Saudi Journal of Biological Sciences 29 (2022) 2007–2013

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Vitamin D deficiency in children with cerebral palsy: A narrative review of epidemiology, contributing factors, clinical consequences and interventions

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ARTICLE INFO

Article history:
Received 27 October 2021
Revised 16 November 2021
Accepted 12 December 2021
Available online 16 December 2021

Keywords:
Cerebral palsy
Developmental disorder
Vitamin D
Deficiency
Epidemiology
Clinical consequences

ABSTRACT

Sufficient vitamin D levels are necessary, not only for mineralization, normal growth and development of bones, but also for the prevention of fatal chronic diseases like diabetes mellitus, metabolic syndrome and cancer. This is of particular importance in children with neuro- and musculoskeletal disorders, especially cerebral palsy (CP). CP is a heterogeneous group of childhood developmental disability disorders described by uncharacteristic posture, balance, and movement. Patients with CP are at an increased risk of vitamin D deficiency and as a result reduced bone mineral density, bone fragility, osteopenia, and rickets. The present review aims to combine and summarize available evidence, regarding the epidemiology, underlying contributing factors, clinical consequences, and treatment interventions of vitamin D deficiency in children with CP.

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2021.12.026
1319-562X/© 2021 The Author(s). Published by Elsevier B.V. on behalf of King Saud University.
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1. Introduction

Cerebral palsy (CP) is a cluster of heterogeneous neurologic childhood developmental, non-progressing, lifelong disabilities, characterized by constellation of bodily signs such as abnormal posture, inability to maintain balance and atypical movement. This clinical syndrome occurs as a result of brain injury or dysfunction (Al-Garni et al., 2021; Toopchizadeh et al., 2018). While motor disturbances may be the prominent features of CP, perceptive, sensory, musculoskeletal, cognitive, learning, behavioral, communicative defects, and even epileptic seizures are often concomitant (Al-Garni et al., 2021; Toopchizadeh et al., 2018; Ajami and Maghsoudlorad, 2016). Moreover, the quality of life in children with CP is severely affected due to limitations in daily life activities, for instance eating, drinking, bathing, dressing, limited range of mobility owing to erratic muscle tone, wobbly gait, uncontrolled movements, poor balance, and deprived social functioning (Toopchizadeh et al., 2018; Sellers et al., 2014).

CP requires long-standing dependent care and involvement of primary care physicians and neurology specialists. Rehabilitation care usually comprises of a number of methods ranging from conservative (muscle stretching, strengthening and massage) to complex approaches (conductive education and motor learning-based neurorehabilitation). With growing evidence on neuroplasticity, the emphasis has lately been diverted more towards neurological rehabilitation in children with CP (Blair et al., 2019).

The disabilities in CP, particularly abnormal muscle tone, precipitates difficulty in swallowing and subsequently result in malnutrition (Toopchizadeh et al., 2018). Also, poor nutrition, inadequate calcium and vitamin D (25-hydroxycholecalciferol or 25-hydroxyvitamin D_3) have been found to be common in CP patients (Akpinar, 2018). Vitamin D is essential for growth of bone, biomineralization and overall musculoskeletal development in childhood as it facilitates the absorption of alimentary calcium and phosphate (Taylor, 2020). Furthermore, not only it mediates copious cellular processes (Umar et al., 2018), but also influences the risk of developing diabetes mellitus (Zhang et al., 2020), metabolic syndrome (Chew et al., 2021), autoimmune disorders (Lemke et al., 2021) and malignancies (Nica-Badea and Udristioiu, 2021). With CP, children are prone to hypocalcemia, metabolic bone disease (low bone mineral density), osteopenia and rickets with extreme deficiency of vitamin D. It often results in painful fractures even with minor injuries (Sahota, 2014; Paksu et al., 2012).

By collating the available and emerging evidence, the present narrative review aims to accentuate the epidemiology, underlying contributing factors, clinical consequences, and treatment interventions of vitamin D deficiency in children with CP. Finally, the review will end with main takeaway points for clinical and research implications.

