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Vitamin D and Immunity: A comprehensive review of its impact on autoimmunity, allergy suppression, antimicrobial defense, and cancer inhibition

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Abstract

Vitamin D, commonly known for its impact on bone metabolism, is vital in various bodily processes, including regulating immune responses. The actions of vitamin D are carried out through its receptor, found in cells of different human organs and tissues, particularly in most immune system cells and epithelial cells. After binding to the receptor, vitamin D forms a complex with vitamin A and its receptor in the cytoplasm. This complex can inhibit or enhance the transcription of hundreds of genes, including those that control cell growth, differentiation, apoptosis, and prevent malignant growth and angiogenesis. Studies have shown that vitamin D weakens antigen presentation by dendritic cells, shifts the balance of Th1/Th2 cell responses towards Th2, and promotes the development and activity of Treg cells. Additionally, vitamin D enhances the production of "endogenous antibiotics" against bacteria, fungi, and viruses. This important nutrient has been linked to preventing autoimmune and atopic diseases, respiratory infections, and tumors. A lack of vitamin D, or hypovitaminosis D, is present in almost half of the population and is a leading cause of weakened immunity and increased morbidity. Thus, detecting, preventing, and treating hypovitaminosis D should be a priority in healthcare in the Kingdom of Saudi Arabia.

Keywords: Vitamin D, Immunity, Immunoregulation, Hypovitaminosis, vitamin D supplements

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Introduction

Approximately half of the global population is affected by vitamin D deficiency. Studies estimated that one billion individuals, spanning all ages and ethnicities, suffer from this deficiency.[1] Vitamin D comprises a set of secosteroids that are soluble in fat and play a crucial role in enhancing the absorption of calcium, magnesium, and phosphate in the intestine, as well as performing various other biological functions. Vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol) (Figure1) are the most significant compounds in this group for human health,[2] Recent research has presented conflicting findings on the link between vitamin D deficiency and various health conditions such

as cancer, autoimmune diseases, diabetes, and heart disease.[3] However, a research study by Chiodini et al., 2021,[4] suggested that vitamin D may play a role in reducing the risk of developing the chronic obstructive pulmonary disease in patients infected with the coronavirus disease 2019 (COVID-19) virus. Additionally, vitamin D-containing dietary supplements have become increasingly popular in recent years, but taking excessive amounts may result in negative effects such as kidney and bone diseases.[4] Vitamin D is important for maintaining the proper growth and development of skeletal muscles and preventing conditions like rickets and osteomalacia in children.[5] In their research, Zemb et al., 2020,[6] examined the connection between vitamin D and immune function and the possible effect of vitamin D deficiency on the likelihood of contracting respiratory infections, including COVID-19. The researchers stated that vitamin D could be acquired through exposure to direct sunlight at specific times and that blood levels of 30 ng/mL to 50 ng/mL are sufficient for maintaining good health in most individuals. A level of 12 ng/mL or below is considered deficient.

A recent study has highlighted the negative effects of low vitamin D levels on health, including metabolic syndrome, cardiovascular disease, and diabetes.[7] Moreover, research indicates an inverse relationship between vitamin D levels and the immune system, with deficiency leading to increased inflammation and reduced control of chronic diseases.[8] Additionally, lack of vitamin D in pregnant mothers can result in rickets and osteoporosis in their children. Al-Alyani et al., 2018,[9] reported that vitamin D deficiency is prevalent in the Saudi society. This research showed that it affects 100 % of the population, leading to a high incidence of osteoporosis among older individuals. The present article aimed to examine the biology of vitamin D and summarize the mechanisms that may underlie the relationship between vitamin D and immunity.

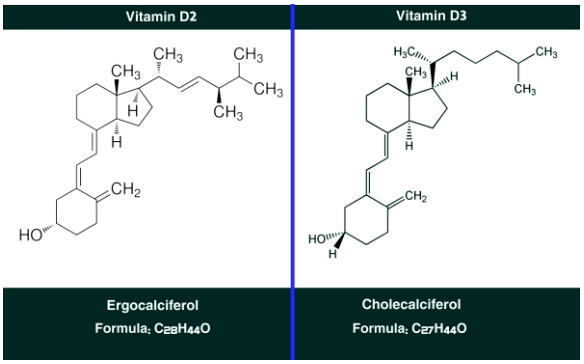

Figure 1. Vitamin D2 and D3 chemical structure.

1. Vitamin D function

Vitamin D plays a crucial role in various physiological processes within the body, including the regulation of normal thyroid function, blood clotting, the state of myelin fibers in nerve cells, muscle strength and endurance, bone strength, and density, prevention of osteoporosis and rickets, enhancement of the production of "endogenous antibiotics," immune responses, prevention of autoimmune and allergic diseases, resistance to infectious diseases, and inhibition of tumor growth.[5,10,11] During the COVID-19 pandemic, vitamin D was found to be beneficial in boosting the activity of COVID-19 vaccines, as reported by Bleizgys, 2021.[12] Sizar et al., 2022,[3] found that vitamin D reduces the incidence of many diseases, regulates blood pressure, and supports cardiovascular health. Littlejohns et al., 2014,[13] revealed that a natural vitamin D level of 50 nmol/l may protect against Alzheimer's or dementia. According to Klampfer, 2014,[14] researchers discovered that those who consumed vitamin D had a 50% decreased risk of getting rectal and early colon cancer. Adequate vitamin D3 intake improved survival of colon cancer patients and polyp recurrence. Gil et al., 2018,[15] mentioned that vitamin D is an antioxidant that fights age.

