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Impact of Vitamin D on Mast Cell Activity, Immunity and Inflammation

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Abstract Vitamin D is involved not only in bone metabolism with an endocrine function, but is also an important regulator/mediator of the innate and inductive immune system and inflammation. Vitamin D shows an inhibitory effect of Th1 cells, both T and B cells, reduces polarization of Th0 cells to Th1 cells and inhibits the generation of cytokines/chemokines. Vitamin D3 plays a role in cell differentiation, such as Th1, Th2, Th17 and Treg cells, promotes the augmentation of anti-inflammatory cytokines IL-4 and IL-10 and inhibits the generation of IFN gamma released by Th1 cells. Mast cells, which participate in innate and acquired immunity, are involved in allergic reactions. Their products can decrease the ability of Treg cells to produce the immunosuppressant and anti-inflammatory IL-10. Vitamin D increases the expression of the soluble decoy receptor sST2 which is capable of inhibiting inflammatory effects. Treatment with vitamin D3 provokes the reduction of transcription and translation of IFN-gamma IL-12p40 and TNF exerting an anti-inflammatory action. Vitamin D leads to the regulation of Bcl2 and modulation of intracellular kinase pathways p38 and P13K. Moreover, it is involved in the activation of several pathways, including MAPK and cAMP/PKA, and others. The mechanism of anti-inflammatory actions of vitamin D is not yet clear, however, it is assumed that vitamin D3 binds to its receptor and inhibits the macrophage cytotoxicity and the release of vasoactive compounds in mast cells. The benefits of vitamin D are widespread in literature, however, to better understand its effect, more studies are needed.

Keywords: *vitamin D, immunity, inflammation, mast cells, macrophages*

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1. Introduction

The concept described in this paper is based on our laboratory studies on chemokines during thirty years of experience and a summary of the latest key findings reported in the scientific literature.

Deficiency of vitamin D (rickets) was described by Soranus Ephesius (130 A.D.). In 1882, Sniadecki, in Poland, suggested that rickets was caused by lack of exposure to sunlight. Almost 120 years ago Palm concluded, in an epidemiological study, that the common denominator in rickets in children was lack of exposure to sunlight. In 1922, Sir Edward Mellanby successfully provoked rickets in dogs in absence of sunlight, and in the same year McCollum established that vitamin D is independent of vitamin A. In 1926, Steenbock showed that irradiation of animals as well as foods produced vitamin D2. In the present study, we review the recent data regarding the role of vitamin D in the genesis of inflammation and its relationship with immune cells, including mast cells.

Vitamin D (cholecalciferol; calciferol; ergocalciferol) is an essential fat-soluble compound which functions as a hormone. The conversion of pro-vitamin D into vitamin D in our skin is due to sunlight; in fact, vitamin D is often called the "sunshine vitamin". The primary function of vitamin D is to enhance the intestinal absorption and metabolization of calcium and phosphorus.

There are several vitamin D isomers and not all are biologically active.

2. Discussion

Malformation of bones and teeth in children are characteristic of rickets, a vitamin D-deficient disease marked by the under-mineralization of skeletal bones which afflicts a large number of children in tropical countries. This disease could be prevented or cured by exposing children to UV light or feeding them with food containing vitamin D. Therefore, vitamin D (active form: 1,25-Dihydroxyvitamin D_3 [$1,25(OH)_2D_3$]) is important in assisting the body in its absorption of the minerals calcium and phosphorus, necessary for the growth and development of bones and teeth. In adults, the counterpart of rickets is osteomalacia, which is also due to the insufficient presence of vitamin D and involves the loss of calcium from the bones. This is due to the marked suppression in intestinal calcium absorption and the impairment of calcium balance [1]. There are 6 types of vitamin D: D1,

