Vitamin D: a Natural Inhibitor of Multiple Sclerosis[1]

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Abstract

Inheriting genetic risk factors for multiple sclerosis (MS) is not sufficient to cause this demyelinating disease of the central nervous system (CNS); exposure to environmental risk factors is also required. MS may be preventable if these unidentified environmental factors can be avoided. MS prevalence increases with decreasing solar radiation, suggesting that sunlight may be protective in MS. Because the vitamin D endocrine system is exquisitely responsive to sunlight, and MS prevalence is highest where environmental supplies of vitamin D are lowest, we have proposed that the hormone, 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$], may protect genetically-susceptible individuals from developing MS. Evidence consistent with this hypothesis comes not only from geographic studies, but also genetic, and biological studies. Over-representation of the vitamin D receptor gene *b* allele was found in Japanese MS patients, suggesting it may confer MS susceptibility. Fish oil is an excellent vitamin D source, and diets rich in fish may lower MS prevalence or severity. Vitamin D deficiency afflicts most MS patients, as demonstrated by their low bone mass and high fracture rates. However, the clearest evidence that vitamin D may be a natural inhibitor of MS comes from experiments with experimental autoimmune encephalomyelitis (EAE) a model of MS. Treatment of mice with 1,25-$(OH)_2D_3$ completely inhibited EAE induction and progression. The hormone stimulated the synthesis of two anti-encephalitogenic cytokines, interleukin-4 (IL-4) and transforming growth factor beta-1 (TGF-β1), and influenced inflammatory cell trafficking or apoptosis. If vitamin D is a natural inhibitor of MS, providing supplemental vitamin D to individuals who are at risk for MS would be advisable.

Key Words

Introduction

Multiple sclerosis is a CNS demyelinating disease of uncertain etiology (Ebers 1998). Genetic epidemiological studies demonstrate that genetic risk factors determine susceptibility and account for familial clustering of MS (reviewed in Ebers & Dyment 1998). Biological first-degree relatives of MS patients show a 20- to 40-fold increased risk of disease compared to unrelated individuals. However, no single locus controlling MS development has been identified, suggesting that genetic MS susceptibility may be polygenic, as originally postulated by Pratt et al. (1951).

Importantly, inheriting MS susceptibility factors is not sufficient for disease development, as evidenced by the finding that 70% of monozygotic twin pairs are discordant for MS (Ebers et al. 1986). Thus, exposure to one or more environmental risk factors is necessary for MS development. Because infections often precede the onset of MS symptoms and/or exacerbations (Sibley et al. 1985; Anderson et al. 1993; Panitch 1994), an infectious MS etiology has been proposed (reviewed by Noseworthy 1999). Despite intense investigation, compelling evidence for this hypothesis has not been forthcoming, and other disease-determining environmental risk factors must be sought.

Multiple sclerosis prevalence shows a striking geographic distribution. It increases with increasing latitude in both hemispheres (Davenport 1922; Ulett 1948; Limburg 1950; Kurland 1952 and others), from a low of 1-2 cases per 10^5 population near the equator to a high of >200 cases per 10^5 population at latitudes >50º. This peculiar distribution suggests that one disease determining environmental risk factor is somehow linked to latitude. Acheson et al. (1960) examined many latitude-linked variables, and showed that average annual hours of sunlight and average December daily solar radiation showed a highly significant inverse correlation with MS prevalence. They concluded that sunshine "could conceivably act directly - a certain skin dose of sunshine per unit time protecting the individual in some way."