2-Vitamin D metabolism

The synthesis of vitamin D (Figure 2) begins with the conversion of its precursor, 7-dehydrocholesterol (7-DHC), which is found in the epidermis, mainly in the stratum basale and stratum spinosum.[16] Alagarasu, 2021,[17] noted

that 7-DHC in the skin is the key raw material for vitamin D synthesis. When 7-DHC is exposed to ultraviolet light B, it breaks down to form pre-D isomers. These pre-D isomers are then rapidly converted to vitamin D3 (cholecalciferol) in a non-catalytic process, whether under natural or artificial ultraviolet sources. Vitamin D3 is then transported via a vitamin D-binding protein into the blood and carried to the liver. In the liver, it is converted to 25-hydroxycalciferol (Calcifediol) through the action of 25-hydroxylase enzymes like cytochrome P450 2R1 enzyme (CYP2R1), cytochrome P450 family 27 subfamily A member 1 protein coding gene (CYP27A1), cytochrome P450 3A4 enzyme (CYP3A4), and cytochrome P450 2J2 enzyme (CYP2J3). The main targets of vitamin D are the intestines, bones, kidneys, and parathyroid glands. Vitamin D plays an important role in the absorption of calcium and minerals in the intestines. It must first be converted into its biologically active form, known as 1,25-dihydroxyvitamin D. This is the most physiologically active form of vitamin D.[18, 19]

In addition to the liver, the active form of vitamin D3, 1,25-dihydroxycholecalciferol, is also formed in many other cells such as those of the proximal tubules of the kidneys, monocytes and dendritic cells, osteoblasts, keratinocytes, large intestine, bronchial wall, prostate, and pancreas, through the action of the enzyme vitamin D 1-hydroxylase, cytochrome P450 family 27 subfamily B member 1 protein coding gene (CYP27B1.) [20, 21, 22] Dominguez et al., 2021, [23] found that vitamin D2 or D3 is retained in fatty tissues after entering the bloodstream, forming a weak link with vitamin D binding protein. It is then metabolized to 25-hydroxy vitamin D in the liver. The rate of conversion to 25-hydroxy vitamin D may be slower in people who receive high doses of vitamin D. Acar and Özkan, 2021, [24] reported that vitamin D3 affects vitamin D2, it contains a double bond between the 22 and 23 carbon atoms, and the methyl group on the 24-carbon atom, thus affecting vitamin D2 to destroy it.

The optimal ultraviolet light B wavelength for the synthesis of vitamin D from the skin is between 295 and 315 nm, according to Young et al., 2021. [2] A double bond is formed between the broken carbon atoms in the B ring through a heat-sensitive, non-enzymatic process, as noted by Acar and Özkan, 2021. [24] Bikle et al., 2021, [21] found that the highest production of vitamin D3 occurs around noon and is greater in the summer than in other seasons. If the body is exposed to enough sunlight, there is no need for additional vitamin D intake. However, clothing and sunscreens can prevent the production of vitamin D3 in covered areas. Additionally, ergocalciferol and ergosterol, found in foods such as seafood, fish liver, cheese, vegetables, butter oils, and raw egg yolks, may contribute to the body's ability to synthesize vitamin D.

The activation of vitamin D 1-hydroxylase transcription is influenced by early-stage inflammatory cytokines as tumor necrosis factor α (TNF-α) and interleukin (IL)-1, according to Overbergh et al., 2000. [26] Vitamin D activation and its impact on cytokine-producing cells also serve as regulators, helping to reduce the inflammatory cascade. A combination of two or more stimulatory signals is typically needed for vitamin D 1-hydroxylase activation, with the most frequent signals being transmitted by interferon gamma (IFN-γ), lipopolysaccharides, and activating factors of kinases.

Hormones that affect the mineral makeup of bone tissue and immune system mediators both influence vitamin D synthesis, as reported by Bikle, 2012.[27] This results in the release of the parathyroid hormone into circulation as the amount of ionized calcium in the extracellular fluid decreases. It works indirectly by altering the transmembrane fluxes of phosphate ions in the cells of the renal tubules to boost vitamin D 1-hydroxylase activity in the kidneys.

When blood vitamin D levels reach approximately 30-40 ng/mL, the release of parathyroid hormone stops. Other hormones such as prolactin, sex steroid hormones, glucocorticoids, and insulin also affect the vitamin D 1-hydroxylase activity and parathyroid hormone. However, the relative importance of each in controlling vitamin D biosynthesis still needs to be determined, as noted by Holick, 2013.[28] IFN-γ and Toll-like receptors, which identify lipopolysaccharides,

lipoproteins, and other molecular components on the surface of bacteria, are two mediators that control vitamin D 1-hydroxylase activity in the immune system, according to Kak et al., 2018.[29]

