ISSN: 2754-4737

Journal of Neurology Research Reviews & Reports

SCIENTIFIC Research and Community

Mini Review

Open Access

Indications for the Use of Vitamin D in Everyday Life Clinical Practice in Individuals with Cerebral Palsy

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ABSTRACT

There is currently an increasing demand for chronic inflammation to be recognized as a comorbidity in cerebral palsy (CP). A broad immunomodulatory and anti- inflammatory strategy in therapy management should be introduced into daily care. Vitamin D status is increasingly recognized as an important aspect, as the steroid hormone is attributed to a complex physiological function. In summary, by 2024 there will be sufficient pathoimmunological evidence that children with CP will benefit significantly from daily high- dose vitamin D supplementation throughout their lives. The reduction of chronic inflammation in the CNS, positive effects on the skeletal and muscular system, prevention and therapeutic support of infections are the target for the active form of vitamin D, 1,25-dihydroxy-vitamin D3 (calcitriol). In particular, quality of life is increased by improving reduced muscle performance and reducing the potential risk of falls. Children with PC are prone to hypovitaminosis D and about half of the children had a vitamin D deficiency. If the Endocrine Society empirically recommends vitamin D supplementation for healthy children and adolescents aged 1 to 18 years to prevent disease , this treatment option should be used because of cytokine dysregulation in CP with poorer neurological development . Proactive therapy with vitamin D supplementation is equally important in women who want to have children, primarily to reduce the risk of CP.

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Received: Janaury 26, 2025; **Accepted:** Janaury 29, 2025; **Published:** February 10, 2025

Keywords: Cerebral Palsy, Interleukin, 1,25(OH)2D3, Bone Health, Vitamin D Supplementation, Infection Prevention

Introduction

Cerebral palsy (CP) is defined as a movement and postural disorder resulting from a non-progressive lesion of an immature brain [1]. PC is described as a condition characterized by abnormal tone, posture and movement and is clinically classified according to the predominant motor syndrome – spastic hemiplegia, spastic diplegia, spastic quadriplegia and extrapyramidal or dyskinetic [2].

The Pathogenesis of CP is Currently Divided into Four Main Stages

Fetal, prenatal, perinatal and postpartum [3].

As part of early rehabilitation, secondary diseases should be prevented or stopped in children with CP so that functional abilities can be positively influenced. One therapeutic option would be daily vitamin D supplementation (Vit D suppl) for four indications. This pluripotent therapeutic agent should be discussed in the rehabilitation plan as a cost-effective measure that is easy to implement worldwide.

In CP, the prevalence of hypovitaminosis D has been observed to be between 19% and 53%, and serum 25-hydroxyvitamin D [25(OH) D] levels should be checked in principle [4-11].

Monitoring is easily possible by determining 25(OH)D [s25(OH) D], Ca, and phosphate in the blood. There is sufficient evidence of severe inflammatory processes and neuroimmunological dysregulations in CP and vitamin D may contribute to achieving immunological homeostasis.

Attenuation of Chronic Neuroinflammation

CP patients showed increased levels of eight cytokines (IFN-γ, GM-CSF, TNF-α, IL-2, IL-4, IL-6, IL-17A and IL-12) compared to control subjects , including IFN-γ, GM-CSF, TNF-α, IL-2, IL-4, IL-6, IL-17A, BAFF, IL-12p70 and IL-10, which were also increased in the cerebrospinal fluid of patients with CP [12]. Increased pro-inflammatory cytokines such as IL-1ß, IL-6 and TNF-alpha have been verified both postnatal and later in life in PC, and increased IL-6 levels are associated with increased pro-inflammatory IL-17A. This cytokine constellation leads to disruption of the blood-brain barrier (BBB) and enables the infiltration of harmful immune cells [3]. The inflammasome of the NOD-like receptor family pyrin domain -containing protein 3 (NLRP3) is also involved in the inflammatory cascade, and calcitriol inhibits the overactivation of the NLRP3 inflammasome, which also has a beneficial effect on infection defense [13,14].

s25(OH)D levels, as established biomarkers for vitamin status, D status showed a significant inverse correlation with proinflammatory cytokines such as IL-1ß, IL-6, IL-8 and IL-17 A [15-19]. The active metabolite of vitamin D, calcitriol, promotes the development of forkhead box protein 3 (FOXP 3)+ regulatory T cells (Treg) and IL-10-producing T regulatory type 1 (TR1) cells . In T cells, 1,25(OH)2D3 reduces the production of IL-2, IL-17 and interferon-γ (IFN γ) and attenuates the cytotoxic activity and proliferation of CD4+ and CD8+ T cells [20-22]. A significant increase in serum Concentrations of IL-10 (and TGF-β1) indicate an anti- inflammatory effect of vitamin D supplementation [20].

