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Vitamin D and Immune System

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Abstract

Vitamin D interaction with immune system is a well-established although it is a non-classical effect of Vitamin D. Several reports have documented the role of 1,25 hydroxycholecalciferol $(OH)_2D_3$ in mediating innate and adaptive immune systems. The 25-hydroxyvitamin D_3 ($25OHD_3$) is the main circulating metabolite of Vitamin D and is the most reliable measurement of an individual's Vitamin D status. It mediates its effect through autocrine or paracrine synthesis of 1, $25(OH)_2D_3$. Therefore, the ability of Vitamin D to influence human immunity is possibly dependent on the vitamin D status of individuals. The vitamin D receptor (VDR) is expressed on various immune cells including B cells, T cells and antigen presenting cells. However, its highest concentration is in immature immune cells of the thymus and mature CD-8 T lymphocytes. These cells can synthesize active Vitamin D metabolite which can act in an autocrine way in a local milieu. As Vitamin D has immune-modulatory effects on both innate and adaptive immune responses, its deficiency or significant insufficiency can be associated with autoimmunity and infection. In autoimmune disease, the immune cells are responsive to ameliorative effects of vitamin D.

Keywords: Vitamin D; Immune system; Innate; Adaptive; Physiology; Kidney; Autoimmune; Infection

Introduction

Vitamin D was considered as vitamin and was known to be one of the four fat soluble vitamins. However, research work showed that Vitamin D is a prohormone and it is established now that it has many other biologic actions outside the musculoskeletal system [1,2].

Vitamin D_3 (cholecalciferol), which is the natural form of Vitamin D, is present in low amount in animal food sources and almost absent in vegetables, and Vitamin D_2 (ergocalciferol) is present in some vegetables. Vitamin D_3 is produced in the skin through the action of sun rays on a derivative of cholesterol, 7-dehydrocholesterol, to produce previtamin D_3. Then, previtamin D_3 is slowly isomerized to vitamin D_3; cholecalciferol. This dual source of Vitamin D, through sunlight in the skin and diet intake, secures sufficient levels of Vitamin D in the body, although the major source for production of vitamin D_3 is through the skin. Exposure of the precursor 7-dehydrocholesterol in the basal and suprabasal layers of the epidermis to ultraviolet B (UVB) light with a wavelength of 290-315 nm is needed for the formation of the previtamin D_3. Thus, the level of production of vitamin D_3 in the skin is mainly affected by the amount of UVB radiation to which the skin is exposed. Other factors affecting this cutaneous synthesis of vitamin D_3 include geographical area, season of the year and time of the day [3].

Vitamin D_3 itself is biologically inactive. Thus, after being synthesized in the skin, vitamin D_3 binds to the vitamin D-binding protein (DBP) in the blood to be transported into the liver where the first hydroxylation at position 25 occurs producing the major circulating metabolite 25-hydroxy vitamin D_3 ($25(OH)D_3$). Although the circulating level of $25(OH)D_3$ is 500-1000-fold greater than the subsequent 1α, 25 dihydroxy D_3, but its bioactivity is 3 times less than the active one. This might be explained on the basis that the serum DBP has more affinity to $25(OH)D_3$, rendering it biologically inactive in vivo. The second hydroxylation at position 1 occurs mainly in the kidney to form 1α, 25 dihydroxy D_3 ($1,25(OH)_2D_3$); the most active circulating metabolite form of vitamin D [4]. Studies have shown that the renal hydroxylation is localized to the proximal tubules, and in some species the cortical nephron proximal to the loop of Henle is also involved [5]. Indeed, researchers have shown that the enzyme, 25 (OH) 1 alpha hydroxylase, is present in at least 10 tissues in addition to the renal tubules, producing $1,25(OH)_2D_3$ in a paracrine fashion. However, this paracrine-generated $1,25(OH)_2D_3$ does not normally spill over into the circulatory system, and consequently, the plasma concentration of $1,25(OH)_2D_3$ does not increase in a measurable way [6]. The biologic importance of such locally produced $1,25(OH)_2D_3$ emerged from its ability to promote cell differentiation in prostate cancer and colon cancer cells [7,8].

There are more than 35 additional vitamin D_3 metabolites are formed by the body. However, it is evident now that all these metabolites are either less active or rapidly cleared and they are considered intermediates in the degradation of the active form, 1, $25(OH)_2D_3$. The most important of these metabolites are 24R, 25-$(OH)_2D_3$ and 1, 24, 25-trihydroxyvitamin D_3 produced by the enzyme CYP24, which is induced by the vitamin D hormone itself [10]. The 24R,25-$(OH)_2$ D_3 has been shown to be an essential hormone in the process of bone fracture healing. The 24R,25-dihydroxyvitamin D_3 most likely initiates its biological responses via binding to the ligand binding domain of a postulated cell membrane receptor VDR mem 24,25, similar to the better studied, but still not cloned cell membrane receptor for 1,25-dihydroxy vitamin D3, VDRmem 1,25. For clinical

purpose, the serum concentration of 25-hydroxyvitamin D levels is the accepted biomarker to test the Vitamin D status among population. It is the major circulating form of Vitamin D that reflects both dietary Vitamin D intake and the endogenous Vitamin D production [11]. For simplification, authors through the following parts of this chapter will refer to $25(OH)D_3$ as vitamin D and to $1,25(OH)_2D_3$ as active Vitamin D.

The production of active Vitamin D is largely controlled by the calcium homeostasis. However, the main factor regulating production of active vitamin D_3 is the level of $1,25(OH)_2D_3$ itself. Thus, when its circulating level in the blood is high, its production by the kidney is down regulated and vice versa. Next is the parathyroid hormone which stimulates the activity of renal 1 hydroxylase in response to a fall in serum calcium level. Serum calcium level would affect the activity of renal hydroxylation step in relation to this dual feedback between calcium level and parathyroid hormone. Other factors that regulate the production of active Vitamin D include also phosphate level and fetal growth factor 23 [1].

The degradation of active D3 hormone and its metabolites is induced by vitamin D3 itself in target tissues. Researchers have indicated that pulses of the Vitamin D hormone program its own death through induction of the 24-hydroxylase which metabolize Vitamin D to its excretion product calcitroic acid [11]. Also, $25(OH)D_3$ can be degraded through this pathway. The regulation of expression of 24-Hydroxylase is an important factor in the determination of the circulating concentrations of the hormonal form of Vitamin D. Early studies says that there is a possible hepatic catabolic pathway where clearance of vitamin D metabolites is conjugated with bile acids in the bile [12].

The vitamin D_3 hormone functions through a single vitamin D receptor (VDR), which has been cloned for several species including humans, rats, and chickens. It is a member of the class II steroid hormones, being closely related to the retinoic acid receptor and the thyroid hormone receptor. Like other receptors, it has a DNA-binding domain called the C-domain, a ligand-binding domain called the E-domain, and an F-domain, which is one of the activating domains. VDRs are either nuclear receptors (VDRnuc) regulating gene transcription (classic genomic response) or cell membrane receptors (VDRmem) regulating non-genomic responses [13]. The VDRnuc, mediating the genomic responses of the hormone D_3, is a protein of 50 kDa, which binds $1,25(OH)_2D_3$ with high affinity. It does not bind either previtamin D_3 or vitamin D_2. It has been reported that about 36 tissues possess VDR and more interestingly research work has shown that VDR can regulate the expression of about 500 genes of the 20488 in the human genome [14]. On the other hand, the rapid non-genomic effects of $1,25(OH)_2D_3$ are mediated by its binding with VDR that is located on the cell membrane. This membrane receptor is the classic receptor found in the nucleus but is found to be associated with caveolae present in the plasma membrane of a variety of cells [15]. Interestingly, it has been found that both nuclear and caveolae VDR share in the rapid modulation of osteoblast ion channel responses by 1, $25(OH)_2D_3$ [16].