2. Prevalence of CP

Globally, CP accounts for significant morbidity and disability burden in pediatric population (Panteliadis et al., 2015). Having mentioned that, CP and many other developmental disorders are still exhaustively untapped themes in both developing and developed nations (Al-Garni et al., 2021). According to global estimates of Global Burden of Disease (GBD) Study 2019, cumulative all-age prevalence of CP is approximately 50.0 million, with age-standardized prevalence of 6.6 per 1000 population. Moreover, it is responsible for 11 million years of life lived with disability (YLD), necessitating long-term rehabilitation support (Cieza et al., 2020). The prevalence of CP is about 2 cases per 1000 live births (Oskoui et al., 2013). In developed nations, CP is very frequent with a prevalence of approximately 1.3–1.9 per 1000 live births (Report of the Australian Cerebral Palsy Register Birth years, 2018). However, as per population-based studies, the prevalence estimates range from approximately 2 to over 4 in children with defined age bracket or per 1000 live births (Winter et al., 2002; Johnson, 2002; Paneth et al., 2006; Bhasin et al., 2006.; Arneson et al., 2009; Van Naarden et al., 2016; Kakooza-Mwesige et al., 2017; Smithers-Sheedy et al., 2016). It is reported that the prevalence of CP in preterm infants is very high in comparison with term infants. Furthermore, the prevalence is inversely related to gestational age and birth weight (Hirvonen et al., 2014; Hafström et al., 2018). Interestingly, a fairly steady pattern has been witnessed in the prevalence of CP by large population-based studies over the years. A population-based study in Iceland estimated the prevalence of CP between 2.2 and 2.3 per 1,000 live births from the year 1990 to 2003, respectively (Sigurdardottir et al., 2009). A self-report of parents for children aged between 2 and 17 years observed a stable prevalence of 2.6 per 1000 live births in the National Survey of Children's Health (NSCH) and 2.9 per 1000 live births in the National Health Interview Survey (NHIS) (Maenner et al., 2016). Another report documented spastic CP prevalence of 1.9 in 1985 to 1.8 in 2002 per 1000 live births (Van Naarden et al., 2016).

3. Prevalence of vitamin D insufficiency and deficiency in children with CP

The exact prevalence estimates for vitamin D insufficiency and deficiency in children with CP are uncertain. Most of the research literature is limited to cross-sectional studies only. Wide ranging prevalence have been documented thus far. A case-control study from India by Manohar and Gangadaran (2017) reported 61% vitamin D insufficiency and 32% deficiency in children with CP (Manohar and Gangadaran, 2017). Seth et al. (2017) reported 60% of the CP children to be vitamin D deficient (Seth et al., 2017). Toopchizadeh et al. (2018), in their case-control study, demonstrated 44.6% prevalence of vitamin D deficiency in Iranian children with CP (Toopchizadeh et al., 2018). A cross-sectional study from Turkey observed that 28.8% and 22.6% of the CP children were vitamin D deficient and insufficient, respectively (Akpinar, 2018). Lately, Le Roy et al. (2021) also found that nearly half (47.8%) of their children participants with CP had vitamin D insufficiency and one-third (30.4%) had deficiency (Le Roy et al., 2021). One of the main reasons of difference in the prevalence could be inconsistencies in definition used for vitamin D insufficiency and deficiency. For instance, vitamin D insufficiency was defined as serum levels below 30 ng/mL and deficiency as serum levels below 10 ng/mL by Manohar and Gangadaran (2017). Toopchizadeh et al. (2018) used 20–30 ng/mL cutoff for vitamin D insufficiency and <20 ng/mL for deficiency (Toopchizadeh et al., 2018). While

Akpinar (2018) defined insufficiency and deficiency as 12–20 ng/mL and ≤ 12 ng/mL, respectively (Akpinar, 2018), Le Roy et al. (2021) used 21–29 ng/mL for insufficiency and ≤ 20 ng/mL for vitamin D deficiency (Le Roy et al., 2021).

