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Review

Vitamin D level and potential impact on immune cells in Behçet's disease

Clinical

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Abstract

Introduction

Vitamin D plays key roles in innate and adaptive immunity through the stimulation of Toll-like receptors, increasing proinflammatory cytokine production, and possibly skewing T helper (Th) responses. Data from human vitamin D supplementation studies have shown beneficial effects of vitamin D on immune function, in particular in the context of autoimmunity. Low levels of this hormone were observed in several autoimmune diseases including Behçet's disease. The data relating vitamin D to autoimmune and inflammatory diseases are equivocal, with studies linking low vitamin D levels to dysregulation of Th1/Th2 and Th17/Treg ratios. We summarised the effects of vitamin D on the immune system in Behçet's disease.

Conclusion

Vitamin D research has confirmed important interactions between vitamin D and cells from the innate as well as from the adaptive immune system. All the data reported in this review show that vitamin D in Behçet's disease inhibits Th17 cytokine production, enhances Treg cells, suppresses Th1 and promotes Th2 cytokine production and thus skews T cells towards Th2 polarisation.

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Introduction

Vitamin D receptor (VDR) and the vitamin D-activating enzyme 1-α-hydroxylase (CYP27B1) are expressed in many cell types and cells of the immune system[1,2]. Poor vitamin D status is associated with a higher risk of numerous diseases, and a large number of autoimmune diseases have been associated with a poor vitamin D status, including multiple sclerosis (MS)[3], diabetes mellitus type I[4], systemic lupus erythematosus (SLE)[5], vasculitis[6], rheumatoid arthritis (RA)[7,8], Behçet's disease (BD)[9] and other autoimmune rheumatological disorders[10]. The aim of this review is to discuss vitamin D levels and its potential impact on immune cells in BD.

Vitamin D and immunologic mechanisms

Vitamin D directly and indirectly regulates the differentiation and activation of $CD4^+$ T lymphocytes and can prevent the development of autoimmune processes[11]. Its role on the regulation of cells of the immune system has been recognised recently with the discovery of VDR on distinct cell types. Specifically, VDRs have been identified on nearly all cells of the immune system including T cells, B cells, neutrophils, macrophages and dendritic cells (DCs)[12,13]. The continued elucidation of the mechanisms surrounding the action of vitamin D through VDRs in autoimmune/inflammatory diseases helped clarify the link between vitamin D and immune functions.

Monocytes and in particular DCs represent antigen-presenting cells (APCs), which are important in the initiation of the adaptive immune response. Monocytes and DCs can be either immunogenic or tolerogenic and hereby modulate T-cell responses[14]. Tolerogenic APCs are characterised by a reduced expression of costimulatory molecules and a cytokine production favouring regulatory T-cell (Treg) induction[15]. Vitamin D has been shown to manipulate monocytes and DCs at different levels, enabling them to exert tolerogenic activities, which could be exploited to better control autoimmune diseases[16]. Monocytes cultured with 1,25(OH)2D display a VDR-dependent loss of major histocompatibility complex-II[17]. Surface costimulatory molecules, such as CD40, CD80 and CD86, are also reduced upon culture with 1,25(OH)2D[18]. Monocytes pretreated with 1,25(OH)2D were less effective in inducing proliferation of T cells upon stimulation with tetanus toxoid[19]. Additionally, 1,25(OH)2D inhibits the production of interleukin-1α (IL-1α), IL-6, IL-12 and tumour necrosis factor-α (TNF-α) by monocytes cultured in the presence of proinflammatory stimuli such as CD40L and LPS[19,20]. On the other hand, transcription levels of IL-10 mRNA are significantly upregulated by LPS-stimulated monocytes in the presence of 1,25(OH)2D[21]. Also *in vivo*, 1,25(OH)2D treatment (1 μg twice daily for 7 days) in healthy volunteers showed a significant reduction in IL-6, but not IL-1α or TNF-α production by peripheral blood mononuclear cells[22]. The cytokines affected by 1,25(OH)2D are typically involved in the differentiation of naïve T cells in distinct effector Th cell subsets. Monocytes activated in the presence of 1,25(OH)2D and co-cultured with anti-CD3-stimulated