Thus, in target tissues, the binding of the $1,25(OH)_2D_3$ hormone with VDR initiates a complex cascade of molecular events resulting in alterations in the rate of transcription of specific genes or gene networks. An essential point in this series is the interaction of VDR with retinoid X receptor (RXR) forming a heterodimeric complex that binds to specific DNA sequence elements [vitamin D response element (VDREs)] in vitamin D-responsive genes. This binding will ultimately influence the rate of RNA polymerase II-mediated transcription [9].

In addition to the known physiologic action of Vitamin D in regulating calcium homeostasis, evidences from recent research have shown that Vitamin D has wider physiologic effects attributed to the wide distribution of the VDR as shown before. Because of this wider scope of biologic actions of Vitamin D, there is now what is termed and accepted as Vitamin D endocrine system signifying its functioning as a pluripotent hormone in 5 systems [17]. These systems include the adaptive immune system, the innate immune system, insulin secretion by the pancreatic β cell, multifactorial heart functioning and blood pressure regulation, and brain and fetal development [17]. The biologic effects of Vitamin D regarding the immune system will be discussed later in this chapter. Here, we will try to focus more on its known function in controlling the serum calcium level.

Acting with parathyroid hormone (PTH), active Vitamin D hormone increases serum calcium concentration through multiple mechanisms. First, active Vitamin D is the only hormone that mediates induction of calcium binding protein (calbindin) involved in intestinal calcium absorption. Whether active Vitamin D regulates the synthesis of calbindin at the gene level or through the activation of increased intracellular calcium levels is not well understood. Also, it stimulates active intestinal absorption of phosphate. Furthermore, active Vitamin D with PTH stimulates reabsorption of the last 1% of filtered load of calcium in renal distal convoluted tubules, saving a reasonable portion to calcium pool in the body [18].

In conditions of decreased serum calcium level with dietary deficiency of calcium, both hormones, D_3 and PTH, act to mobilize calcium from bones to the blood. A decrease in serum calcium level below the normal range (9-11 mg/dl) will be sensed by Calcium-sensing proteins in the cell membranes of parathyroid gland cells [19]. Consequently, this will initiate cascade reactions through these transmembrane proteins-G protein coupled system, stimulating the secretion of PTH. Circulating PTH will mediate a very important effect; activation of renal 1 α hydroxylase, increasing production of active Vitamin D hormone. Then, together with PTH, active Vitamin D stimulates mobilization of bone calcium and renal reabsorption of calcium. Active Vitamin D hormone stimulates osteoblasts to produce receptor activator nuclear factor κB ligand (RANKL) which by its turn stimulates osteoclastogenesis and activates resting osteoclasts inducing bone resorption [20]. Another bone action of active Vitamin D is recruiting osteoclasts from the monocyte-macrophage lineage of cells [21]. This additional action of recruitment of osteoclasts might explain the effect of toxic levels of Vitamin D resulting in hypercalcemia rather than hyperostosis [21]. On the other hand, active Vitamin D induces the synthesis of alkaline phosphatase, osteocalcin, and matrix g-glutamic acid-containing protein in the osteoblasts, but inhibits the synthesis of type I collagen [22]. Accordingly, it seems that active Vitamin D is exerting a dual role in bone through modulation of the normal interaction between osteoblast and osteoclast function.

Thus, the Vitamin D hormone plays an important role in allowing individuals to mobilize calcium from bone when it is absent from the diet. When serum calcium is increased, this will inhibit the sensing mechanism in parathyroid gland, and consequently the renal production of active D_3. On the other hand, in conditions of abnormally high plasma calcium concentrations, the C-cells of the thyroid gland secrete calcitonin, which blocks bone calcium mobilization. Interestingly, under normocalcemic conditions,

Calcitonin activates the renal 1α hydroxylase enzyme producing the Vitamin D hormone for non-calcemic needs [23].

Vitamin D expression on immune system

The serum level of Vitamin D was correlated inversely with level of parathyroid hormone and this observation has urged the introduction of a new term called Vitamin D insufficiency [24-26]. The Vitamin D insufficiency is defined by sub-optima level of Vitamin D that is not rachitic [4]. Geographical, social, or economic factors can affect the Vitamin D status in different populations and Vitamin D insufficiency is considered as worldwide epidemic [25-28]. Vitamin D has important function other than calcium and bone homeostasis and epidemiological studies documented the possible link between Vitamin D insufficiency and various human diseases including autoimmune, infectious, cardiovascular, neurologic, immune deficiency and even cancer [28-30].

Vitamin D has a paracrine or autocrine function beside the endocrine function. The active Vitamin D manifests its diverse biological effects by binding to the VDR. In the same time, many tissues beside the kidney express 1-α-hydroxylase and can convert the 25 D to 1,25 D [31]. VDR is expressed in organs and tissues involved in bone metabolism and in more than thirty-five target tissues that are not involved in bone metabolism and explains the pleiotropic effect of Vitamin D hormone [32,33]. These tissues include T/B lymphocytes, antigen presenting cells (APCs), monocytes, hematopoietic cells, cardiac and skeletal muscle cells, endothelial cells, islet cells of the pancreas, neurons and placental cells [33]. VDR activation either directly or indirectly regulate about 100-1250 genes that represent about 0.5-5% of the total human genome and include the genes responsible for the regulation of cellular proliferation, differentiation, apoptosis and angiogenesis [32,34]. Because the immune cells express VDR and can synthesize the active Vitamin D metabolite and in the same time, Vitamin D can modulate the innate and adaptive immune responses, it is reasonable that the Vitamin D deficiency will be associated with increased autoimmunity and increased susceptibility to infection [29].

The VDR gene is located on chromosome 12 and is a member of trans-acting transcriptional regulatory factors that include the steroid and thyroid hormone receptors [35]. The VDR gene contains 11 exons and spans approximately 75 kb. The exons 1A, 1B, and 1C are present in the noncoding 5-prime end and its translated product is encoded by 8 additional exons. Exons 2 and 3 are involved in DNA binding, and exons 7-9 are involved in binding to Vitamin D [35-37]. Vitamin D binds to VDR and then dimerise with the retinoid X receptor (RXR). This complex of vitamin D-VDR-RXR translocates to the nucleus and binds in the promoter of Vitamin D responsive genes to Vitamin D responsive elements (VDRE) with subsequent expression of these Vitamin D responsive genes [29].

DNA sequence variations "polymorphisms" which occur frequently in the population, can have modest and subtle but true biological effects. Their abundance in the human genome as well as their high frequencies in the human population have made them targets to explain variation in risk of common diseases. Recent studies have indicated many polymorphisms to exist in the VDR gene [38]. Over 470 VDR single nucleotide polymorphisms (SNPs) are known [38,39]. Their distribution and frequency vary among ethnic groups. Most of the work done on VDR polymorphisms has been conducted in Caucasian populations and has focused on six SNPs: rs10735810 or FokI in exon 2, rs1544410 or BsmI in intron 8, rs731236 or TaqI in exon9, rs7975232 or ApaI in intron 8, rs757343 or Tru91 in intron 8 and the poly (A) mononucleotide repeat in the 3′-untranslated region (UTR) [40,41].