D2, D3, D4, D5 and D6, among which vitamins D2 (ergocalciferol) and D3 (cholecalciferol) are the two major physiologically relevant forms in humans, where vitamin D3 seems to be more effective than vitamin D2. These two vitamins are able to restore the transport of calcium and phosphorus in animals displaying abnormalities and might prevent the exacerbation of inflammatory diseases [2]. It is generally accepted that an insufficient vitamin D status contributes to osteoporosis in the elderly [3]. Vitamin D, provided in the diet or produced in the skin, is absorbed from the intestinal tract in association with fats and requires the presence of bile salts. In the skin, after exposure to UVB rays, 7-dehydrocholesterol is converted into pre-vitamin D3, which is subsequently transformed into vitamin D3. A plateau of daily vitamin D production is reached after only 30 min of u.v. B irradiation [4]. Epidemiologic studies suggest an association between vitamin D deficiency and inflammatory diseases, including atopic diseases, respiratory infections, type 1 diabetes mellitus and asthma [5,6] (Table 1). However, vitamin D has been found to be the most toxic of all vitamins and an overdose causes nausea, headache and diarrhea, as well as hypercalcemia, a serious and irreversible disease which can lead to calcium deposits in several tissues, including heart and kidneys. For these reasons, large amounts of vitamin D should be avoided [7]. The administration of high-dose vitamin D in patients with arthritis, or other chronic inflammatory diseases, can cause hypercalcemia and does not produce any benefit, therefore it is no longer used [8]. However, vitamin D signal pathway is not only involved in bone metabolism with an endocrine function, but also is an important regulatory mediator of the innate and adaptive immune system and inflammation [9]. It is well documented that vitamin D has a protective role in cancer with a large reduction in the incidence of tumor and also plays a role in a plethora of cellular immune processes [10].

Table 1. Here we report some biological effects of Vitamin D in several immunological and inflammatory reactions

PHYSIOPATHOLOGICAL ROLE OF VITAMIN D3 IN IMMUNITY AND INFLAMMATION
• It regulates macrophage function
• its active metabolites can be generated within the skin
• It partially inhibits antigen and mitogen-driven lymphocyte stimulation
• It is a natural regulator of human immune functions
• vitamin D3-binding protein has a potent adjuvant activity for immunization
• It plays a role in endocrine system and in immunological health
• Vitamin D-binding protein (DBP) has been reported to contribute to innate immunity
• Its receptor gene polymorphism is associated with chronic periodontitis
• Polymorphism in vitamin D-binding protein is associated with MAF activity
• It down-regulates monocyte TLR expression and triggers hyporesponsiveness
• It has an anti-inflammatory effects in the skin of hairless mice
• It mediates mast cell maturation
• It promotes mast cell-dependent reduction of chronic UVB-induced skin pathology
• It acts via genomic and a non-genomic signalling pathway
• It modulates contraction, inflammation and remodeling tissue
• It represses IgE-dependent mast cell activation.
• It enhances the production of soluble ST2 and inhibits the action of IL-33
• It reduces severe asthma in patients
• It has a positive effect on autoimmune diseases and other immune disorders
• Induces high phagocytic capability in macrophage-like tumor cell line
• It acts as one of the immunoregulatory factors in vivo and in vitro
• It is involved on differentiation and growth of pluripotent (CFU-mix), erythroid (BFU-E), and myeloid (CFU-C) progenitor cell
• It has an effects on human preleukemic and leukemic cells
• It influences the production of interleukins 1, 2 and 3
• It affects human T lymphocyte activation, proliferation and cell cycle
• It inhibits mitogen-stimulated human B-cell activation
• It regulates proliferation of activated T-lymphocyte subsets
• It has synergism and antagonism with retinoic acid, and dexamethasone, on phagocytosis and transglutaminase activity
• It suppresses human T helper/inducer lymphocyte activity in vitro
• It regulates the differentiation and function of macrophages and granulocytes

To date, many laboratory and clinical data have indicated that vitamin D expresses a pivotal role in the immune system. The vitamin D-dependent immune responses are controlled through intracrine and paracrine vitamin D signaling mechanisms and enhance the body's defense against infections, demonstrating the physiological importance of the vitamin D pathway in the immune system [11].