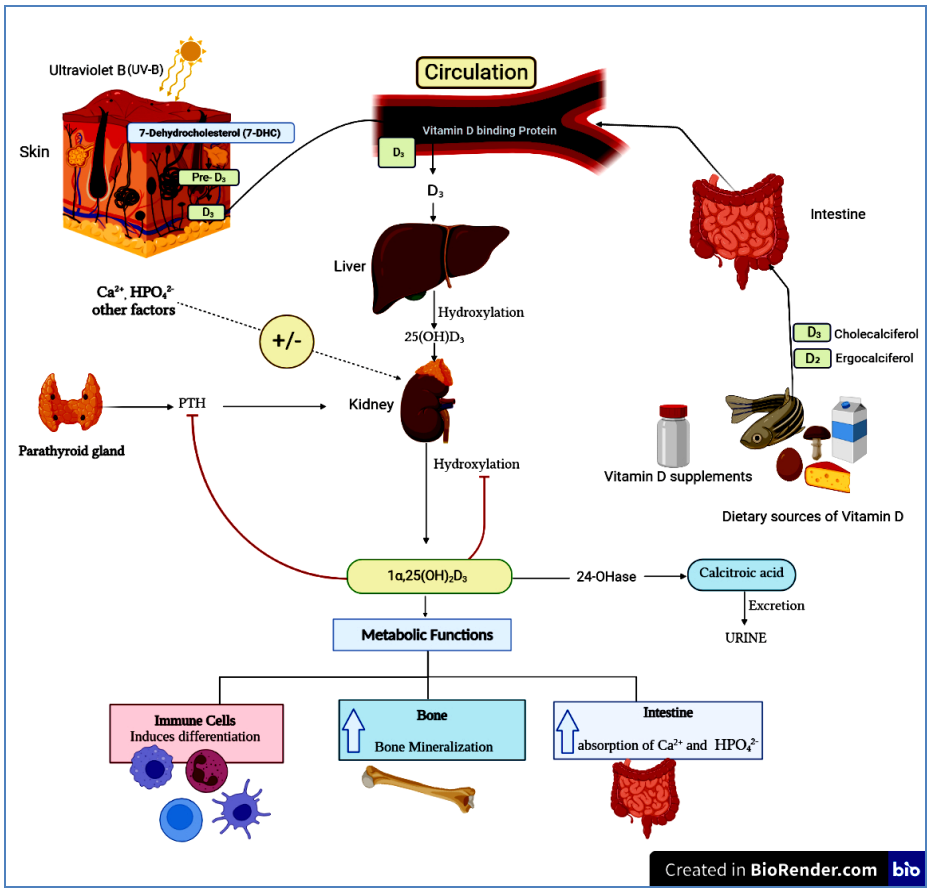

Figure 2. Vitamin D metabolism involves synthesizing vitamin D3 through the conversion of pro-vitamin D_3 to pre-vitamin D_3 in response to sunlight exposure. Vitamin D_3 is obtained from pre-vitamin D3 through isomerization in the skin or absorption through diet. Once in the bloodstream, vitamin D3 binds to vitamin D-binding protein and is transported to the liver, where the liver 25-hydroxylases hydroxylate it. The resulting 25-hydroxycholecalciferol is then further hydroxylated in the kidney by 25-hydroxyvitamin D_3-1α-hydroxylase to produce the active secosteroid 1α, 25$(OH)_2$ D_3. The synthesis of 1α, 25$(OH)_2$ D_3 is regulated by various factors such as parathyroid hormone and calcium levels. Catabolism of 25(OH) D_3 and 1α,25$(OH)_2$ D_3 occurs through 24-hydroxylation by 25-hydroxyvitamin D 24-hydroxylase encoded by the CYP24A1 gene—the main effects of 1α, 25$(OH)_2$ D_3 on different target tissues.

3- Interactions between Vitamin D, Receptors, and Transcription Factors

The vitamin D receptor (VDR) is a member of the family of ligand-activated nuclear receptors for transcription factors. It is a phosphoprotein with a molecular weight of 50 kDa, structurally resembling steroid, thyroid, and retinoid receptors.[21] The vitamin D receptor contains a specific vitamin D ligand and a DNA-binding domain.[30] Vitamin D receptor can be found in various cell locations, including cell membranes, cytoplasm, the perinuclear zone, and mitochondria [31]. This receptor is present in cells of a wide variety of tissues and regulates intracellular calcium metabolism, cell growth, and differentiation. Vitamin D receptor is particularly prevalent in immune cells, with high concentrations in monocytes, dendritic cells, and T-lymphocytes.[32-35] In stimulated T cells, vitamin D receptor expression is increased and persistent and is associated with cell proliferation, cytokine production, and activation of the extracellular signal-regulated

kinase (ERK)1/2 kinase enzyme.[36] Additionally, the stage of development of specialized T cells affects vitamin D receptors expression, with high levels found in naive and early memory T cells, which initiate the graft versus host reaction.[37] After vitamin D binds to the vitamin D receptors, a vitamin receptor complex is formed in the cytoplasm, which then combines with another vitamin-receptor complex, the retinoid X receptor (RXR), to create a heterodimeric structure. These VDR/RXR heterodimers bind to the promoter regions of various genes in the nucleus, attracting co-regulatory proteins and resulting in changes to the chemical structure of histones, leading to chromatin rearrangement, changes in RNA polymerase II binding and transcription initiation.[38,39] There are about 3000 such regions in the genome, called Vitamin D Responsive Elements (VDREs), consisting of hexanucleotide repeats with spacers of three nucleotides.[40,41] In these regions, vitamin D receptor can regulate the transcription of over 900 genes.[42] Vitamin D receptor plays a crucial role in regulating gene expression. It directly affects many genes, estimated to be around 3% of the human genome, involved in immune functions.[42,43] Vitamin D receptor acts as a coactivator or corepressor on even more genes, further expanding its influence.[44]

One of the keyways in which vitamin D receptor regulates gene expression is by inhibiting the phosphorylation of the p65 subunit of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), which prevents the translocation of NF-kB to the nucleus.[45] This, in turn, blocks the activity of the nuclear factor of activated T-cells, a common transcription factor expressed in most immune system cells. Vitamin D receptor also sequesters runt-related transcription factor 1 (RUNX1), a transcription factor that regulates the differentiation of hematopoietic cells. Furthermore, it affects the induction of the transcription factor FoxP3+, one of the main regulators of the development and functioning of T cells.[46]

Vitamin D receptor also increases the expression of immunoglobulin-like transcripts 3 and 4 (ILT3 and ILT4) on the dendritic cells surface[47] and activates histone deacetylase, which coils DNA on histones more tightly, preventing transcription of this DNA.[48,49] A negative feedback mechanism is also present, as bound vitamin D receptor suppresses the transcription of the vitamin D receptor gene. Additionally, vitamin D receptor enhances the expression of 24-hydroxylase, an enzyme that produces a less active form of vitamin D.[50]