The discovery of the VDR in the cells of the immune system and the fact that activated dendritic cells produce the Vitamin D hormone suggested that Vitamin D could have immunoregulatory properties. The most evident effects of the D-hormone on the immune system seem to be in the down-regulation of the Th1-driven autoimmunity. Low serum levels of Vitamin D might be partially related, among other factors, to prolonged daily darkness (reduced activation of the pre-vitamin D by the ultra violet B sunlight), different genetic background (i.e. VDR polymorphism) and nutritional factors and explain to the latitude-related prevalence of autoimmune diseases such as rheumatoid arthritis by considering the potential immunosuppressive roles of Vitamin D. The Vitamin D plasma levels have been found inversely correlated at least with the RA disease activity showing a circannual rhythm (more severe in winter). Recently, greater intake of Vitamin D was associated with a lower risk of RA as well as a significant clinical improvement was strongly correlated with the immunomodulating potential in Vitamin D-treated RA patients [40,42].

In immune cells, activation of VDR leads to production of downstream gene products. These proteins have potent anti-proliferative, pro-differentiative, and immunomodulatory effects [43]. Active Vitamin D inhibits several intracellular pathways such as the nuclear factor-κB (NF-κB) signaling pathway, X-box binding protein 1 (XBP1) and endoplasmic reticulum to nucleus signaling 1 (ERN1). This inhibition has been observed in T cells, monocytes or macrophages [44] and subsequently may influence the expression of various essential secreted molecules on the cell surface. On the other hand, the active Vitamin D has no inhibitory effect on the expression of other transcriptional regulators such as Paired box-5 (PAX-5), B-cell lymphoma 6 (BCL-6), activation, and IFN-regulatory factor 4 (IRF4) [43].

Vitamin D and innate immune system

The innate immune system is the immediate, non-specific first line of the defense against pathogens and includes complement, antimicrobial peptides produced by neutrophils and macrophages, in addition to antigen presentation [45]. It is important to review the levels of innate defense to understand the role of Vitamin D in innate immune response. The epithelial cells of the skin, gut, respiratory and urinary tract is the first line of defense which protects against invasion by organisms. The active Vitamin D is important in up-regulating genes of the proteins required for the tight, gap and adheres junctions [46].

The Vitamin D is a potent stimulator of antimicrobial peptides in innate immunity and sufficient level of Vitamin D is necessary for production of cathelicidin and some types of defensins (defensins hBD-2) [46-48]. In mammals, pathogens have pathogen-associated molecular patterns (PAMP's) that trigger pathogen recognition receptors called toll-like receptors (TLRs). In humans, triggering of TLR2/1 and TLR4 results in increased expression of 1-α-hydroxylase and VDR. Induction of 1-α-hydroxylase induces the production of active Vitamin D. Then complex of vitamin D-VDR-RXR translocates to the nucleus and binds to VDREs of genes of cathelicidin and beta defensin 4 with subsequent transcription of these proteins [29,49]. It is now clear that the transcription of cathelicidin is dependent on sufficient Vitamin D and transcription of beta defensin 4 requires

binding of NFkB to appropriate response elements on the beta defensin 4 RNA [29,50].

The active Vitamin D enhances the secretion of hydrogen peroxide in monocytes and increases oxidative burst [51]. Also, Vitamin D has a role in the attraction of other immune cells to promote wound healing or fight infection and is essential in activating antigen specific T-cell [52,53]. Vitamin D prevents inflammatory response overreaction and prevents further cell or tissue damage by inflammation [54]. Vitamin D also suppress the inflammation by limiting excessive production of proinflammatory cytokines such as TNFα and IL-12 [46,55].

The macrophages recognize lipopolysaccharide (LPS) of bacterial infection through TLRs. As mentioned above, engagement of TLRs leads to a cascade of events that produce peptides with potent bactericidal activity (e.g., cathelicidin and beta defensin 4). These peptides co-localize with the ingested bacteria inside the phagosome where they disrupt bacterial cell membranes [56].

Vitamin D appears to show promise in aiding the body's own natural defenses against viruses, bacteria and fungi and there is evidence that Vitamin D may strengthen the physical epithelial barrier via stimulating junction genes. With increasing antibiotic-resistant bacteria, there is a need for the development of new strategies for treatment of infections. Cathelicidin (LL-37) has a potent anti-endotoxin and some direct antimicrobial activity [57]. In critically ill patients, correlation was reported between low levels of Vitamin D and those of LL-37 and there was an evidence for the regulation of LL-37 levels by vitamin D status [56]. Also, the LL-37 is known to be effective against Methicillin-resistant *S. aureus* (MRSA), that may cause serious illness such as pneumonia, toxic shock syndrome, food poisoning or staphylococcal-scalded skin syndrome and no strains show complete resistance to LL-37 until now [46,58-60].

The effects of Vitamin D on macrophage function have been central to many of the new observations implicating Vitamin D in the regulation of immune responses. In common with natural killer cells (NK) and cytotoxic T-lymphocytes (cytotoxic T-cells), macrophages and their monocyte precursors play a central role in initial non-specific immune responses to pathogenic organisms or tissue damage-so called cell-mediated immunity. Their role is to phagocytose pathogens or cell debris and then eliminate or assimilate the resulting waste material. In addition, macrophages can interface with the adaptive immune system by utilizing phagocytic material for antigen presentation to T-lymphocytes (T-cells) [28].

It was thought that the key action of Vitamin D on macrophages was to stimulate differentiation of precursor monocytes to more mature phagocytic macrophages and this was supported by differential expression of VDR and 1α-hydroxylase during the differentiation of human monocytes macrophages [61]. Also, stimulation of human macrophages with interferon gamma (IFNγ) resulted synthesis of active Vitamin D, localized activation of Vitamin D and expression of endogenous VDR (i.e., autocrine or intracrine action of Vitamin D) [62,63].

Macrophages possess both enzymes essential to produce active Vitamin D leading to intracrine and paracrine effects. The high expression of VDR by monocytes ensures sensitivity of these cells to the differentiating effects of active Vitamin D. In the same time, the active Vitamin D down-regulates the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF), stimulates production of immunosuppressant prostaglandin E_2 from macrophages and modulates macrophage responses, thus, inhibiting the release of more inflammatory cytokines and chemokines [42].Therefore, Vitamin D deficiency will impair the antimicrobial function of macrophages due to decreased capacity to mature, to produce lysosomal enzymes, to secrete H_2O_2 and to produce specific surface antigens by down-regulating the expression of HLA-II [64,65].

Monocytes isolated from normal human peripheral blood mononuclear cells (PBMCs) when treated with cytokines such as IFN-γ [66] or bacterial antigens such as lipopolysaccharide [61] can synthesize active Vitamin D [54]. The presence of CYP27B1 in macrophages is important for the physiological action of active Vitamin D in immune-regulation. In activated macrophages, the CYP27B1 expression is regulated by immune inputs, mainly IFN-γ and agonists of TLRs, the pattern recognition receptors [67].

The immune system is responsive to the circulating levels of Vitamin D as evidenced by; stimulation of TLR1/2 heterodimers in human macrophages by bacterial lipopeptides induced expression of CYP27B1 and VDR; the downstream VDR-driven responses were strongly dependent on serum concentration of active Vitamin D cultured in the presence of human serum and these responses were attenuated or absent in Vitamin D-deficient individuals and were restored by active Vitamin D supplementation [26,28,68].

In human cells, the expression of the co-receptor of TLR4 and CD14, is strongly regulated by active Vitamin D and a correlation was found between induction by LPS and expression of CYP27B1 via TLR4/CD14 receptor complexes [67,68]. Treatment of human monocytes with active Vitamin D inhibits the expression of TLR2, TLR4, TLR9 and alters the TLR9-dependent production of IL-6 [69]. While, the active Vitamin D promotes the antimicrobial activities of myeloid cells, it inhibits TLR2 expression and TLR4 expression on monocytes, therefore, inducing a state of hypo-responsiveness to pathogen-associated molecular patterns. This is may be a negative feedback mechanism, preventing excessive TLR activation and inflammation at a later stage of infection [70]. Therefore, the down-regulation of pattern recognition receptors by active Vitamin D in APCs may contribute to its ability to attenuate abnormal Th1-driven inflammatory responses and potential autoimmunity [71].

