Republic of Iraq

And Scientific Research

Al-Hilla University College

Department of Medical Physics

((Relation ship between vitamin D deficiency and vheumatioid arthritis))

Research submitted to the Council of Al-Hilla University cooege

It is part of the requirements for obtaining a Bachelor's degree in Medical Physics

Submitted by

Mohammed Haider Jaber

Ali Hussein Kazem

Saif Abdul Hassan Abbas

Zainab Musa Kazem

Zahraa Raad Fadl

Dunia Ahmed Odeh

Supervised by

Dr. Ahmed Salam Abood

2024 1445

((وَعَلَّمَكَ مَا لَمْ تَكُنْ تَعْلَمُ ۚ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا))

صدق الله العلي العظيم

سورة النساء - الآية ١١٣

Dedication

Praise be to God, who fills the heavens and the earth and all that is between them. We thank Him, Glory be to Him, the Most High, for granting us the blessing of reason, hope, and patience, and prayers and peace be upon the most .honorable messengers and after him

With all love, I dedicate my graduation thesis to those whom the Most Merciful said, and I hold for them the wing of humility out of mercy and say, “My Lord, have mercy on them as they raised me when I was young

To the one whom God placed Paradise under her feet, to the one who carried me while they were weak, and the one who struggled for me to reach this day, and whose heart embraced me before her hand, and made adversity easy for me with her prayers, to the compassionate heart and the secret of my strength and success, my paradise my mother

To the one who decorated my name with the most beautiful titles and who supported me without limits and gave me something in return. To the one who taught me that the world is a struggle whose weapon is knowledge and knowledge. My first supporter in my path and my support, my strength and my refuge after God. My pride and pride: My father

To all those who provided me with strength and guidance, believed in me, and .supported me to reach where I am now. To every brother and sister

Finally, whoever said, “I am hers,” he “gets her,” and I am hers. If she refuses against her will, I bring her, and I would not have done this if it were not for God’s grace

.

Thanks and gratitude

قال تعالى (وَمَن يَشۡكُرۡ فَإِنَّمَا يَشۡكُرُ لِنَفۡسِهِۦۖ)

{لقمان :12 }

وقال رسوله الكريم (ص)

(من لم يشكر الناس؛ لم يشكر الله عز وجل)

Successes have people who appreciate their meaning, and creativity has people who reap it. Therefore, we appreciate your strenuous efforts. You are deserving of gratitude and appreciation. We must appreciate you, and you have all our praise and appreciation. I especially mention our honorable supervisor professor, Dr. Ahmed Salam Abboud, for the time and effort he spent with us.

We also extend our sincerest expressions of thanks and gratitude to the Deanship of Hilla University College and to the Department of Medical Physics. You have all our thanks and appreciation

Abstract

Vitamin D plays an important role in maintaining a healthy mineralized skeleton. It is also considered an immunomodulatory agent that regulates innate and adaptive immune systems. The aim of this narrative review is to provide general concepts of vitamin D for the skeletal and immune health, and to summarize the mechanistic, epidemiological, and clinical evidence on the relationship between vitamin D and rheumatic diseases. Multiple observational studies have demonstrated the association between a low level of serum 25-hydroxyvitamin D [25(OH)D] and the presence and severity of several rheumatic diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), spondyloarthropathies, and osteoarthritis (OA). Nevertheless, the specific benefits of vitamin D supplements for the treatment and prevention of rheumatic diseases are less accepted as the results from randomized clinical trials are inconsistent, although some conceivable benefits of vitamin D for the improvement of disease activity of RA, SLE, and OA have been demonstrated in meta-analyses. It is also possible that some individuals might benefit from vitamin D differently than others, as inter-individual difference in responsiveness to vitamin D supplementation has been observed in genomic studies.Althoughtheoptimallevelfserum25(OH)Disstill debatable,it is advisable it is advisable thatp atients with rheumatic diseases should maintain aserum 25(OH)D level of at least 30 ng/mL (75 nmol/L) to prevent osteomalacia, secondary osteoporosis, and fracture, and possibly 40–60 ng/mL (100–150 nmol/L) to achieve maximal benefit from vitamin D for immune health and overall health

