

# VITAMIN D

## IN AUTOIMMUNE & NEURODEGENERATIVE DISORDERS

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### ABSTRACT

Vitamin D, a secosteroid exhibiting a pleiotropic action, plays important functions in the nervous system and immune system. By suppressing dendritic cell survival, it impairs the activation of allo-reactive T-lymphocytes. It induces apoptosis of B-lymphocytes, reducing the production of autoantibodies. Its neuroprotective roles are linked with its influence on neurotrophin production, calcium ion homeostasis and in controlling oxidative damage. It is therefore not surprising that hypovitaminosis D is linked to both autoimmune and neurodegenerative disorders.

**Keywords:** Vitamin D, autoimmunity, neurodegeneration.

### INTRODUCTION

Vitamin D is a secosteroid existing in two major forms: ergocalciferol and cholecalciferol. The most recognized function of this vitamin is in maintenance of calcium homeostasis.<sup>1</sup> However more recent evidence supports a role of vitamin D in brain development and function, in regulation of insulin production, in controlling immune responses and in cardiovascular and musculoskeletal health.<sup>2</sup>

### 1. VITAMIN D AND ITS MODULATORY FUNCTION

#### A. THE NERVOUS SYSTEM

Vitamin D alters the synthesis and secretion of neurotrophic factors, nerve growth factors and the neurotrophin receptor p75NTR. Its deficit results in decreased expression of neurotrophins and p75NTR, leading to a loss of the survival, differentiation and maintenance function that these exert in nerve cells, contributing to neurodegeneration.<sup>3</sup>

By interacting with and reducing reactive oxidative species (ROS), vitamin D prevents oxidative stress-induced neuronal damage. Even nanomolar concentrations of vitamin D (0.1-100 nM) help to protect neurons from such damage.<sup>4</sup> Vitamin D inhibits  $\gamma$ -glutamyl transpeptidase and nitric oxide synthase. This leads to lower levels of intracellular hydrogen peroxide and nitric oxide respectively, further exerting anti-oxidant effects.<sup>5</sup>

Vitamin D is also involved in sustaining intracellular calcium ion ( $\text{Ca}^{2+}$ ) homeostasis by suppressing L-type  $\text{Ca}^{2+}$  channels. Physiologically elevated levels of  $\text{Ca}^{2+}$  ions in the cytosol lead to exocytosis of various stimulating amino acids neurotransmitters, resulting in excitotoxicity.<sup>5</sup>

#### B. THE IMMUNE SYSTEM

Inhibition of memory- and plasma- cell production, as well as promotion of apoptosis of B-lymphocytes are direct effects exerted by vitamin D on B-cells. By controlling B-lymphocyte activation and proliferation, vitamin D reduces the production of autoantibodies, which are involved in the pathophysiology of autoimmune disorders.<sup>5</sup>

Vitamin D suppresses T helper cell (Th) proliferation and differentiation. Through down regulation of the major histocompatibility complex-II (MHC-II) antigen and the production of interleukin (IL)-23 and IL-12, vitamin D shifts the polarization of T-lymphocytes from a Th17 and Th1 phenotype towards a Th2 phenotype. This results in reduced production of pro-inflammatory cytokines like IL-17 and interferon- $\gamma$  and promotes the synthesis of anti-inflammatory Th2 cytokines, including IL-3 and IL-10. By suppressing dendritic cell survival, vitamin D further promotes the development of T regulatory cells and Th2 cells.<sup>6</sup>

Lucas *et al.*<sup>7</sup> have shown that vitamin D helps in maintaining the ratio of activated Th1/Th17 cells in the systemic circulation and prevents their movement across the blood-brain barrier. This reduces the expression of the chemokine receptor CXCR3. Increased expression of this receptor increases intracellular  $\text{Ca}^{2+}$  levels by activating the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase pathways, leading to excitotoxicity.<sup>8</sup>

Another target through which vitamin D mediates suppression of self-reactive T-lymphocytes is the Fas ligand. The Fas-FasL pathway regulates activation-induced cell death in T-lymphocytes, thereby maintaining central and peripheral

**IN UTERO LEVELS OF VITAMIN D ALSO AFFECT THE RISK OF DEVELOPMENT MS LATER IN LIFE**

tolerance to self-antigens. Through downregulation of this ligand vitamin D alters the immune response at various levels, preventing the development of autoimmune diseases.<sup>9</sup>