Vitamin D also affects microRNAs, small noncoding RNA molecules regulating transcriptional and posttranscriptional gene expression.[51] Vitamin D modulates the expression of microRNA in adipocytes in vitro and in adipose tissue in vivo through its impact on the NF-kB signaling system. It may represent a new mechanism by which vitamin D regulates inflammation.[52]

Beyond its impact on gene transcription, vitamin D receptor also has an immediate extra genomic influence on the second messengers of many physiological processes, such as cyclic adenosine monophosphate (cAMP), inositol triphosphate, and arachidonic acid. For example, vitamin D receptor modifies the calcium-dependent process of megakaryocyte and platelet activation through the effect of vitamin D on mitochondria.[31] Mitochondrial enzymes, such as cytochrome P450 family 24 subfamily A member 1 (CYP24A1) and cytochrome P450 family 27 subfamily A member 1 (CYP27A1), start the breakdown of vitamin D and vitamin D receptor in cellular mitochondria.[2]

It is worth noting that variants in the vitamin D receptor have been linked to a number of health conditions, including asthma, atopy, autoimmune disorders, and cancer.[53] Thus, it is important to understand the role of vitamin D receptor in gene regulation and its potential implications for health and disease.

4-Vitamin D and Vitamin D receptors in the regulation of the immune system

4.1. The Effect of Vitamin D on innate immunity

Innate immunity plays a crucial role in the immune response, including various cellular components such as macrophages and natural killer cells. However, these cells decrease as we

age, making the elderly more susceptible to multiple infections.[54] Vitamin D, by binding to the vitamin D receptor, promotes the expression of the cathelicidin antimicrobial peptide (CAMP) and beta-defensin-2 (DEFB2) genes, leading to the transcription of cathelicidin and β-defensins, which are low molecular weight (2-6 kDa) cationic proteins referred to as endogenous antibiotics.[32,35] These peptides have an antibacterial effect against various bacteria, fungi, and some viruses and are found in multiple body parts such as the skin, cornea, tongue, salivary glands, esophagus, and respiratory system.[55,56] Urry et al., 2009,[57] stated that beta-defensins are present in almost all types of leukocytes and epithelial cells. At the same time, alpha-defensins are mostly found in neutrophilic granulocytes, natural killer (NK) cells, T lymphocytes, and small intestinal epithelial cells. Most defensins are lodged in a microbial cell's membrane, and by "perforating," they result in membrane depolarization or lysis. These peptides have a very powerful protective effect.

A study by White, 2008,[33] reported that some β-defensins and CAMP could act as chemo-attractants for monocytes, neutrophils, and other immune system cell types. Defensins, described as antimicrobial peptides, are also involved in the adaptive immune response. For example, defensin-1, a human neutrophil peptide found in the mucosal epithelium, chemotactically attracts monocytes, T-lymphocytes, dendritic cells, and mast cells to the infected site.[58,59] The innate immune system also includes natural killer T (NKT) cells, which protect the body from autoimmune diseases. Vitamin D receptor is essential for the growth of these cells,[60] but it is still unclear how vitamin D and vitamin D receptors affect the control of mature NKT activity.[61] In experimental models, NKT cell counts are decreased, IL-4, IL-5, and IL-13 production is inhibited, and airway hyperresponsiveness is not induced in knockout mice missing vitamin D receptors.[62]

4.2. The effect of Vitamin D on Monocytes and Dendritic cells

Vitamin D has been shown to prevent the activation of phagocytic monocytes and human dendritic cells by binding to vitamin D receptors and suppressing the expression of Toll-like receptors (TLR proteins 2 and 4).[63-66] This reduces the ability of monocytes to recognize pathogens and weakens the translocation of the NF-kB/RELA factor into the nucleus, which is necessary for the transcription of pro-inflammatory mediators.[63,67] In dendritic cells, vitamin D receptors inhibit the transcription of proteins required for their phagocytic and antigen-presenting functions, making these cells (at least a subgroup of these cells) immunologically tolerogenic.[68,69] In addition to preventing TLR expression, vitamin D also suppresses the appearance of costimulatory molecules such as cluster of differentiation 40 (CD40), CD80, CD83, and CD86 on the surface of dendritic cells.[69,70] These dendritic cells produce less IL-2 and IFN-γ than non-tolerogenic dendritic cells and secrete more IL-10 instead of IL-12.[71,72] It is well known that dendritic cells differentiate from bone marrow progenitor cells into immature dendritic cells, which then mature in the phagocytosis of pathogenic microorganisms, followed by their destruction (primarily by oxidative burst) and transformation into class II major histocompatibility complex (MHC) antigens. At the same time, dendritic cells express costimulatory molecules such as CD40, CD80, and CD86 and acquire the ability to migrate to the lymph nodes, where they present the finished MHC-II complex to T cells.[63,73-75] In addition, dendritic cells are immune cells that produce the cytokine IL-12, which converts Th0 cells into Th1 lymphocytes that produce IFN-γ.[76] Studies have shown that both in rodents and humans, dendritic cells can become tolerogenic in the absence of microbial stimulation or under the influence of certain cytokines such as IL-10 and transforming growth factor-beta (TGF-β), as well as vitamin D. When dendritic cells become tolerogenic, they lose their ability to process and present MHC class II antigens to Th1 or Th2 cells, but instead promote the differentiation of naive Th0 cells into CD4+CD25+Foxp3+ regulatory T (Treg) cells. Treg cells are produced during thymocyte development and are essential in avoiding immune system attacks on human tissues and cells.[77,78] In addition to its

effect on dendritic cells differentiation, vitamin D also reduces the total number of dendritic cells, most likely by promoting their spontaneous apoptosis.[79,80] Furthermore, it inhibits the proliferation, promotes the apoptosis of activated B cells, and reduces the expression of MHC class I and II molecules on the cell surface.[81, 82] Vitamin D-induced suppression of IL-23 production also contributes to a decrease in the response of tolerogenic dendritic cells to the antigen.[83,84]

