

VITAMIN D AND ITS FUNDAMENTAL ROLE FOR THE IMMUNE SYSTEM

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INTRODUCTION

Vitamin D (25-(OH)2-D3) is not just a vitamin but it has both endocrine and paracrine functions (Nair & Maseeh, 2012). 25-(OH)2-D3 plays a fundamental role for the immune response and protection. Vitamin D target tissues which contain a specific vitamin D nuclear receptor (VDR). VDRs are present in more than 30 cell types particularly those responsible for calcium homeostasis, immune function, endocrine, hematopoiesis and tumors (Kongsbak et al., 2013). Bsm1 (rs1544410), Apal, and Taql are fragment length polymorphisms (RFLP) located next to each other in the region of intron 8 and exon 9 on the vitamin D receptor gene (VDR) (Colombini et al; 2016). These polymorphisms, as will be discussed below have been commonly associated with several diseases.

ASTHMA

Most studies have linked low levels of 25-OH-D3 with increased risk for asthma (Nair & Maseeh, 2012). On the other hand Ramadan et al; (2019) highlight that VDR expression in asthmatic children was found to be low. Calcitriol is the active form of Vitamin D and when calcitriol binds to VDR receptors it has been seen to regulate lymphocyte and monocyte sensitivity to glucocorticoids by inducing expression of FOXP3. FOXP3, the immune response protein, is the master transcription factor which determines the Treg phenotype (Nair & Maseeh, 2012). According to Marques et al; (2015), FOXP3 gene expression has been seen to decrease in asthmatic patients. In fact, in vitro studies have deduced that vitamin D treatment in asthmatic patients reduces airway proliferation of smooth muscle cells (Nair & Maseeh, 2012). The advantage of vitamin D treatment in asthma has been observed in VDR-knockout mice which in the presence of induced asthma do not show inflammatory responses suggesting how in fact calcitriol may be immunosuppressive as it inhibits signs/symptoms of Th1 autoimmune illness (Wittke et al; 2004). The Taql VDR genotype is associated with increased risk of asthma primarily when conditions of vitamin D levels are normal (>20 ng/ml) (Papadopoulou et al; 2015).

RHEUMATOID ARTHRITIS

Rheumatoid Arthritis an autoimmune disease of unknown cause characterized by inflammation of the joints. Vitamin D deficiency is known to result in diffuse musculoskeletal pain (Meena et al; 2018). Vitamin D is known to prompt immunologic tolerance. Kostoglou-Athanassiou et al. (2012) explain how vitamin D deficiency impacts immune tolerance inducing autoimmune diseases including rheumatoid arthritis. As shown in figure 1., Meena et al; (2008) demonstrate how low serum vitamin D in fact leads to high rheumatoid arthritis disease activity by discovering that F allele present in F/F FokI VDR polymorphism are associated with RA. The f variant in the VDR has three more amino acids when compared with the F allele and the FokI alleles differ functionally because VDR affinity and VDR elements transactivation are altered (Meena et al; 2008).

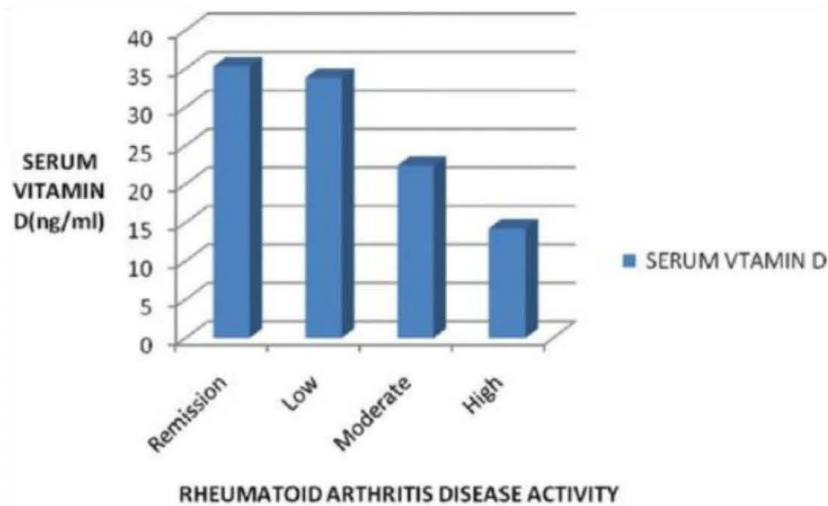


Figure 1: Inverse relationship of serum vitamin D (ng/ml) with Rheumatoid Arthritis Disease Activity (Meena et al; 2008)

MULTIPLE SCLEROSIS (MS)