4. Prevalence of fracture in children with CP

Fracture is one of the most common consequent features in patients suffering from CP due to inadequate vitamin D levels. A study by King et al. (2003) reported 39% fracture history in children with quadriplegic CP (King et al., 2003). A handful of longitudinal studies have also been conducted to determine the prevalence and factors associated with fractures in children with CP. Leet et al. (2006), in their study of 763 patients, documented 12% prevalence of fracture in CP children (Leet et al., 2006). Another study reported 6% occurrence of fracture CP patients (Presedo et al., 2007). A study from Japan by Maruyama et al. (2010), conducted on a very large cohort of CP children representing 38 schools, communicated 3.6% and 9.7% prevalence of 1-year and lifetime fracture, respectively (Maruyama et al., 2010). Previous study by Bischof et al. (2002) conveyed a very high prevalence of fracture; 23% in quadriplegic CP children (Bischof et al., 2002). A study from UK reported 12.5% prevalence of fracture. The study further found that 66% of the fractures were in severe cases (GMFCS V) of CP children, with knee being the most common site (Patel et al., 2015). One study reported incidence to be 4%/year in children with moderate-to-severe CP (Gross Motor Functional Classification System [GMFCS] III to V) (Stevenson et al., 2006). Brunner and Doderlein (1996) identified that 74% of multiple fractures in CP children were in femoral shaft and supracondylar area (Brunner and Doderlein, 1996). Over two-thirds of the lower limb fractures were reported by another study in CP children (Leet et al., 2006). In contrast, Presedo et al. (2007) reported greater than 80% of the fractures in lower extremities. They also confirmed 10% post-fracture complications such as more fragility fractures, nonunion, malunion and pneumonia (Presedo et al., 2007).

5. Contributing factors of vitamin D deficiency in children with CP

5.1. Immobility

One of the classic features of children with CP is zero mobility. Immobility is a triggering factor for osteopenia; severely low bone mass. In most cases where CP children are non-ambulatory for chronic duration, osteopenia is imminent (Duncan et al., 1999). Immobility is considered as the antecedent of poor sunlight exposure which in turn can precipitate vitamin D deficiency. Another explanation of low serum vitamin D level in non-ambulatory CP children is obesity (now commonly observed in CP). This is because adipose tissue sequesters vitamin D and therefore obesity due to long-term immobility may contribute to false vitamin D deficiency (Thacher and Clarke, 2011). Abdominal obesity has been documented as an independent risk factor of vitamin D deficiency (Peterson et al., 2014). Furthermore, immobility in CP children stems from abnormal or no muscular function which results in poor and chronic deprivation of nutrition (Agarwal and Verma, 2012), indirectly contributing to hypovitmainosis D.

5.2. Poor sunlight exposure

Sunlight exposure is a well-established determinant of serum vitamin D levels. Interestingly, over 90% of body's vitamin D requirement is fulfilled by sunlight exposure (Seth et al., 2017). Inadequate exposure to sunlight has been cited as one of the most common factors contributing to vitamin D deficiency in children with CP (Manohar and Gangadaran, 2017). The key precipitating element here is loss of ambulation. Quantification of sunlight exposure is complex and merely few studies have attempted to ascertain the relationship between quantitative sunlight exposure and vitamin D deficiency in CP children (Seth et al., 2017). A case-control study by Seth et al. (2017) found that the mean ultraviolet radiation exposure in healthy cohort was comparatively higher than in children with CP (10.3 ± 2.6 and 5.4 ± 2.3 min/m^2/day, respectively). Similarly, in ambulatory children with CP, the mean ultraviolet radiation score was relatively higher. They also reported mean ultraviolet radiation score as an independent predictor of moderate to severe vitamin D deficiency in CP children (Seth et al., 2017).

5.3. Difficulty in feeding and poor nutritional status

Problems with appropriate feeding disrupts intake of optimal nutrition. Difficulty in feeding develops simultaneously with increasing severity of motor disability, and in turn worsens the nutritional status (reduced calcium intake) of children with CP and eventually vitamin D deficiency (Le Roy et al., 2021). Feeding issues associated with difficulty in swallowing, dysfunctional lip and tongue control, tooth decay and malabsorption syndrome significantly damages skeletal health and enhances growth delay (Akpinar, 2018). Manohar and Gangadaran (2017) reported association between vitamin D deficiency and difficulty in feeding (Manohar and Gangadaran, 2017). Another report delineated that almost three-fourth of the CP children in their study failed to meet the daily requirements of dietary calcium intake. Low calcium disrupts vitamin D levels and bone mineralization status by triggering PTH-induced bone resorption (Seth et al., 2017). One main reason for poor nutritional status besides the disease itself is difficulty in managing the incapacitated CP child. It would not be wrong to say that parental neglect is very often anticipated in such dire scenarios.