4.3. The effect of Vitamin D on B-lymphocytes and T-lymphocytes

Early phases of B-cell formation take place in complex microenvironments called "niches" formed by bone marrow stromal cells, where the stimuli need to start a chain of cell signaling come from B cells that are a crucial source of plasma cells, which produce antibodies while also controlling autoimmune reactions and the generation of T cells.[85,86] Vitamin D has numerous effects on cells within the immune system. According to previous studies, vitamin D has an inhibitory effect on progenitors of B-lymphocytes (as well as progenitors of T-cells). It prevents B cells from differentiating, reduces the level of immunoglobulins they produce, and promotes apoptosis. However, most authors believe that vitamin D affects B cells indirectly through the suppression of T cells and a decrease in IL-2 and IFN-γ release, preventing B cells from activating, proliferating, and producing immunoglobulins IgM and IgE in both human and animals.[87-89] Vitamin D/vitamin D receptor (VD/VDR) affect the activity of transcription factors in dendritic cells and T cells, change their receptor and cytokine profiles, and prevents polarization of naive Th0-lymphocytes into Th1 cells and, to a lesser extent, Th2 cells, shift the Th1/Th2 balance towards the Th2 response, suppress the formation Th17 cells and their production of IL-17 and activate Treg cells. The integral effect of VD/VDR on immunity is more complex and yet to be explored. Thus, if the suppressive effect of VD/VDR on Th1 cells can be considered established, then there is no complete clarity regarding the Th2-response. There are indications that VD/VDR also attenuates the Th2 response. For example, in the primary culture of mouse CD4+T cells, vitamin D receptor inhibited the transcription of both IFN-γ and IL-4, the main promoters of Th1 and Th2 cell differentiation, respectively, and the use of vitamin D in the treatment of allergic inflammation, led to a decrease in the levels of both IFN-γ and IL-4, IL-5, and IL-13.[90,91] Therefore, it is more correct to assume that vitamin D and vitamin D receptor can reduce both Th1 and Th2 responses. Vitamin D would accelerate the progression of Th2-mediated diseases, raise the chance of acquiring asthma, allergies, and eczema, and alter the Th1/Th2 balance in favor of the Th2 response. Vitamin D boosted allergen-induced T-cell proliferation in experimental research.[92,93] Also, in allergen-specific immunotherapy, the only curative treatment for type I allergy, supplementation with 25-hydroxyvitamin D3 (inactive precursor of vitamin D3) increased the positive effects in sensitized, vitamin D deficient mice.[94] In contrast, vitamin D appears to be successful as adjuvant therapy and, in clinical practice, does not aggravate the course of these diseases; it rather inhibits the development of asthma and other atopic disorders linked to the activation of the Th2 response. Furthermore, vitamin D receptor-deficient mice fail to induce experimental asthma.[95]

5-Effect of Vitamin D on cytokine production

Vitamin D has been found to possess immunomodulatory properties that involve the regulation of cytokine production. Cytokines act as signaling molecules in the immune response and can have either pro-inflammatory or anti-inflammatory effects depending on their concentration and type. The immune cells, including T cells, B cells, dendritic cells, and macrophages, express the vitamin D receptor are regulated by vitamin D through binding. Upon binding to vitamin D receptor, vitamin D can regulate the transcription of various genes related to immune system function, including those involved in cytokine production. Several studies have investigated the effect of vitamin D on cytokine production, and the results were

inconsistent. Some studies have shown that vitamin D can decrease the production of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α while increasing the production of anti-inflammatory cytokines such as IL-10.[95-97] Previous studies have demonstrated that vitamin D can suppress the expression of IL-1β and IL-6 in human monocytes and macrophages stimulated with lipopolysaccharide.[4,5] Other studies have shown no significant effect of vitamin D on cytokine production.[98,99] Anti-inflammatory cytokines are a class of cytokines that help to inhibit the immune response and reduce inflammation. They include IL-10, TGF-β, and others.[100] IL-10 is a potent anti-inflammatory cytokine that can suppress the production of pro-inflammatory cytokines, while TGF-β can regulate immune cell function and promote anti-inflammatory responses.[101] Several studies have investigated the effects of vitamin D on the expression and production of anti-inflammatory cytokines. One study showed that vitamin D supplementation increased the expression of IL-10 and TGF-β in human monocytes and dendritic cells.[102] Another study demonstrated that vitamin D supplementation increased IL-10 production in T cells from healthy individuals.[103]

Additionally, vitamin D supplementation was shown to increase the expression of IL-10 and decrease the expression of pro-inflammatory cytokines.[104] Similarly, in patients with multiple sclerosis, vitamin D supplementation was found to increase the production of IL-10 and reduce the production of pro-inflammatory cytokines.[105] One mechanism by which vitamin D may upregulate anti-inflammatory cytokines is through the inhibition of NF-κB, a transcription factor that plays a central role in regulating pro-inflammatory cytokines. Vitamin D has been shown to inhibit NF-κB signaling in several immune cell types, leading to decreased production of pro-inflammatory cytokines and increased production of anti-inflammatory cytokines, such as IL-10.[106] Another mechanism by which vitamin D may regulate anti-inflammatory cytokines is through the activation of regulatory T cells (Tregs), a type of immune cell that plays a critical role in immune tolerance and the prevention of autoimmunity. Vitamin D has been shown to promote the differentiation of Tregs and enhance their suppressive function, which can lead to the suppression of pro-inflammatory cytokine production and the promotion of anti-inflammatory cytokine production.[107] In addition, vitamin D may also modulate the expression and activation of cytokine signaling pathways, such as the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which is involved in the regulation of several cytokines, including IL-10. Vitamin D has been shown to inhibit the activity of the JAK/STAT pathway in certain immune cell types, leading to decreased production of pro-inflammatory cytokines and increased production of anti-inflammatory cytokines.[108]