Macrophages / microglia are defense cells of the immune system and are characterized by binary M1/M2 macrophage polarization. The polarization of macrophages / microglia is an important

regulatory factor in the development of inflammation processes [23]. Calcitriol promotes the polarization of M2 macrophages by increasing the expression of T cells immunoglobulin mucin3 (Tim-3), which leads to a decrease in TNFα and IL-6 and an increase in IL-10 [21,24]. Vit D thus indirectly inhibits Th17 cells and Th1 by inhibiting the production of IL-6 and TNFα by macrophages [21].

To achieve immunological homeostasis, a relatively high Vit D supplement dose of at least 1000IU/ day in children seems to be necessary, which is not associated with hypercalcemia or other adverse effects [18,25,26].

Bone Health in CP

Another indication for Vit D suppl is reduced bone mineral density (BMD) in children with CP. Children with CP can be affected by mild to multiple disabilities. When 77% of non- ambulatory children with CP have low bone mineral density (BMD) and an increased risk of fractures (about 4% per year), especially of the vertebrae and distal femur, attention to bone health is *a sine qua non* [27,28].

Vitamin D deficiency is a major factor in reduced BMD in children with CP [6]. Treatment with antiepileptic drugs increases the risk of hypovitaminosis [8]. In addition, there is an association between bone loss and IL- 17 with reduced vitamin D levels [29].

Adequate vitamin D intake in childhood improved bone mineralization and, in combination with high-dose vitamin D supplementation before birth and later in life, reduced the risk of bone fractures [30]. A positive correlation between s25(OH) D levels and total BMD and an inverted U- shaped relationship between serum calcium and total BMD were verified [31].

A study indicated that serum 25(OH)Vit-D levels were lower in pediatric patients with fractures. S25(OH)Vit-D ≤ 50 nmol /L was associated with increased fracture risk in children [32].

A correlation was also found between s25(OH) D and bone turnover markers osteocalcin (OC) and β- cross-laps (β- CTx) in children . An increase in s25(OH)D values by 10 nmol /L was significantly associated with a decrease in β- CTx by 10.5 ng /L [33].

Increased serum IL-35 levels were associated with increased 25(OH)VitD3, suggesting that IL-35 may play an important role in bone health and the immune system [34]. IL-35 induces the expansion of lymphocytes into regulatory B (135-Breg) and T cells (iTR35) [35].

Low vitamin D levels in children with CP are also associated with decreased muscle strength, balance, muscle pain, paresthesia, and poor muscular coordination [36].

Prevention of PC

As part of proactive therapy, PC in pregnancy should be diagnosed early and high- dose Vit D suppl should be administered immediately. A 60% lower rate of premature births and thus also prevention of PC could be achieved with high- dose Vit D supplementation with s25 (OH)D values ≥ 40 ng / mL [37,38]. As part of prenatal care, this option should be offered to every pregnant woman and thus indirectly contribute to reducing CP [39]. If biomarkers or imaging procedures indicate a suspicion of possible PC in pregnancy, Vit D suppl could be a possible intervention [40,41].

Numerous studies have shown that hypovitaminosis D is associated with the occurrence of pre-eclampsia, premature birth, low birth weight , low gestational age (small infants), indication for cesarean section and gestational diabetes [42,43]. Effects of hypovitaminosis D on the newborn and on child development in terms of poor immune and skeletal development, allergies and respiratory infections have shown that neural, musculoskeletal, and psychomotor growth as well as bone health are negatively affected [43].

For women who want to have children, as part of prevention for the course of pregnancy and for maternal and child health, it is crucial to start Vit D suppl at least 2 months before conception (before placentation and trophoblast invasion) with around 5000 IU/ day Vit D to achieve an optimal Vit D serum level (serum level over 100nmol/L=40ng/mL) [44].

Vit D deficiency can also be the cause of recurrent embryo implantation failure and recurrent fetal loss [45-47].

The influence of Vit D on placental genes expression and inflammation within the placenta creates an optimal starting position for the children [46-48].

