ASSOCIATION BETWEEN VITAMIN D DEFICIENCY AND AUTOIMMUNE DISEASES

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ABSTRACT

Vitamin D is a secosteroid rather than a vitamin. Vitamin D plays a role in the maintenance of immune homeostasis. Low levels of 25-hydroxyvitamin D [25(OH)D] are frequently noted in patients with autoimmune diseases, leading to a current consensus that a deficiency of the secosteroid may contribute to the autoimmune disease process. Low levels of vitamin D in patients with autoimmune disease may be a result rather than a cause of disease. The discovery of the vitamin D receptor (VDR) in the cells of the immune system and the fact that several of these cells produce the vitamin D hormone suggested that it could have immunoregulatory properties. Vitamin D has multiple immunosuppressant properties. Definitive mechanisms by which vitamin D protects against autoimmune disease have yet to be identified. This review describes the importance of vitamin D deficiency in autoimmune diseases.

Keywords: vitamin D, deficiency, pathophysiology, autoimmune diseases

VITAMIN D AND THE IMMUNE SYSTEM

Adequate vitamin D levels can be achieved only by sunlight exposure or supplementation. Lack of sunlight, gastrointestinal inflammation, aging, darker skin and elevated cortisol can cause a vitamin D deficiency. Some years ago, molecular biology identified 25-D as a secosteroid. Vitamin D is involved in bone and calcium metabolism. It is involved in the regulation of calcium homeostasis, as it regulates calcium absorption from the gastrointestinal system. The hormone is synthesized in the skin by the action of ultraviolet irradiation. Vitamin D has extraskeletal effects as well (1).

The nonclassical actions of vitamin D are currently under discussion. It is increasingly recognized that vitamin D also has important roles in multiple other systems, including effects on muscles, vasculature, reproduction, cellular growth and differentiation, malignancy and the immune system. Vitamin D can modulate the innate and adaptive immune responses. Vitamin D plays an important role in the immune system's battle against infection and control of inflammation. The definition of deficiency of 25(OH)D is variable. Vitamin D deficiency is also frequent among young subjects. Vitamin D insufficiently is emerging as a clinical problem of global proportions and epidemiology has linked vitamin D status with autoimmune disease susceptibility and severity. These low levels of 25(OH)D are a result, rather than a cause, of the disease process. Vitamin D has a pivotal role in the maintenance of immune homeostasis (2).

THE ROLE OF VITAMIN D IN REGULATING IMMUNE RESPONSES

Emerging evidence suggests that vitamin D plays an important role in immune regulation. Vitamin D's regulatory role of vitamin D in modulating the immune response includes inhibitory effects on

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T cells, B cells and dendritic cells (3). The identification of vitamin D receptors (VDR) in peripheral blood mononuclear cells sparked the early interest in vitamin D as an immune system regulator (4). Vitamin D may be a physiological regulator of T-cell development. In the light of recent research, the VDR is now known to transcribe at least 913 genes and largely control the innate immune response. Immune cells have vitamin D receptors, and activated vitamin D is a very effective modulator of immune functioning, reducing the inflammatory response and limiting autoimmune attacks. Vitamin D plays an important role in balancing the Th1 (cell-mediated) and Th2 (humoral) arms of the immune system (5).

Vitamin D receptors are expressed on B cells. The insights are based on molecular research showing that 25(OH)D inactivates rather than activates its native receptor. Additional vitamin D activates the VDR being converted into 1,25(OH)D. The VDR is ultimately a control system for the innate immune response (6).

Deficiency in vitamin D is associated with increased autoimmunity and an increased susceptibility to infection. Interestingly, vitamin D has been shown to inhibit antibody secretion and autoantibody production (7). Therefore, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], the biologically active metabolite of vitamin D_3 exerts immunomodulation via the nuclear VDR expressed in antigen-presenting cells and activates T/B cells. Moreover, $1,25(OH)_2D_3$ enhances IL-10 production and promotes dendritic cells (DC) apoptosis. Together, these effects of $1,25\ (OH)_2D_3$ inhibit DC-dependent T-cell activation. The synthesis of other T-lymphocyte cytokines can also be influenced by $1,25(OH)_2D_3$ (8).

$1,25(OH)_2D_3$ inhibits B cell proliferation before differentiation to immunoglobulin-secreting cells, consequently reducing immunoglobulin production. In vitro, $1,25(OH)_2D_3$ inhibits the differentiation of monocytes into dendritic cells (DCs) and interferes with the stimulatory activity that T-cells exert on them (9). In vivo, $1,25(OH)_2D_3$ has a direct immunosuppressive effect on DC, reduces IL-12 production and IFN-γ and IL-2. $1,25(OH)_2D_3$ stimulates phagocytosis and killing of bacteria by macrophages but suppresses the antigen-presenting capacity of these cells and of DCs (10,11).