5.4. Tube feeding

Children with CP are often on tube feeding, like nasogastric or gastrostomy tube feeding, for fulfillment of nutritional requirements. Because feeding problems mostly begin early and restricted growth is likely with advancing age, it is imperative to make sure optimal nutrition supply as soon as possible (Andrew and Sullivan, 2010). While use of tube feeding, based on the condition of CP children, may not directly impact vitamin D deficiency, it can still potentiate the impact of vitamin D deficiency by increasing the risk of fracture in children with CP. Only countable studies have studied the role of tube feeding and fracture risk in CP (Stevenson et al., 2006; Duncan et al., 1999; Uddenfeldt Wort et al., 2013). Duncan et al. (1999) reported osteopenia and inadequate micronutrients including vitamin D in non-ambulatory CP children on gastrostomy tube feeding (Duncan et al., 1999). A study by Stevenson et al. (2006) demonstrated high fracture rate in CP children on gastrostomy tube feeding in comparison with those patients without gastrostomy tube feeding (Stevenson et al., 2006). Ideally, we would expect gastrostomy feeding to be osteoprotective by ensuring sufficient delivery of micronutrients including vitamin D. Another key finding of study was association between higher body fat percentage and risk of fracture (Stevenson et al., 2006). This can be explained by the fact that gastrostomy can increase body fat percentage, which in turn reflects comparatively low muscle, as demonstrated by previous study on children with CP (Stevenson et al., 1994). High muscle and simultaneous pressure on bone tissue might have effect on bone formation, perhaps decreasing the risk of fracture. Another study

reported conflicting findings with regards to risk of fracture and gastrostomy tube feeding in children with CP. They reported gastrostomy to be associated with lesser fracture risk with trauma; however, 4-fold high risk of fracture without trauma was also noted (Uddenfeldt Wort et al., 2013). The reasons reported were long-term undernourishment of severely CP children (GMFCS IV–V) with fractures however with no trauma prior to gastrostomy. Another reason suggested was nutritional support given may not have adequate micronutrients, leading to increased risk of fracture.

5.5. Formula feeding

Another factor that can synergistically potentiate the vitamin D deficiency in children with CP is formula feeding (Kim, 2013). For obvious reasons of malnutrition and growth stunting and even death, CP children are exposed to synthetic nutritional support (Dipasquale et al., 2018). A retrospective research study by Duncan et al. (1999) reported significant deficiency of micronutrients along with vitamin D in CP children on commercially standard formulas (Ensure®, Jevity®, Pediasure® etc). They cited that 74% of CP children received < 75% of the Recommended Daily Allowance (RDA) (Duncan et al., 1999). Another study by Choi et al. (2013), but not on CP patients, reported 17.5% vitamin D deficiency in infants aged one to six months (Choi et al., 2013). A study from Canada by Gross et al. (2013) also reported severe vitamin D deficiency in six children on cow milk based infant formula added with vitamin D (400 IU/L) (Gross et al., 2013). These findings highlight that children formula feeding may not always adequately fulfill the bodily requirements of vitamin D and may contribute to fragile bones and fracture unless sufficiently supplemented in the formula according to the needs of the children with. Besides being diligent in actively monitoring the vitamin D levels, physicians should also be mindful of selecting the appropriate nutritional formula for micronutrients and vitamin D supplementation, if need be.

5.6. Use of antiepileptic drugs

CP children on antiepileptic drugs commonly encounter vitamin D deficiency and subsequently osteomalacia and rickets (Fong and Riney, 2014). Contrasting results have been communicated in this regard (Toopchizadeh et al., 2018; Manohar and Gangadaran, 2017; Le Roy et al., 2021). Literature suggests that cytochrome P450 enzyme inducers like carbamazepine, phenytoin, phenobarbitone and primidone, and inhibitors such as valproic acid drastically affect bone health by accelerating the metabolism of vitamin D (Seth et al., 2017; Yaghini et al., 2015). Of late, a systematic review and meta-analysis by found that pediatric patients on cytochrome P450 enzyme inducing antiepileptic drugs had statistically significant prevalence of vitamin D deficiency (OR 0.33, 95% CI 0.21–0.47). When they stratified analysis by study design of cross-sectional and cohort studies, they reported prevalence of OR 0.28, 95% CI 0.21–0.37 and OR 0.52, 95% CI 0.40–0.64, respectively (Junges et al., 2020).