To prevent PC, a proactive approach could also be used to prevent infection both during pregnancy and during PC.

Infection Prophylaxis

Lack of standard guidelines for adjunctive vitamin D therapy in diseases with an immunological basis/component could promote complications such as infections. Preventive measures are therefore justified because multiorgan dysfunction in PC is generally accepted [49].

The most common cause of morbidity and mortality in people with CP is respiratory disease [50].

In PC, a high rate of carriage of abnormal bacteria/potential pathogens, antibiotic-resistant bacteria and infections have been observed [51,52]. The complex pathology has not yet led to evidence-based treatment guidelines for respiratory diseases in PC [53]. In PC, a higher complication rate is also to be expected in influenza infections [54].

Urinary tract infections (UTI) in children with CP range from 8.5% to 56.7% in industrialized countries, while in Africa, particularly in Nigeria, a prevalence of 38.5% has been found [55].

Hypovitaminosis D can increase susceptibility to respiratory tract infections (Covid- 19)/ urinary tract infections [56-58]. From the beginning of fetal development and throughout life, Vit D exerts its effects on the lungs. Any vitamin D dysfunction during fetal development has long-term consequences for lung health after birth. The fetus is solely dependent on the supply of Vit D from the mother. Many cells in the lung express the Vit D receptor (VDR) and respond to 1,25(OH)2D3 [59].

Calcitriol increases the physical barrier by creating integrity in the mucous membranes of the respiratory and urogenital tract through integrity of Tight Junctions (TJs), Adherence junctions (AJs) and E-cadherin [60]. The promotion of TJs by Vit D is also beneficial because the BBB is disrupted in Covid-19 [61].

Structure of the Blood–Brain Barrier (BBB). (A) The blood–brain barrier (BBB) consists of endothelial cells, pericytes, astrocytes, and the basement membrane. The neurovascular unit (NVU) is composed of endothelial cells, pericytes, and astrocytes of the BBB and neurons, oligodendrocytes, and microglia, which closely communicate with each other in order to regulate brain homeostasis. (B) Tight junctions (claudin-5, occludin, ZO-1, ZO-2, and ZO-3) and adhesion junctions (JAMs and VE-cadherin) between BBB endothelial cells (BBB-ECs) form the BBB. (C) Transcellular migration of lymphocytes involves the following 4 steps: (1) in the rolling process, activated lymphocytes slow their flow speed due to the interaction of VLA-4 from the surface of lymphocytes with vascular cell adhesion molecules 1 (VCAM-1) on BBB-ECs; (2) in adhesion pathways, the lymphocytes adhere to endothelial cells and transverse the BBB by coupling the VLA-4 and LFA-1 expressed on lymphocytes with the endothelial cell receptor (VCAM-1 and intracellular adhesion molecules (ICAM-1); (3) during adhesion, interaction between VCAM-1 and ICAM on BBB-ECs and their ligands (LFA-1 and VLA-4) on leukocytes induces the arrest of immune cells from the blood by the brain endothelial cells; and (4) interaction between ICAM-1 and ICAM-2 and their ligands (LFA-1 and LFA-2) is involved in crawling and migration.

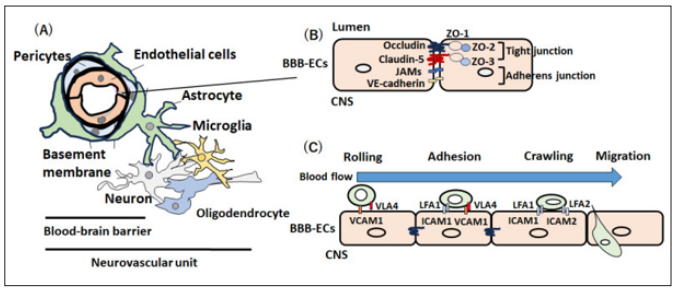

Figure 1: *from Shimizu F et al. Blood-Brain- Barrier Disruption in Neuroimmunological Disease.(2024) Int J Mol Sci;25(19):10625*

1,25(OH)2D3 promotes the formation of the antimicrobial peptides (AMPs) ß- defensin 2 and cathelicidin 2 [63]. Calcitriol reduces the production of proinflammatory cytokines and chemokines in various cells of the lung [59,60].

Inhibition of NLRP3 inflammasome activation by Vit D may also be helpful in respiratory infections [64].