FOR CITATION PURPOSES: *Hamzaoui K, Hamzaoui A.* Vitamin D level and potential impact on immune cells in Behçet's disease. OA Inflammation 2013 Jun 01;1(1):6.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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purified CD4+ T cells show a decreased interferon-γ (IFN-γ) and increased IL-10 production by CD4+ T cells. Furthermore, IL-6 has been described to prevent the development of TGF-β-induced Tregs and together with TGF-β to induce Th17 cell differentiation[23]. Thus, by decreasing IL-6 production and by increasing IL-10 production in monocytes, vitamin D could modulate the T-cell response in a more anti-inflammatory and regulatory direction[24].

Behçet's disease

BD is an immune-mediated disease, mainly driven by Th1 cells. The characteristic features of the disease are orogenital ulcers, cutaneous manifestations and uveitis. The disease can also lead to vascular complications such as arterial and venous thrombosis, central nervous system vasculitis, arthritis and gastrointestinal involvement[25]. The aetiology of BD is not fully understood. Autoimmunity and genetic and environmental factors are thought to play a part in the pathogenesis of BD[25]. CD4+ T lymphocytes seem to be the major cell type in inflammatory infiltrates, and increased concentrations of tumour necrosis factor-α (TNF-α)and IFN-γ have been described[26]. Treatment remains insufficient and relies on non-specific immunosuppressive medications, with significant side effects.

There is an increasing interest in the role of vitamin D as a potential treatment for a number of disparate diseases. 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 in people of particular geographical, climate and therefore ethnic background[11]. As in type I diabetes mellitus, MS, RA, SLE and inflammatory bowel diseases, a correlation between the reduced intake of vitamin D and the prevalence of the diseases can be found, it raises the possibility that serum vitamin D levels may be important in the pathogenesis of these autoimmune diseases[7,27]. A growing body of evidence supports the hypothesis that vitamin D is an environmental factor important in the aetiology of T-cell-mediated autoimmune diseases.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Low serum vitamin D levels in BD

In patients with BD, 25-hydroxyvitamin D values were significantly lower than those of the healthy controls[9,28]. When vitamin D was measured according to clinical BD activity, lower serum vitamin D levels were found in active BD patients compared to inactive BD patients and healthy controls[9]. We also observed decreased levels of vitamin D in active BD patients in the same way as in RA and MS patients[9]. No differences were observed in the vitamin D levels between BD patients HLA-B51+ and HLA-B51−[9].

In our study, we observed that vitamin D levels were correlated to the age of active BD patients. A significant negative correlation was observed between the age of active BD patients and their respective vitamin D value ($r = -0.298$; $p = 0.0023$)[9]. Recently, Searing et al.[29] reported that the age of asthmatics was inversely correlated with serum vitamin D levels. The calcium status of the host may influence the effect of vitamin D on immunity as reported by Yu et al.[30] This could explain the inverse correlation observed in aged BD patients. Contrasted results found by Karatay et al.[28] reported the absence of correlation between 25-hydroxyvitamin D levels and age and body mass index. Vitamin D concentrations and clinical parameters were also investigated[9]. Levels of vitamin D resulted significantly lower in active BD patients with pulmonary involvement or neurological manifestations compared to other patients without these manifestations. Serum vitamin D levels were significantly and negatively correlated with CRP ($r = -0.363$; $p = 0.0002$) and erythrocyte sedimentation rate(ESR) in active BD patients ($r = -0.256$; $p = 0.0092$). Our data suggested that disease activity is associated with lower vitamin D serum levels in active BD patients. The epidemiological studies suggest that adequate vitamin D levels decrease the risk of developing autoimmune diseases such as observed in MS, RA and inflammatory bowel disease[1].