5.7. Use of proton pump inhibitors

Children with CP are vulnerable to develop gastroesophageal reflux disease (GERD). The contributing factors are long-standing supine positioning and displacement of stomach due to scoliosis which stretches the lower esophageal sphincter, and increases intra-abdominal pressure from heightened spasticity (Fernando and Goldman, 2019). Moreover, the antiepileptic drugs used for treatment of CP also exacerbates GERD manifestations like nausea, vomiting and dyspepsia (Gjikopulli et al., 2019). To treat for the GERD, the proton pump inhibitors are administered. Apart from antiepileptic drugs, the proton pump inhibitors commonly used for managing GERD in CP children also possess adverse effects on bone health by depriving body of vitamin D, including reduced absorption of calcium and magnesium (Yaşar et al., 2018). It is to be highlighted that given the nature of the disease, CP children remain chronically on proton pump inhibitors. Physiologically, both direct impact of proton pump inhibitors on calcium and magnesium and decreased levels of vitamin D on calcium imbalance will lead to fatal consequences such as tetanus as earlier reported in literature (non-CP patient) (Sivakumar, 2016). It enhances the bone fragility and thus increases th risk of bone fractures (Hant and Bolster, 2016). The research data in this regard is very scarce; however, it can be conceived that while using antiepileptic drugs and proton pump inhibitors together may be necessary but can bring harmful consequences to CP children.

6. Formula feeding and exacerbation of risk of bone disease in children with CP

Like any other children, CP pediatric patients also require ongoing nutritional support via formula feeding. These nutritional formulas are manufactured by following national and international guiding principles to ensure adequate nutritional support and safety. When utilized as the only medium of nutrition, consumption is determined by energy needs and therefore micronutrient consumption differs. Micronutrient consumption from formula feeding is generally sufficient to meet daily needs till consumption descents normal levels for age, despite variable intake. Therefore, micronutrient deficiencies in children consuming formula feed is uncommon. Moreover, when consumption of formula feed is less owing to reduced energy needs, overall consumption of all micronutrients also plummets, ensuing multiple micronutrients deficiency. Hence, formula feeding associated deficit in isolated micronutrient is not very frequent. One recent case series study by Gonzalez Ballesteros et al. 2017 described 51 children from 17 different institutions manifesting hypophosphatemia with each one of them using a same nutritional formula (amino acid based), termed as elemental formula associated hypophosphatemia (Gonzalez Ballesteros et al., 2017). This has very important implication in children with CP if they are prescribed amino acid based nutritional formula like Neocate® as they encounter multiple deficiency disorder, including calcium and vitamin D, which can further deteriorate bone health. Therefore, periodic assessment of calcium, phosphate and vitamin D levels are highly recommended.

7. Clinical consequences of vitamin D deficiency in children with CP

A plethora of papers have highlighted the importance of vitamin D with respect to bone health such as risk of pathological bone fracture (Toopchizadeh et al., 2018; Akpinar, 2018; Leonard et al., 2020; Manohar and Gangadaran, 2017; Seth et al., 2017; Le Roy et al., 2021). In this regard, one research studied the relationship between vitamin D and insulin growth factor 1 (IGF-1) in children with CP. They found reduced levels of vitamin D with IGF in cases. Moreover, they hypothesized that vitamin D/IGF axis could have a role in osteopenia in CP children (Nazif et al., 2017). However, the role of vitamin D deficiency in orchestrating fatal cardiometabolic risk factors and diseases cannot be underestimated. A recent study reported vitamin D insufficiency and deficiency, independent of body mass index (BMI), to be associated with high triglyceride levels in contrast to those with normal vitamin D in children and adolescents suffering from CP, indicating vitamin D deficiency as a proxy biomarker for developing cardiometabolic diseases (Barja et al., 2020). Of great curiosity and interest, one study cited abdominal obesity as an independent predictor of vitamin D deficiency in