An s25(OH)D level <20 ng/ mL increased the risk of UTI, just as an s25(OH)D level < 20 ng/ mL can lead to an increased risk of respiratory diseases [65,66]. Most studies defined 25(OH)D levels below 20 ng /mL as deficient and levels above 20 ng /mL and below 30 ng /mL as insufficient [65]. The importance of the daily dose of Vit D (dose-effect relationship) was demonstrated by the fact that the mean s25(OH)D level in UTI was 7.73 ng/ mL lower than in control subjects [65]. In acute infections, a loading dose of Vit D is required [67].

A Vit D supplement at a dosage of 10,000 IU/kg (max. 400,000 IU) significantly increased 25(OH)D3 levels in critically ill pediatric patients [68].

In adults, s25(OH)D levels of over 50 ng/ mL were necessary to overcome infections (including Covid-19) [69,70]. A Vit D suppl of over 1000 IU/day was beneficial in preventing colds/flu [71,72].

A liquid, oily, ready-to-use Formulation of Vit D (e.g. Vit D drops day) facilitates the possibility of a complication-free and safe application even in tube feeding. A current study in the United Kingdom (UK) is investigating PC patients with gastrostomy / jejunostomy require a Vit D supplement [73].

Discussion

There is currently a growing call to recognize chronic inflammation as a comorbidity in CP. A broad immunomodulatory and anti-inflammatory strategy is warranted [74]. In summary, by 2025 there will be sufficient pathoimmunological evidence to show that children with CP benefit significantly from relatively high-dose daily vitamin D supplementation throughout their lives. A reduction in chronic inflammation in the CNS by sealing the BBB and positive effects on the skeletal system can be expected [62,75]. With increasing age, children showed lower s25(OH)D values [76]. Vitamin D supplementation helps improve reduced muscle performance and reduce the potential risk of falls [77,78]. Secondary sarcopenia (muscle atrophy and weakness due to disuse, inflammation or malnutrition) is no longer in doubt in PC and a beneficial effect of Vit D suppl is evident [79,80]. Vit D is involved in the transcription of a number of proteins essential for skeletal muscle function and therefore Vit D is essential for muscle function and muscle strength [79]. The susceptibility of children with PC to non-traumatic fractures continues into adulthood and therefore Vit D intervention is necessary for skeletal health across the lifespan [81]. Evidence-based health benefits of vitamin D for the general population and recommendations exist, and this message applies even more to individuals with PC [82].

A benefit can only be expected if the s25[OH]D values are between 40 and 70ng/mL and, depending on individual absorption, can be achieved with an intake of around 4000-6000 IU/day Vit D [82].

If the Endocrine Society recommends vitamin D supplementation for healthy children and adolescents aged 1 to 18 years to prevent infections, it should be a mandatory part of treatment management for CP patients [83]. In addition to the usefulness of vitamin D as a potential adjuvant form of therapy, the pluripotency of this hormone during pregnancy should also be part of the global prevention strategy to prevent PC.

Conclusions

Optimizing the resilience of parents/caregivers when caring for individuals with PC is an essential factor in the long-term therapy of this patient group. This resilience is at risk if comorbidities occur alongside the underlying PC disease. A proactive action to prevent chronic inflammation, fractures, infections, comorbidities through the transmission of new pathophysiological/pathoimmunological findings by general practitioners and neurologists is required. The increase in disability can be slowed down by sufficient s25(OH)D values. In order to combat PC preventively, all pregnant women should take advantage of this inexpensive, easy-to-implement and widely available adjuvant therapy from the beginning of pregnancy up to and including the breastfeeding period.

Conflict of Interest: The author declares that there is no conflict of interest.

Ethical Approval and Consent to Participate: Not applicable.