Epidemiological studies are confounded by the problem of separating genetic and environmental influences. However, some evidence from studies involving genetically similar

populations reinforces the possibility that sunlight may be protective in MS. In Switzerland, districts at low altitudes ($\leq$1000 m) have high MS rates, whereas districts at high altitudes ($\geq$2000 m) have low MS rates, despite the relative genetic similarity of the two populations (Kurtzke 1967). This anomaly may reflect the increased short-wavelength ultraviolet (UV) radiation received at high altitudes compared to low altitudes (Geiger 1965). Further, within genetically similar migrating populations, those migrating to regions with increased solar radiation had reduced MS rates, whereas those migrating to regions with decreased solar radiation had increased MS rates (reviewed by Ebers & Sadovnick 1994). The greatest benefits of sunlight may accrue to migrating individuals less than age 14 or 15 (Kurtzke et al. 1970). Together these epidemiological studies indicate that MS may be a preventable disease in individuals who are genetically at risk, if the pertinent environmental risk factors can be correctly identified and avoided. Sunlight appears to be the protective environmental factor linked to latitude.

Sunlight, the vitamin D endocrine system, and MS

The vitamin D endocrine system is exquisitely responsive to sunlight. Sunlight is required for previtamin D_3 synthesis in skin (Velluz et al. 1949), and previtamin D_3 is the precursor of the biologically active hormone, 1,25-$(OH)_2D_3$ (Holick et al. 1971; Norman et al. 1971). Goldberg (1974a & 1974b) first proposed that sunlight might protect individuals from developing MS through the actions of 1,25-$(OH)_2D_3$, since geographic areas with low supplies of vitamin D due to low intensity solar radiation and inadequate dietary vitamin D correlated with regions of high MS prevalence. Conversely, MS prevalence is low where vitamin D is abundant, as in sunny climates, high altitudes, and areas with diets rich in fish oil. We reinforced this hypothesis (Hayes et al. 1997), and provided strong experimental evidence from the EAE model in mice, summarized below, showing that 1,25-$(OH)_2D_3$ is a natural inhibitor of the autoimmune-mediated processes that underlie MS (Cantorna et al. 1996; Cantorna et al. 1998; Nashold et al. 2000).

All vertebrates, including humans, obtain their vitamin D requirement mainly from exposure of their skin to sunlight rather from their diet (Holick 1995). The energy of UV B photons that penetrate the epidermis is absorbed by the abundant cholesterol metabolite, 7-dehydrocholesterol, rupturing the 9-10 carbon-carbon bond and yielding an unstable intermediate, previtamin D_3. This compound spontaneously undergoes an internal sigmatropic shift of a proton and isomerization to the thermodynamically stable vitamin D_3. Vitamin D_3 is transported from the skin to the liver bound to the serum vitamin D binding protein. In hepatocytes, C-25 hydroxylation produces the major circulating form of vitamin D, 25-hydroxyvitamin D_3, which is biologically inactive at physiological concentrations. In the kidney, a further C-1 hydroxylation forms the biologically active hormone, $1,25\text{-}(OH)_2D_3$ (Holick et al. 1971; Norman et al. 1971). The production of the hormone is highly regulated by the need for calcium and phosphorus.

Latitude and season affect the intensity of solar radiation reaching earth's surface, and therefore the rate of vitamin D_3 synthesis (Webb et al. 1988). In Boston, Massachusetts (42°N), human skin exposed to sunlight produced no previtamin D_3 from November through February due to insufficient intensity of solar radiation. Further north in Edmonton (52°N), Canada, this period of no previtamin D_3 synthesis extended from October through March. In Los Angeles, California (34°N), previtamin D_3 synthesis occurred throughout the year. People living at northerly or southerly latitudes who do not eat vitamin D-rich foods or supplements become vitamin D deficient during the winter.

Genetic evidence for the vitamin D - MS hypothesis

Evidence consistent with the hypothesis that vitamin D may be a natural inhibitor of MS comes from geographic (above), genetic, and biological studies. The hormone exerts most of its biological effects only after it has bound to the vitamin D hormone receptor (VDR) (Haussler et al. 1997). New genetic evidence indicates that one allele of the VDR gene may be associated with MS susceptibility. Fukazawa et al. (1999) found over representation of the VDR gene *b*

allele (chromosome 12q14) in Japanese MS patients. This allele is distinguished by a *Bsm*I endonuclease site, and it was also implicated in susceptibility to insulin-dependent diabetes in Indian Asians (McDermott et al. 1997). In Canadian families, Steckley et al. (2000) found no association between MS and genetic markers at the VDR locus, the nearby gene encoding the 25-hydroxyvitamin D_3 1-α-hydroxylase (12q13), or the vitamin D binding protein locus (4q12). However, the report by Fukazawa et al. (1999) indicates that a VDR polymorphism may contribute to MS susceptibility, consistent with the vitamin D - MS hypothesis.