Preventive treatment with vitamin D of individuals considered at high risk of developing autoimmune diseases has been proposed[31]. Our results in BD were in accord with those reported by Do et al. who found that the serum vitamin D levels were inversely correlated with the serum CRP and the ESR levels in BD[32].

Immune cells and vitamin D

We reviewed the effects of vitamin D on immune cells in BD, with a focus on the peripheral immune system Th1, Th2, Th17 and Treg cells. According to serum vitamin D levels, we speculate that this hormone is not an immunosuppressive agent, but rather an immune regulatory agent. The beneficial effects of vitamin D in autoimmunity include the induction of tolerogenic DC, which includes the downregulation of costimulatory molecules, a decreased IL-12 secretion and increased IL-10 secretion in APC, and the ability of these APCs to induce Treg rather than effector T cells. Vitamin D can also directly promote the development and function

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All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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of Treg *in vitro*. Furthermore, effector T cells are both directly and indirectly affected, resulting in a shift in the Th1/Th2 balance towards Th2 and in a reduction of the Th17 response.

The balance between Th1 and Th2 in BD is used to indicate the inflammatory status of the T-cell compartment as we have recently reported[26]. This balance is described by the ratio of IFN-γ$^+$ and IL-4$^+$CD4$^+$ T cells. The IFN-γ/IL-4 ratio correlated negatively with serum 25(OH)D levels (r = –0.599; p = 0.0053). This ratio is commonly used to describe the balance in the immune system between proinflammatory IFN-γ$^+$ Th1 cells and anti-inflammatory IL-4$^+$ Th2 cells. Smolders et al.[33] reported that vitamin D skews the T-cell compartment from a Th1 towards a Th2 phenotype, and high 25(OH)D levels appear to be associated with a less proinflammatory T-cell compartment[33].

IL-17$^+$ cells were less significantly correlated with vitamin D levels (r = –0.462; p = 0.0403). More recently, Tian et al.[34] reported that stimulation of naive CD4$^+$ T cells under Th17 polarising conditions showed a higher Th17 cell differentiation in active BD patients. The addition of vitamin D significantly inhibited Th17 cell differentiation both in BD patients and in normal controls[34].

Regulatory cells within the CD4$^+$ T-cell compartment were defined as CD25^{high}FoxP3$^+$cells. Serum levels of 25(OH)D were positively correlated with the percentage of Treg cells (r = 0.640; p = 0.0024). A significant positive correlation was also observed with IL-10 levels. The decreasing Th1/Th2 ratio reflected a skewing of the IFN-γ/IL-4 balance towards a more Th2 phenotype in patients with higher serum 25(OH)D levels. The fluctuations of immunological parameters associated to the fluctuation of serum 25(OH)D levels were probably specific to disease inflammation. Several studies suggested that vitamin D deficiency could lead to immune malfunctioning[7,27]. T and B lymphocytes, macrophages and dendritic cells express VDR. The cells mostly affected by vitamin D are probably dendritic cells, modulating their maturational state[35].