Financing: No financial support

References

1. (2023) Cerebral Palsy. National Institute of Neurological Disorders and Stroke https://www.ninds.nih.gov/health-information/disorders/cerebral-palsy.
2. Patel DR, Neelakantan M, Pandher K, Merrick J (2020) Cerebral palsy in children: a clinical overview. Transl Pediatr 9: S125-S135.
3. Hu M, Bai Ch, Zhao H, Wu J, Luan X (2024) Research Progress on the Role of the Interleukin Family in the Pathogenesis of Cerebral Palsy in Children. J Integr Neurosci 23: 213.
4. Ware T, Whitelaw CH, Flett P, Parameswaran (2013) Vitamin D status in Tasmanian children with cerebral palsy. J Paediatr Child Health 49: 349-350.
5. Henderson RC (1997) Vitamin D levels in noninstitutionalized children with cerebral palsy. J Child Neurol 12: 443-447.
6. Alenazi KA, Alanezi AA (2024) Prevalence of Vitamin D Deficiency in Children with Cerebral Palsy: A Meta-Analysis. Pediatr Neurol 159: 56-61.
7. Pancheva R, Toneva A, Bocheva Y, Georgieva M, Koleva K, et al. (2024) Prevalence of vitamin D deficiency in children with cerebral palsy and autism spectrum disorder: a comparative pilot study. Folia Med (Plovdiv) 66: 787-794.
8. Madhava Vijayakumar, Ajitha BK, Biju George, Vijayalakshmi Bhatia (2022) Vitamin D Status in Children on Anticonvulsant Therapy. Indian J Pediatr 89: 541-545.
9. Toopchizadeh V, Barzegar M, Masoumi S, Jahanjoo F (2018) Prevalence of Vitamin D Deficiency and Associated Risk Factors in Cerebral Palsy A study in North-West of Iran. Iran J Child Neurol 12: 25-32.
10. Akpinar P (2018) Vitamin D status of children with cerebral palsy: Should vitamin D levels be checked in children with cerebral palsy?. North Clin Istanb 5: 341-347.
11. Paker N, Yavuz Mollavelioglu T, Bugdaycı D, Ones K, Bardak AN, et al. (2023) Vitamin D levels in children with cerebral palsy. J Pediatr Rehabil Med 16: 163-169.
12. Than UTT, Nguyen LT, Nguyen PH, Nguyen XH, Trinh DP, et al. (2023) Inflammatory mediators drive neuroinflammation in autism spectrum disorder and cerebral palsy. Sci Rep 13: 22587.
13. Basma A, Abdelrahman, Olfat A Hammam, Aiman S El-Khatib, Yasmeen M Attia (2023) The role of vitamin D3 in modulating the interplay between NLRP3 inflammasome and autophagy in NASH. Biophys Re Com 688: 149122.
14. Khalil B, Sharif Askari NS, Hafezi S, Sharif Askari FS, Al Anouti F, et al. (2024) Vitamin D regulates COVID-19 associated severity by suppressing the NLRP3 inflammasome pathway. PLoS ONE 19: e0302818.
15. Blondon M, Cushman M, Jenny N, Michos ED, Smith NL, et al. (2016) Associations of Serum 25-Hydroxyvitamin D with Hemostatic and Inflammatory Biomarkers in the Multi-Ethnic Study of Atherosclerosis. J Clin Endocrinol Metab 101: 2348-2357.
16. Roffe Vazquez DN, Huerta Delgado AS, Castillo EC, Villarreal Calderón JR, Gonzalez Gil AM, et al. (2019) Correlation of Vitamin D with Inflammatory Cytokines, Atherosclerotic Parameters and Lifestyle Factors in the Setting of Heart Failure: A 12-Month Follow-Up Study. Int J Mol Sci 20: 5811.
17. Plantone D, Primiano G, Manco C, Locci S, Servidei S, et al. (2022) Vitamin D in Neurological Diseases. Int J Mol Sci 24: 87.
18. Wolters M, Foraita R, Moreno LA, Molnár D, Russo P, et al. (2024) Longitudinal associations between vitamin D status and biomarkers of inflammation in a pan-European cohort of children and adolescents. Eur J Nutr 63: 3047-3060.