Vitamin D has found to promote the induction of monocytic differentiation to macrophages and modulate macrophage responses, preventing them from releasing inflammatory cytokines and chemokines (12). Because macrophages also play important roles in several autoimmune diseases, this may be special clinical importance (13).

Finally, $1,25(OH)_2D_3$ can decrease the antigen-presenting activity of macrophages to lymphocytes by reducing the expression of major histocompatibility complex II molecules on the cell surface. Under such circumstances, supplementation with extra vitamin D is not only counterproductive but harmful. Administering supplemental vitamin D will stimulate 1,25(OH)D production (14).

VITAMIN D DEFICIENCY IN AUTOIMMUNE DISEASES

Epidemiological studies suggest that the development of systemic autoimmune disease is affected by geographical areas and lifestyle. Presumably, in these processes, vitamin D is a significant environmental factor. Both experimental and clinical data provide evidence that vitamin D is one of those important environmental factors that can increase the prevalence of certain autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis RA), type 1 diabetes mellitus, and inflammatory bowel disease. Vitamin D deficiency is common in patients with Crohn disease even when the disease is in remission.

Autoimmunity is an inflammatory response to normal cells or proteins caused by a lack or loss of tolerance by the immune system. There is increasing interest for understanding of the role of vitamin D deficiency in a number of chronic health problems including autoimmune diseases. Vitamin D action may to preserve balance in the T-cell reaction and thus avoid autoimmunity. A number of studies have suggested that patients with autoimmune diagnoses are deficient in 25-hydroxyvitamin D [25(OH)D] (15,16).

Low levels of 25(OH)D are frequently noted in patients with autoimmune disease, leading to a current consensus that a deficiency of the secosteroid may contribute to the autoimmune disease process (17).

It is unclear whether vitamin D insufficiently is a cause or a result of autoimmunity and/or corticosteroid therapies, which are commonly used to treat these patients (18,19).

Like corticosteroid medications, vitamin D may provide short-term relief by lowering inflammation but may exacerbate disease symptoms over the long-term. For example, a higher incidence in brain lesions, allergies, and atopy in response to vitamin D supplementation have been noted of supplementation with the secosteroid (20-22).

Vitamin D supplementation leads to the formation of 25(OH)D rather than 1,25(OH)D. It seems that high vitamin D intake, regardless of sunlight exposure, is associated with a reduced risk of developing type 1 diabetes mellitus, RA, and multiple sclerosis (MS). High levels of 25(OH)D do not appear to prevent inflammatory disease. In contrast, 1,25(OH)D appears to be a highly sensitive clinical marker both in diagnosis of autoimmune and associated diseases. Moreover, critically low levels of the vitamin clearly correlated with the progression to well-established connective tissue disease (CTD) (23).

VITAMIN D DEFICIENCY IN SYSTEMIC LUPUS ERYTHEMATOSUS

The suppressive immunologic properties have led to considering its role in autoimmune diseases such as SLE. A number of recent studies have highlighted the association between SLE and vitamin D deficiency (24-28). People with low levels of vitamin D are more prone to develop SLE than those with higher levels. Researchers have just found that vitamin D levels among SLE patients directly relates to the severity of the disease (29,30). Prospective studies of vitamin D in SLE are limited, but most cross-sectional studies show an inverse relationship between levels of vitamin D and disease activity. Vitamin D deficiency as a possible risk factor for SLE and provide guidance for future studies looking at a potential role of vitamin D in the prevention and/or treatment of SLE. Vitamin D deficiency was found in 18% of the SLE patients with the presence of severe renal disease and photosensitivity. As another vitamin D-reducing factor, anti-vitamin D antibodies have been described in patients with SLE, antiphospholipid syndrome, and pemphigus vulgaris, and these autoantibodies were associated with anti-dsDNA antibodies in SLE (31-33).

VITAMIN D DEFICIENCY IN RHEUMATOID ARTHRITIS

Previous research has indicated an association between vitamin D deficiency and rheumatoid arthritis (RA). Reduced vitamin D intake has been linked to increased susceptibility to the development of RA and vitamin D deficiency has been found to be associated with disease activity in patients with RA. Vitamin D supplementation may be needed both for the prevention of osteoporosis as well as for pain relief in patients with RA (32). Some authors reported an inverse relationship between serum levels of vitamin D metabolites and disease activity or disability in patients with RA or early inflammatory polyarthritis (33). Vitamin D supplementation should be commonly given to RA patients taking corticosteroids to prevent corticosteroid-induced osteoporosis through modulation of the Th1/Th17 and Th2 cytokine balance (34).