Disturbances in vitamin homoeostasis may contribute to the inflammatory process in active BD patients. Th1 cells, Th2 cells and Treg cells have been shown to express the VDR and to be vitamin D targets[36]. They also demonstrated the effect of vitamin D on innate immunity-mediated inflammation, enhancing the antimicrobial properties of immune cells such as monocytes and macrophages[37]. In BD, vitamin D could be considered as an important mediator, whose fluctuation is correlated to the inflammatory state of the disease. The development of certain immune cells requires the expression of the VDR both intrinsically and extrinsically as reported by Maruotti et al.[38]. The alteration of innate immune systems could critically be involved in the pathogenesis of BD. However, it is not clear what kind of stimuli and mechanisms are responsible for the *in vivo* activation of the immune system of BD patients. Vitamin D modulates dendritic cells that favour the suppressive activity of Tregs[39] by inhibiting the production of IL-12 and IL-23, and enhancing the release of IL-10 and MIP-3α[40]. IL-10 was significantly correlated with vitamin D level in active BD. This result should indicate that vitamin D levels, IL-10 and Treg cells operate intimately to abrogate inflammation *in vivo*. This result together with the inverse correlation between IFN-γ/IL-4 ratio and vitamin D indicates that the increase in vitamin D level is associated with improvement of the patients. During the BD active phase, T cells and particularly CD4$^+$ lymphocytes are intensively stimulated and switched from naïve to memory CD4$^+$ T[41]. Our explanation for the decreased vitamin D in the active stage is that CD4 cells consumed intrinsic vitamin D levels during their activation. It has been reported that quiescent CD4$^+$ T cells express VDRs at low concentrations, which increase fivefold after their activation[42]. Addition of 1,25(OH)2D3 leads to decreased secretion of IL-2 and IFN-γ by CD4 T-cells and promotes IL-5 and IL-10 production, which further shifts the T-cell response towards Th2 dominance[37]. Importantly, immune cells are able to activate vitamin D locally, arguing for an autocrine or paracrine role for this hormone within the immune system. The fact that Th1, Th2 and Th17 were correlated to serum vitamin D implies the origin of vitamin D deficiency in BD. More studies are needed to clarify the mechanisms by which vitamin D regulates cellular immunity and whether there are any genetic factors modifying the production of 1,25(OH)2D3 and signalling through the VDR.

Effects of vitamin D on expression of Toll-like receptors

Toll-like receptors (TLRs) are crucial players in the innate immune response to microbial invaders, enabling vertebrates to detect the pathogen-associated molecular patterns early and subsequently activating the adaptive immune response[43]. Recent data found that the expression of TLRs was enhanced in BD patients, resulting in an excess production of Th1 cytokine[44,45]. As the initiating cause of BD is unknown, but an aberrant response to infection has been suggested, single-nucleotide polymorphisms in TLRs were analysed in patients with BD[46]. A study from Do et al.[32] established an association between the TLR expression and the serum vitamin D concentration in BD. Monocytes of active BD patients showed higher expressions of TLR2 and TLR4 than those of healthy controls, and serum 25(OH)D levels tended to be lower in active BD. Levels of vitamin D were inversely correlated with the expressions of TLR2, TLR4. *In vitro* analysis showed that

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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vitamin D was found to dose dependently suppress the protein and mRNA expressions of TLR2 and TLR4. Do et al.[32] reported that TNF-α synthesis known as inflammatory mediator was also decreased upon TLR ligand stimulation in vitamin D(3)-treated monocytes. These results suggested that the inflammation triggered through TLR2 and TLR4 is important in the pathogenesis of BD and that vitamin D may be used as a therapeutic option by modulating TLR2 and TLR4 expression of monocytes in BD. A study from Choi et al.[47] analysed the role of vitamin D through the regulation of TLR in herpes simplex virus-induced BD-like mice. Treatment with 1,25(OH)2D3 improved the symptoms in BD-like mice and downregulated the frequency of TLRs associated and proinflammatory cytokines (IL-6 and TNF-α) expression.

Endothelial function in BD

Endothelial dysfunction is a marker of vascular involvement in any disease affecting the vascular structure. Histopathological features of vascular BD are mainly characterised by vasculitis, with prominent neutrophil and monocyte infiltration in the perivascular regions[48]. Several studies have revealed indirect evidences of endothelial dysfunction in BD, such as increased von Willebrand factor, VEGF, MMPs and thrombomodulin levels as well as coagulation and fibrinolytic pathway abnormalities[49–51]. Can et al.[52] reported that vitamin D deficiency is associated with disease activity, endothelial function and carotid intima media thickness in patients with BD. A high presence of vitamin D deficiency was observed in BD patients, and replacement of vitamin D had favourable effects on endothelial function[52].