adults with CP (Peterson et al., 2014). It is, however, to be noted that increased obesity has also been observed in pediatric patients with CP (Rogozinski et al., 2007; Hurvitz et al., 2008). A scoping review reported obesity in children with CP between 3% and 18% (Ryan et al., 2018). A study conducted on Chinese children concluded that even insufficiency of vitamin D can enhance the risk of abnormal blood glucose among children, with girls being at potential risk of high total cholesterol and hypertension (Xiao et al., 2020). Dolinsky et al. (2013), in their systematic review found inverse association between vitamin D and blood pressure among children and adolescents (Dolinsky et al., 2013). The conceivable biological explanation of these could be presence of vitamin D receptors on smooth muscle cells, endothelial cells and myocytes, by acting on which vitamin D helps reduce proinflammatory cytokines, and thereby overall inflammation (Norman, 2008; Sugden et al., 2008; Tarcin et al., 2009; Schleithoff et al., 2006). The discussed evidence may not be adequate to cement the role of vitamin D deficiency in increasing the propensity of cardiometabolic syndrome in children with CP; however, the findings of cardiometabolic risk in children in general population are of substance to implicate as vitamin D deficiency along with malnutrition is far more severe in disabled children.

8. Interventions for vitamin D deficiency in children with CP

The principal approach to deal with the issue of vitamin D deficiency should be the minimization or eradication of etiology. Optimal bone mineral density can be attained via a blend of modifiable factors such as sunlight exposure, calcium and vitamin D supplementation and weight-bearing activities. Drugs or their doses that causes vitamin D deficiency should be reconsidered for adjustment and non-ambulatory periods must be minimized (Toopchizadeh et al., 2018; Akpinar, 2018; Seth et al., 2017; Le Roy et al., 2021; Fehlings et al., 2012; Wagner and Greer, 2008).

8.1. Vitamin D supplementation

Vitamin D is essential for bone mineralization and appropriate functioning of musculoskeletal system. In children with CP, vitamin D supplementation can be considered as an alternative. According to a systematic review, there is no consensus on clinical formulation and dosage of vitamin D supplementation (Fehlings et al., 2012). Biologically, upon exposure to ultraviolet radiation from sun, skin can synthesize vitamin D_3 and even both vitamin D_2 or D_3 can be acquired through food sources (Wagner and Greer, 2008). CP children are often not sufficiently exposed to sunlight, and therefore may require dietary and/or vitamin D supplementation. The hydroxylation of inactivate vitamin D_2/D_3 in the liver and final activation in the kidney produces 25-hydroxyvitamin D (25-OH-D) and 1, 25-dihydroxyvitamin D, respectively. The form of vitamin D supplementation can be either inactive or inactive. If children with CP have liver or kidney disease, then activated 1, 25-dihydroxyvitamin D form can be supplemented. It has been emphasized that inactive form of vitamin D_2/D_3 supplementation should be given to CP children to avert vitamin D toxicity such as hypercalciuria) because most children CP possess adequate liver and kidney function to process vitamin D_2/D_3 (Fehlings et al., 2012). The daily recommendation of vitamin D intake for healthy children is 600 IU/day. On the other hand, higher doses of 800–1000 IU/day are required to cater the vitamin D needs of CP child as per bone health specialists (Misra et al., 2008). This is acceptable to maintain sufficient vitamin D state; vitamin D levels over 50 nmol/L (Calvo et al., 2005). Vitamin D levels should be regularly monitored. Levels must be checked at baseline to determine the adequacy, insufficiency, and deficiency and then vitamin D supplementation should be planned accordingly.

8.2. Role of bisphosphonates

Bisphosphonates are yet another viable option to treat bone mineral density in children with CP. While it does not act directly to increase vitamin D levels; however, it can act synergistically to increase bone mineral density and diminishing risk of fracture by antagonizing osteoclasts that reabsorb bone tissue. While bisphosphonates are commonly used for osteoporosis in adults, their utilization in children with bone disease is still debatable due to efficacy and safety concerns (Allington et al., 2005; Boyce et al., 2014).

It is important to note here that children with CP primarily possess defect in bone formation, for which ideal treatment would be anabolic drugs like teriparatide. However, due to risk of osteosarcoma, present recommendations do not allow anabolic treatment for developing bone tissue (Vahle et al., 2002). Therefore, bisphosphonate remains the ideal therapy for children with CP for bone disease.