It is generally believed that Vitamin D is important for the physiological activity of immune cells and may be associated with disorders of human immune functions [12,13].

In the literature, numerous laboratory and clinical data indicate that vitamin D may influence the activation of thousands of genes involved in cell growth, development and functions, and it has been confirmed that it is indispensable for normal calcium and phosphorus homeostasis [14,15]. In addition, vitamin D shows an inhibitory effect on T-helper (Th)1 cell activation where these cells participate in immune and inflammatory diseases by producing inflammatory cytokines, such as interleukin (IL)-1 and TNF. Therefore, vitamin D plays a key role in the inhibition, differentiation and proliferation of both T and B cells, reduces polarization of Th0 cells to Th1 cells, and inhibits the generation and production of cytokines [16].

The pathophysiology of some inflammatory diseases, where the level of vitamin D is very low, *e.g.* atopic asthma, is initiated by mast cell activation in response to many triggers, such as neuropeptide substance P and corticotrophin-releasing hormone (CRH) [17]. Through activation of $CD4^+$ T cells by antigen, Th cells differentiate into Th1, Th2, Th17 and Treg cells that

secrete distinct sets of cytokines, and vitamin D is an important determinant in this cell differentiation [18]. The expression of T-helper cells and an imbalance of Th1 and Th2 cells can also lead to chronic inflammation and autoimmune diseases. It has been reported that vitamin D3 promotes TH2 cells by augmenting the production of the anti-inflammatory cytokine IL-4 and inhibiting the generation of IFN-gamma released by TH1 cells [19].

In addition, vitamin D3 may inhibit the generation and differentiation of Th17 cell, contributing to its anti-inflammatory activity [20]. In this respect, vitamin D displays selected types of anti-inflammatory activity by inhibiting antigen presentation, proliferation, differentiation of both T and B lymphocytes, reduction on polarization of Th0 cells to Th1 cells, inhibiting production of cytokines from the immune cells and helping to prevent inflammatory response in asthma. In chronic inflammatory diseases, MCs, as well as TH2 cell activation, generate cytokines and chemokines which are involved in the inflammatory response [21]. These inflammatory responses can be inhibited by vitamin D, as well as the dysregulation of the immune cells, such as Tregs. Inflammatory cytokines and chemokines can be inhibited by vitamin D by altering the transcription of immune cell genes [22]. This inhibitory effect downregulates the activity of TH2 cells and mast cell-mediated inflammation. However, in some studies, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-13 were unchanged following vitamin D supplementation, while IL-2 mRNA levels decreased [23].

Mast cells (MCs) participate in innate, acquired immunity, and autoimmunity, as well as in inflammatory and immunological diseases [24,25]. Their involvement in maintaining homeostasis is primarily under the control of peptides, hormones and environmental factors. MCs are involved in allergic reactions through cross-linking of their surface high affinity receptors for IgE (FcεRI), leading to immediate degranulation and release of newly synthesized vasoactive, pro-inflammatory and nociceptive mediators, such as histamine, cytokines/chemokines, platelet activating factor (PAF), proteolytic enzymes and arachidonic acid metabolites [26,27]. Some of these compounds (cytokines/chemokines) are released selectively without degranulation, while others (histamine, protelytic compounds) are released in seconds [28,29]. MC products can decrease the ability of Treg cells to produce the immunosuppressant IL-10, thus further increasing inflammation. MCs are characterized by the surface expression of the stem cell factor (SCF) receptor c-*kit*, and the high affinity receptor for immunoglobulin E (FcεRI) [30]. However, mast cells do not always express their c-*kit* receptor or FcεRI, but do so during inflammation [31]. MC proliferation is dependent on activation of the tyrosine-kinase receptor c-*kit*, induced by binding of the ligand stem cell factor (SCF) [32].

