

# The Role of Vitamin D in Immunity



Vitamin D is well-known for the important role it plays in calcium utilization and the proper development of bones. For example, most people are aware that vitamin D deficiency in young children can lead to rickets, a condition where the bones become weak and soft.<sup>1</sup> More recently, however, vitamin D has gained attention for a plethora of other important benefits, and low levels of vitamin D have now been linked to increased hypertension, increased autoimmune diseases, an increased risk for various forms of cancer including breast, prostate and skin, chronic pain, premenstrual syndrome (PMS), poor immune system, diabetes, seasonally affective disorders and even an increased risk of mortality by all causes.<sup>2-7</sup>

## Immune System Modulation

Many of the benefits of vitamin D relate to the very important role the vitamin plays in the normal functioning of the immune system. The immune system is made up of a number of different types of cells that work together to protect the body from threats. Dendritic cells are important for activating the rest of the immune system, and are specialized in antigen presentation. This means that they will engulf invaders, and then display markers of the invader, or antigens, which in turn activate other cells of the immune system, such as helper T-cells. Activated helper T-cells then stimulate other cells including killer T-cells, which attack and kill cells infected by the invader, and B-cells, which produce antibodies that identify and attach to the invader, marking it for elimination.

This is an extremely complicated process, and requires a delicate balance for proper functioning. The immune system is critical for protecting our bodies from foreign pathogens and invaders. However, it must also be able to distinguish between a dangerous invader and harmless food proteins, friendly bacteria and cells of the body. In other words, the immune system must

develop “tolerance” for these types of proteins and cells. When tolerance fails, an inappropriate immune response occurs – resulting in allergies, where the immune system reacts to normally harmless molecules as if they were dangerous invaders, or even autoimmunity, where the body attacks its own cells.

This delicate balance is mostly established by the helper T-cells, which are responsible for the moderation and regulation of the immune response. There are two types of helper T-cells– Th1 and Th2. Autoimmunity seems to be related to an overabundance of Th1, whereas allergies have been linked to an overactive Th2 response.<sup>8</sup> The active metabolite of vitamin D3, 1,25(OH)<sub>2</sub>D<sub>3</sub>, has been shown to affect both the Th1 and Th2 responses, and plays a very important role in immune system regulation.

## The Regulatory Role of Vitamin D

Firstly, vitamin D inhibits the formation of dendritic cells, which in turn reduces the activation of T-cells, and the T-cell mediated immune response.<sup>8,9</sup> Vitamin D also acts on T-cells themselves, regulating the differentiation and activation of Th1 and Th2. Studies have shown that vitamin D3 down-regulates Th1, whose expression is related to autoimmunity. Vitamin D’s actions on Th2 are less certain, with some studies showing increased Th2 function and others showing suppressed function.<sup>8,9</sup> Vitamin D has also been shown to increase the production of regulatory T-cells, which play a very important role in self-tolerance, and therefore in the prevention of autoimmunity.<sup>8</sup>

In addition to the regulation of T-cells, vitamin D also has an effect on the actions of B-cells. It seems to act on them in two primary ways; first, it stimulates increased production of interleukin (IL)-10, which inhibits antigen presentation by dendritic cells and prevents T-cell activation, and second, it inhibits the production of IgE antibodies, the primary antibody associated with the allergic response.<sup>10</sup>

Overall, vitamin D is critical for the regulation and proper functioning of the immune system, and may act to prevent inappropriate immune system responses and help to restore proper immune system balance.

## Innate Immunity

Beyond its role in immune system modulation, vitamin D is also critically involved in the body’s innate immune response. Specifically, vitamin D has been shown to activate important antibacterial proteins called defensin and cathelicidin.<sup>8</sup> Researchers have related these actions to numerous beneficial effects, including a reduction in the risk of skin infection in individuals with atopic dermatitis<sup>11</sup>, a reduced risk of placental infections during pregnancy<sup>12</sup>, and even a reduction in the occurrence of the common cold.<sup>13</sup>



Figure 1. Asthma is a chronic inflammatory disease of the airways that is often associated with allergies. Asthma affects 8.4% of Canadians and 12% of Canadian children (Statistics Canada, 2001).

### The Link to Allergies and Asthma

Recent research on vitamin D has established a clear link between vitamin D and autoimmune disorders, and with self-tolerance. For example, low vitamin D levels have been related to the occurrence of autoimmune diseases including multiple sclerosis (MS) and inflammatory bowel disease (IBD).<sup>8,14,15</sup> Furthermore, studies in mice have suggested that treatment with vitamin D could be beneficial for a wide range of autoimmune diseases including MS, IBD and rheumatoid arthritis.<sup>8</sup>

With vitamin D playing such a major role in the function of the human immune system, it seems evident that there must also be some link to allergies, and indeed this seems to be the case. However, the role of vitamin D in the allergic response has not yet been fully clarified. For example, one study in mice has suggested potentially dual influences of vitamin D on allergies, with administration of active vitamin D resulting in increased T-cell activation and cytokine production in the mice, while at the same time reducing airway eosinophilia – a key pathological feature of asthma.<sup>14</sup>