1 Introduction

Vitamin D is a steroid hormone responsible for the regulation of calcium and phosphate metabolism and for maintaining a healthy mineralized skeleton [1,2,3]. In addition, it is known to exert various non-skeletal actions due to the presence of the vitamin D receptor (VDR) in most tissues, including the skin, adipose tissue, skeletal muscle, endocrine pancreas, immune cells, breast, blood vessels, and brain [1,2,4].

Rheumatic diseases are a spectrum of autoimmune and/or inflammatory diseases that cause damage to joints, muscles, and bones, as well as vital organs such as the lungs, heart, kidneys, and nervous system. In rheumatology, vitamin D supplementation is recommended to prevent glucocorticoid-induced osteoporosis and to reduce the risk of fracture in patients with osteoporosis [5]. It is proposed that the improvement of vitamin D status may help protect against the development and severity of rheumatic diseases, given the specific actions of vitamin D on the skeletal and immune systems [2,6,7]. The purpose of this review is to provide general concepts of vitamin D for the skeletal and immune health, and to summarize the mechanistic, epidemiological, and clinical evidence on the relationship between vitamin D and several types of rheumatic diseases, including rheumatoid arthritis **(**RA), systemic lupus erythematous (SLE) sp0ndyioarthropathyies (Spa), gout and hyperuricemia osteoarthritis (OA) and other

2 Physiology of Vitamin D

Humans gets vitamin D from dietary consumption, supplements, and endogenous synthesis in the skin. The two major forms of vitamin D are vitamin D2 and vitamin D3.

Vitamin D2, synthesized from ergosterol, can be found in ultraviolet irradiated and sundried mushrooms and yeasts. As shown in Figure 1, vitamin D3, synthesized from 7-dehydrocholesterol, can be found in animal products such as cod liver oil and oily fish, and is synthesized endogenously in the skin [1–3]. After entering circulation, vitamin D (D2 and D3) is metabolized in the liver by the enzyme vitamin D-25-hydroxylase (CYP2R1) to 25-hydroxyvitamin D [25(OH)D], which is the major circulating form of vitamin D that is clinically measured to reflect vitamin D status [1,2,8]. Circulating 25(OH)D is then further metabolized by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to 1,25-dihydroxyvitamin D [1,25(OH)2D], the biologically active form. 1,25(OH)2D exerts its functions in the target tissue by binding to the vitamin D receptor (VDR) in the nucleus, where it triggers the up- or down-regulation of multitudes of genes in multiple types of tissues including renal tubular cells, intestinal epithelium, parathyroid glands, bone cells, and immune cells [1–3,8]. Those include genes involved in calcium and phosphate metabolism, and genes associated with risks of certain autoimmune diseases [1,9,10].