Vitamin D plays a vital role in regulating the balance between the production of Th1 and Th2 cytokines. Th1 cells produce cytokines like IFN-γ and IL-2, which are essential in cell-mediated immunity and play a significant role in eliminating intracellular pathogens. In contrast, Th2 cells produce cytokines such as IL-4, IL-5, and IL-13, which are crucial in humoral immunity and play a significant role in removing extracellular pathogens. Moreover, research has shown that vitamin D promotes the differentiation of Treg cells, which are involved in suppressing Th1 and Th2 immune responses [109]. Vitamin D receptors are found on many immune cells, including T cells, B cells, and antigen-presenting cells.[110] Studies have demonstrated that vitamin D can suppress pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 while increasing anti-inflammatory cytokines such as IL-10 and TGF-β.[111,112]

Research has indicated that vitamin D can boost the production and efficacy of several anti-inflammatory cytokines, such as IL-27, IL-35, and IL-37, which regulate immune cell function.[112-114] Furthermore, vitamin D can reduce the production of Th1 cytokines, such as IFN-γ, while increasing Th2 cytokines, such as IL-4 and IL-5.[115] Vitamin D supplementation in healthy individuals has been shown to decrease the production of IFN-γ and IL-17 while increasing the production of IL-4 and IL-10.[116] Vitamin D can also regulate the differentiation and activation of immune cells, including

promoting the differentiation of Tregs and inhibiting the differentiation of Th17 cells by downregulating the expression of IL-17.[110,112]

Additionally, vitamin D has been shown to increase the production and efficacy of TGF-β and IL-1 receptor antagonist (IL-1Ra), which are essential for controlling immune cell differentiation and activity.[111,112] In some conditions, vitamin D has been demonstrated to decrease the production of IL-4 and IL-13, which are cytokines that promote inflammation, potentially mitigating inflammation.[112] Moreover, vitamin D can increase the expression of tumor necrosis factor receptor 2 (TNFR2), a receptor for the pro-inflammatory cytokine TNF-α and reduce the production of the soluble TNF receptor (sTNFR), a marker of inflammation, potentially mitigating inflammation.[106,118]

Furthermore, vitamin D can suppress the production of IL-1β, IL-6, TNF-α, IL-12, IL-17, IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8, and monocyte chemoattractant protein-1 (MCP-1) in various cell types, including monocytes, macrophages, dendritic cells, and T cells.[108,116] These effects suggest that vitamin D has significant immunomodulatory properties and potential therapeutic implications for various autoimmune and inflammatory conditions.

6-Vitamin D level in the blood and hypovitaminosis

Vitamin D levels are assessed in the body by determining the concentration of 25-hydroxyvitamin D in the blood serum. This is due to its connection with the vitamin D-binding protein, which is genetically determined and phenotypically different among individuals, contributing to their varying vitamin D content in the blood.[117] This variability also affects the susceptibility of individuals to respiratory tract infections and autoimmune disorders.[117,118]

According to the Institute of Medicine of the National Academies and the 2011 US government guidelines, blood levels of 25-hydroxyvitamin D below 30 nM/L (or 12 ng/mL) indicate severe vitamin D deficiency, leading to rickets and bone softening in children.[119] Levels between 30-50 nM/L (12-20 ng/mL) indicate inadequate intake and the risk of vitamin D deficiency, while levels between 50-125 nM/L (20-50 ng/mL) are considered adequate for bone metabolism and overall health in adults. Levels above 150 nM/L (>50 ng/mL) may be harmful. However, several leading American vitamin D experts consider these limits to be low and believe that serum vitamin D levels around 40-60 nM/L (ideally 100 ng/mL) are sufficient and levels above 200-250 ng/mL are toxic, as the poisonous effect of vitamin D, manifested as hypercalcemia, is not observed until the level of 25-hydroxyvitamin D reaches 375 nM/L (150 ng/mL).[118]

According to a meta-analysis study in 2021, the prevalence of vitamin D deficiency in Saudi Arabia was high. The study analyzed 64 articles published between 2008 and 2020 which included 67, 262 participants. The overall prevalence of vitamin D deficiency was 56.6%, with a higher prevalence among females (67.7%) than males (44.7%). The study also found that vitamin D deficiency was more common among older adults, those with low socioeconomic status, and those with chronic illnesses such as diabetes and hypertension.[120] The findings of this meta-analysis suggested that vitamin D deficiency is a significant health concern in Saudi Arabia, and efforts should be made to raise awareness about the importance of vitamin D and to promote strategies to prevent and treat deficiency. This can include promoting sunlight exposure, increasing the consumption of vitamin D-rich foods, and considering vitamin D supplementation for those at high risk of deficiency. In addition, according to a study by Aljabri et al., 2020,[121] 73.3% of Saudi Arabian adolescents aged 12-18 years were found to have a deficiency in vitamin D. The research also revealed that deficiency in vitamin D was more common in females and individuals with a lower body mass index. There are needs to generate more data on the comparison of vitamin D levels among the population of Saudi Arabia's regions. However, some studies suggested that the prevalence of vitamin D deficiency is high in the country, with varying rates across different areas. For example, a survey conducted in 2017 found that the prevalence of vitamin D deficiency among

adult males in Riyadh, the capital city of Saudi Arabia, was around 70%.[122] Another study conducted in 2016 found that the prevalence of vitamin D deficiency among pregnant women in the Eastern Province of Saudi Arabia was around 80%.[123] Overall, the prevalence of vitamin D deficiency in Saudi Arabia is believed to be higher among females, older adults, and those with limited sun exposure due to cultural practices and clothing norms.[124] It is important to note that these studies have limitations, including small sample sizes and regional variations in data collection and analysis. More comprehensive studies are needed to provide a clearer understanding of vitamin D levels among the population of Saudi Arabia's regions.

