.[6,43]

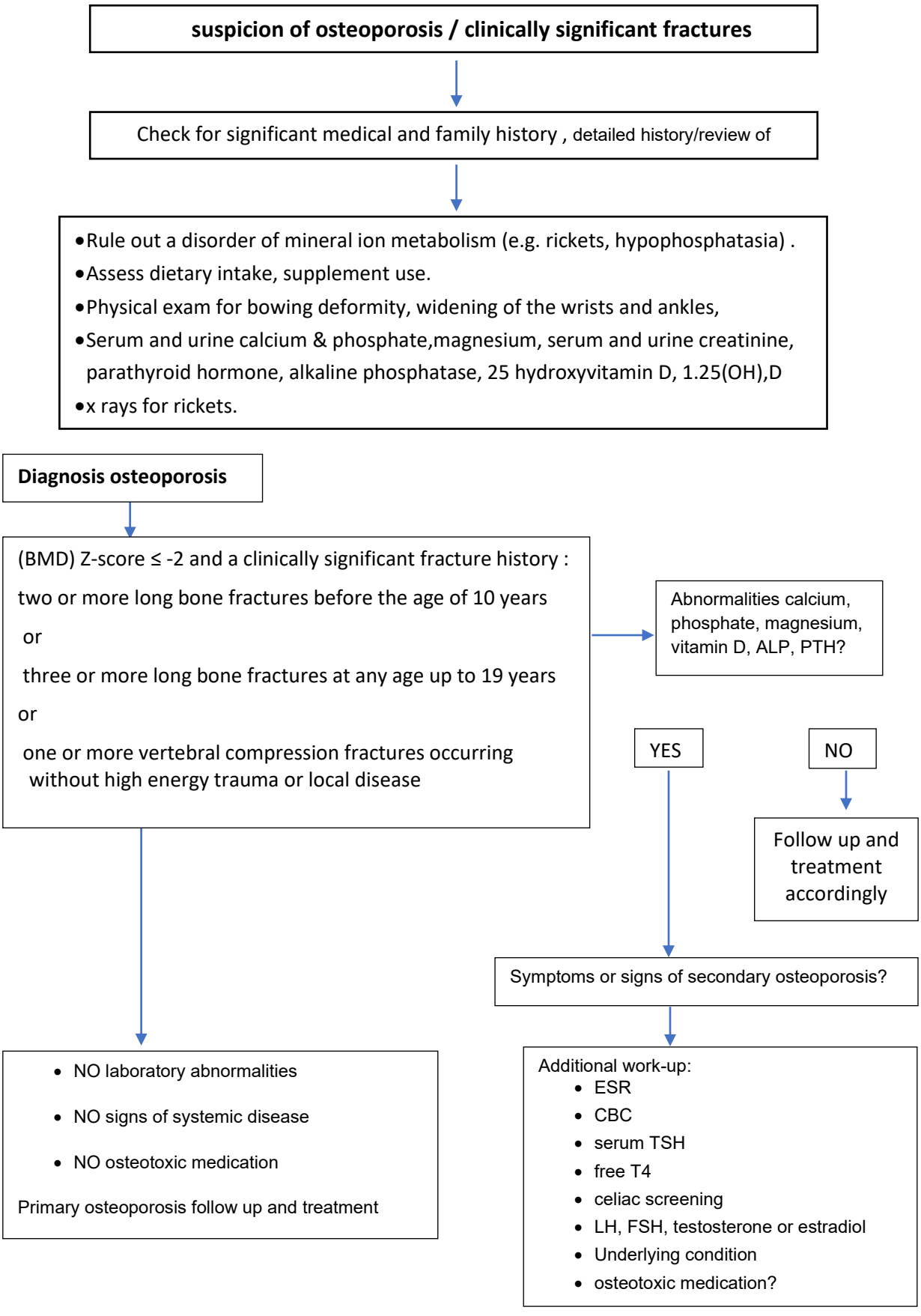
Dual-energy X-ray absorptiometry (DXA) is widely recognized as the gold standard method for diagnosing osteoporosis and low bone mass. It is currently utilized to evaluate skeletal status in the field of pediatrics. In order to diagnose osteoporosis in premenopausal women and assess low bone mass in postmenopausal women, both the lumbar spine (L1 to L4) and the femoral neck are recommended, as per the guidelines outlined by the World Health Organization (WHO). Within the Swedish pediatric normal reference cohort, growth is considered to be the primary factor that can affect lumbar spine bone mass measurements. Therefore, it has been proposed that the inclusion of L1 and L2, in addition to L1 to L4, may be beneficial when evaluating patients in the pubertal stage. Moreover, when assessing children with DXA, it is important to consider the area that provides the least amount of beam-hardening for the femoral neck. When utilizing DXA to evaluate low bone mass, it is crucial to report height velocity and bone age alongside the bone mineral density (BMD) and bone mineral apparent density (BMAD) Z-scores. It should be noted that the pubertal stage of a patient may also influence the BMD Z-score. . In addition, disrupting factors, such as movement during measurement, scoliosis, and metalwork, can give non-interpretable results .[41, 44]

If DXA-LS cannot be performed, alternative sites are the distal forearm, the proximal hip, and the lateral distal femur.[18]

During periods of growth, it is recommended to use a Z-score cut-off of -2, while a T-score cut-off of -2.5 is advisable for identifying osteoporosis or assessing adults within high-risk age groups who may be prone to pathologic fractures.