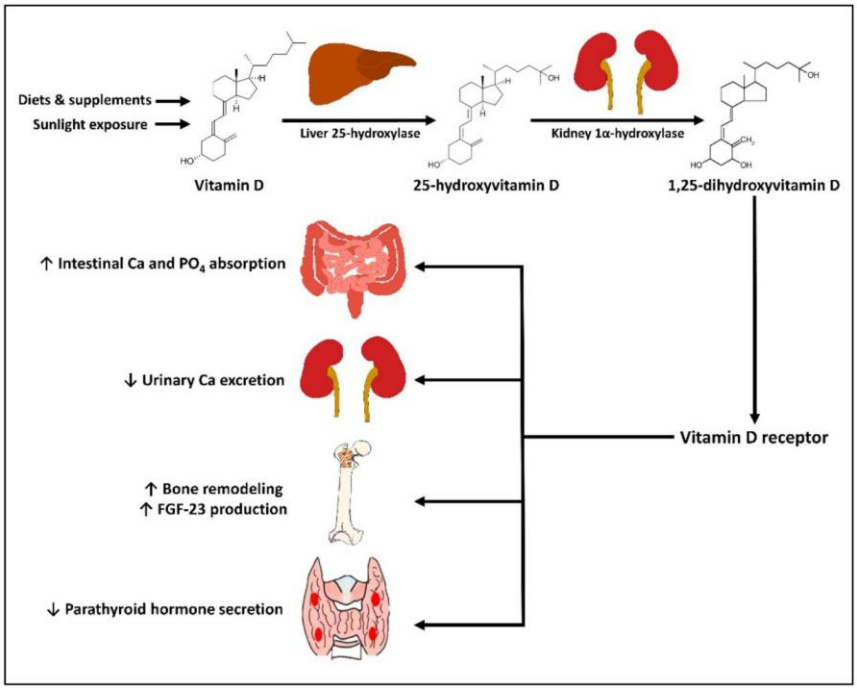

Figure 1. Schematic representation of the synthesis, sources, and metabolism of vitamin D for skeletal function. ↑: Increased; ↓: Decreased; CA: Calcium; FGF-23: fibroblast growth factor-23; PO_4: phosphate.

The main site of conversion of 25(OH)D into the systemically bioavailable 1,25(OH)2D is the kidneys, where CYP27B1 is expressed and regulated by parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23) [11]. CYP27B1 expressed by many other tissues (e.g., immune cells, parathyroid glands, microglia, breast, colon, and keratinocytes) can also convert 25(OH)D into $1,25(OH)_2D$, resulting in intracranial and paracrine signaling, without being regulated by PTH or FGF-23 [12]. Both 25(OH)D and $1,25(OH)_2D$ are metabolized by the enzyme 24-hydroxylase (CYP24A1), expressed mainly by the intestine, bone, and kidneys into inactive water-soluble carboxylic acids, which are then excreted in the bile [13].

3. General Concepts of Vitamin D for Skeletal and Immune Health

3.1. Effects of Vitamin D on Bone and Mineral Metabolism

Vitamin D exerts its effects on bone and mineral metabolism mainly by altering the expressions of several genes in the small intestine, kidneys, parathyroid glands, and bone [2,3]. Activation of VDR by $1,25(OH)_2D$ promotes intestinal calcium and phosphate absorption and renal tubular calcium reabsorption, which help maintain an adequate calcium−phosphate product that crystallizes in the collagen matrix in the bone. $1,25(OH)_2D$ also has direct effects on the bone by stimulating the receptor activator of nuclear factor kappa-B-dependent bone desorption and inducing the expression of 0steocalcin, the major non-collagenous protein in the skeleton [14,15,16]. Furthermore, $1,25(OH)_2D$ directly inhibits PTH production, leading to decreased bone resumption and induces FGF-23 production by the osteocytes, leading to increased urinary phosphate excretion [11,17,18].

The pathophysiology of vitamin D deficiency causing rickets, 0steomalacia, and osteoporosis is mainly mediated by secondary hyperparathyroidism (Figure 2) [1,19]. A low level of serum 25(OH)D results in inadequate intestinal calcium absorption, which, in turn, leads to a transient decrease in serum ionized calcium. This subsequently results in secondary hyperparathyroidism, causing increased bone resumption, which precipitates osteoporosis. Secondary hyperparathyroidism also causes increased urinary phosphate excretion leading to an inadequate calcium-phosphate product, thereby precipitating rickets in children and 0steomalacia in adults [1,19]