Biological evidence for the vitamin D - MS hypothesis

Fish oil is a rich source of vitamin D_3, and there is limited evidence that diets rich in fish may lower the incidence and/or severity of MS. Lower MS prevalence rates are found along the Atlantic coast of Norway than inland (Swank et al. 1952; Presthus 1960; Westlund 1970). The coastal Norwegians consumed the equivalent of about 1300 IU of vitamin D_3 daily, about 3-fold higher than individuals living in inland (Goldberg 1974a). Furthermore, in a small clinical trial, MS patients ingested cod liver oil (20 g/day; 5000 IU/day of vitamin D), along with calcium and magnesium supplements, which reportedly lowered their rate of exacerbations (Goldberg et al. 1986). A second small trial of fish oil also lessened MS symptoms (Bates et al. 1989). These trials involved very few subjects and had other methodological shortcomings. Nevertheless, the available evidence on fish oil consumption and MS is consistent with the vitamin D - MS hypothesis.

There is clear evidence that the majority of MS patients exhibit long-term vitamin D deficiency, as characterized by low bone mass and high fracture rates. The serum 25-hydroxyvitamin D_3 level, the best indicator of near-term vitamin D nutrition, was less than adequate (<50 nmol/L) in 69% of MS patients tested (Nieves et al. 1994). In addition, MS patients had significantly reduced bone mass compared to their age- and gender-matched healthy peers (Nieves et al. 1994), indicative of long-term vitamin D malnutrition. A follow-up study found that MS patients lost bone mass at a 3- to 7-fold higher rate and experienced fractures at a

10-fold higher rate than their peers (Cosman et al. 1998). These findings indicate that significant vitamin D deficiency of some duration exists in most MS patients, consistent with the hypothesis that this deficiency may pose a risk factor for MS.

Experimental evidence for the vitamin D - MS hypothesis

The clearest evidence that vitamin D may be a natural inhibitor of MS comes from experiments done using the EAE system as a model of MS. Immunizing mice with spinal cord homogenate containing myelin basic protein induces a progressively paralytic autoimmune disease, EAE, with strong similarities to MS (Olitsky & Yager 1949). Lemire and Archer (1991) and Branisteanu et al. (1995) used the EAE model to show that feeding a low calcium diet and injecting $1,25\text{-}(OH)_2D_3$ prolonged the survival of SJL/J mice with severe EAE, but these treatments did not completely inhibit the morbidity or mortality of the disease. We studied relapsing-remitting EAE in B10.PL mice and demonstrated that $1,25\text{-}(OH)_2D_3$ pre-treatment completely eliminated EAE, while hormone treatment at the first sign of symptoms inhibited EAE progression (Cantorna et al. 1996). The lower the dietary calcium level, the higher was the $1,25\text{-}(OH)_2D_3$ dose needed to completely prevent EAE symptoms, suggesting that adequate dietary calcium is important for EAE inhibition (Cantorna et al. 1999).

In further experiments, we tested the hypothesis that $1,25\text{-}(OH)_2D_3$ might stimulate the development of anti-encephalitogenic cells and the cytokines they produce (Cantorna et al. 1998). Consistent with this hypothesis, we detected interleukin-4 (IL-4) and transforming growth factor beta-1 (TGF-β1) transcripts in the lymph nodes and CNS of hormone-treated mice, where EAE was prevented, but not mock-treated mice with EAE. The IL-4 and TGF-β1 cytokines have strong anti-inflammatory activity in EAE (Racke et al. 1991; Johns et al. 1991; Kuruvilla et al. 1991; Inobe et al. 1996). In other experiments, we induced severe EAE, administered hormone treatment or mock treatment, and examined the CNS for infiltrating inflammatory cells (Nashold et al. 2000). Whereas the mock-treated mice remained severely paralyzed, most hormone-treated animals regained the partial use of both hind limbs within 72 hr