19. Dauletbaev N, Herscovitch K, Das M, Chen H, Bernier J, et al. (2015) Down-regulation of IL-8 by high-dose vitamin D is specific to hyperinflammatory macrophages and involves mechanisms beyond up-regulation of DUSP1. Br J Pharmacol 172: 4757-4771.
20. Sparaco M, Bonavita S (2024) Vitamin D Supplementation: Effect on Cytokine Profile in Multiple Sclerosis. Journal of Clinical Medicine 13: 835.
21. Galoppin M, Kari S, Soldati S, Pal A, Rival M, et al. (2022) Full spectrum of vitamin D immunomodulation in multiple sclerosis: mechanisms and therapeutic implications. Brain Communications 4.
22. Sintzel MB, Rametta M, Reder AT (2018) Vitamin D and Multiple Sclerosis: A Comprehensive Review. Neurol Ther 7: 59-85.
23. Chen S, Saeed AFUH, Liu Q, Jiang Q, Xu H, et al. (2023) Macrophages in immunoregulation and therapeutics. Signal Transduct Target Ther 8: 207.
24. Liang S, Cai J, Li Y, Yang R (2019) 1,25-Dihydroxy-Vitamin D3 induces macrophage polarization to M2 by upregulating T-cell Ig-mucin-3 expression. Mol Med Rep 19: 3707-3713.
25. Kilpinen Loisa P, Nenonen H, Pihko H, Mäkitie O (2007) High-dose vitamin D supplementation in children with cerebral palsy or neuromuscular disorder. Neuropediatrics 38: 167-172.
26. Calton EK, Keane KN, Newsholme P, Zhao Y, Soares MJ (2017) The impact of cholecalciferol supplementation on the systemic inflammatory profile: a systematic review and meta-analysis of high-quality randomized controlled trials. Eur J Clin Nutr 71: 931-943.
27. Mergler S, Evenhuis HM, Boot AM, De Man SA, Bindels De Heus KGCB, et al. (2009) Epidemiology of low bone mineral density and fractures in children with severe cerebral palsy: a systematic review. Dev Med Child Neurol 51: 773-778.
28. Barbier V, Goeb V, Gouron R, Fritot S, Mentaverri R, et al. (2023) Bone health in children with severe cerebral palsy. Front Pediatr 11: 1264111.
29. Albarzinji N, Albustany MD (2022) Association of 25-Hydroxy Vitamin D with IL-17 Inflammatory Cytokines and Osteoporosis in patients with Rheumatoid Arthritis in Kurdish nation / Iraq. The Open Rheumatology Journal 16: 1-6.
30. Brustad N, Thorsen J, Chawes BL, Krakauer M, Lasky Su J, et al. (2022) High-dose vitamin D supplementation in pregnancy and 25(OH)D sufficiency in childhood reduce the risk of fractures and improve bone mineralization in childhood: Follow-up of a randomized clinical trial. eClinical Medicine 43: 101254.
31. Pan K, Tu R, Yao X, Zhu Z (2021) Associations between serum calcium, 25(OH)D level and bone mineral density in adolescents. Adv Rheumatol 61: 16.
32. Yang G, Lee WYW, Hung ALH, Tang MF, Li X, et al. (2021) Association of serum 25(OH)Vit-D levels with risk of pediatric fractures: a systematic review and meta-analysis. Osteoporos Int 32: 1287-1300.
33. Thiering E, Brüske I, Kratzsch J, Hofbauer LC, Berdel D, et al. (2016) Associations between serum 25-hydroxyvitamin D and bone turnover markers in a population based sample of German children. Sci Rep 5: 18138.
34. Li Y, Yao L, Liu S, Jisheng Wu, Xia L, et al. (2019) Correlation between Serum IL-35 Levels and Bone Loss in Postmenopausal Women with Rheumatoid Arthritis. Mediators Inflamm 26: 9139145.