Few adverse effects have been documented in children with CP with use of bisphosphonates. Symptoms like pyrexia, fatigue and flu have been reported after initial infusion. Moreover, gastrointestinal symptoms such as nausea, vomiting and abdominal pain are also common. Other cited side effects are low serum phosphate and calcium levels, bone ache, temporary uveitis, delayed healing of fracture, increase deposition of calcium in kidneys (nephrocalcinosis) and acute renal tubular necrosis. Noteworthy to mention that length of use of bisphosphonate is yet another factor in determining the adverse effects, for instance chronic use (>5 years) in has been linked with high occurrence of atypical femoral fractures (Shane et al., 2014) and jaw osteonecrosis (Khosla et al., 2007).

A study by Moon et al. 2017 found improved lumbar spine z-scores with bisphosphonate treatment (pamidronate); pre-treatment score of -4.22 ± 1.24 and post-treatment score of -2.61 ± 1.69. In fact, they also reported significant decline in alkaline phosphatase levels, and therefore concluded improved bone mineral density in lumbar spine and decreased fracture incidence (Moon et al., 2017). A meta-analysis by Kim et al. (2015) established that bisphosphonates significantly improve bone mineral density in children with CP. They found that lumbar spine and femur z-scores statistically improved post-treatment with bisphosphonates in comparison with pre-treatment scores (Kim et al., 2015). A very recent Cochrane review aimed to investigate the safety and effectiveness of bisphosphonates for treatment of low bone mineral density/osteoporosis/both in severe CP children (GMFCS III-V). The study reviewed two relevant randomized control trials (RCTs), of which only one could be finalized for effect estimation. They concluded uncertainty towards use of bisphosphonate for improvement of bone health in CP children (Hurley et al., 2021). More clinical trials are required indeed, with optimal treatment strategy regarding vitamin D and calcium supplementation and frequency of fracture as main outcome should be thoroughly considered.

9. Takeaway points for clinicians and researchers

Given the crippling nature of the disease, vitamin D status in children with CP cannot be disregarded. Clinical physicians, very often, emphasis on treating frequent symptoms like pain, spasticity and restricted mobility, and the effectiveness of relevant interventions. In actuality, most of such symptoms are further aggravated by vitamin D deficiency itself. Ironically, the focus on bone health in children with CP has been very marginal. Checking for vitamin D status in CP children is not a regular practice of most clinicians.

Simply testing for serum vitamin D levels on constant basis in children with CP would do no financial harm but may delay factors that exacerbate the symptoms emerging from this debilitating disease. We cannot deny the fact that normal bone growth is out of question in CP children; however, enabling bone development and plummeting the incidence and prevalence of injuries and fractures can certainly optimize their quality of life.

Research data is also meager with respect to vitamin D deficiency in children with CP. Majority of the published studies are conducted in single-centers. The vitamin D deficiency cutoffs used in studies are diverse and therefore further limits the generalization of findings. Most importantly, the exact prevalence and the burden of this entity is unknown. A meta-analysis collating studies to identify the prevalence of vitamin D deficiency would perhaps ascertain the gravity of this prevailing yet ignored health condition in pediatric population. Similar applies to prevalence of fracture in children with CP. Moreover, research data regarding cardiometabolic risk of vitamin D deficiency is also meager. Therefore, retrospective and prospective multicenter research studies are required to establish the prevalence, cardiometabolic risk of vitamin D deficiency in children with CP and suitable dosing and timing of vitamin D supplementation in children with CP.

10. Conclusion

The vitamin D deficiency in children with CP is common; however, the precise extent to which this condition prevails is unknown. Factors that contribute to increase risk of vitamin D deficiency in such population are poor sunlight exposure, difficulty in feeding, poor nutritional status and use of antiepileptic drugs. Continuous monitoring of vitamin D levels, early identification and appropriate vitamin D supplementation must be religiously followed by clinicians and is of significance in reducing the risk of injury and fractures, even more so in CP children with history of epilepsy, developmental and intellectual disability, and growth and mental retardation. Further research is highly warranted in this regard.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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