In the cells of monocytic and epithelial origins, the active Vitamin D induces the expression of gene encoding NOD2/CARD15/IBD1. This pattern recognition receptor detects muramyl dipeptide (MDP), a lysosomal breakdown product of bacterial peptidoglycan common to Gram-negative and Gram-positive bacteria. The MDP-induced NOD2 activation stimulates NF-κB, which induces expression of the defensin β2 gene [72]. One pathway, concerns the inactivation of active Vitamin D by the enzyme 24-hydroxylase (CYP24), mitochondrial enzyme that initiates active Vitamin D catabolism. While expression of CYP24, is sensitive to the presence of active Vitamin D, the negative feedback loop appears to be defective in macrophages and the 24-hydroxylase gene is induced by Vitamin D following TLR2/1 activation of monocytes [73].

While the expression of CYP24 transcripts in macrophages is induced by active Vitamin D, the corresponding enzymatic activity is undetectable and the enzyme is trapped in the cytosol in inactive form [74]. This suggests in macrophage that the active Vitamin D signaling is maintained for extended time, and would be advantageous for combating intracellular pathogens such as Mycobacterium tuberculosis [75].

In M. tuberculosis-infected PBMCs, the active Vitamin D attenuates the expression of matrix metalloproteinases (MMP) 7 and 10,

suppresses secretion of MMP-7 and inhibits secretion and activity of MMP-9, induces secretion of IL-10 and prostaglandin E2 [76]. In human monocytes, neutrophils and other human cell lines, the active Vitamin D induces genetic expression of antimicrobial peptides (AMPs), such as defensins and cathelicidin (hCAP). The AMPs display a broad-spectrum of antimicrobial and antiviral activities including the influenza virus and these endogenous antibiotics destroy invading microorganisms [28,77].

DCs are heterogeneous in their location, phenotype and function and per their origin, they are divided into two groups: myeloid (mDCs) and plasmacytoid (pDCs). The mDCs are professional APCs [78] and the pDCs are more closely associated with immune tolerance [79,80] All cells of innate immunity are capable of; identifying and removing foreign substances present in organs, tissues, into the blood and lymph stream; interacting with pathogens and with each other and modulating the adaptive immune response by regulating timing, type, and number of cytokines [81].

It is now documented that the active Vitamin D can change the function and morphology of DCs to tolerogenic DCs (tolDCs) [82,83]. In the same time, the active Vitamin D and its analogs can inhibit DCs differentiation and maturation, therefore, impairing normal turnover of DCs in tissues and locking them in an immature-like state. In human and murine DC cultures, vitamin D down-regulate; the expression of MHC-Class II, co-stimulatory molecules such as CD40, CD80, CD86; other maturation molecules such as CD1a and CD83 and chemokine (c-x-c motif) ligand 10 (CXCL10) which is involved in the recruitment of T helper 1 (Th1) cells [54,84-87]. On the other hand, active Vitamin D up-regulate; inhibitory molecules (e.g., programmed death-1 ligand (PD-L1) and immunoglobulin-like transcript 3 (ILT3) on DCs; the secretion of chemokines (CCL2, CCL18 and CCL22) which are implicated in the recruitment/induction of regulatory T cells (Tregs), polarization of Th2 subset, maintenance of the immature state of DCs [88,89]. Additionally, Vitamin D-modulated DCs produce more anti-inflammatory cytokine (IL-10) and less pro-inflammatory cytokines IL-12 (Th1 driving) and IL-23 (Th17-driving) and this might dampen Th1 and Th17 responses, render T cells anergic and recruit and differentiate Treg subsets [28,45,78,80].

The mDCs are efficient promoters of naïve T cell function [89] and the pDCs are more associated with attenuation of T cell function [90]. In vitro, the active Vitamin D regulates mainly mDCs, with associated suppression of naïve T cell activation. This can be explained by expression of similar levels of VDR by both mDC and pDC, therefore, the tolorogenic pDC may respond to active Vitamin D via local, intracrine mechanisms [28,90]. Also, active Vitamin D generated by pDCs may not act to regulate pDC maturation but may act in a paracrine fashion on VDR-expressing T-cells. The ability of Vitamin D to influence the differentiation and function of DCs provides another layer of innate immune function that complements its antibacterial properties. However, this interaction between active Vitamin D and DC will also have downstream effects on cells that interact with APCs, namely cells from the adaptive immune system [90,91].

Vitamin D and adaptive immune system

The expression of VDR on active and proliferating T and B lymphocytes suggesting that the active Vitamin D has anti-proliferative role on these cells. Also, variations in Vitamin D levels can influence T cells and in patients with multiple sclerosis (MS) a correlation between the activity of T regulatory cells (Tregs) and circulating levels of Vitamin D have been reported [92].There are four possible mechanisms explaining how the serum Vitamin D can influence T-cell function : direct effect of systemic active Vitamin D on T cells ; indirect effects of localized DC expression of CYP27B1 and intracrine synthesis of active Vitamin D on antigen presentation to T cells; paracrine mechanism through direct effects of active Vitamin D on T cells following synthesis of the active Vitamin D by CYP27B1-expressing monocytes or DCs; intracrine conversion of Vitamin D (25OHD) to active Vitamin D ($1,25(OH)_2D$) by T cells [93].

The VDR expression is undetectable in quiescent T lymphocytes and upon T cell activation, it increases five times [94]. The active Vitamin D regulates T-cell development and migratory function and Th1 and Th2 cells are direct targets for the active Vitamin D. Direct actions on T cells represent a different route for active Vitamin D to shape T-cell responses and to control T-cell antigen receptor signaling, which through the alternative p38 pathway induces VDR expression [28,93].

When active Vitamin D binds to the VDR, the VDR translocates to the nucleus and activates phospholipase C-γ1(PLC-γ1) gene. Due to PLC-γ1 gene activation, PLC-γ1 protein accumulates in the cytoplasm of primed T cells after 48 hours of initial activation [94]. The PLC-γ1 has a central role in classical T-cell receptor signaling and T-cell activation, therefore, the differences in PLC-γ1 expression in naive and primed T cells explain the process of functional avidity maturation observed in T cells. Activation of the VDR by active Vitamin D changes the cytokine secretion patterns, suppresses effector T-cell activation and induces Tregs [95,96].

The active Vitamin D inhibits the migration of T cells to lymph nodes [96]. This can be explained by stimulating expression of chemokine receptor 10 (CCR10) by active Vitamin D on T lymphocytes and the CCR10 recognizes the chemokine CCL27 secreted by epidermal keratinocytes [97]. Also, the active Vitamin D affects the phenotype of T cells by inhibiting the Th1, thus, it will able to promote the translocation and/or retention of T cells within the skin [98]. In contrast, in the gastrointestinal tract (GIT), the Vitamin D has a negative effect on chemokines and chemokine receptors [96] and Vitamin D promotes a T-cell shift from Th1 to Th2 and may limit the potential tissue damage associated with Th1 cellular immune responses [42,99].

The active Vitamin D decreases the proliferation and inhibits the production of IL-2, IFN-γ, tumor necrosis factor-α and IL-5 from Th1 cells [97,99]. In the same time, administration of Vitamin D enhances transforming growth factor-β1 (TGF-β1) and IL-4 transcripts, therefore, it exerts in an immunosuppressive action and increases the Th2 cell function [96].

