MINIREVIEW

Vitamin D and Autoimmunity: Is Vitamin D Status an Environmental Factor Affecting Autoimmune Disease Prevalence? (44485)

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Abstract. **The environment in which the encounter of antigen with the immune system occurs determines whether tolerance, infectious immunity, or autoimmunity results. Geographical areas with low supplies of vitamin D (for example Scandinavia) correlate with regions with high incidences of multiple sclerosis, arthritis, and diabetes. The active form of vitamin D has been shown to suppress the development of autoimmunity in experimental animal models. Furthermore, vitamin D deficiency increases the severity of at least experimental autoimmune encephalomyelitis (mouse multiple sclerosis). Targets for vitamin D in the immune system have been identified, and the mechanisms of vitamin D-mediated immunoregulation are beginning to be understood. This review discusses the possibility that vitamin D status is an environmental factor, which by shaping the immune system affects the prevalence rate for autoimmune diseases such as multiple sclerosis, arthritis, and juvenile diabetes.**

[P.S.E.B.M. 2000, Vol 223]

The immune system is able to distinguish between foreign invaders (bacteria and viruses) and the "self" body tissues in normal, healthy individuals. Autoimmune diseases result when the immune system inappropriately attacks self tissues. Although autoimmune diseases may occur in any organ, some tissues are more frequently affected than others. Examples of three prevalent autoimmune diseases include juvenile diabetes or insulin-dependent diabetes mellitus (IDDM), multiple sclerosis (MS), and rheumatoid arthritis (RA). In IDDM, the autoimmune targets are the islet beta cells in the pancreas, in MS the targets are the myelin-producing cells in the central nervous system (CNS), and in RA the targets are the collagen-producing cells in the joints. For each of these diseases there is a strong genetic component underlying prevalence (i.e., they occur most frequently in people with a blood relative who also has the disease). There are also a number of ill-defined environmental factors that contribute to the etiology of IDDM, MS, and RA. The possibility that vitamin D status is an environmental factor affecting the prevalence of IDDM, MS, and RA is explored in this review.

Vitamin D Status in IDDM, MS, and RA

There is a large body of anecdotal information suggesting a link between MS and vitamin D status. Epidemiological studies show that MS is more prevalent in temperate high latitudes than at equatorial latitude (1). The environmental factor that explains the link between geography and MS has been extremely elusive. However, in 1974, Goldberg first suggested that the amount of vitamin D available in the environment either from sunshine exposure or from the diet might affect the prevalence of MS (2). Ultraviolet irradiation of the skin is a major source of vitamin D, and the prevalence of MS is lower in regions where vitamin D

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0037-9727/00/2233-0230$15.00/0

is abundant as in sunny climates and high altitudes. In addition, areas with diets rich in fish oil, a major dietary source of vitamin D, have lower incidence of MS (1, 2). Conversely, areas with low supplies of vitamin D correlate with geographic regions associated with a high risk for MS (1, 2).

The geographic distribution for MS is now sufficiently well established that any satisfactory theory of its etiology must account for the geographic variations. Although the geographic distributions of IDDM and RA are not clearly delineated, there are also suggestive geographic variations for the prevalence of juvenile diabetes and arthritis (3, 4). Generally RA and juvenile diabetes are more prevalent in higher latitudes than in the latitudes of the tropics and subtropics (3, 4). In addition, there is seasonal variation in IDDM with the largest proportion of IDDM cases diagnosed during fall-winter and the lowest during the summer (3). Sunlight exposure and vitamin D status are highest in the summer and lowest during the fall and winter in the northern latitudes (5). Whether these suggestive geographic and seasonal anomalies are linked to vitamin D status is presently unknown.

Vitamin D deficiency or insufficiency has been documented in MS, IDDM, and RA patients (6–9). Vitamin D status is most often assessed because of reduced bone mass or osteopenia in these patients. It is unclear whether vitamin D insufficiency is a cause or a result of autoimmunity and/or corticosteroid therapies, which are commonly used to treat these patients (6–9). Vitamin D supplements have been used in MS, RA, and IDDM patients to improve bone mineral density, but the effects of these supplements on the underlying autoimmune diseases have not been explored.