35. Charles E Egwuagu, Cheng Rong Yu, Lin Sun, Renxi Wang (2015) Interleukin 35: Critical regulator of immunity and lymphocyte-mediated diseases. Cytokine & Growth Factor Reviews 26: 587-593.
36. Kumar R, Kumar G, Runu R, Gupta AK, Sharma DK, et al. (2022) Vitamin D Status in Children with Cerebral Palsy: A Tertiary Care center Study. Int J Health Sci 1: 11438-11445.
37. McDonnell SL, Baggerly KA, Baggerly CA, Aliano JL, French CB, et al. (2017) Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. PLoS One 12: e0180483.
38. Trønnes H, Wilcox AJ, Lie RT, Markestad T, Moster D (2014) Risk of cerebral palsy in relation to pregnancy disorders and preterm birth: a national cohort study. Dev Med Child Neurol 56: 779-785.
39. Bearzi CF, Finamor DC, Marim G, Durante FR (2023) Vitamin D deficiency and preterm birth: a comprehensive review. International Journal of Nutrology 16.
40. Larsen ML, Rackauskaite G, Pihl K, Uldal Pl, Greisen G, et al. (2022) First-trimester biomarkers and the risk of cerebral palsy. Early Human Development 167: 105564.
41. Haataja L (2020) Early diagnosis of cerebral palsy. J Pediatric Medicine 3.
42. Mansur JL, Oliveri B, Giacoia E, Fusaro D, Costanzo PR (2022) Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children. Nutrients 14: 1900.
43. Vasdeki D, Tsamos G, Koufakis T, Goulis DG, Asimakopoulos B, et al. (2023) You are my sunshine, my only sunshine: maternal vitamin D status and supplementation in pregnancy and their effect on neonatal and childhood outcomes. Hormones (Athens) 22: 547-562.
44. Mumford SL, Garbose RA, Kim K, Kissell K, Kuhr DL, et al. (2018) Association of preconception serum 25-hydroxyvitamin D concentrations with livebirth and pregnancy loss: a prospective cohort study. Lancet Diabetes Endocrinol 6: 725-732.
45. Durá Travé T, Gallinas Victoriano F (2023) Pregnancy, Breastfeeding, and Vitamin D. Int J Mol Sci 24: 11881.
46. Hou W, Yan XT, Bai CM, Zhang XW, Hui LY, et al. (2016) Decreased serum vitamin D levels in early spontaneous pregnancy loss. Eur J Clin Nutr 70: 1004-1008.
47. Dai M, Xu Y, Zhang Y (2023) Roles of immune microenvironment in the female reproductive maintenance and regulation: novel insights into the crosstalk of immune cells Sec. Immunological Tolerance and Regulation Front Immunol 14.
48. Hollis BW, Wagner CL (2017) Vitamin D supplementation during pregnancy: Improvements in birth outcomes and complications through direct genomic alteration. Molecular and Cellular Endocrinology 453: 113-130.
49. Allen J, Zareen Z, Doyle S, Whitla L, Afzal Z, et al. (2021) Multi-Organ Dysfunction in Cerebral Palsy. Front Pediatr 9: 668544.
50. Blair E, Langdon K, McIntyre S, Lawrence D, Watson L (2019) Survival and mortality in cerebral palsy: observations to the sixth decade from a data linkage study of a total population register and national death index. BMC Neurol 19: 1-11.
51. Thorburn K, Jardine M, Taylor N, Reilly N, Sarginson R, et al. (2009) Antibiotic-resistant bacteria and infection in children with cerebral palsy requiring mechanical ventilation. Pediatric Critical Care Medicine 10: 222-226.
52. Gregson E, Thomas L, Elphick HE (2021) Pseudomonas aeruginosa infection in respiratory samples in children with neurodisability-to treat or not to treat?. Eur J Pediatr 180: 2897-2905.
53. Marpole R, Blackmore AM, Gibson N, Cooper MS, Langdon K, et al. (2020) Evaluation andManagement of Respiratory Illness in Children with Cerebral Palsy. Front Pediatr 8: 333.
54. Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, et al. (2020) Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2020-21 Influenza Season. MMWR Recomm Rep 69: 1-24.
55. Ryakitimbo A, Philemon R, Mazuguni F, Msuya L (2018) Prevalence and antimicrobial sensitivity pattern of urinary tract infection among children with cerebral palsy, Moshi, Tanzania. Pediatric Health Med Ther 9: 59-65.
56. Engin MMN, Özdemir Ö (2024) Role of vitamin D in COVID-19 and other viral infections. World J Virol 13: 95349.
57. Li X, Yu Q, Qin F, Zhang B, Lu Y (2021) Serum Vitamin D Level and the Risk of Urinary Tract Infection in Children: A Systematic Review and Meta-Analysis. Front Public Health 9: 637529.
58. Mercy DJ, Girigoswami A, Girigoswam K (2024) Relationship between urinary tract infections and serum vitamin D level in adults and children-a literature review. Mol Biol Rep 51: 955.
59. Gayan Ramirez G, Janssens W (2021) Vitamin D Actions: The Lung Is a Major Target for Vitamin D, FGF23, and Klotho. JBMR Plus 5: e10569.
60. Schrumpf JA, van der Does AM, Hiemstra (2020) Impact of the Local Inflammatory Environment on Mucosal Vitamin D Metabolism and Signaling in Chronic Inflammatory. Lung Diseases Front Immunol 11: 1433.
61. Kempuraj D, Aenlle KK, Cohen J, Mathew A, Isler D, et al. (2024) COVID-19 and Long COVID: Disruption of the Neurovascular Unit, Blood-Brain Barrier and Tight Junctions. Neuroscientist 30: 421-439.
62. Shimizu F, Nakamori M (2024) Blood-Brain Barrier Disruption in Neuroimmunological Disease. Int J Mol Sci 25: 10625.
63. Bishop EL, Aiten Ismailova, Sarah Dimeloe, Martin Hewison, John H White (2021) Vitamin D and Immune Regulation: Antibacterial, Antiviral, Anti-Inflammatory. JBMR Plus 5: e10405.
64. Tunbridge M, França Gois PH (2020) Vitamin D and the NLRP3 Inflammasome. Applied Sciences 10: 8462.
65. Gan Y, You S, Ying J, Mu D (2023) The Association between Serum Vitamin D Levels and Urinary Tract Infection Risk in Children: A Systematic Review and Meta-Analysis. Nutrients 15: 2690.
66. Kuang L, Liang Z, Wang C, Lin T, Zhang Y, et al. (2023) Serum 25-Hydroxy Vitamin D Levels in Children with Acute Respiratory Infections Caused by Respiratory Virus or Atypical Pathogen Infection. Nutrients 15: 1486.
67. van Groningen L, Opdenoordt S, van Sorge A, Telting D, Giesen A, et al. (2010) Cholecalciferol loading dose guideline for vitamin D-deficient adults. Eur J Endocrinol 162: 805-811.
68. Covington EW, Jasper Trotter SL, Arnold RD, Amin R, Egbert S, et al. (2023) Prospective pilot study evaluating a vitamin D3 loading dose in critically ill children with vitamin D deficiency. Fundam Clin Pharmacol 38: 588-595.
69. Wimalawansa SJ (2024) Physiology of Vitamin D-Focusing on Disease Prevention. Nutrients 16: 1666.
70. Wimalawansa SJ (2022) Overcoming Infections Including COVID-19, by Maintaining Circulating 25(OH)D Concentrations Above 50 ng/mL. Pathol Lab Med Int 14:

37-60.

71. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, et al. (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 356: i6583.
72. Carboo JA, Dolman Macleod RC, Malan L, Lombard MJ (2024) High dose oral vitamin D supplementation for prevention of infections in children aged 0 to 59 months: a systematic review and meta-analysis. Nutrition Reviews 82: 579-599.
73. Vitamin D status in Children and Young People with Cerebral Palsy. NHS Health Research Authority https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/vitamin-d-status-in-children-and-young-people-with-cerebral-palsy/.
74. Paton MCB, Finch Edmondson M, Dale RC, Fahey MC, Nold Petry CA, et al. (2022) Persistent Inflammation in Cerebral Palsy: Pathogenic Mediator or Comorbidity?. A Scoping Review. J Clin Med 11: 7368.
75. Galoppin M, Kari S, Soldati S, Pal A, Rival M, et al. (2022) Full spectrum of vitamin D immunomodulation in multiple sclerosis: mechanisms and therapeutic implications. Brain Commun 4: 171.
76. Xing W, Liang L, Dong N, Chen L, Liu Z (2023) Abnormal changes of bone metabolism markers with age in children with cerebral palsy. Front Pediatr 11: 1214608.
77. Langley CK, Onambélé Pearson GL, Sims DT, Hussain A, Buffey AJ, et al. (2021) Musculoskeletal Health in Active Ambulatory Men with Cerebral Palsy and the Impact of Vitamin D. Nutrients 13: 2481.
78. Clarke, Nicholas MP (2012) Page, Jonathan E. Vitamin D deficiency: a paediatric orthopaedic perspective. Current Opinion in Pediatrics 24: 46-49.
79. Verschuren O, Smorenburg ARP, Luiking Y, Bell K, Barber L, et al. (2018) Determinants of muscle preservation in individuals with cerebral palsy across the lifespan: a narrative review of the literature. J Cachexia Sarcopenia Muscle 9: 453-464.
80. Morley JE, Argiles JM, Evans WJ, Bhasin S, Cella D, et al. (2010) Nutritional recommendations for the management of sarcopenia. J Am Med Dir Assoc 11: 391-396.
81. Whitney DG, Hurvitz EA, Caird MS (2021) The Effect of Osteoporosis Medication on Risk Attenuation of Non-Trauma Fracture Among Adults with Cerebral Palsy: A Propensity Score-Matched Observational Study. Clin Epidemiol 13: 91-102.
82. Grant WB, Wimalawansa SJ, Pludowski P, Cheng RZ (2025) Vitamin D: Evidence-Based Health Benefits and Recommendations for Population Guidelines. Nutrients 17: 277.
83. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, et al. (2024) Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 109: 1907-1947.