The initial studies evaluating the effects of Vitamin D on T-cells focused on the ability of active Vitamin D to suppress T-cell proliferation and subsequent studies showed that Vitamin D influences the phenotype of T-cells by inhibiting Th1 cells (i.e., cellular immune response) and enhancing cytokine of Th2 cells (i.e., humoral immunity) [100]. By switching the immune response from Th1 to Th2, the Vitamin D may help to limit the tissue damage associated with excessive Th1 immune responses. However, studies using VDR gene knockout mice showed reduced Th1 levels [101], therefore, the in vivo effects of Vitamin D on T cells are more complex [28].

Th17 cells is a third group of Th cells and is named so because of their capacity to secrete IL-17 [102]. Th17 cells are important for promoting immune responses to some pathogens and have been linked to inflammatory tissue damage [103]. In vitro treatment of T-cells with

active Vitamin D suppresses Th17 development and inhibits production of IL-17 [104]. Also, in vivo treatment of mouse models of irritable bowel disease (IBD) with active Vitamin D down-regulates expression of IL-17 and in CYP27B1 gene knockout mouse, loss of active Vitamin D leads to elevation of IL-17 [90,105].

T regulatory or suppressor T cells (Tregs) is a fourth group of CD4 T cells and exert suppressor functions. The active Vitamin D modulates the T-cell phenotype and promotes the development of Tregs [106]. Topical application of active Vitamin D affects the differentiation and functions of Tregs, increases the suppressive activity and the in vivo expansion of antigen-specific Tregs [107]. In mice with induced experimental autoimmune encephalomyelitis (EAE), oral administration of active Vitamin D reduces the number of lymphocytes especially CD4+ T cells in the central nervous system (CNS) [108]. The explanation for this may be the death of activated T cells due to intake of active Vitamin D especially with the absence of Th17-polarizing conditions or regulation of Th17 cell recruitment via chemokine and chemokine receptors [28,109]. Negative regulation of the expression of CCR6 on Th17 by active Vitamin D may be essential for the entry of Th17 into the CNS and the initiation of EAE [108]. The active Vitamin D inhibits the lineage commitment of Th17 and induces IL-10 production, which, suppresses EAE initiation [110,111]. In the same time, the combination of active Vitamin D and dexamethasone increase the frequency of generation of IL-10-producing Tregs [112].

The active Vitamin D may induce the production of IL-10 via help to TGF-β via the generation of IL-27 [111]. In either case, the active Vitamin D requires the presence of TGF-β and IL-6 to increase the number of IL-27-mediated IL-10-producing T cells and it is possible that active Vitamin D may cooperate with IL-27 to protect against EAE through IL-10 [113]. IL-27 blocks the generation of Th17 cells through transcription factor STAT1 and active Vitamin D mediates suppression of Th1 and Th17 cell by induction of Foxp3+ Treg-cell expansion [42,90].

In contrast, active Vitamin D inhibits the expression of TGF-β-mediated Foxp3 through VDR signal on CD4+ T cells [114]. Also, in vitro treatment of active Vitamin D decreases the production of interleukin-2 (IL-2) by activated CD4+ [115] suggesting that IL-2 may be crucial for inhibiting Treg differentiation by active Vitamin D [114]. However, both active Vitamin D and IL-2 may have synergistically limit the production of IL-17. The inhibitory effect of active Vitamin D is evident on effecto/memory than naïve T cells because the level of VDR expression on naïve T cells is low. Hence, the VDR signal on the CD4+ inhibits the expression of IL-17, IL-2, Foxp3 and CCR6 and enhances the expression of IL-10 [42,115].

Although the expression of VDR by B cells is controversial, the results indicate that B cells may respond to active Vitamin D in autocrine/intracrine way [116]. The resting B cells do not contain VDR [117], the human tonsil B cells express VDR and can be up-regulated by activation [118], the B-cell lymphoma cell lines SUDHL4 and SUDHL5 express VDR [119], the human primary B cells express VDR mRNA at low levels and active Vitamin D up-regulated the expression [120]. The regulation of VDR expression by active Vitamin D in B cells suggests that the effects of active Vitamin D may differ according to its serum level in individuals and the state of B cells (i.e., active or resting). The VDR up-regulation by active Vitamin D is needed for inhibition of B-cells proliferation by active Vitamin D and there may be a threshold level of VDR engagement needed for the anti-proliferative effect to be apparent [116].

The resting B cells express CYP27B1 mRNA and incubation of B cells with active Vitamin D up-regulate the expression. Therefore, the activity of Vitamin D on B cells may be affected by VDR expression and the ability to degrade the active molecule. However, the CYP24A1 level was not altered by B-cell activation indicating that human B cells can respond directly to active Vitamin D. Also, the increased susceptibility of activated B cells to many of the effects of active Vitamin D may be due to up-regulation of VDR and the B lymphocytes may metabolize the Vitamin D to active Vitamin D and this is a source for the extra-renal synthesis of active Vitamin D [120].

The active Vitamin D inhibit B cell proliferation and this is associated with apoptosis of both activated and dividing B cells. In cultures using combination of IL-21 and anti-CD40 with or without B-cell receptor cross linking, the active Vitamin D inhibits also the plasma cell differentiation and immunoglobulin production. However, if B cell were treated with active Vitamin D after 5 days of culture, the inhibition was not evident. This indicates that the Vitamin D inhibits the generation of plasma cells but not their subsequent persistence and is responsible for decreased immunoglobulin secretion [120-122].

The active Vitamin D up-regulate the mRNA level of p27 and down-regulate the levels CDK4, CDK6 and cyclin D. Thus, it inhibits the B cell proliferation by inhibiting the previous cycling B cells from entering the cell cycle. These results suggest that the effect of active Vitamin D on plasma and memory cell differentiation may be due to suppression of ongoing B-cell proliferation [120].

Vitamin D and kidney disease

The kidney is the major organ involved in the formation of bioactive forms of Vitamin D and is the major target organ (VDR is highly expressed) for the classical and non-classical actions of Vitamin D. The progression of chronic kidney disease (CKD) and many of the cardiovascular complications may be linked to Vitamin D deficiency [123]. Patients with CKD have two problems; a high rate of severe Vitamin D and reduced ability to convert Vitamin D to active Vitamin D [124]. Vitamin D deficiency is observed in nearly all CKD patients; therefore, Vitamin D is recommended to be prescribed for stage 3-5 CKD patients who have low Vitamin D and high serum PTH levels [125,126]

Many mechanisms were postulated to explain the decrease in Vitamin D during the course of CKD [126]. First, Low Vitamin D in a substrate-product relationship [127]. Patients with CKD will have impaired production of cholecalciferol in the skin (due to low exposure to sunlight, impaired response and malnutrition) and decreased amount of Vitamin D that enter the renal tubules and then uptake in the circulation (due to decreased renal mass/GFR and decreased expression of megalin). In addition, proteinuria will damage the proximal tubular cells and limits the number of megalin receptors and Vitamin D binding to the megalin receptor [128].

Second, Low 1-α-hydroxylase activity (i.e., decreased active Vitamin D) and high 24-hydroxylase activity (i.e., increased 24, 25(OH)2D). Therefore, there will be marked reduction in endogenous Vitamin D and active Vitamin D with increased decay [129]. Third, Elevated FGF-23 which is a phosphaturic hormone (i.e., keeping serum phosphate homeostasis in early renal dysfunction) [130]. FGF-23 inhibits 1-α-hydroxylase activity in the renal proximal tubule and reduce active Vitamin D production and stimulates 24-hydroxylase to produce $24,25(OH)_2D$ [131].