We recently reported that MCs are necessary for the development of allergic reactions, are involved in asthma, a chronic inflammatory disease of the lungs, and can be activated by various immune and environmental triggers, such as chymase and tryptase, stem cell factor (SCF), TNF, TLR ligands, and IL-33 [28]. IL-33, designated as IL-1F11, is a member of the IL-1 family that signals through the IL-1 receptor-related protein ST2, and has been found to be a potent inducer of Th2 cell responses and Th2-associated cytokines IL-4, IL-5, and IL-13, but not Th1 [33]. IL-33 is an *alarmin* cytokine which has a sequence similar to that of IL-1 and fibroblast growth factor, however, IL-18 is the most closely related to this cytokine, and plays an important role in asthma and other allergic-type diseases, and is also capable of inducing MCP-1 [34,35]. In studies on genome, IL-33 genes have been repeatedly identified as predisposing to asthma risk and allergic inflammation.

Vitamin D has been strongly associated with asthma and its pathology [36]. In T cells, vitamin D increases the expression of the soluble decoy receptor sST2 which is capable of inhibiting the inflammatory effects of IL-33 [37]. Therefore, the active precursor 1,25-hydroxyvitamin D3 up-regulates the production of sST2 and the induction of regulatory mechanisms.

It is likely that vitamin D stimulates some cytokine inhibitor/s in situ, with a beneficial effect on the inflammatory processes [38].

Current consensus holds that vitamin D contributes to inhibition of inflammatory mediators, such as cytokines/chemokines, reactive oxygen, nitrogen species and prostaglandins, decreasing the activation of multiple signaling pathways and generation, such as the nuclear factor NF-κB in inflammatory diseases [39]. Vitamin D may also play a role in phagocyte defense and contribute to protection against bacteria by provoking an anti-inflammatory action and may serve as a new anti-inflammatory agent for the future treatment of allergic, autoimmune, acute and chronic inflammatory diseases [40]. Therefore, it is believed that vitamin D plays an anti-inflammatory role, and its deficiency is often associated with increased risk of inflammatory, immunological and autoimmune diseases.

The biological active metabolite of vitamin D, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] is a potent regulator of the immune response and functions by binding to the vitamin D receptor [41]. It has pleiotropic immune effects, is involved in innate immunity, and may enhance macrophage activity to release RANTES/CCL5 and nitric oxide through Toll-like receptor 4 (TLR4) [42].

Stimulation of MCs provokes NF-kB and AP-1 activation, and production of many cytokines such as TNF-alpha (which is the only cytokine that can be stored in the granules of MCs), GM-CSF, IL-33, IL-6, IL-5, IL-4, IL-1, and IL-13, as well as various chemokines *e.g.* MIP-1alpha, MIP-1beta and MCP-1 (CCL2) [43] (which is inhibited by IgG1 monoclonal antibody anti-MCP-1). MCP-1, which binds to chemokine receptors CCR2 and CCR4, is a member of the CC subfamily chemokines, characterized by two adjacent cysteine residues which display chemotactic activity for monocytes, MCs and basophils, but not for neutrophils [44,45]. MCP-1 has been implicated in the pathogenesis of inflammatory diseases characterized by macrophage and/or MC infiltrates, including psoriasis, rheumatoid arthritis, and atherosclerosis [46,47].

We previously reported, for the first time, that injection of chemokines RANTES and MCP-1 in rat skin provokes the recruitment of inflammatory cells, including MCs, release of cytokines and activation of transcription of histidine decarboxylase (HCD), the enzyme responsible for the production of histamine from histidine, involved in anaphylactic shock [48]. This effect was absent in genetically MC-deficient W/Wv mice.

TNF, like biogenic amines and enzymes, can also be rapidly released after MC stimulation [49,50]. Some of the above-mentioned cytokines are also produced by T cells which are recruited by specific chemokines into the site of inflammation [51]. The activation of chemokines recruits other inflammatory cells, thereby increasing the inflammatory response, an effect which may be mostly regulated by vitamin D2 and D3 [52]. *In vitro* treatments with vitamin $1\alpha,25(OH)_2D_3$ of activated macrophages cause a reduction of transcription and production of IFN-γ, IL-12p40, and TNF, exerting an anti-inflammatory action [53].