Common causes and associated conditions for secondary osteoporosis in children

Critical Organ Dysfunction	Endocrine disorders	Inflammatory Disorders	Lifestyle	Medications
•Hematological disorders (malignancy, thalassemia) •Glucocorticoid-treated liver and kidney diseases •Diabetes mellitus, Cystic fibrosis •Short bowel syndrome •Inflammatory bowel disease •Neuromuscular disorders (e.g. duchenne muscular dystrophy,CP)	•Hypogonadism •Hyperthyroidism •Growth hormone deficiency •Hyperparathyroidism •Endogenous hypercortisolemia •Amenorrhea due to anorexia nervosa •Hypercortisolism •Hypogonadism	•Systemic vasculitis •Systemic juvenile arthritis •Juvenile dermatomyositis •Systemic lupus erythematosus •Mixed connective tissue disease •Inflammatory bowel disease •Celiac disease	•Limited sunlight exposure •Inadequate calcium and vitamin D intake •Lack of physical activity •Poor nutrition	•Glucocorticoids •Anti-epileptic drugs •Anti-coagulants •Methotrexate •Anti-retroviral agents •Calcineurin inhibitors •Proton pump inhibitors •Chemotherapy


suspicion of osteoporosis / clinically significant fractures
Check for significant medical and family history , detailed history/review of
•Rule out a disorder of mineral ion metabolism (e.g. rickets, hypophosphatasia) .
•Assess dietary intake, supplement use.
•Physical exam for bowing deformity, widening of the wrists and ankles,
•Serum and urine calcium & phosphate,magnesium, serum and urine creatinine, parathyroid hormone, alkaline phosphatase, 25 hydroxyvitamin D, 1.25(OH),D
•x rays for rickets.
Diagnosis osteoporosis
(BMD) Z-score ≤ -2 and a clinically significant fracture history :
two or more long bone fractures before the age of 10 years
or
three or more long bone fractures at any age up to 19 years
or
one or more vertebral compression fractures occurring without high energy trauma or local disease
Abnormalities calcium, phosphate, magnesium, vitamin D, ALP, PTH?
YES
NO
Follow up and treatment accordingly
Symptoms or signs of secondary osteoporosis?
• NO laboratory abnormalities
• NO signs of systemic disease
• NO osteotoxic medication
Primary osteoporosis follow up and treatment
Additional work-up:
• ESR
• CBC
• serum TSH
• free T4
• celiac screening
• LH, FSH, testosterone or estradiol
• Underlying condition
• osteotoxic medication?

Treatment Approaches

Strategies for Improving Bone Health in Children with Low Bone Density :

The team treating a child with low bone density should focus on managing the underlying condition while also implementing general methods to enhance bone health. For instance, weight gain and a return to normal estrogen production can improve bone density in adolescents with anorexia nervosa, and vitamin D and calcium supplementation can further promote bone remineralization. Bisphosphonates are generally not recommended as the first-line treatment for otherwise healthy pediatric patients with low bone density. They should be considered for children with severe osteoporosis or certain conditions like osteogenesis imperfecta, where recurrent fractures and vertebral collapse may occur despite disease management. Pediatricians should ensure that at-risk patients receive adequate vitamin D and calcium, even though there are no standardized amounts recommended for children with these conditions. Currently, the recommended daily intake for vitamin D is 400 IU/d for infants younger than 1 year and 600 IU/d for children 1 year and older. Calcium intake should match the recommended daily allowance for healthy children, which varies based on age. Collaborating with pediatric physical therapists can also help safely maximize activity in children at higher risk for osteoporosis and fractures.

The main strategy in treating pediatric patients with osteoporosis is to improve their bone mineral status. Although osteoporosis of childhood due to chronic illness is often irreversible, worsening can be prevented, leading to improved growth in affected prepubertal children or minimizing the decrease in bone mass and fractures associated with chronic illness in affected pubertal and postpubertal children. Treatment for idiopathic juvenile osteoporosis, secondary juvenile osteoporosis may include some combination of higher calorie diets, improved nutrition, increasing weight-bearing activity, medical therapy designed to supplement the bones with an anabolic agent, or for those with germline LRP5 or LRP5-associated phenotypes, possibly pharmacologic inhibition or gene editing strategies for particular scenarios.[44, 45]

In all osteoporotic prepubertal pediatric patients due to chronic illness affecting both cancellous and cortical bone, we generally recommend supplementation with calcitriol 0.25 mcg daily to 0.5 mcg every other day and oral calcium 250 mg two to three times daily within 30 minutes of a meal, improving weight-bearing activity carefully, and (when weight-bearing activity can be tolerated by prepubertal children) providing a higher calorie diet to meet estimated metabolic demands, meaning to promote bone health with normal bodyweight status.