Animal Models of Autoimmunity

The development of animal models for MS, diabetes, and arthritis have increased our understanding of the autoimmune disease process. In these model systems, T lymphocytes orchestrate the attack against self-tissue (10). T cells are thymus-derived cells that are characterized by their ability to discriminate among antigens. The discriminatory ability of T cells is what normally prevents autoimmunity. For reasons that are not fully understood, people and animals with autoimmune disease have many T cells that recognize self tissues. In particular, a subset of T cells called the T-helper (Th) cells that express the CD4 marker on their surface have been shown to transfer experimental autoimmune encephalomyelitis (EAE, mouse MS), and diabetes to naive mice (11, 12). Furthermore, CD4 + cell depletion eliminates symptoms of EAE, diabetes, and arthritis in mice (13–15). Although there are certainly important differences in the etiology of EAE, arthritis, and diabetes, T cells drive all of these diseases; therefore, for the purpose of this review, EAE will be used as the example.

EAE has been employed extensively to determine the efficacy of pharmacological agents that may be of ultimate use in the treatment of MS (16). Susceptible strains of mice develop EAE following injection with CNS proteins like myelin basic protein (MBP). EAE is mediated by CD4 + T cells, and more specifically type-1 helper (Th1) cells that recognize proteins in the CNS (17). MBP-specific Th1 cells, which make interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF-α), and are isolated from paralyzed mice, transfer disease when injected into naive mice (Fig. 1) (17). Conversely, transfer of type-2 helper (Th2) cells specific for CNS proteins (make IL-10 and IL-4) suppress EAE in mice (18, 19). Normally the immune response is a balanced one in which both Th1 and Th2 cells are activated. In EAE there is a skewed immune response with many Th1 cells and few Th2 cells. Many experimental therapies aim to correct this imbalance either by suppressing/eliminating Th1 cells or by stimulating Th2 cells (18–20).

IL-4 regulates the development of CD4 + Th lymphocyte subsets by stimulating precursor cells to mature into Th2 cells while inhibiting the generation of Th1 cells (Fig. 1) (21). Conversely, IL-12 expression stimulates precursor (Th0) cells to mature into Th1 cells while inhibiting the generation of Th2 cells (Fig. 1) (21). The production of other cytokines such as transforming growth factor (TGF)-β1, and IFN-γ has also been shown to affect the development of Th cell subsets *in vitro* and *in vivo*. The microenvironment in which the Th0 cell develops determines which Th subset predominates. Factors that are known to direct the differentiation of Th0 cells include antigen dose, route of antigen administration, and the antigen-presenting cells. All of these factors are thought to act by changing the cytokine milieu present during antigen stimulation.

Vitamin D and the Immune System

The identification of vitamin D receptors (VDR) in peripheral blood mononuclear cells sparked the early interest in vitamin D as an immune system regulator (22, 23). The classical functions of vitamin D are in the regulation of calcium homeostasis and thus bone formation and resorption. However, it has recently been shown that the active

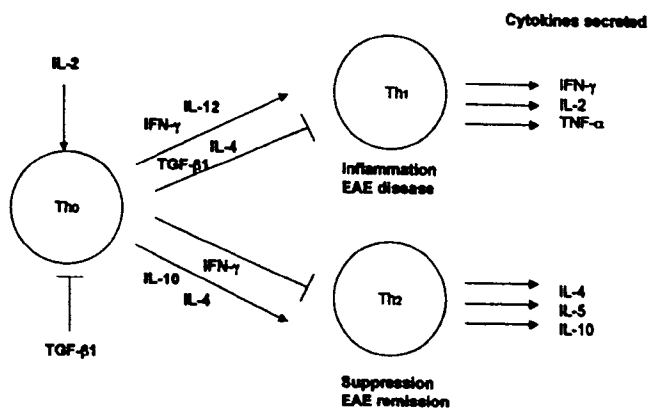

Figure 1. Cytokines that regulate Th cell differentiation. Arrows → represent cytokines that are positive regulators, and lines —| represent cytokines that inhibit or are negative regulators of Th cell development.

form of vitamin D ($1,25\text{-}(OH)_2D_3$) profoundly affects immune responses. *In vivo*, $1,25\text{-}(OH)_2D_3$ supplementation prevents EAE and arthritis development (24, 25), and injected $1,25\text{-}(OH)_2D_3$ has been shown to prolong the time to the development of murine IDDM (26). Furthermore, vitamin D deficiency has been shown to increase the susceptibility of mice to EAE (24). *In vitro*, $1,25\text{-}(OH)_2D_3$ inhibits T-cell proliferation and decreases the production of the Th1 cytokines IL-2, IFN-γ, and TNF-α (27). *In vivo*, $1,25\text{-}(OH)_2D_3$ injections were shown to inhibit the Th1-driven delayed-type hypersensitivity response (28, 29). The targets of vitamin D in the immune system have begun to be identified, and one vitamin D target is the Th1 cell that causes EAE.