This shows that vitamin D is an environmental factor, related to both autoimmune and neurodegenerative disorders. In fact, studies suggest that hypovitaminosis D, which is defined as a vitamin D serum concentration of being less than 25nmol/L, negatively impacts such disorders.<sup>10</sup>

## 2. VITAMIN D AND AUTOIMMUNITY

With insufficient vitamin D serum levels, the immune system allows the up-regulation of B-cells and self-reactive T-cells. The production of inflammatory cytokines, together with increased production of immunoglobulin producing B-cells, contributes to the development of autoimmune diseases.<sup>11</sup>

Vitamin D deficiency has also been implicated in facilitating the progression of existing autoimmune disorders. In a study carried out by Zold *et al.*<sup>12</sup> 161 patients with an early connective tissue disorder were followed for about 2 years. There was no progression of the disease in most of the patients. However 21% of the patients developed a specific rheumatologic disorder including systemic lupus erythematosus (SLE). Lower vitamin D levels were present in the population in which the disease progressed to a definitive state.<sup>12</sup>

Hypovitaminosis D is linked to several autoimmune disorders, including multiple sclerosis (MS), type 1 diabetes mellitus (T1DM) and inflammatory bowel disease (IBD).<sup>5</sup> MS is the only autoimmune disease in which the effects of vitamin D have been well-established.

### A. MULTIPLE SCLEROSIS

MS is an autoimmune neurodegenerative disease, driven by myelin auto-reactive T- lymphocytes, which leads to the recruitment of macrophages, with subsequent myelin destruction and axon degeneration.<sup>5</sup>

Vitamin D deficiency leads to loss of balance between the inflammatory and anti-inflammatory pathways. This is because activation of immature dendritic cells results in mature dendritic cell production, leading to reduced differentiation of immunosuppressive regulatory T-cells and increase in Th1 cells. These synthesize and secrete inflammatory cytokines, including IL-23 and interferon- $\gamma$ , leading to demyelination. Prolonged toxic insults to neurons results in the release of neural antigens, stimulating further inflammatory responses, enhancing demyelination.<sup>13</sup>

Vitamin D acts as a specific inhibitor of osteopontin, a pro-inflammatory cytokine involved in the progression of MS. Osteopontin increases the production of IL-12, tumor necrosis factor and interferon- $\gamma$  by T-lymphocytes, inhibits IL-10 production and lengthens the life-span of activated T-lymphocytes. In fact, higher levels of osteopontin transcripts are found in patients suffering from MS.<sup>5</sup>

In utero levels of vitamin D also affect the risk of development MS later in life. Eyles *et al.*<sup>14</sup> showed that in utero vitamin D deficiency led to the dysregulation of various mRNA transcripts, including the enzyme calcineurin and FK506 binding protein 1a in the brain tissue of the offspring. These function to limit the synthesis of IL-2, which results in cytotoxic T-cell activation and tissue damage.

## IN A STUDY INVOLVING 10,366 CHILDREN ... DAILY SUPPLEMENTATION OF 2000IU OF VITAMIN D IN THE FIRST YEAR OF LIFE REDUCED THE RISK OF DEVELOPING T1DM ... BY ABOUT 80%

### Genetic Risk Factors

#### Vitamin D receptor gene

The *FokI* polymorphism of the vitamin D receptor (VDR) gene affects in vitro vitamin D-mediated inhibition of IL-12 transcription and protein production by dendritic cells and monocytes. IL-12 induces Th1 cells, contributing to neuronal inflammation.<sup>15</sup> The *TaqI* variant of the VDR gene is also weakly related to MS.<sup>16</sup>

#### HLA-DRB1 gene

The MHC gene on chromosome 6 provides the single largest contribution to disease susceptibility in the entire genome. The classical human leukocyte antigen (*HLA*)-*DRB1\*15:01* allele has been documented as the strongest genetic association to the risk of developing MS.<sup>17</sup> The vitamin D response element in the *HLA-DRB1* promoter, corresponding to the *HLA-DRB1\*15* haplotype, binds VDR with higher affinity than other elements. Vitamin D stimulation of B-lymphocytes transfected with *HLA-DRB1* gene constructs, including the *HLA-DRB1\*15* sequence, doubles the expression of *HLA-DRB1\*15:01*. This suggests that the *HLA-DRB1\*15:01* haplotype greatly contributes to the effect exerted by vitamin D in MS.<sup>18</sup> A lack of vitamin D during the early life of *HLA-DRB1\*15*-bearing individuals could allow autoreactive T-cells to escape thymic deletion, increasing the risk of the development of autoimmune disorders.<sup>19</sup>

