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Pediatric Bone Health Update

Assessment and management of low bone mineral density in children with cerebral palsy

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ABSTRACT

Cerebral palsy (CP) is an impairment in motor function and coordination due to a nonprogressive brain injury that occurs pre-, peri-, or postnatally until 2 years of age with a prevalence of 1 to 4 per 1,000 live births. Along with impaired motor function, decreased bone mineral density (BMD) in children with CP is of concern for providers. An algorithm has been created to help identify patients at risk for decreased BMD who are seen by providers. Factors included in the algorithm are medication history, fracture history, ketogenic diet, ambulation status, history of endocrinopathy, and pubertal stage.

BMD levels are measured using dual-energy x-ray absorptiometry scans. Once a patient is identified as having decreased BMD several treatment options are available. BMD can be increased through stander use, diet, and bisphosphonate treatment. This paper serves as a summary of the current ways in which children with CP are assessed at each visit, as well as how to treat low BMD once it has been identified.

Key Concepts:

(1) Explain the algorithm used to identify patients at risk for decreased BMD.
(2) Review how to assess patients with decreased BMD.
(3) Summarize treatment recommendations to increase BMD in children with CP.

Introduction

The basis of skeletal health is established during childhood and adolescence; any insults occurring during these time periods increase the lifetime risk for osteoporosis and fracture. Children with cerebral palsy (CP) have a higher incidence of fragility fractures than their age-matched peers. The incidence of fractures among children in the United States ranges from 1.6% to 3.6% per year [1]. However, the risk of fracture in children with CP ranges from 4% to 12% with ambulatory status having a significant contribution to higher fracture incidence [2]. Children with CP have multiple risk factors related to poor bone health including decreased mobility, poor nutrition or restricted diets, use of medications that may have adverse effects on bone health and vitamin D metabolism, comorbid chronic conditions, and changes in pubertal tempo. In this review, the authors will (1) provide the background for the development of a screening algorithm to understand which children with CP may benefit from a more formalized assessment of their bone health, (2) review the tools used in the assessment of skeletal health and maturation, and (3) discuss approaches for treatment of bone health in children with CP.

Background

CP is commonly defined as a nonprogressive injury to the brain occurring during the pre-, peri-, or postnatal period up until 2 years of age. Its incidence is reportedly as high as 1 to 4 per 1,000 live births per year [3]. Motor function is assessed using the Gross Motor Function Classification System (GMFCS), which uses a scale of 5 different levels. Level I corresponds to the ability to walk with no limitation, and the scale progresses to level V, which requires a wheelchair for mobility [4]. Lack of weight-bearing leads to decreased bone density because of the lack of a feedback mechanism of weight and standing on bone