VITAMIN D DEFICIENCY IN DIABETES MELLITUS

Epidemiological studies suggest a link between vitamin D deficiency in early life and the later onset of type 1 diabetes. Several observational studies have suggested that either low vitamin D levels or low vitamin D intake may predispose to the development of both type 1 and type 2 diabetes mellitus. Vitamin D deficiency has been implicated in the pathogenesis of type 1 diabetes mellitus. Vitamin D has another little-known role. It regulates insulin secretion and sensitivity and balances blood sugar. Vitamin D deficiency is associated with insulin resistance. Low vitamin D levels, low sun exposure, and low intake of vitamin D have each been associated with an increased risk for the development of type 1 diabetes mellitus. Low 25(OH)-vitamin D levels have been shown to correlate with the presence of cardiovascular disease in diabetics. Generally RA and juvenile diabetes are more prevalent in higher latitudes than in the latitudes of the tropics and subtropics. In addition, there is seasonal variation in type 1 diabetes mellitus with the largest proportion of type 1 diabetes mellitus cases diagnosed during fall-winter and the lowest during the summer (35,36).

VITAMIN D DEFICIENCY IN MULTIPLE SCLEROSIS

Vitamin D deficiency has been implicated in the pathogenesis of multiple sclerosis (MS). In addition, areas with diets rich in fish oil, a major dietary source of vitamin D, have lower incidence of MS. The maintenance of an adequate vitamin D level may have a protective effect in individuals predisposed to MS. Ultraviolet irradiation of the skin is a major source of vitamin D, and the prevalence of MS is lower in regions where vitamin D is abundant as in sunny climates and high altitudes. Further studies are needed to determine whether vitamin D alone or combined with other treatments is effective in individuals with active MS (37-39).

VITAMIN D DEFICIENCY IN UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

The term "undifferentiated connective tissue disease" (UCTD) has been used since 1980 to describe a group of connective tissue diseases (CTDs) that lack the characteristics of any distinctive disease. About 30% to 40% of patients with UCTD will evolve to defined CTD during the years of follow-up. Several factors can lead to low levels of vitamin D in our patients with UCTD. Although the physical activity of most patients was not limited, patients with photosensitive rashes do seem to have a reduced exposure to sunlight and generally use very high UV protection. UCTD has specific signs and/or autoantibodies that are characteristic of autoimmune disease. Vitamin D may be a key regulator of autoimmune processes in patients with UCTD. Vitamin D deficiency in UCTD patients may play a role in the subsequent progression into well-defined CTDs. The measurement of serum vitamin D is crucial in UCTD patients and that the effective supplementation of vitamin D may be important in these patients (40-42).

VITAMIN D DEFICIENCY IN AUTOIMMUNE THYROID DISORDERS

Autoimmune thyroiditis tends to be an innocent bystander with other autoimmune diseases such as type 1 diabetes, RA, SLE, etc. Autoimmune thyroiditis is also the most common undiagnosed autoimmune disease in the world. More women are diagnosed with this condition than men. Several studies have established a relationship between low vitamin D levels and autoimmune thyroid disorders. Vitamin D helps to balance the immune system that is out of balance and attacking the thyroid gland. Insulin resistance and dysglyemcia adversely affect thyroid physiology in several ways. Since vitamin D is absorbed in the small intestine, a **leaky and inflamed gastrointestinal tract** – which is extremely common in people with low thyroid function – reduces the absorption of vitamin D. There is evidence for a role of the vitamin D in the pathogenesis of thyroid autoimmunity. Vitamin D deficiency was also strongly correlated with antithyroid antibodies and poor thyroid functions. In humans, serum levels of $1,25(OH)_2D_3$ were found to be significantly lower in autoimmune than in non-autoimmune hyperthyroidism. Patients with autoimmune thyroid disease have been shown to be deficient in vitamin D with genetic abnormalities in their VDR. Studies have shown that a significant number of patients with autoimmune Hashimoto's disease have VDR polymorphisms (43).

CONCLUSION

The main source of vitamin D comes from the endogenous production in the skin after exposure to ultraviolet B light. Vitamin D influences immune system cells, particularly dendrites (D-cells). Vitamin D may regulate the immune response. The active form of vitamin D has immunosuppressive actions. Deficiencies of vitamin D interfere with D-cell function and contribute to autoimmunity Low levels of vitamin D in patients with autoimmune disease may be a result rather than a cause of disease. Vitamin D deficiency may have a role in the pathogenesis of systemic autoimmune diseases.

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