Epigenetic changes in the genes encoding cytochrome P450 reductase (CYP) 27B1 and CYP24A1, which are involved in vitamin D metabolism and catabolism respectively, also affect vitamin D serum levels, contributing to the pathogenesis of the disease.<sup>17</sup>

### B. OTHER AUTOIMMUNE DISORDERS

#### i. Type 1 Diabetes Mellitus

T1DM results from immune-mediated destruction of  $\beta$ -pancreatic cells. Apart from acting at a peripheral level and controlling the cellular-mediated pathogenesis of this disease, vitamin D reduces the selection of self-reactive T-cells in the thymus.<sup>20</sup> Vitamin D supplementation also decreases the risk of developing T1DM. In a study<sup>21</sup> involving 10,366 children carried out in Finland, daily supplementation of 2000IU of vitamin D in the first year of life reduced the risk of developing T1DM in the next 31 years by about 80%.<sup>21</sup>

#### ii. Inflammatory Bowel Disease

IBD includes ulcerative colitis and Crohn's disease, both of which are characterized by chronic inflammation of the intestine. Reduced levels and/or dysfunctional auto-phagocytosis have been implicated as contributing factors in IBD.<sup>22</sup> By enhancing the co-localization of pathogen-harboring phagosomes with autophagosomes in a



cathelicidin-dependent manner, vitamin D increases the basal levels of autophagy.<sup>23</sup> Vitamin D down-regulates the expression of the protein kinase mammalian target of rapamycin (mTOR), a negative regulator of autophagy.<sup>24</sup> Furthermore, through the activation of the PI3K signaling pathway, it enhances beclin-1 expression, which stimulates auto-phagocytic processes.<sup>23</sup>

### 3. VITAMIN D AND NEURODEGENERATION

Insufficient levels of vitamin D results in increased levels of Ca<sup>2+</sup> ions and ROS, which together with reduced neurotrophin levels, contribute to neuronal degeneration. Hypovitaminosis D also contributes to immune-mediated degeneration. Interactions between Th1, Th17 cells and inflammatory cytokines result in microglia activation and inflammation, resulting in cytotoxicity and neuronal damage.<sup>5</sup> Apart from MS, low levels of vitamin D are linked to several neurodegenerative disorders including amyotrophic lateral sclerosis (ALS) and Alzheimer's dementia (AD).<sup>5,25</sup>

#### A. AMYOTROPHIC LATERAL SCLEROSIS

Multiple effector pathways contribute to ALS pathology including deficiency of neurotrophic factors, glutamate toxicity and damage from ROS, all of which are kept in control by vitamin D. An abnormal calcium-parathyroid hormone-vitamin D level has been detected in patients with ALS, with vitamin D serum concentrations being significantly lower in ALS patients than in transgenic mouse control models of ALS. Such patients showed improvements in their functional capacity following dietary vitamin D supplementation.<sup>25</sup>

Several of the ALS susceptibility genes with related VDR-binding sites have been indicated in salient brain functions such as neuritogenesis and axonal growth.<sup>26</sup> In fact, the Gc2 polymorphism of vitamin D-binding protein was recorded in the plasma of a cohort of Portuguese patients with familial ALS.<sup>27</sup>

#### B. ALZHEIMER'S DEMENTIA

Given the role of vitamin D in facilitating neurotransmitter synthesis, protecting against oxidative stress, reducing pro-inflammatory responses, and maintaining neurite outgrowth,<sup>5</sup> a biological basis exists that supports the role of vitamin D in the pathogenesis of cognitive impairment and AD. 72% of the 25 cross-sectional studies analyzed by van der Schaft *et al.* report a statistically significant worse outcome on one or more cognitive function tests or a higher frequency of dementia with lower vitamin D levels or intake. 66.7% prospective studies show a higher risk of cognitive decline after a follow-up period of 4–7 years in participants with lower vitamin D levels at baseline.<sup>28</sup>

### CONCLUSION

Vitamin D exhibits the main characteristics of a true neuroactive steroid, with clinical and experimental evidence that vitamin D deficiency is an important factor involved in autoimmune and neurodegenerative disorders. However little is still known whether its supplementation helps in the prevention and treatment of such disorders. ❄

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