In specific settings, additional anabolic agents such as testosterone or other anabolic steroids, insulin-like growth factor 1 or 3, teriparatide may be considered on a case-by-approach in addition to support for diet, weight-bearing activity, and normalized underlying disease states, as clinical experience and data become available.

Pharmacological Interventions

This topic has not been well studied in most long-term studies on pediatric osteoporosis treatment. Bisphosphonates have been used in adolescents as young as 12.5 years old, but treatment regimens and long-term effects are uncertain. Calcitonin and raloxifene are not FDA-approved for pediatric use. Vitamin D therapy may be considered for patients with deficiency, and adequate intake for infants is 400 IU/d and for children 1 year and older is 600 IU/d. Vitamin D levels do not require routine measurement but may be reasonable in children with significant fractures. Severe cases may require oral or intravenous calcium therapy. Insufficiency or deficiency cases must be monitored to avoid hypercalcemia and kidney stones. Diet is crucial for bone health management.[46]

Nutritional and Lifestyle Modifications

Calcium and vitamin D are crucial for healthy bone development. Requirements vary by age, diet, and sun exposure. Puberty and growth spurts require increased calcium intake. Many pediatric patients have low calcium intake, so supplemental calcium is important. Vitamin D levels can be challenging to maintain, especially in areas with less sun. Daily supplementation is important. Calcium-rich foods and exercise also help with bone health and fracture reduction.[47-49]

Monitoring and Follow-up

Patients with low bone mineral density should undergo monitoring and follow-up studies. Initial DXA Z-score should be tested annually for height, weight, and either BMI or pubertal status evaluation. Spine DXA should be done every 24 months if Z-score is worsening. Long bone length measurements can track growth velocity. Patients with growth velocity less than 5 cm per year should receive appropriate investigations. Additional DXA T-scores should be obtained at Z-score of -2.0 or less. Annual bone-specific alkaline phosphatase or serum cross-linked C-telopeptide evaluation is recommended for those with predicted below normal puberty age. Dietary counseling is important for weight gain failure. Counseling should be given in cases of significant menstrual irregularities, absent menarche at age 15, or only one menstrual cycle in the past 6 months. Monitoring of BMD after stopping anti-osteoporosis medication is necessary. The American Society for Bone and Mineral Research recommends repeating DXA every 2 years for patients with at least one major osteoporosis risk factor. In patients with a DXA at femoral neck T-score -2.0 or lower, more frequent DXA monitoring is appropriate.[50-52]

Assessment of Treatment Efficacy

Currently, dual-energy X-ray absorptiometry (DXA) is the only established imaging technique that is validated for assessing diagnosis and treatment efficacy for osteoporosis.[53-56]

The International Society for Clinical Densitometry (ISCD) recommends at least a one-year interval for T-scores determined by DXA at two different body sites, such as lumbar vertebrae (L1-L4) and total proximal femora (hip; TPF), in order to monitor treatment efficacy. Bone mineral content (BMC) is usually normalized by total body weight and transformed into Z-scores based on the same sex, age, and body size in a pediatric population. Of note, spine enlargement may not be reflected by an improvement in the BMC Z-score after antiresorptive treatment, and thus vertebral volumetric BMD, as assessed by quantitative computed tomography, should be considered a more suitable marker of evaluation. Periodic radiation exposure is one of the main concerns for quantitative imaging. [41, 57, 58]

5.2. Long-term Management Strategies

Despite being off-label, anabolic agents are widely recognized for their growth-promoting effects in short children with osteoporosis. These agents have also shown to improve final height in children with severe osteogenesis imperfecta (OI) and can be used for pubertal children with anorexia nervosa and low bone mineral density (BMD). The standard anabolic agent for this is rhIGF-1. Alternatively, luteinizing hormone-releasing hormone analogues (LHRHa) can be used for children with growth retardation due to early puberty. Bisphosphonates are the gold standard therapy for pediatric osteoporosis, but their use should be limited due to potential harm on the growing skeleton. Instead, medication that can be used long-term without side effects is being developed. Management of osteoporosis in children should include fracture treatment, addressing high-risk conditions, proper nutrition, exercise, and avoiding smoking and alcohol. Regular BMD measurements and fracture risk assessment are important to prevent further fractures.[46, 50, 59, 60]

Conclusion

It is of utmost importance for pediatricians to possess extensive knowledge about both genetic and acquired pediatric bone disorders, as these conditions can result in substantial morbidity and necessitate early identification. In the context of osteoporosis in children, it is absolutely imperative to consult with or make a referral to a specialized pediatric bone expert. This aspect holds even greater significance owing to the fact that children possess an extraordinary capacity for natural and medication-facilitated recuperation, inclusive of the reshaping of vertebral fractures. Consequently, pediatricians assume a pivotal role in augmenting bone mass accumulation and ensuring optimal musculoskeletal well-being in children afflicted with osteoporosis.

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