MS is a chronic disease which affects the central nervous system and occurs when the immune system attacks the nerve fibers and myelin sheathing in the brain and spinal cord. When studying on the prevalence of MS, Sintzel, Rametta & Reder (2018) have observed how MS is more predominant in northern countries than in the tropics due to the number of hours of sunlight in winter and/or annually. In fact MS patients, like in asthma and rheumatoid arthritis have lower plasma calcitriol levels (Sintzel, Rametta & Reder, 2018). Mansouri et al; (2014) performed several studies which have shown how increased sunlight exposure leads to decreased vitamin D deficiency, decreasing MS risk. In fact they also explain how this decrease in risk is higher when sun exposure in particular occurred during childhood and puberty stage. Other studies have also shown how the birth month is related to MS risk. Individuals who were born in the fall means that their mother when pregnant has been exposed to summer sunlight. These individuals had a lower MS risk. On the other hand, individuals who were born during spring means that their mother when pregnant were less exposed to summer sunlight. These individuals were found to have a higher risk of MS. This indicates an observational relationship between maternal sunlight exposure during pregnancy and risk of MS (Sintzel, Rametta & Reder, 2018).

The most recent meta-analysis to date, have studied VDR polymorphisms risk of acquiring MS. It was found that based on geographical location, Asians who had the Bsml variant had an increased risk of MS while Apal showed lesser risk. Yet no association was found in variants and MS risk in the EU. The Fok1 variant was not related with increased MS risk or by geographical location (Imani et al; 2019).

INFLAMMATORY BOWEL DISEASE (IBS)

Vitamin D deficiency is present in patients' with Crohn's disease or ulcerative colitis. Vitamin D maintains a healthy microbiome in the gut because of VDR gut epithelial signaling. This has been seen to inhibit inflammation-induced epithelial cell apoptosis and prevents pathogenic CD8+ T cells proliferation therefore protecting the mucus barrier. Therefore, by affecting the gut microbiome vitamin D can ensure immune function of the host (Sheng et al; 2019).

ADIPOSE TISSUE AND DIABETES

Sequestration of calcitriol depends on the amount of adipose tissue. The more adipose tissue present results in a reduction in circulating calcitriol plasma levels. Therefore decreased 25-OH-D3 plasma levels could stimulate fat accumulation leading to metabolic syndrome. Vitamin D deficiency can lead to obesity. In fact, 1,25-(OH)₂-D₃ can result in adipocyte apoptosis by competition between VDR and RXR to bind with peroxisome-proliferator activation receptor (PPAR γ) which suppresses fat deposition, and stimulating steroid-metabolism enzyme expression of 11 β -hydroxysteroid hydroxylase- a steroid-metabolizing enzyme. Together with caloric restriction, Vitamin D can result in weight loss.

Berridge (2017) suggests that Vitamin D increases insulin sensitivity as calcitriol leads to the upregulation of the translocation of glucose transporter 4 (GLUT4) and adipocyte insulin signaling. On the other hand vitamin D may also play a role in decreasing the risk of Type 1 Diabetes (T1DM). It does this by destructing insulin-producing pancreatic- β cells which are secreted by cytokines and the free radicals released from inflammatory infiltrates; a process referred to as T-cell dependent. 1,25-(OH)₂-D₃ downregulates IL-12 production. Therefore IL-12-dependent Th1 cells will have suppressed activity, triggering cytotoxic CD8+ lymphocytes and macrophages activity. Risk of T1D is positively related to latitude and inversely proportional to hours of sunlight (Berridge, 2017).

Vitamin D deficiency also appears to increase the risk of noninsulin-dependent diabetes (type 2 diabetes, T2DM). As discussed above Vitamin D reduces inflammation. In fact according to Martine & Cambell, 2011, when Vitamin D is not present, chronic inflammation associated with insulin resistance will increase. In fact it has been found that serum calcitriol is inversely proportional to insulin resistance, body fat mass and body mass index (BMI). In fact studies have proven that the highest risk of T1/2DM is higher in winter because circulating levels of calcitriol are at their lowest. Bsm1 and Apal are two VDR polymorphisms which have been linked to high fasting glucose levels, hyperinsulinemia, and higher T2D risk. The greatest relationship between levels of vitamin D and T2DM are highest among overweight and obese people (Martin & Campbell, 2011 & Berridge, 2017).

CONCLUSION

In asthma, rheumatoid arthritis, MS, IBS and diabetes vitamin D supplementation can be given to either prevent or reduce the severity of such conditions. Yet further studies focusing on vitamin D administration and sufficient levels of Vitamin D administration are necessary to conclude this.

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