Vitamin D supplementation may inhibit the synthesis of mRNA on MCs and macrophage-derived pro-inflammatory cytokines, interleukin (IL)-1, IL-6, IL-33 and TNF [54], and may also suppress the IL-2 secretion of Th1 cells [55]. Some clinical studies reported that vitamin D receptor is expressed in several immune cells which are involved in allergic inflammation, and vitamin D3 inhibits the release of IL-6 and CRP, and is essential for the generation of IL-4 and IL-10, which possess anti-inflammatory activity [56]. Furthermore, in an experimental animal model, it has been reported that vitamin D supplementation, in IL-10 knockout mice, significantly ameliorates the symptoms of diarrhea, cachexia, and the rate of mortality [57].

A number of reports indicated in experimental studies that the vitamin D hormone, calcitriol, operating at the DNA level to regulate genes to reduce inflammation and pain, can suppress the release of TNF, and that it has beneficial effects on inflammatory diseases [58]. Moreover, macrophages treated *in vitro* with vitamin D prevent TNF induction and release in MCs through a process likely to be mediated by the vitamin D receptor. These effects can be prevented by addition of the vitamin D receptor antagonist TEI-9647 [59].

The activation of expression of vitamin D receptor on macrophages is influenced and regulated by both Toll-like receptor and cytokines/chemokines [60]. It is believed that the anti-inflammatory action of vitamin D is partly due to the inhibition of transcription and translation of inflammatory cytokines/chemokines. Vitamin $1,25(OH)_2D_3$ can modulate the immune response of T cells. In fact, in tuberculosis patients, vitamin D modulates the immune response to *Mycobacterium tuberculosis* and improves their medical condition, an action linked to Toll-like receptor activation, and does not directly involve the effect of vitamin D on *Mycobacterium tuberculosis* [61]. Platelet-derived growth factor (PDGF), which is a cytokine generated by platelets and macrophages, and acts as a chemoattractant for neutrophils, monocytes, and fibroblasts, is inhibited by vitamin 1,25-dihydroxyvitamin D_3. Vitamin D modulates growth factor activity and up-regulates the gene expression, provoking cell cycle arrest, including the inhibition of proliferation and differentiation [62]. In addition, it may provoke the down regulation of Bcl2 and the modulation of the intracellular kinase pathways p38, mitogen-activated protein kinase (MAPK), extracellular regulated kinase (ERK), and phosphatidylinositol3-kinase (PI3K) [63]. Vitamin D reduces efficiency of DNA repair mechanisms as well as promotion of epigenetic and transcriptional effects through DNA methylation changes. [64]. Vitamin D is involved in the activation of several pathways including multiple MAPKs such as ERK1/2, p38, and JNK1/2 and cAMP/PKA, PKC, calmodulin/CaM-kinase, PKB/Akt [64] (Figure 1).

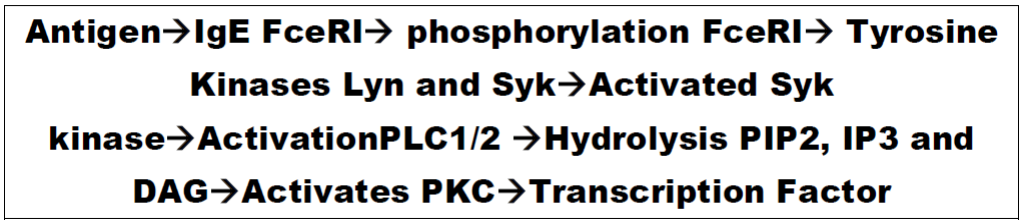

Figure 1. Schematic representation of FcεRI-mediated mast cell signal transduction. Inhibition of signal pathway tyrosine kinase and PKC by vitamin D. This results in mast cell inhibition of degranulation and cytokine production