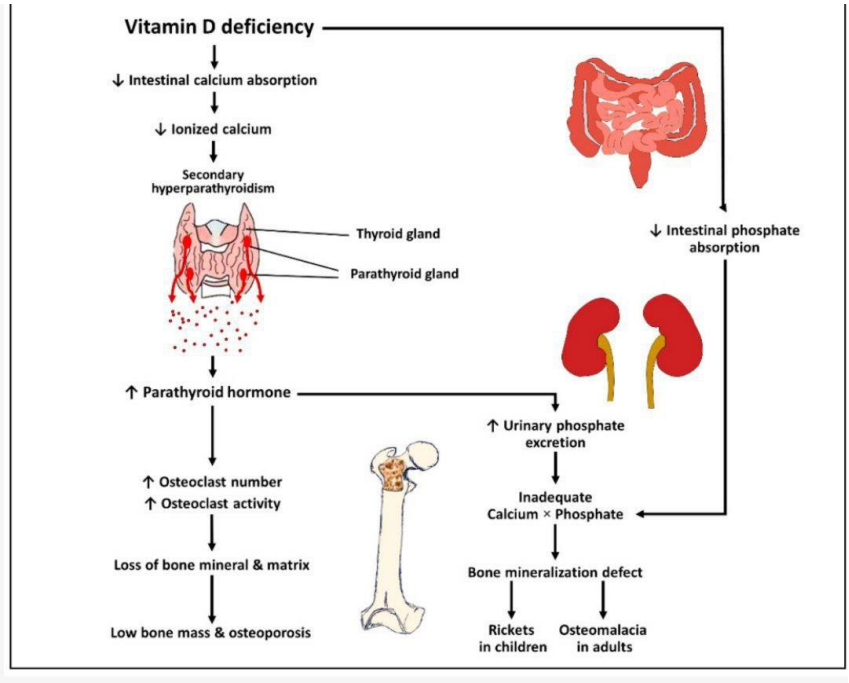

Figure 2. Schematic representation of the pathophysiology of vitamin D deficiency causing rickets, 0steomalacia, and osteoporosis. ↑: Increased; ↓: Decreased.

A low level of serum 25-hydroxyvitamin D causes a significant decrease in the intestinal absorption of calcium and phosphate. This leads to a transient decrease in the serum concentration of ionized calcium and subsequent secondary hyperparathyroidism. Elevated parathyroid hormone induces the differentiation of Preosteoclast into mature osteoclast, thereby leading to an increased osteoclast number and activity. This causes increased bone resumption, loss of bone mineral and matrix, and subsequent low bone mass and osteoporosis. Furthermore, parathyroid hormone exhibits a phosphaturic effect, resulting in an increase in urinary phosphate excretion. Urinary phosphate loss along with decreased intestinal phosphate absorption due to vitamin D deficiency contributes to an inadequate calcium−phosphate product, thereby leading to bone mineralization defects and the development of rickets and osteomaiacia.

3.2. Effects of Vitamin D on the Immune System

Vitamin D is known not only for its functions in maintaining calcium and phosphate homeostasis, but also for its immunomodulatory effects on several components of the innate and adaptive immune systems [6,20]. Evidence on the effects of VDR activation on the proliferation, differentiation, and function of each immune cell type is to be reviewed in this section, which is summarized in.

