

VITAMIN D AND PEDIATRIC MS: AN INFORMATION LEAFLET

Background

Epidemiological observations have suggested a link between latitude at place of residence, sunlight exposure and multiple sclerosis (MS) risk.¹ Large observational studies have indicated that high oral vitamin D intake (> approximately 600 IU/day) and high serum 25-hydroxyvitamin D (25OHD) levels (> 100 nmol/L) are associated with a reduced risk of subsequent MS development.^{2,3}

In established adult-onset MS, studies have shown that serum 25OHD levels are lower in MS patients as compared to healthy controls.⁴⁻⁶ In adult MS patients, vitamin D levels appear to be lower during times of relapse as compared to remission.⁶ Carefully designed prospective studies in adult MS patients have shown an inverse relationship between serum 25(OH)D levels and relapse risk in the subsequent 4 weeks to 6 months.^{7,8} Higher 25(OH)D levels have also been associated with reduced risk of developing new or enhancing brain MRI lesions and reduced disability progression in adults with MS.^{9,10}

There is limited evidence for the role of vitamin D in pediatric MS. A large Canadian national prospective cohort study in pediatric patients with incident demyelination showed that low serum 25OHD level at first presentation was associated with increased risk of MS diagnosis (HR 1.1 95% CI 1.00-1.25 for every 10 nmol/L decrease).¹¹ A US study suggested that relapse risk in pediatric patients with either MS or clinically isolated syndromes (CIS) was inversely related to serum 25OHD level with a 34% decrease in relapse risk for every 10 ng/mL* increase in serum vitamin D level (incidence risk ratio 0.66 95% CI 0.46-0.95).¹²

What are the Sources of Vitamin D?

Vitamin D₂ (ergocalciferol) is derived from fungus/yeast exposed to UV light. Vitamin D₃ (cholecalciferol) is synthesized after skin exposure to sunlight and is also consumed in the diet where it is found in high levels in oily fish and, in some countries, fortified dairy products. Vitamin D₃ may also be obtained in an oral supplement form. All of these sources appear able to raise serum 25OHD levels, but it remains unclear whether they are equally potent and if they have differential effects on immune function.

How Much Vitamin D is Enough?

It is unclear what the optimal amount of vitamin D is for pediatric MS patients. The Recommended Dietary Allowance (RDA) for vitamin D suggested by the National Institute of Medicine is 600 IU/day for all individuals over 1 year of age. This RDA was established to target a serum 25(OH)D level of 50 nmol/L, which

was determined with particular concern for maintaining bone health and preventing rickets, not for modulating immune function. Optimal vitamin D intake for improving MS disease course in children has yet to be established.

Serum 25(OH)D level is often used as a marker of vitamin D sufficiency status. Reference ranges vary by laboratory and definitions of deficiency (typically < 30 nmol/L) and sufficiency (typically > 75 nmol/L) are again largely based on bone health outcomes. The optimal 25OHD level for pediatric MS patients still needs to be determined.

How Much Vitamin D is Too Much?

Vitamin D toxicity is largely related to increased bone resorption and hypercalcemia. The National Institute of Medicine's upper limit for vitamin D intake varies by age and is 4000 IU/day for individuals over the age 9 years. Vitamin D toxicity in adults has not been observed below a daily intake of 10,000 IU daily and is usually associated with a serum 25OHD level above 200 nmol/L. Studies in adult MS patients have examined dose-response relationships for vitamin D and established short-term safety for daily doses as high as 40,000 IU daily.^{13, 14} Dose-response relationships and defining a safe range of serum 25OHD levels in children with MS still need to be defined.

How Might Vitamin D Affect MS Course?

Vitamin D likely has immunomodulatory effects.¹⁵ Vitamin D receptors are located on monocytes, macrophages, dendritic cells, and activated T cells. Vitamin D suppresses T cell proliferation, induces a Th1 to Th2 shift, reduces Th17 responses and increases regulatory T cell production. Vitamin D indirectly reduces B cell proliferation and antibody production. There are no studies of the effects of vitamin D on immune cell function in pediatric MS patients.

Conclusions and Priorities for Future Work

There is much to learn about vitamin D and its effects in children with MS. Current evidence suggests that in children older than 9 years of age, oral vitamin D intake up to 4000 IU/day and maintenance of 25OHD levels in the upper end of reference ranges (75-100 nmol/L) is likely safe and may have beneficial effects on clinical and radiological disease course.

Establishing age-related oral vitamin D doses that are able to raise serum levels into the desired range, determining optimal frequency and timing of doses with respect to season and establishing the safe range of supplemental oral vitamin D doses in children with MS will only occur through carefully designed prospective studies and randomized clinical trials.

1 ng/mL = 2.496 nmol/ml

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