Finally, active Vitamin D inhibits through feedback mechanism the 1-α-hydroxylase and 25-hydroxylase. A pharmacological dose of active Vitamin D may down-regulate Vitamin D levels and reduce Vitamin D availability in extrarenal tissues and organs, thus increasing Vitamin D deficiency [132]. In the same time, lower concentration of Vitamin D, as the case in CKD patients, will decrease the activity of 1-α-hydroxylase [126].

Vitamin D status in CKD may have clinical implications on cardiovascular system (CVS) through its effect on renin-angiotensin-aldosterone system (RAAS). RAAS have multiple effects on CVS; it regulates blood pressure, electrolytes, volume homeostasis, endothelial function, vascular remodeling and fibro genesis [133,134]. The active Vitamin D has a negative effect on the RAAS and this pathway appears to be regulated by the autocrine function of Vitamin D in CKD patients [135,136]. Some observations in VDR null mice, both intrarenal mRNA renin and plasma angiotensin II concentrations, showed marked increase which were associated with hypertension and cardiac muscle hypertrophy in VDR null mice. Inhibition the synthesis of active Vitamin D in wild type mice showed increase in the intrarenal expression of renin [133-136].

The level of Vitamin D showed an inverse relationship with the degree of albuminuria in CKD suggesting its anti-proteinuric effects which may be mediated through RAS-angiotensin II mechanism [136]. In addition, the local synthesized intrarenal angiotensin II has an effect on the CVS (i.e., its effect on blood pressure, vascular smooth muscle cells and cardiac myocytes) [123]. Therefore, Vitamin D therapy may affect premature mortality associated with CKD [137].

NF-κB pathway is another pathway in CKD, which may be regulated by the non-classical autocrine actions of Vitamin D. The NF-κB may play a role in progression of renal disease and in diabetic nephropathy in CKD patients [124]. Activation of the NF-κb pathway will trigger secretion of many cytokines, chemokines and other inflammatory factors, which exacerbate tissue injury in CKD [136]. In hyperglycemia, angiotensin II may activate NF-κB and then activates angiotensinogen expression in renal cells [138]. Vitamin D inhibits the activation of NF-κB and its level has inverse relationship with the degree of tissue inflammation present in various types of kidney disease [124,136,138].

Vitamin D therapy improves the rates of morbidity and mortality in CKD either through immune-dependent or immune-independent mechanisms beyond mineral and bone. Vitamin D has a direct protective action on both renal and cardiovascular tissue and has an immune-modulatory effect in CKD patients. Vitamin D has anti-inflammatory actions which will reduce the state of chronic inflammation associated with the progression in CKD, therefore, Vitamin D will limit infiltration of renal tissues with immune cells and inflammation-related cardiovascular complications. In addition, Vitamin D has potent antimicrobial actions and thereby will improve the ability of those patients to combat infectious pathogens [139].

Active Vitamin D Reno protective effect is mediated via suppression of RAAS, reduction of proteinuria, protection of structural and functional integrity of podocytes [140]. Combination of Vitamin D with RAAS blockades can ameliorate renal fibrosis [141]. Active Vitamin D anti-inflammatory properties may be due to suppression of NF-B pathway which via regulation of many inflammatory cytokine enhances both inflammation and fibro genesis [140, 142]. Active Vitamin D has immune modulatory effects in CKD patients which will ameliorate renal fibrosis and slow-down proteinuria development. This can be done by enhancing Th2 cell differentiation, decreasing IL-6 expression, decreasing inflammatory and oxidative stress, altering T cell behavior, thus favoring tolerance development and reduce proinflammatory activity (140,143-145].

6-vitamin D and infection

In humans, Vitamin D triggers effective antimicrobial pathways, in the cells of innate immune system, against bacterial, fungal and viral pathogens, therefore, it has emerged as a central regulator of host defense against infections. However, Vitamin D attenuates inflammation and acquired immunity via its potent tolerogenic effects and hens limits the collateral tissue damage. On the other hand, Vitamin D promotes aspects of acquired host defense and epidemiological studies reported association between Vitamin D deficiency and increased risk of various infectious diseases [146].

The relationship between Vitamin D and infection was suggested about more than 100 years ago, and before the advent of effective antibiotics, Vitamin D has been used to treat infections such as tuberculosis [147]. Several studies have been associated between Vitamin D deficiency and increased risk for infection. Upper respiratory tract infection was reported in individuals with Vitamin D level below 30 ng/ml [148]. Military recruits from Finland with low Vitamin D lost more days from active duty (i.e. secondary to upper respiratory infections) than those with high serum levels [149]. Also, other studies reported association between low level of Vitamin D and increased rate of infection with influenza [150], bacterial vaginosis [151] and HIV [152].

VDR is an important element in host immune response to different infection. Some organisms either down-regulate or even block its activity which lead to impairment of innate immune response such as TB [153], Mycobacterium leprae [154], Epstein-Barr virus (EBV) [155], Aspergillus fumigatus [156] and HIV infection that completely inhibits VDR activity [157]. The Vitamin D has been linked to infection susceptibility through the genetic studies on VDR. Genetic polymorphisms of VDR were linked to TB susceptibility, extent infection, response to treatment and time of microbiological resolution by different studies [158-160].

The potential role of Vitamin D in host resistance to infections was based on the following four findings: conversion of circulating Vitamin D to the active Vitamin D requires the CYP27B1 enzyme (cytochrome 27B1, 25-hydroxyvitamin D_3 1-α-hydroxylase) and the immune system is able to produce this enzyme; the majority of immune system cells express VDR especially after stimulation; the production of active Vitamin D in the immune system led to the induction of antibacterial products such as cathelicidin which in turn inhibited the replication of Mycobacterium tuberculosis in vitro; and impaired Vitamin D status is a common health problem across the globe and may be responsible for the increased incidence of common infectious diseases across the world [28,42,81].

Active Vitamin D increased the expression of TLR4 and CD14 in human cells [161] and mouse model [162]. Increased TLR2 expression by about two folds after stimulation with Vitamin D in human keratinocytes. Microarray analysis of VDREs genes showed active Vitamin D increased CD 14 by more than 20-fold in well-differentiated human squamous carcinoma cells [163,164]. Also, the cathelicidin antimicrobial peptide (CAMP) and β-defensin 2 (DEFB2) genes were increased in response to active Vitamin D. The CAMP and defensins act as chemo-attractant for immune cells such as neutrophil and

monocytes and other components of immune response [165]. Liu et al. found that in African-American, the level of serum Vitamin D was lower than those in Caucasian and the level of TLR 2/1 activation and the expression of cathelicidin were also lower. Supplementation of Vitamin D to succeed to restore the normal activity of TLR 2/1 and expression of cathelicidin [56].

Kroner et al. [146] proposed a model for the vitamin D-dependent antimicrobial pathway. In Human, both innate immune mechanism (i.e., TLR-2/1 ligand and TLR-8 ligand) and adaptive immune mechanisms (i.e., IFN-γ and CD40 ligand) induce antimicrobial response in monocytes/macrophages through different signaling pathways. Then, up-regulation of CYP27B1 and VDR will occur and Vitamin D will be converted to active Vitamin D. The Active Vitamin D will trigger VDR mediated up-regulation of antimicrobial peptides (CAMP, DEFB4 and NOD2). At the same time, the active Vitamin D will bind to VDR and mediate down-regulation of hepcidin (HAMP) which will favor the cellular export of iron, therefore, the intracellular compartment will be inconvenient for the survival/proliferation of pathogens. In addition, cathelicidin promotes autophagy, which enhances auto-phagolysosomal fusion and antimicrobial activity.