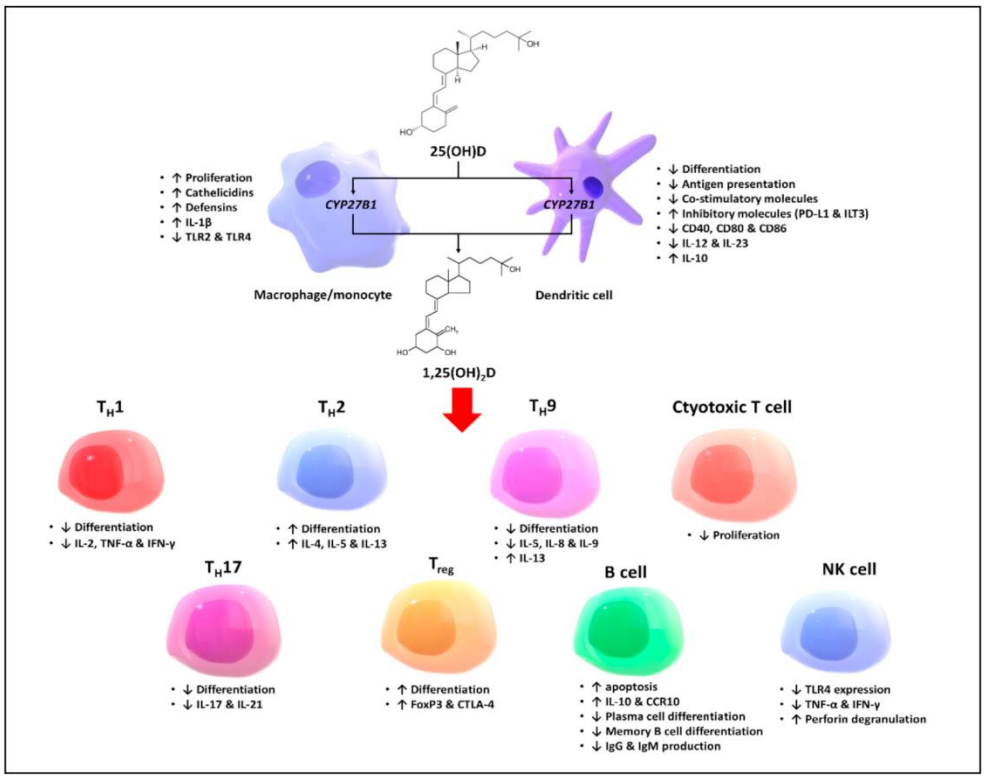

Figure 3.

: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D. macrophage proliferation and the production of the proinflammatory cytokine interleukin Effects of vitamin D on different cell types of the innate and adaptive immune systems. ↑: Increased; ↓: Decreased; $1,25(OH)_2D$

Activated macrophages and monocytes, induced by exposure to inflammatory cytokines (e.g., IFN-Y) and toll-like receptor signaling,

an autocrine and paracrine fashion to regulate the innate and adaptive immune systems [21]. It has been shown that $1,25(OH)_2D$ stimulates macrophage proliferation and the production of the proinflammatory cytokine interleukin-1β, as well as endogenous antimicrobial peptides, cathelicidins, and defensins [22,23]. In the presence of granulomatous inflammation (e.g., TB, sarcoidosis, fungal infections and some lymphomas), an excessive amount of $1,25(OH)_2D$ can be produced by the macrophages, causing unregulated increased $1,25(OH)_2D$ in the systemic circulation, which results in hypercalcemia and hypercalciuria [24].

$1,25(OH)_2D$ regulates the functions and differentiation of antigen-presenting cells (APCs) by decreasing the antigen presentation and increasing the expression of inhibitory molecules on the cell surface, causing the APCs to become tolerogenic and more immature [25,26,27]. It does so by decreasing the expression of MHC class II and co-stimulatory molecules, inhibiting the production of IL-12 and IL-23, and stimulating the production of IL-10, a tolerogenic cytokine [25,28,29]. $1,25(OH)_2D$, in addition, is shown to downregulate the expression of toll-like receptors on the monocytes and inhibit the production of proinflammatory cytokines (i.e., IL-2, IL-6, and IL-17) [6,20,30].

$1,25(OH)_2D$ is known to modulate the adaptive immune system by activating the VDR expressed by the APCs and activated T and B lymphocytes, which, in general, results in a shift of immune status from a proinflammatory to tolerogenic state. $1,25(OH)_2D$ inhibits the proliferation of T lymphocytes and regulates cytokine production and differentiation with various effects on different subgroups of T lymphocytes. It promotes a shift from T helper 1 (T_H1), T helper 9 (T_H9), and T helper 17 (T_H17) immune profiles to the T helper 2 (T_H2)

immune profile, and facilitates the differentiation of regulatory T cells (T_{reg}) [31,32,33]. Although little is known about the direct effect of $1,25(OH)_2D$ on the cytotoxic lymphocytes, it is believed that $1,25(OH)_2D$ may suppress the proliferation of cytotoxic lymphocytes based on the observation that the oral administration of high-dose vitamin D_3 is associated with an increase in the CD4/CD8 ratio [34,35].