Vitamin D may be a physiological regulator of T-cell development. *In vitro*, $1,25\text{-}(OH)_2D_3$ has been shown to be a differentiation factor for monocytes and other cell types including tumor cells (30). In T cells, $1,25\text{-}(OH)_2D_3$ seems to preferentially downregulate type-1 helper (Th1) cells both by decreasing proliferation and decreasing cytokine secretion (31). Furthermore, $1,25\text{-}(OH)_2D_3$ decreases IL-12 production, and IL-12 is an important T-cell differentiation factor (Fig. 1) (32). *In vivo* $1,25\text{-}(OH)_2D_3$ treatment increased the proportion of antiencephalitogenic Th2 cytokines IL-4 and TGF-β1 (33). In the absence of vitamin D, EAE developed more rapidly as compared with vitamin D–sufficient mice (24). Figure 2 shows a model of the development of EAE in the absence and presence of vitamin D. It seems probable that vitamin D is a factor that shapes the development of the T-cell compartment and therefore the development of EAE.

The molecular mechanisms underlying cytokine-driven, Th-cell differentiation are beginning to be understood and include the differential induction of a number of transcription factors including Stat 1, Stat 4, Stat 6, and GATA-3 in Th1 and Th2 cells (34–36). The identification of VDRs in Th cells suggests that vitamin D is likely to have a role in either the function or the development of Th cells. The molecular $1,25\text{-}(OH)_2D_3$ regulation of IL-2 and IL-12 has been studied. For cells that secrete IL-2 or IL-12, regulation may include inhibition of the nuclear factor of activated T cells and the nuclear factor-*k*B transcription signal by $1,25\text{-}(OH)_2D_3$ (32, 37, 38). Vitamin D is a transcription factor itself (39). Vitamin D receptors are found in the nuclease of cells and when bound to the VDR ligand ($1,25\text{-}(OH)_2D_3$) they regulate transcription of targeted genes (39). Vitamin D response elements are sequences of DNA found in the promotors of vitamin D–regulated genes (39). Vitamin D might act as a transcriptional regulator of Th cell cytokine synthesis (as it does for IL-2 and IL-12), as a regulator of Stat 1, 4, or 6, as a regulator of GATA-3, or perhaps as the latest transcription factor to regulate Th-cell differentiation.

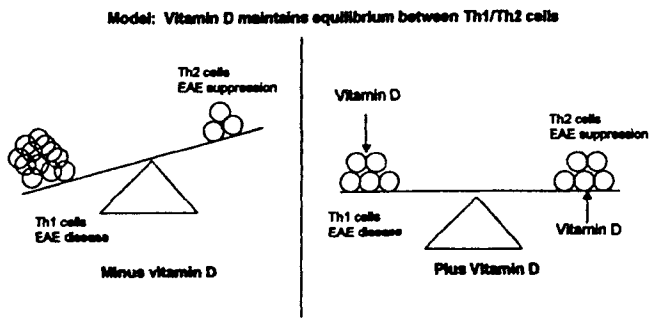

Figure 2. A model for the development of EAE (left) in the absence of vitamin D and (right) in the presence of vitamin D is presented. The hypothesis is that vitamin D regulates Th-cell development either by negatively regulating Th1 cells or by positively regulating Th2 cells or, the most likely scenario, both by regulating Th1 and Th2 cells.

Summary

Vitamin D is one of many potential new therapies for MS, arthritis, and juvenile diabetes. The appeal of vitamin D therapy for these diseases is in the possibility of concomitantly reducing autoimmunity and building stronger bones. The potential for vitamin D deficiency to exacerbate symptoms of MS, arthritis, and diabetes warrants further investigation. If vitamin D deficiency is occurring at a higher rate in autoimmune disease patients, then appropriate supplementation may be indicated. Similarly, in patients with osteopenia, there is a clear and rational reason to suggest vitamin D treatment. Bone loss and osteopenia are two of the most crippling side effects of standard corticosteroid therapy (6–9). The most serious side effect of vitamin D treatment is hypercalcemia, which itself can be lethal. Therefore, caution is warranted in the use of vitamin D as a treatment for MS, RA, and IDDM, but so is further investigation into the possible connections between vitamin D status and autoimmune diseases.

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