Regarding infections, effect of Vitamin D on proinflammatory cytokines remains controversial (i.e., suppress or even enhance). Zhang et al. [166] reported up-regulation of MKP-1 by Vitamin D to mediate suppression of pro-inflammatory cytokines in monocytes/macrophages. However, these suppressive effects are attributed to vitamin D feedback mechanisms to reduce tissue damage [167]. Thus, it seems that first, the Vitamin D triggers antimicrobial host defense and enhances early inflammatory reactions needed for cell recruitment and efficient coordination of immune responses, later, after a while, Vitamin D by negative feedback mechanism, prevents extensive inflammation and tissue destruction [146].

Mangin et al. [168] hypothesized that the extra-renal production of active Vitamin D increases when nucleated cells are infected by intracellular bacteria. The kidneys lose its control of active Vitamin D production and due to rapid conversion of Vitamin D to active Vitamin D, the level of Vitamin D will decrease. The following mechanisms may be responsible; inflammatory cytokines will activate the CYP27B1 enzyme which will cause more Vitamin D conversion to active [169]; VDR are repressed by microbes and cannot transcribe CYP24A1 enzyme that breaks down the excess active Vitamin D [170]; increased active Vitamin D will bind to pregnane X receptor (PXR) and will inhibit conversion of vitamin D_3 to 25(OH)D [171] and active Vitamin D inhibits the hepatic synthesis of Vitamin D [172]. Therefore, low Vitamin D may be a consequence and not a cause of the inflammatory process [168].

7- vitamin D and autoimmunity

Autoimmune diseases (AIDs) are characterized by a loss of self-tolerance to self-antigen and development of autoreactive immune cells with subsequent body tissue destruction [173]. Interplay between endogenous and exogenous factors characterize the mosaic of autoimmunity. Complex genetic predisposition, hormonal, epidemiological and environmental risk factors contribute to the development of AIDs [93].

Epidemiological studies suggested an association between Vitamin D insufficiency/deficiency and increased incidence of AIDs such as SLE, RA, T1D and MS. Vitamin D supplement in AID animal models prevented or ameliorated autoimmunity. Increased incidence of inflammation and susceptibility to AIDs was observed in VDR knock-out or Vitamin D deficient animals [174]. In the same time, Vitamin D deficiency is considered as an epidemic and the incidence of AIDs was increased dramatically in the last decades. Also, a link between low sun exposure and increased incidence of AIDs was reported especially in Northern latitudes [175]. Epstein-Barr virus (EBV), is one of the most inducing infectious risk factor for autoimmunity. It was reported that EBV down-regulates the expression of VDR and thus decreases beneficial effects of Vitamin D [174]. Therefore, the availability of sufficient level of Vitamin D represents an exogenous and endogenous player in AIDs [175].

The Vitamin D has multiple effects on various cell lineages of immune system and its anti-inflammatory and immune-modulatory roles were suggested to explain the association between Vitamin D and autoimmunity. Vitamin D inhibits activity of Th1 and secretion of proinflammatory cytokines (e.g., IL-2, IFN-γ and NTF-α). On the other hand, Vitamin D enhances Th2 immune response and secretion of anti-inflammatory cytokines (e.g., IL-4, IL-5 and IL-10), therefore, shift the T cell immune response from an inflammatory Th1 to anti-inflammatory Th2 state. Vitamin D may increase activity of Tregs and inhibits activity of IL-17. Also, Vitamin D is required for the development of natural killer T cells (NKT) and increased secretion of IL-4 and IFN-γ [98,100,145,176,177].

Several associations were reported between serum level of Vitamin D and AIDs. Low serum level of Vitamin D was associated with increased incidence, severity and seasonality (i.e., more frequent flares in springtime due to less sunshine) of MS [178]. The frequency of MS was 40% less in females with high level of Vitamin D [179] and regular Vitamin D supplement decreased the risk of developing RA in about 30,000 patients [180]. Also, infants with regular Vitamin D intake had a reduced incidence of developing T1D [181].

The mechanism explaining how the Vitamin D intake affects the development of AIDs is still unknown. However, Mahon et al. [182] described that daily intake of 1000 IU of Vitamin D with 800 mg Calcium; increased secretion of TGF-β1. The increased level of this anti-inflammatory cytokine was associated with inhibition of harmful auto-reactive T-cell functions [179,183].

Vitamin D insufficiency and deficiency have been reported in SLE patients (38-96% and 8-30% respectively). The observed wide variation may be due to age of the patients, disease duration, ethnicity, seasonality, medications, geographic causes and method of assay [184-187]. Also, Vitamin D deficiency was noted in European American female patients with SLE and in obese healthy controls with positive anti-nuclear antibodies indicating that Vitamin D deficiency may play a role in initiating autoimmunity [188]. On the other hand, no associations were found between SLE development and Vitamin D dietary intake [189,190]. However, these studies were dependent on questionnaire for dietary Vitamin D intake and the serum levels of Vitamin D were not reported [179].

There are several causes that can explain the vulnerability of SLE patients to Vitamin D deficiency; those patients always advised to avoid exposure to sunlight due to photosensitivity [191]; renal involvement with subsequent defect in the 1-hydroxylation of Vitamin D [179]; chronic use of corticosteroid and may be high doses, as the case in lupus nephritis, decreases dietary absorption from intestine and increases the catabolism of Vitamin D [192] and the genetic variation [193].

8-vitamin D and therapy

Vitamin D deficiency is very important health problem because it affects many biological activities and bone mineralization. This problem is well known in both highly developed and underdeveloped countries. In winter months, a little Vitamin D is made in individuals living in northern and southern regions of the planet, therefore, adequate concentrations of Vitamin D are needed [17]. Many reasons were suggested to explain the epidemic of Vitamin D deficiency; skin melanin pigmentation, clothing as a barrier to Vitamin D photosynthesis, pollution as a block for some ultraviolet radiation, ageing of the skin, inflammatory process and latitude that dramatically influences the amount of solar radiation available to synthesize vitamin D_3 [168].

The Vitamin D (25(OH)D) is the marker for vitamin D status and its level determines whether a person is deficient, sufficient or toxic. Until now, there is a controversy about the precise level of Vitamin D and the level of Vitamin D categories (i.e., deficient, sufficient or toxic). However, the Vitamin D Council (VDC) [194] recommended maintaining serum levels of 50 ng/ml as the precise level with the following reference ranges; deficient: 0-40 ng/ml; sufficient: 40-80 ng/ml; high Normal: 80-100 ng/ml; undesirable: >100 ng/ml and toxic: >150 ng/ml. The Endocrine Society definition stated that Vitamin D deficiency means levels below or equal 20 ng/ml and insufficiency means levels equal to 20 -29 ng/ml [195]. The values stated by the Institute of Medicine definition [196] is lower than the others with levels less than or equal 12 ng/ml for risk/deficiency, levels from 12 to 20 ng/ml for risk/insufficiency and levels equal 20 ng/ml for sufficient.

The reasons for VDC recommendations regarding the precise level and categories of Vitamin D categories are; Vitamin D blood levels between 40-80 ng/ml was maintained in peoples living near the equator from sun exposure alone and human evolved in this area synthesizing in the skin a robust quantities of Vitamin D [197]; the anti-rachitic activity in breast milk occurs at 45 ng/ml or higher, but not at 38.4 ng/ml or lower [198], therefore the VDC believes that the maternal status of Vitamin D is necessary to provide anti-rachitic activity for offspring and should be considered a biomarker for optimal Vitamin D status in humans; the parathyroid hormone is maximally suppressed at 40 ng/ml or higher and this should be also considered a biomarker for optimal vitamin D status [199]. On Sun exposure alone, human body cannot achieve levels above 100 ng/ml from Vitamin D [200]. Hypercalcemia and calcuria are the manifestation of Vitamin D toxicity and no relation was reported between Vitamin D levels up to 257 ng/ml and serum calcium. In the same time, Vitamin D toxicity have been reported at levels as low as 194 ng/ml [201], therefore, the threshold of 150 ng/ml should be considered the lower limit of toxicity.