Besides its effects on the T lymphocytes, $1,25(OH)_2D$ has been shown to have a negative effect on antibody production by the B lymphocytes when in a hyperactive state via multiple mechanisms. It induces the apoptosis of activated B cells and plasma cells, thereby inhibiting plasma cell formation [36,37]. Furthermore, $1,25(OH)_2D$ directly promotes the production of anti-inflammatory cytokines, such as interleukin-10 and CCR10, and inhibits the differentiation from mature B cells to memory B cells and plasma cells [38,39,40]. It is therefore believed that, by dampening antibody production, $1,25(OH)_2D$ may benefit by reducing the risk and severity for autoantibody-mediated autoimmune disorders such as SLE and type 1 diabetes [41,42].

It is important to note that supplementation of vitamin D or raising serum 25(OH)D is not equivalent to activating the VDR in the immune cells, as circulating $1,25(OH)_2D$ is regulated by PTH and FGF-23, and patients with low levels of 25(OH)D may have normal or even a high level of circulating $1,25(OH)_2D$ due to secondary hyperparathyroidism [11,43]. However, it is reasonable to postulate that circulating 25(OH)D may be converted into $1,25(OH)_2D$ by the enzyme CYP27B1 expressed by the immune cells, where it triggers intracrine and paracrine signaling, as clinical studies have demonstrated changes in immune

profiles in response to vitamin D supplementation similar to what is expected from treating the immune cells with 1,25$(OH)_2$D in vitro [44,45].

Equally important is the concept of individual responsiveness to vitamin D supplementation, as studies have demonstrated a high inter-individual difference in the genome-wide expression in human peripheral blood mononuclear cells following vitamin D supplementation. In a recent clinical trial by Shirvani et al. [46], approximately 60% of healthy adults with a vitamin D deficiency or insufficiency (25(OH)D < 30 ng/mL or 75 nmol/L) who received 10,000 IUs per day of vitamin D_3 for 6 months had a robust response in their genome-wide expression compared with the other 40% who had mild to moderate responses, although all subjects increased their serum concentrations of 25(OH)D to the same range of 60–90 ng/mL (150–225 nmol/L). Moreover, they observed that subjects with a robust genomic response to vitamin D supplementation exhibited different patterns of serum metabolomic profiles compared with those with lower degree of responsiveness [47]. This observation is in line with that of the prior study by Carlberg et al. [48], showing robust changes in broad gene expression in about half of the 71 patients with prediabetes who were given 3200 IUs of vitamin D_3 daily for 5 months. Therefore, it is reasonable to postulate that vitamin D may affect the immune system differently among individuals, which is hypothesized to be due to inter-individual differences in genetic polymorphisms associated with vitamin D metabolism and signaling pathway (e.g., genes encoding VDR, vitamin D binding protein (DBP), and VDR responsive element in the target genes), as well as some undisclosed epigenetic factors [6]**.**

3.3. Defining Optimal Serum 25-hydroxyvitamin D

mortality, cardiovascular disease, falls, and some cancers) at levels higher than It is still controversial as to what concentration of serum 25(OH)D would provide optimal benefits for bone health and overall health. A serum 25(OH)D concentration of 15 to 20 ng/mL (37.5–50 nmol/L) is considered sufficient for the prevention of rickets and osteomalacia [19]. It is, however, recommended by the Endocrine Society's Clinical Practice Guideline that serum 25(OH)D concentration should be above 30 ng/mL (75 nmol/L) to maximize the calcemic effects of vitamin D and to minimize the risk of secondary hyperparathyroidism that predisposes for osteoporosis [8]. According to this guideline, vitamin D deficiency and insufficiency are defined as a serum 25(OH)D level of <20 ng/mL (<50 nmol/L) and 20 ≤ 30 ng/mL (50 ≤ 75 nmol/L), respectively [8]. On the other hand, the Institute of Medicine (IOM) concluded that a serum 25(OH)D level of 20 ng/mL is the level necessary for good bone health for practically all individuals [49]. It is also worth acknowledging the historical evidence to postulate vitamin D status in our hunter-gatherer ancestors. It has been reported that indigenous populations in East Africa have serum 25(OH)D in the range of 40–60 ng/mL (100–150 nmol/L) [50]. This range is consistent with that reported in populational-based studies, which is associated with the lowest risk of chronic diseases and all-cause mortality [51]. However, some studies suggest that there may be a U-shaped relationship between 25(OH)D and some adverse outcomes (e.g50 ng/mL (125 nmol/L) [52,53].