In inflamed tissue, the breakdown of membrane phospholipids by phospholipase A2 leads to generation of prostaglandin, leukotrienes and platelet-activating factor (PAF) [65]. Prostaglandins, which are lipid autacoids derived from arachidonic acid, play a key role in the generation of inflammatory diseases [66]. It is generally accepted that cyclooxygenase-2 (COX-2), the enzyme responsible for PG synthesis, is an important molecular target in inflammation therapy. Cyclooxygenase COX-2, which is elevated in inflammatory diseases and inhibited by non-steroidal anti-inflammatory drugs (NSAIDs), is fast induced by mitogens and cytokines such as IL-1, an effect regulated by vitamin D [67]. Therefore, vitamin D metabolites may also regulate and activate phospholipase A_2 activity in macrophages and mast cells with the consequence of arachidonic acid activity and production of PGE2 and PGD2, respectively, effects mediated by IL-1. However, little is known about vitamin D and AA metabolism and mobilization. The induction of calcium mobilization is induced by vitamin D3 and is regulated by activation of phospholipase C (PLC) gamma and the production of inositol triphosphate (IP_3) [68]. PLCγ can be activated by c-Src and phosphoinositide 3-kinase (PI-3 kinase) [69]. Vitamin D_3 induces the release of arachidonic acid (AA) and promotes its mobilization, an effect dependent on influx of extracellular calcium and activation of phospholipase A_2 (PLA_2), enhanced by activation of PKC [70,71]. These effects may also alter cell membrane fluidity and permeability. When arachidonic acid products are injected into rat skin they produce a long-lived wheal and flare reaction along with preformed mediators, dependent on immune cell activation, including MCs [72]. An imbalance of immunological reaction, occurring for example in asthma where MCs are involved, provokes in these cells the *de novo* synthesis of lipid-derived mediators, such as prostaglandin D2, platelet-activating factor (PAF) and leukotrienes LTC4, LTD4 and LTE4, which are called slow-reacting substance of anaphylaxis (SRS-A). These effects are often regulated by vitamin D3

which also inhibits the genesis of both Th1 and Th2 cell-mediated diseases [73].

The mechanism of the anti-inflammatory action of vitamin D is not yet clear, but it is assumed that vitamin $1,25(OH)_2D_3$ binds to its receptor and acts on the fusion of phagolysosomes of activated macrophages, facilitates cytotoxic activity by enhancing the rate of phagocytosis, and increases the activity of lysosomal enzymes, resulting in a protective innate immune response [74]. Another hypothesis is that vitamin D increases the transcription and translation of IFN-gamma which stimulates macrophages and activates the innate immunity [75]. Therefore, it is evident that low vitamin D status may contribute to the pathogenesis and symptoms of several inflammatory diseases. Experimental animals lacking vitamin D receptor exhibit abnormal bone formation, and knockout animals are more susceptible to inflammatory diseases [76], however, some authors reported that vitamin D administration in experimental animal models shows no effect on the pathogenesis of asthma, which is often associated with allergy mediated by MCs [77].

The deficiency of vitamin D may lead to a higher risk of developing atopic dermatitis, and supplementation of vitamin D may lower blood pressure, and have a direct effect on calcium metabolism and vascular cells [78].

Vitamin D supplementation has a modulating effect on the specific immune system and may be effective for the prevention of asthma exacerbations, where MCs play a determinant role [79,80], but these last observations need to be confirmed by clinical trials [78].

The health benefits of vitamin D are widespread and its deficiency in immunological diseases has long been described in literature, in fact, this shortage may contribute to the onset of allergic and inflammatory diseases mediated by MCs [81].

3. Conclusion

This systematic review is intended to present an update on the physiopathology of inflammation in relation to vitamin D, however, some studies do not confirm the beneficial effects of vitamin D supplementation in subjects with inflammatory diseases, therefore more studies are needed *in vitro* and *in vivo* to better understand the effectiveness and safety of vitamin D and its potential role in immune-regulation. These findings have implications for future research even though the mechanism of action of vitamin D is still unclear.

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