6- Relationship between Vitamin D and Allergic Diseases

Vitamin D has been found to play a significant role in the development and progression of allergic diseases. Several studies have shown that vitamin D acts as an immune modulator and helps reduce allergy symptoms[125]. It is believed that vitamin D helps regulate the immune system's response to allergens, and deficiency of vitamin D can lead to an increased risk of developing allergic conditions such as asthma, allergic rhinitis, eczema, and food allergies. Vitamin D acts as an immune modulator in allergies and reduces allergy symptoms. According to Huang et al., 2019,[126] there is a relationship between vitamin D and allergic conditions such as asthma, allergic rhinitis, eczema, and food allergy. However, the association between vitamin D levels and sensitivity is weak. According to Di and Chen, 2021,[127] vitamin D helps to maintain the intestinal mucosal barrier and prevents exposure to food allergens. Mirzakhani et al., 2015,[128] highlighted the importance of vitamin D in the development of allergic diseases, and deficiency can cause skin aging, itching, darkening, and pigmentation. Two studies, Reinholz et al., 2012,[129] and Martineau et al., 2017,[130] emphasized the significant role of vitamin D in regulating the functions of both innate and adaptive immunity, which can worsen allergic diseases.

According to Özdemir, 2016,[131] consuming vitamin D can decrease the likelihood and intensity of asthma, allergic rhinitis, and atopic dermatitis. Lipińska et al., 2021,[132] reported that vitamin D levels in children with allergies were lower than in those without allergies. A study conducted by Mehmet et al., 2014,[133] found that insufficient vitamin D increases the likelihood of developing asthma and allergic rhinitis. A study by Sikorska et al., 2020,[134] uncovered that taking vitamin D supplements during pregnancy can safeguard against asthma in children until the age of six. While these supplements may not entirely prevent asthma, they offer other advantages, including lessening jaundice in newborns with a family history of allergies. Research has shown that low levels of vitamin D in pregnant women may increase the risk of their children developing food allergies, as highlighted by the study conducted by Woon et al., 2020.[135] This highlights the importance of maintaining adequate vitamin D levels during pregnancy to promote optimal health outcomes for the child.

7- Vitamin D and autoimmune diseases

Vitamin D has been shown to regulate immune function and suppress the development of autoimmune diseases. Several studies have shown that vitamin D protects against autoimmune diseases. For example, in a study of patients with systemic lupus erythematosus, vitamin D supplementation reduced disease activity and improved quality of life.[136] Another study showed that vitamin D supplementation reduced the risk of developing multiple sclerosis in women.[137] Furthermore, a systematic review and meta-analysis of 25 randomized controlled trials found that vitamin D supplementation reduced the risk of developing multiple sclerosis.[138]

Székely and Pataki, 2012,[139] reported that vitamin D is involved in preventing certain pathological immune responses that can lead to autoimmune disorders such as type 1 diabetes, colitis, multiple sclerosis, rheumatoid arthritis, and graft rejection. Vitamin D deficiency is associated with an increased risk of rheumatoid arthritis.[140] Vitamin D has been shown to regulate the immune system and inhibit the

production of pro-inflammatory cytokines, which may contribute to rheumatoid arthritis.[141] In addition, vitamin D supplementation has been shown to reduce disease activity and improve symptoms in patients with rheumatoid arthritis.[142] Immune diseases that depend on Th1 cells by inhibiting antigen presentation, then polarizing Th0 cells to Th1 cells and reducing cytokine production, and the presence of an appropriate amount of vitamin D in the body may lead to the prevention and protection of autoimmune diseases. Dupuis et al., 2021,[143] mentioned that women are more affected by autoimmune diseases than men, as researchers have found that gender differences in immunity, sex hormones (such as estrogen) that enhance vitamin D function, and environmental triggers, may play a role in developing these conditions and increase risks for women. Antico et al., 2012,[144] showed indications for the relationship between vitamin D deficiency and autoimmune aggression in all autoimmune diseases, including rheumatoid arthritis, lupus erythematosus, and scleroderma, which confirms that vitamin D can attack oneself. According to Bellan et al., 2020,[145] insufficient vitamin D levels may increase infection rates. Lupus erythematosus is a chronic disease that can cause many symptoms, including bone damage and poor kidney function. It is important to take vitamin D supplements to prevent and treat this condition. Kostoglou et al., 2019,[146] stated that vitamin D deficiency is linked to the development of autoimmune diseases. It may be strongly associated with rheumatoid arthritis, an autoimmune condition. The immune system may attack healthy tissues in the joints, thus causing joint swelling. Moreover, Yang et al., 2013,[147] found that multiple sclerosis is also an autoimmune disease. There is a correlation between vitamin D and multiple sclerosis, particularly when environmental factors such as inadequate sunlight exposure during the winter are considered risk factors for the disease.