Studies in humans have also demonstrated an important link between vitamin D levels and the development of asthma. Two recently published studies have reported that children under the age of 5, whose mothers had higher vitamin D intakes during pregnancy, had a reduced incidence of wheezing symptoms.<sup>17,18</sup> In fact, it has been demonstrated that higher vitamin D intakes during pregnancy may reduce the risk of childhood asthma by as much as 40%, and suggest a dose of 2000 IU daily during pregnancy to achieve adequate levels.<sup>19</sup> In yet another study involving 616 asthmatic children, low serum vitamin D levels were associated with increased levels of well-known markers of asthma and allergy severity, including IgE and eosinophil levels.<sup>20</sup>

The association between asthma and vitamin D is also supported by genetic studies, which have revealed variations in the vitamin D receptor in asthmatic individuals.<sup>21,22</sup> Furthermore, research has indicated that vitamin D is vital for proper lung development, and may also influence lung function later in life.<sup>23,19</sup> Two studies, one involving 2112 adolescents and the other 14901 adults, found that higher vitamin D intake is associated with improved lung function.<sup>24,25</sup>

Another interesting link between vitamin D and allergies was established by a group of American researchers examining the prevalence of EpiPen prescriptions across the United States.<sup>26</sup> EpiPens are autoinjectors that administer epinephrine as an emergency treatment for severe and potentially deadly allergic reactions called anaphylaxis. The study revealed a strong north-south gradient in EpiPen prescriptions, with northern states having a significantly higher number of prescriptions than southern states. The Researchers inferred that this gradient is related to sunshine exposure, and thus vitamin D levels.<sup>26</sup>

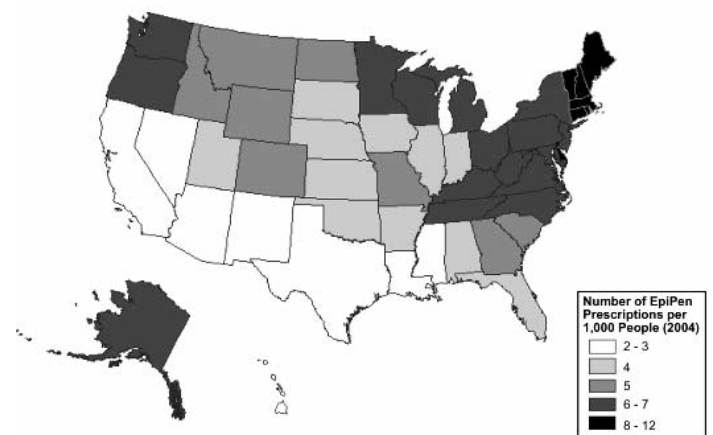


Figure 2. Regional Difference in EpiPen prescriptions per 1000 persons.<sup>26</sup>

### How it works

The mechanism by which vitamin D influences allergies and asthma is quite complex. Vitamin D has been shown to influence IgE levels, which is highly significant as IgE is the main antibody involved in the initiation of the allergic response. There have, however, been some conflicting results regarding vitamin D's influence on IgE. A recent study conducted in Europe offers some potential insight into this conflict. Scientists in Europe and the UK examined both the IgE and serum vitamin D levels of 7288 individuals and found that those with both extremely low (< 25 nmol/L) and extremely high (> 135 nmol/L) vitamin D levels in the blood expressed elevated IgE levels, and thus a higher potential for allergies.<sup>28</sup> These results indicate the importance of balanced vitamin D

levels, and are consistent with other studies suggesting a lower threshold of 75-100 nmo/L for serum vitamin D levels.<sup>28</sup>

More and more evidence suggests, however, that the most important role of vitamin D may be during early development, especially before birth.<sup>19</sup> As mentioned above, vitamin D's effects on Th2 are inconsistent, with some studies showing upregulation of Th2 cytokines associated with allergies, and others showing their suppression.<sup>8,9</sup> Researchers have suggested that these seemingly contradictory effects may relate to the timing of vitamin D exposure (i.e. pre or post-natal) and also to the role of regulatory T-cells (Tregs).<sup>19</sup> Vitamin D has been shown to increase Tregs, and also to increase the secretion of IL-10. Both of these actions have been shown to benefit individuals with steroid-resistant asthma – a well-established Th2 disorder.<sup>27</sup>



## Achieving Balance

Vitamin D3 has wide-ranging effects on the immune system. Due to its actions on both Th1 and Th2 mediated immune responses, vitamin D deficiency has been purported as a potential unifying factor in the rise of the prevalence of both Th1 disorders (autoimmunity) and Th2 disorders (allergies) over a similar time span.<sup>19</sup> Vitamin D may be of particularly critical importance at early stages of development to ensure proper immune function later in life. It has been hypothesized that vitamin D is essential for normal Treg development, and in turn the suppression of improper Th1 and Th2 responses and a more balanced immune response.<sup>19</sup> Although more research and clinical trials are required, it is clear that the "Sunshine" vitamin is an essential component of good health and in the development and maintenance of a healthy, balanced immune system.

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