3.4. Recommended Vitamin D Intake

It is recommended by the Institute of Medicine that children aged≥1 year old and adults should ingest at least 600 IUs of vitamin D per day to achieve a serum 25(OH)D level of at

least 20 ng/mL (50 nmol/L) [49]. The Endocrine Society Clinical Practice Guideline on vitamin D, however, recommends a higher dose of daily vitamin D intake in order to achieve a level of serum 25(OH)D of at least 30 ng/mL (children aged 0–1 year: 400–1000 IUs, upper limit 2000 IUs; children aged 1–18 years: 600–1000 IUs, upper limit 4000 IUs; adults aged >18 years 1500–2000 IUs, upper limit 10,000 IUs) [8]. Some experts also suggest that adults should be on 4000–6000 IUs to maintain a serum 25(OH)D level in the preferred range of 40–60 ng/mL (100–150 nmol/L) [54]. Notably, patients with obesity and intestinal malabsorption require a two to three times higher amount of vitamin D to maintain the same serum 25(OH)D concentrations [8]. In addition, patients who receive chronic glucocorticoid therapy need two to three increased doses of vitamin D intake as glucocorticoids can cause increased catabolism of both 25(OH)D and 1,25(OH)2D [8].

3.5. Vitamin D from Sunlight Exposure and Diets

Humans get vitamin D from sunlight exposure, diet, and supplements. The amount of vitamin D synthesized by the skin is known to be dependent on the intensity and duration of exposure to ultraviolet B radiation at wavelength of 290–315 nm and skin pigmentation. It is estimated that sunlight exposure 1/4 of a minimal erythemal dose (MED) over 1/4 of the body surface area is equivalent to ingestion of oral 1000 IUs of vitamin D3 [55]. People living in high-latitude regions are more susceptible to vitamin D deficiency, especially in the wintertime, because of the oblique zenith angle of the sun. It is documented that when living above or below 33◦ latitude, little or no vitamin D can be produced in the skin during the winter. During the summertime or near the equator, vitamin D can be synthesized effectively only during 10:00 a.m.–15:00 p.m. [1,56]. Given the limited availability of vitamin D from

sunlight exposure, many people rely on oral vitamin D intake to achieve vitamin D sufficiency. It should be noted that only few foods naturally contain vitamin D. These include oily fish (up to 1000 IUs of D3/3.5oz), cod liver oil (up to 1000 IUs of D3/tsp), sun-dried or ultraviolet-irradiated mushrooms (up to 1000 IUs of D2/3.5oz), egg yolk (20 IUs of D2 or D3), and meat (variable amount in the form of D3 and 25(OH)D3). Fortified milk, yogurt, and orange juice in the US contains 100 IUs of vitamin D2 or D3 per serving (8 oz) [1,2]. Taken together, with minimal sunlight exposure, it is difficult to achieve adequate vitamin D intake solely from foods, and, therefore, many individuals may require vitamin D supplementation to prevent vitamin D deficiency and insufficiency