8-Vitamin D Deficiency and Its Role in Infectious Diseases

Vitamin D has been shown to modulate both innate and adaptive immune responses, including the production of antimicrobial peptides, cytokines, and chemokines. These immune-modulating effects of vitamin D are mediated by the vitamin D receptors, which are expressed on immune cells such as macrophages, dendritic cells, and T cells.[97] Several studies have suggested that vitamin D deficiency may increase the risk of developing infectious diseases, including respiratory infections, tuberculosis, sepsis, and human immunodeficiency virus (HIV).[148,149] For example, a meta-analysis of randomized controlled trials found that vitamin D supplementation reduced the risk of acute respiratory infections in individuals who were vitamin D deficient.[101] Similarly, a study of tuberculosis patients found that vitamin D supplementation improved the clinical outcome of the disease.[150]

Furthermore, vitamin D deficiency has been associated with increased mortality in critically ill patients with sepsis.[151] Additionally, low vitamin D levels have been linked to an increased risk of mother-to-child transmission of HIV.[152] The mechanisms by which vitamin D deficiency may increase the risk of infectious diseases are not fully understood. However, vitamin D may enhance the innate immune response by stimulating the production of antimicrobial peptides such as cathelicidin and defensins. Additionally, vitamin D may modulate the adaptive immune response by promoting the differentiation of regulatory T cells and inhibiting the production of pro-inflammatory cytokines.[153] Rehan et al., 2019,[154] mentioned that vitamin D plays a vital role in preventing and treating infection-related diseases. It is an important source for treating many infectious diseases, as it is good at avoiding infection and other than that, it is inexpensive.

9-Impact of Vitamin D on Chronic Obstructive Pulmonary Disease (COPD)

According to various studies, vitamin D deficiency is prevalent in individuals with COPD, a serious lung disease that makes breathing difficult. Janssens et al., 2013,[155] found that taking calcium and vitamin D supplements may prevent the deterioration of lung function in COPD patients. Zhu et al., 2016,[156] conducted a

systematic review and meta-analysis to investigate the association between vitamin D deficiency and COPD risk. Their study included 14 observational studies with a total of 24,194 participants. The results showed that vitamin D deficiency was significantly associated with an increased risk of developing COPD (odds ratio: 1.61, 95% confidence interval: 1.33-1.95). Janssens et al., 2010,[157] suggested that reduced exposure to sunlight may be linked to decreased serum vitamin D levels, which could contribute to the development and progression of various chronic diseases, including respiratory disorders such as COPD. Kokturk et al., 2018,[158] conducted a study on the effect of vitamin D supplementation on patients with COPD. The study found that a combination of a nutritious diet, physical activity, and vitamin D supplementation reduced the risk of vitamin D deficiency and improved lung function in COPD patients. The authors suggested that this may provide a potential treatment option for COPD.[159,160]

Additionally, Saleem et al., 2021,[161] conducted a systematic review and meta-analysis of observational studies and found that low vitamin D levels were associated with an increased risk of developing COPD; the study recommended that increasing vitamin D levels may be a potential strategy for reducing the risk of developing COPD. COPD is the third leading cause of death globally. Vitamin D deficiency is prevalent in 40-80% of COPD patients, associated with the severity and exacerbation of the disease.[153] Janssens et al., 2012,[162] reported that both COPD and vitamin D are affected by pathophysiology, leading to a negative relationship between vitamin D and respiratory disease. Lokesh et al., 2021,[163] suggested that people with COPD may experience bone weakening and bone loss due to a shortage of vitamin D. They recommend taking vitamin D supplements as a preventative measure.

In a recent study, Lokesh et al., 2021,[163] determined that COPD patients with low vitamin D levels tend to have worse lung function and experience more severe anxiety and depression. Additionally, Hughes and Norton, 2009,[164] highlighted the importance of vitamin D in the mechanism of COPD, including its impact on lung tissue remodeling, pulmonary fibrosis, and airway inflammation, all of which can lead to lung function obstruction. A lack of outdoor activity is one possible reason for vitamin D deficiency in people with COPD.

Conclusions

Vitamin D was once believed to only affect infant bone growth and maintain bone structure in older people. However, recent studies have revealed other key effects of vitamin D on the body, such as suppressing autoimmune reactions and allergies that damage tissues, promoting the production of antimicrobial peptides to protect against infectious diseases, and inhibiting cancer growth in various organs. This review focused on the effects and mechanisms of vitamin D in preventing pathological immune reactions and autoimmune diseases, such as diabetes, colitis, and asthma.

The impact of vitamin D on infectious diseases and cancer is well-established, and numerous studies have shown that adequate levels of vitamin D can lower the risk of respiratory infections and reduce the severity of the symptoms. Additionally, several studies reported that individuals with higher levels of vitamin D have a lower risk of developing certain types of cancer, such as colon and breast cancer.

Epidemiological studies have shown that roughly half the population in various countries and continents suffer from vitamin D deficiency. Still, most cases go unnoticed due to a lack of symptoms and inadequate attention from healthcare providers. Even subclinical vitamin D deficiency can contribute to developing immune disorders and increase susceptibility to various diseases. In Saudi Arabia, where the hot climate leads to widespread of indoor living, vitamin D deficiency is particularly prevalent, and addressing it is crucial to population health.

Overall, it is important to recognize the medical significance of vitamin D and take steps to ensure adequate levels in the body for maintaining good health. To address this issue, healthcare providers should conduct tests for vitamin D content in the blood, develop ultraviolet radiation equipment and test new,

advanced vitamin D drugs for oral and dermal application. New technologies are also recommended to create epidemiological, clinical, and experimental study programs. It is also important to raise awareness about the importance of vitamin D in maintaining overall health and the potential consequences of deficiency. Moreover, supplementing with vitamin D through food sources and supplements and spending time in sunlight are ways to maintain a healthy vitamin D level.

Author Contributions

MA and HH were responsible for conceiving and designing the study, as well as creating the figure that beautifully enhanced the article. HH contributed to data collection. MA and NE participated in the data collection process. The manuscript was drafted by MA, HH, and NE, who also conducted a thorough review of the references. All authors had the opportunity to review the data and provided valuable feedback to shape the final version of the manuscript. The authors are in agreement with the content of this article and have approved its publication.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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