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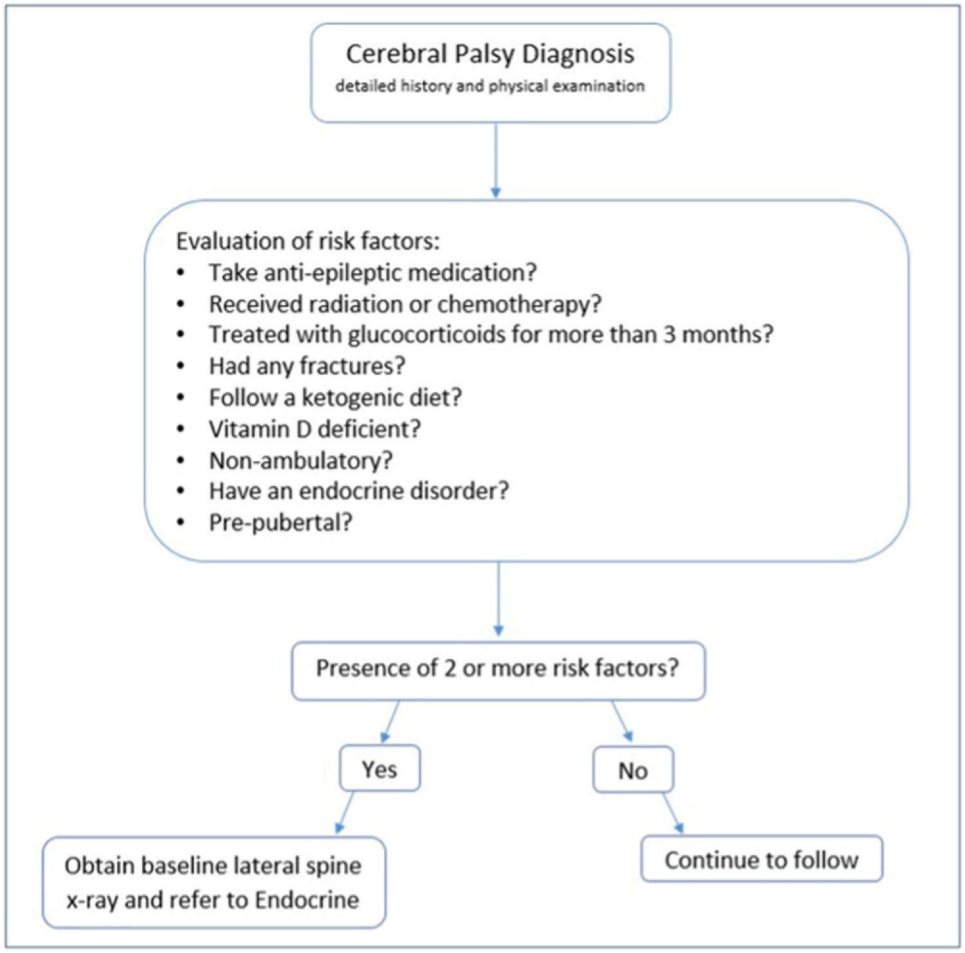

Figure 1. Algorithm created for determining the risk of low bone mineral density.

growth [5]. As a result, patients with a GMFCS classification of IV to V often have decreased bone mineral density (BMD), due to limited weight-bearing status.

Certain aspects of the patient's medical history are important when considering bone health. An algorithm has been created in collaboration with a pediatric endocrinologist specializing in bone health and the CP team to help identify patients at risk for decreased BMD who are seen in a multidisciplinary CP clinic. A comprehensive history of the child's medication, fractures, and nutrition should be obtained since this may impact BMD levels. A baseline radiograph of the lateral spine should be considered, particularly in patients who have a history of fragility fractures, glucocorticoid exposure, and/or back pain [6,7]. Referral to a pediatric bone health specialist or endocrinologist should be made if the patient is at risk for low BMD based on having 2 or more risk factors described in Fig. 1.

Medication history

Medication history is important because many medications affect bone resorption, remodeling, and osteoporosis. Antiepileptics drugs are of concern for children with CP. Children with CP often have epilepsy and are treated with antiepileptics drugs such as phenytoin and phenobarbital [8]. These drugs alter BMD levels by inducing the activity of the enzyme cytochrome P450, metabolizing 25-hydroxy Vitamin D (25OHD3) to its inactive metabolites. Low 25OHD3 levels decrease calcium absorption leading to increased levels of parathyroid hormone (PTH). Increased release of PTH leads to increased bone turnover and promotes phosphaturia, resulting in decreased BMD levels. Although rarely used in patients with CP, questions about the use of chemotherapeutics and radiation in the history are important because they can reduce BMD through a variety of mechanisms [9]. Chronic glucocorticoid use is often seen in patients with CP who have respiratory disease due to bronchopulmonary dysplasia and other lung diseases. The prolonged use of steroids increases bone resorption and decreases bone formation [10].

Fracture history

The location and the circumstances surrounding a fracture (low energy vs high energy) are important to obtain. In patients with CP who have a history of 1 fracture, the odds of obtaining another fracture are 1.9 times higher than average, whereas after the second fracture, the odds increase to 3.04 times more likely to fracture again [8]. Children with GMFCS levels I to III experience fractures in typical locations for a child their age, whereas levels IV and V tend to experience fractures in the distal femur and lower extremities [8].

Fractures related to low BMD are often caused by low-energy mechanisms. When diagnosing osteoporosis, it is important to assess a patient's history for fragility fractures and vertebral fractures. Fragility fractures occur under stress levels which would not ordinarily result in a fracture. Vertebral fractures are commonly missed in the clinical setting. They are of significance because they are a predictor of future fractures as well as decreased quality of life and survival [11].