Vitamin D insufficiency indicates biochemical low levels without clinical evidence of deficiency (i.e., rickets or osteomalacia). Vitamin D insufficiency may cause muscle weakness, fractures in elderly when associated with osteoporosis. Also, Vitamin D insufficiency and deficiency were reported to be associated with colorectal cancer, prostate cancer, multiple sclerosis, type 1 diabetes, cardiovascular diseases and TB [202].

The best indicator for Vitamin D status assessment in patients with a Vitamin D related disease is to measure the range of $25(OH)D_3$ serum concentration in a population of healthy subjects [1]. This view is supported;1) absence of Vitamin D clinical assay; 2) the serum concentration of $25(OH)D_3$ is an accurate indicator for Vitamin D_3 derived from cutaneous UV-stimulated synthesis and dietary intake (the metabolism of vitamin D_3 into $25(OH)D_3$ by the liver vitamin D-25-hydroxylase is not regulated); 3) a variety of clinical assays are available to measure 25(OH)D; and 4) the plasma concentrations of $25(OH)D_3$ correlate with many clinical diseases [203,204].

To achieve adequate Vitamin D status, various strategies have been suggested; healthy lifestyle with normal body mass index (i.e., a varied diet with vitamin D-containing foods, adequate outdoor activities and sun exposure); improving vitamin D status (i.e., dietary recommendations, food fortification, vitamin D supplementation and sun exposure) and Vitamin D oral supplementation for high-risk groups (i.e., pregnant and breastfeeding females, teenagers, young children and infants, people over 65 years, people with low or no exposure to sun and dark skin people) [205].

The Institute of Medicine (IOM) recommended daily intakes of 600 IU/day for adults and up to 800 IU/day for elderly people living in North America. The IOM also stated that adequate amount of Vitamin D can be supplied from the regular sun exposure for 15 minutes in summer without sunscreen 3 to 4 times per week and Vitamin D supplement with D_2 or D_3 can be used [206,207].

In UK, Vitamin D supplement of 400 IU/day was advised to be given on for people over 65 years old with the aim of achieving Vitamin D level about 20 ng/ml [207].

The Endocrine Society Clinician Vitamin D Guideline of 2011 recommended Vitamin D serum of at least 30 ng/ml. This level is required to achieve a plateau in the reduction of serum PTH with increasing Vitamin D among healthy adults. Also, at this level of Vitamin D, it will be possible to reduce falls or fracture rates in older people [208]. Encouraging data suggested that adequate Vitamin D supplement can reduce the risks of cancer [209] and the risk of developing a first cardiovascular event [207].

While, Vitamin D supplement must be ensured in high risk groups, however, there is no need to measure serum Vitamin D concentrations on healthy people [210]. On the other hand, assessment of Vitamin D, D-status should be done for people presenting for medical advice with suspicious of Vitamin D deficiency as a cause of the problems presented. Follow-up monitoring is needed; to be sure that a good clinical response to initial supplement is achieved; if the health problems or medication require routine Vitamin D supplement or to ensure that the treatment is adequate [207].

Measuring serum level of 25(OH)D is used currently to assess Vitamin D status, however, this will not provide enough information about Vitamin D endocrine function. In the same time, it is not clear why active Vitamin D is measured, but associations between active Vitamin D and diseases are present [168,211]. On the other hand, active Vitamin D is not measured to assess Vitamin D nutritional status, as marker related to health outcomes or for Vitamin D research. To assess Vitamin D status as a clinical marker of chronic disease, it is better to measure both Vitamin D and active Vitamin D in addition to calcium, phosphorous and PTH when indicated [212,213]. Measuring serum level of active Vitamin D should be considered in cases with low Vitamin D serum level and in autoimmune or chronic inflammatory diseases and abnormal laboratory results such as inflammatory markers [168].

Measurement of serum level of Vitamin D is indicated in; when there is clinical or laboratory suspicious of Vitamin D deficiency (e.g., rickets in children or osteomalacia in adults, bone pain, low level of serum calcium or phosphorous or high level of alkaline phosphatase or

PTH); elderly people; patients with osteoporosis and peoples with increased risk of falls or fractures [214,215].

The physiological serum level of active Vitamin D is in picomole and nanomole doses of active Vitamin D are needed to obtain its non-classical effects. Active Vitamin D supra-physiological doses will result in hypercalcemia. To avoid this and to have tissue and organ targeted Vitamin D effects, active Vitamin D analogs were developed. Presently, enormous number of Vitamin D analogs are manufactured and some analogs have tissue-specific effects, low calcemic side effects and can be given at higher dose [216].

Vitamin D analogs are commonly used to treat secondary hyperparathyroidism complicating CKD or ESRD. They suppress PTH without inducing severe hypercalcemia. Also, Vitamin D analogs are used for psoriasis either alone or in combination with topical steroids. They have anti-inflammatory properties and exert pro-differentiating and anti-proliferative effects on keratinocytes. Furthermore, Vitamin D analogs are used for treating osteoporosis as they increase bone mineral density. Because of the potent anti-proliferative and pro-differentiating effects on normal and malignant cell lines, the active Vitamin D and its analogs are used also for cancer treatment [216].

Active Vitamin D and Vitamin D analogs modulate several cell processes such as growth, apoptosis, adhesion, immune function and signaling pathways. However, comparison of different cell lines showed overlap of few active Vitamin D/analog-regulated genes and this suggested the cell type and tissue-specific effect of active Vitamin D and its analogs [216]. For example, results of active Vitamin D analogs studies using human T-cells showed regulation of genes responsible for cell growth, cell death, cell signaling and migration indicating that these analogs affect human T-cells with a migratory signature and direct them toward sites of inflammation [202].

Several studies have tried to explain the exact mechanism of tissue-specific action of Vitamin D analogs. First, the catabolism of Vitamin D analogs affects their potency. Modification of active Vitamin D side chain slow down its catabolism leading to longer exposure to tissues [217,218]. The metabolites formed after catabolism are more active than active Vitamin D [219]. Some analogs more effective in slowing down the VDR degradation. Some cell types prefer specific catabolism pathways and enzymes above others and the degradation process may also contribute to the tissue-specific activity of Vitamin D analogs. The affinity for the Vitamin D binding protein (DBP) also plays a role in the activity of Vitamin D analogs [216]. Second, the interaction between Vitamin D analogs and VDR, co-activators and VDREs. Some analogs promote hetero-dimerization between VDR and retinoid X receptor (RXR). Vitamin D analogs might also be able to induce tissue-specific effects by favoring binding to specific VDRE motifs in target gene promoters. Another mechanism need to be investigated is the effect of proteomics and epigenetics [216].

Conclusion

VDR is expressed on immune cells (B cells, T cells and antigen presenting cells) and these immunologic cells are all are capable of synthesizing and responding to Vitamin D. Vitamin D interaction with immune system is one of the most well-established non-classical effects of Vitamin D. Vitamin D can modulate the innate and adaptive immune responses. The ability of Vitamin D to influence normal human immunity will be highly dependent on the vitamin D status of individuals, therefore, deficiency or insufficiency of Vitamin D is associated with increased autoimmunity and infection. The 25-hydroxyvitamin D3 (25OHD3) is the main circulating metabolite of Vitamin D and is the most reliable measurement of an individual's Vitamin D status. The Vitamin D supplements in deficient individuals will have beneficial immune-modulatory effects on the autoimmune status.

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