Associations of VDR gene polymorphisms in BD

The *VDR* gene is located on chromosome 12 (12q13.11). It has 11 exons and contains four polymorphic regions. Three of these polymorphic regions are located at the 3'-end of the gene, and these restriction fragment length polymorphisms are detected by the restriction enzymes *Bsm*I, *Apa*I (intron 8) and *Taq*I (exon 9)[53]. The other polymorphic region is located in the start codon and is detected by restriction enzyme *Fok*I. The B allele (of the *Bsm*I polymorphism) is in tight linkage with the t allele of the *Taq*I polymorphism. The function of these *VDR* alleles is not fully understood, and they have been associated with autoimmune diseases[54]. The effects of these polymorphisms on *VDR* function or gene transcription are unclear, suggesting that these polymorphisms may occur in linkage disequilibrium with other functional polymorphisms in the *VDR* gene[55].

The simultaneous influence of *VDR* polymorphisms was recently explored in BD population compared to RA patients and healthy controls[8,56]. One hundred and thirty one BD patients, 108 RA patients and 152 healthy controls were genotyped for the *VDR* FokI, *Bsm*I, *Apa*I and *Taq*I polymorphisms.

The FokI polymorphism alleles and genotype were significantly more common in the RA and BD groups than in healthy controls. The FokI F allele and F/F genotype were significantly associated with BD. According to clinical manifestations in BD, FokI polymorphism was significantly associated with the presence of vascular manifestations ($p = 0.006$). No significant associations were found between the Bsm1 polymorphism and RA or BD[8]. We observed also a significant association between *TaqI* polymorphism and BD ($p = 0.037$). Analysis of the genotypic distribution of *ApaI* polymorphism did not show any significant difference ($p > 0.05$) between BD patients and healthy controls. However, the minor *ApaI* allele tended to confer an increased risk for BD susceptibility ($p = 0.087$; $OR = 1.32$, $CI = 0.95–1.84$). BD patients with VDR homozygous AA or aa genotypes were at increased risk for development of erythema nodosum skin manifestation ($p = 0.038$; $OR = 2.79$, $CI = 1.02–7.59$). *TaqI* and *ApaI* polymorphisms might be modestly implicated in BD pathogenesis. In contrast, *TaqI* and *ApaI* seemed not to be implicated in RA pathogenesis[56].

The association of VDR FokI polymorphism with susceptibility to BD in Tunisian population was similar to reported studies in other inflammatory/autoimmune diseases such as RA[57,58].

Findings from our herein study should be interpreted with caution for several reasons. Only four polymorphisms in the *VDR* gene have been studied in BD, although there exist several other functional *VDR* SNPs as evident in databases, such as the International HapMap Consortium and dbSNP. The results of our smaller study described above need to be replicated in prospective multicentre trials with large numbers of patients before any valid conclusions can be drawn about such associations.

Conclusion

Vitamin D research has confirmed important interactions between vitamin D and cells from the innate as well as from the adaptive immune system. All the data reported in this review show that vitamin D in BD inhibits Th17 cytokine production, enhances Treg cells, suppresses Th1 and promotes Th2 cytokine production and thus skews T cells towards Th2 polarisation. These preliminary results suggested that genetic components might account for vitamin D status in BD subjects. Other studies are needed to tease out the genetic versus environmental underpinnings of vitamin D status in our population. Accumulating evidence suggest that VDR polymorphisms and serum vitamin D status are both closely associated with disease risk of BD and

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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reported in autoimmune diseases. Further mechanistic studies are also needed to understand the mechanisms by which vitamin D exerts its effects both in healthy individuals and in subjects with autoimmune/inflammatory disorders such as BD.

Abbreviations list

APC, antigen-presenting cell; BD, Behçet's disease; DC, dendritic cell; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; TNF, tumour necrosis factor; VDR, vitamin D receptor

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Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
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FOR CITATION PURPOSES: *Hamzaoui K, Hamzaoui A.* Vitamin D level and potential impact on immune cells in Behçet's disease. OA Inflammation 2013 Jun 01;1(1):6.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.