The International Society for Clinic Densitometry defined pediatric osteoporosis by:

1. One or more vertebral fractures in the absence of disease or trauma regardless of z-score;

2. In the absence of vertebral fractures, osteoporosis is diagnosed with the presence of a clinically significant fracture and BMD z-score less than or equal to 2;
3. Two or more long bone fractures before the age of 10; or
4. Three or more long bone fractures before the age of 19 [12].

Ward et al. [13] recommended refraining from diagnosing osteoporosis in children with only the International Society for Clinic Densitometry criteria, and also using clinical context and fracture characteristics to aid in diagnosis. Based on clinical history and further testing a diagnosis of primary or secondary osteoporosis could be made [13].

Nutrition assessment

Children with CP can have challenges with nutrition. Dysphagia may cause the child to eat more slowly and in smaller amounts. Patients who are GMFCS IV or V may not have the motor ability to feed themselves and have increased energy requirements [14]. Some children require a gastrostomy tube for feeding. Tube-fed children have lower BMDs and weights than those who can feed themselves [15]. Working closely with a dietitian is often needed to meet the nutritional needs of a child with CP.

Calcium is important for bone health and is regulated primarily by intestinal absorption and secondarily by bone turnover and renal absorption. Low levels of calcium triggers a release of PTH from the parathyroid gland. PTH acts to increase 1,25-OHD3, which causes increased calcium absorption from the gut. This also increases calcium release from the bones by resorption and increases calcium reabsorption by the kidney [16]. Thus, nutritional deficits in calcium intake have substantial implications in calcium metabolism. Impaired functioning of any of these pathways may result in decreased levels of calcium resulting in decreased BMD [17]. A nutritional history uncovering risk factors for calcium deficiency, including lactose intolerance, should prompt a consultation to a dietitian.

Ketogenic diets may be prescribed for children with CP who also have epilepsy. Low levels of BMD have been linked to ketogenic diets [18]. The ketogenic diet creates a high acid load. The acidic load leads to a process resulting in the release of calcium carbonate from bone which acts as a buffer resulting in hypercalciuria [19]. The ensuing hypercalciuria leads to a net calcium loss from bone and contributes to low BMD levels [20].

Ambulation status

Mechanical stress from standing and bearing weight while walking works in a feedback mechanism to stimulate bone growth [5]. Physical activity stimulates the proliferation and activation of osteoblasts resulting in thicker bone and higher BMD, while a lack of weight-bearing or exercise negatively impacts the action of osteoblasts resulting in lower BMD [21]. The effect of low ambulation on patients with CP has been investigated; children with a GMFCS level of V were found to have lower BMD levels than their GMFCS levels III-IV counterparts [15].

Endocrinopathies

Proper bone growth and mineralization require various exogenous and endogenous processes. The endogenous processes that mediate bone growth are regulated by hormones. If a child has an endocrinopathy, this can contribute to their low BMD. Hormones that are essential for bone growth are growth hormone (GH), sex hormones, and thyroid hormones.

GH stimulates the release of insulin-like growth factor-1 from the liver. There is evidence that locally expressed insulin-like growth factor-1 (autocrine/paracrine) regulates longitudinal bone growth in the growth plate [22]. Ultimately, the actions of GH/IGF1 lead to the widening of the epiphyseal plate, increased bone mineralization, and bone remodeling, resulting in increased bone mass [23]. If one is deficient or resistant to GH, then BMD is also affected.

Pubertal development assessment

Puberty increases the rate of bone growth. An increase in bone density occurs late in the course of puberty. Children with CP often enter puberty faster than those without CP, but complete it later [24]. The most accurate evaluation of the pubertal stage is by a physical examination that includes an assessment of genital structures and secondary sexual characteristics. Assessments are categorized into 1 of 5 Sexual Maturity Rating (SMR) stages, formally known as Tanner stages. The main criteria assessed for development are pubic hair growth and breast development in females and pubic hair, testicular enlargement, and genital development in males. Worley et al. [24] studied the effects of CP on maturation using SMR staging and found that children with CP grew slower in every SMR stage compared to children without CP.