7

of hormone treatment. Histopathological examination and flow cytometric analyses indicated that about 5 million inflammatory macrophages were lost from the inflamed CNS within 24 hr of the $1,25\text{-}(OH)_2D_3$ treatment, suggesting a possible influence of the hormone on inflammatory cell trafficking or apoptosis.

Vitamin D nutrition and MS

If vitamin D is a natural inhibitor of MS, it would be reasonable to provide supplemental vitamin D to individuals who are at risk for MS. It is noteworthy that vitamin D supplementation during childhood significantly decreased the risk of Type I diabetes mellitus, an autoimmune disease (EURODIAB Substudy 2 Study Group 1999). A reassessment of vitamin D nutrition is underway, and there is good evidence that the currently recommended adequate intakes are too low (Vieth 1999). The adequate intake for adults is currently 200 IU/day (5 μg/day), but this does not prevent osteoporosis and secondary hyperparathyroidism (Holick 1998; Malabanan et al. 1998). To prevent secondary hyperparathyroidism, a serum 25-hydroxyvitamin D_3 concentration >50 nmol/L is required (Malabanan et al. 1998). Adults living or working in sunny environments, where MS prevalence is lowest, have circulating 25-hydroxyvitamin D_3 levels between 105 and 163 nmol/L (Vieth 1999). Thus, a serum 25-hydroxyvitamin D_3 concentration $\geq$100 nmol/L may be optimal to prevent MS. To maintain a serum 25-hydroxyvitamin D_3 ~100 nmol/L, an adult who is not exposed to sunlight would need to ingest 4000 IU/day (Vieth 1999). This estimate is between the 3800 IU/day that Goldberg calculated might prevent MS (Goldberg 1974b), and the 5000 IU/day that was given in the small clinical trial of fish oil (Goldberg et al. 1986).

Very high doses of vitamin D can cause hypercalcemia, which is potentially fatal. Accordingly, a tolerable safe upper limit for vitamin D supplementation has been set at 2000 IU/day for age >1, and 1000 IU/day for age <1 (Holick 1998). However, the panel that established this limit overlooked information indicating that the safe upper limit is actually much higher. Adults living or working in sunny environments easily generate >10,000 IU/day of

vitamin D through sun exposure without adverse effects, so the safe upper limit for total vitamin D nutrition is at least 10,000 IU/day (Vieth 1999). Moreover, all documented cases of vitamin D toxicity with hypercalcemia involved intakes $\geq$40,000 IU/day (Vieth 1999). Thus, the 4000 IU/day needed by an adult without sun exposure to maintain serum 25-hydroxyvitamin D_3 ~100 nmol/L would be safe, since it is well below the 10,000 IU/day generated by adults living or working in sunny environments.

The 4000 IU/day of vitamin D supplementation that might be needed to prevent MS is significantly higher than the intake required to prevent rickets, a metabolic bone disease attributable to vitamin D deficiency. The intake recommended to prevent rickets in children (0-18 yrs) living in far northern and southern latitudes is 200 IU/day (Holick 1998). It is interesting to note that the geographies of rickets (Hess 1929) and MS are very similar; the geography of rickets led Sniadecki to suggest in 1822 that sunlight might cure rickets (cited by Holick 1995). Regrettably, rickets continued to cripple children for a full century, before investigators proved the benefits of sunlight or cod liver oil (Hess & Unger 1921; Chick et al. 1922), and cod liver oil became a winter staple for children living in northerly latitudes. The evidence that vitamin D might be a natural inhibitor of MS is compelling. Examining the benefit of vitamin D supplementation for MS prevention will require a major effort on the part of the scientific community, but it is clearly justified.

Footnotes

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