A secondary tool for the evaluation of pubertal status is the measurement of gonadotrophins and sex steroids, such as estrogen and androgens. Estrogen is important for bone development because it inhibits excessive bone resorption through the inhibition of osteoclasts. Decreased levels of androgens also lead to lower BMD in both men and women. Including gonadotrophins and sex steroids in pubertal assessment is important as a secondary measure in children with delayed or nonprogressive pubertal development, as hypogonadism negatively influences BMD and increases fracture risk [25].

BMD assessment

Dual-energy X-ray absorptiometry (DXA)

DXA as an assessment tool, is efficacious, accurate, precise, and minimally invasive and has low radiation exposure. The lateral distal femur and lumbar spine are preferred sites for evaluation. The lateral distal femur measurement is used to assess bone mineral density in children who are nonambulatory, have difficulties with positioning, have hardware or tubes that cannot be removed, abnormal skeletal anatomy, and/or severe scoliosis that may interfere with DXA procurement at other skeletal sites [26,27]. DXA scans are also used to conduct vertebral fracture assessments. Identifying vertebral fractures is an important part of bone health monitoring in patients with CP as they are at risk for decreased BMD. Therefore, a vertebral fracture assessment via DXA is indicated [26]. A vertebral fracture alone is enough to satisfy the criteria for osteoporosis [28]. DXA should not be used as first-line imaging in someone who is having back pain as lateral spine radiographs still remain the gold standard for diagnosis of vertebral compression fracture.

A Z-score provides a means of comparison between a patient's measurement and that of an average child in their same age group, sex, and race, whereas, a T-score is a standard deviation calculation in relation to the average BMD measurement of a 30-year-old [29]. For clinical use in children, a Z-score is used. A score of -2.0 or lower is considered low [8]. Height should be taken into consideration as children who are shorter than their peers may have falsely low measurements. Height can be measured using a tibial length in patients with CP who have associated contractures [30,31]. Measurements are manufacturer-specific, so measurements should be compared from the same machine [32] (Fig. 2).

Treatments

The treatment of low bone density can be influenced by both mechanical and pharmacologic methods [15].

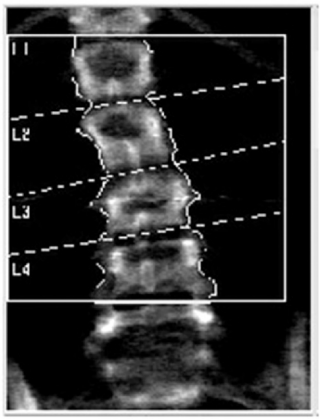

Figure 2. DXA image of the lumbar spine.

Stander use

Standard mechanical treatment describes the use of a stander to stimulate bone growth by allowing a patient to stand for longer periods of time than could be achieved alone. One issue with this treatment is that there is no standard prescription or regulated threshold of time in a stander for observable benefit. Commonly quoted in the literature, is the use of a stander 5 days a week in 60- to 90-minute increments [33].

Initial research into the benefits of weight-bearing standers has been inconclusive. Some studies have reported that there were no observable benefits, whereas others have reported BMD levels that were increased and then plateaued after some time [34] Eisenberg et al. [35] cited an increase in BMD levels measured in the femur with the use of a stander. Weight distribution within the stander itself may not replicate natural standing, confounding the results of such studies [36]. Other modified standers that have been shown to have moderate benefits are vibrational standers [33], but the research so far is very minimal.

While it is known that exercise increases bone mineral density, the effect of a gait trainer in children with CP on bone mineral density has not been studied. Gait trainers are used in children with CP to improve mobility and ambulation by supporting the trunk and pelvis to aid in ambulation [37]. The overall goal of a gait trainer is to improve activity and participation in walking. Although gait trainers are not expected to achieve a goal of unassisted ambulation [37], they will allow for weight-bearing which may have positive effects on bone mineral density.

Diet

Malnutrition has been linked to lower BMD levels with subsequent increased frequency of fractures. Vitamin D and calcium are necessary for successful bone growth. Although optimal doses of vitamin D remain unclear for children with CP, 400 IU/day vitamin D supplementation in infancy, and 600 to 1,000 IU/day supplementation in childhood may be enough to prevent secondary osteoporosis [18,38].

The recommended daily intake of calcium by age group is listed in Table 1.

Bisphosphonates

Pharmacological efforts have also been pursued to increase bone density. Bisphosphonates are commonly used medications used to treat osteoporosis for fracture prevention in adults. The decision to use bisphosphonate therapy in CP children with decreased BMD should be made on an individual basis. Initial therapy starts by addressing low 25OHD3 levels, hypocalcemia, decreased ambulation, and hypogonadism before bisphosphonate therapy is considered [40]. Intravenous (IV) or oral bisphosphonate administration can be used. However, due to the favorable pharmacokinetic profile in children and high rates of gastrointestinal reflux or dysphagia in patients with CP, IV formulations are often preferred [41].

Table 1
Calcium recommended daily allowance by age.

Age	Male (mg)	Female (mg)
0 to 6 months	200	200
7 to 12 months	260	260
1 to 3 years	700	700
4 to 8 years	1,000	1,000
9 to 13 years	1,300	1,300
14 to 18 years	1,300	1,300
19 to 50 years	1,000	1,000

Adapted from National Institutes of Health. Calcium Fact Sheet for Health Professionals. October 6, 2022. Available at: https://ods.od.nih.gov/factsheets/calcium-HealthProfessional/. Accessed November 29, 2022 [39].

Recommended dosing and duration of therapy are still under investigation. In a study by Nasomyont et al. [42], a 1.5 mg/kg/dose infusion of pamidronate every 3 months was preferred, whereas other investigators preferred a 1 mg/kg/dose infusion every 3 months [40,42]. Zolendronic acid has also become more widely used in the last 5 years, with varying regimens. Bachrach and Ward [43] documented that bisphosphonate use was associated with a 21% to 89% gain in BMD with the use of pamidronate, and a reduced incidence of bone pain and fractures. Nasomyont et al. [42] found that among patients with greater than 2-year follow-up, fracture rates decreased from 1.4 to 0.1 fracture/year. Hurley et al. [41] reported after bisphosphonate treatment the fracture rate decreased from 2.4 to 0.1 fractures/year, with a follow-up of 6.4 years.

The duration of bisphosphonate therapy in children is still ill-defined. In children with osteogenesis imperfecta (OI), Bachrach and Ward [40] have shown that the effects of therapy tend to plateau after 2 to 4 years. Generally speaking, in the osteogenesis imperfecta population, bisphosphonate treatment continues until growth plates have closed to avoid creating areas of stress risers in bone [43]. It has been observed that the lasting effects on bone mass after therapy depend on the age of the child. Children close to adult height maintained bone mass in their spine 2 years after treatment was stopped; however, bone mass declined in children still growing [40].

Bisphosphonate therapy tends to be well tolerated in children. Avascular necrosis of the jaw is rarely if ever, described in children, but dental evaluations are still indicated [40]. A consistent adverse effect observed is a febrile reaction to IV administration of the drug [41,42]. The majority of research on the use of bisphosphonates is in patients with osteogenesis imperfecta. As a result, many clinicians follow these protocols in the absence of CP-specific recommendations [40].

Summary

Children with CP should have a bone health risk stratification performed at each visit. If more than 2 risk factors are identified, the patient should be referred to an endocrinologist or bone health specialist and sent for lateral spine radiographs for vertebral fracture assessment. BMD is measured using DXA as it is highly efficient, minimally invasive, and accurate. To decrease the risk for low BMD levels and subsequent fragility fractures in patients with CP, treatment is centered on increasing weight-bearing activity with stander use, optimizing nutrition, and potentially initiating pharmacologic intervention.

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Author contributions

Jeffrey R Sawyer: Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **David D Spence:** Conceptualization, Visualization, Writing – original draft, Writing – review & editing. **William C Warner:** Conceptualization, Data curation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Leslie N Rhodes:** Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Alicia Diaz-Thomas:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **Woodi Hazel Woodland:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing.

Declarations of competing interests

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