3.6. Screening for Vitamin D Status

The Endocrine Society Clinical Practice Guideline on vitamin D recommends that screening for vitamin D deficiency should be performed in individuals who are at risk for vitamin D deficiency, such as older adults with a history of falls or fractures; patients with chronic illnesses, obesity, and intestinal malabsorption; or individuals taking medications that interfere vitamin D metabolism (e.g., glucocorticoids, antiepileptics, antiretrovirals, and antifungals) [8]. Nonetheless, the US Preventive Services Task Force reported that evidence on the benefits of screening for vitamin D deficiency in the general population is still lacking [57]. It is, however, advisable that patients with chronic inflammatory disorderswithorwithoutcorticosteroidtherapyshouldbescreenedandtreatedforvitamin D deficiency and supplemented with adequate calcium and vitamin D to prevent further bone resorption on top of chronic inflammation-associated bone loss

4. Evidence on Vitamin D for Prevention and Treatment of Rheumatic Diseases

Multitudes of observational studies have demonstrated the association of low level of 25(OH)D with the presence and severity of several rheumatic diseases. However, the benefits of vitamin D supplementation for the prevention and treatment of these diseases tends to be is less accepted, as the association can be explained in part by confounders such as limited physical outdoor activities and sunlight exposure in patients with chronic illnesses. In this section, the relationship between vitamin D and rheumatic diseases and evidence fromclinicalstudiesdemonstratingtheimpactofvitaminDsupplementationarereviewed, which is summarized

4.1. Rheumatoid Arthritis

RA is a chronic inflammatory disease characterized by synovial inflammation causing symmetrical polyarthritis, affecting approximately 4 cases per 10,000 person−years [58]. RA was classically considered a TH1-mediated disease [59]. However, recent studies have suggested that increased TH17 and TH22 activities and dysfunctional Treg also play a role in the pathogenesis of RA [60,61]. Individuals with certain genetic variations of the human leukocyte antigen (HLA) genes are known to be susceptible to RA, while the only wellestablished environmental risk factor of RA is cigarette smoking [62]. Vitamin D is believed to play a role in modulating the pathogenesis and disease activity of RA, based on the actions of 1,25(OH)2D on the adaptive immune response that suppresses the proliferation and activity of TH1 and TH17 and enhances the Treg activity [63]. Furthermore, genomic studies have shown that certain polymorphisms of the gene encoding VDR and DBP are

associated with susceptibility to RA, suggesting that the vitamin D signaling pathway may be involved in the pathogenesis of RA [64,65]. Multiple observational studies have shown the association of vitamin D status or intake with incidence and severity of RA [66]. For example, in a prospective cohort study by Merlino et al., women in the highest tertile of vitamin D intake had a lower risk for RA by 33% compared with those in the lowest tertile [67]. Moreover, a higher amount of ultraviolet B exposure was shown to be associated with a decreased risk of incident RA in the Nurse Health Study cohort of 106,368 women aged 30–55 years old [68]. This finding is in line with the evidence that the risks of some immune-mediated diseases (e.g., type 1 diabetes, multiple sclerosis, and RA) are higher in high-latitude regions where there is a relatively low amount of ultraviolet radiation and a high prevalence of vitamin D deficiency [69,70]. These observations, therefore, support that vitamin D obtained from either oral intake or sunlight exposure could possibly be protective against RA. In the COMOrbidities in Rheumatoid Arthritis (COMORA) study consisting of 1413 patients with RA from 15 countries, the serum level of 25(OH)D was inversely correlated with disease activity, as assessed by the Disease Activity Score-28 (DAS28) after adjusting for potential confounders [71]. Although the observed association between vitamin D status and RA incidence and severity, like in other diseases, could be partly explained by confounders, the results from clinical trials have suggested that giving vitamin D to patients with RA may help mitigate the disease activity. In a meta-analysis of six studies including 438 RA patients, vitamin D supplementation resulted in a significant improvement in the DAS28 (weighted mean difference (WMD)−0.41, 95%CI:−0.59–−0.23), erythrocyte sedimentation rate (WMD−3.40, 95%CI:−6.62–−0.18), and tender joint count (WMD−1.44, 95%CI:−2.74–−0.14), but not inpainvisualanalogscale[72]. Itwasalsoshowninanothermeta-

analysisoftworandom ized studies that vitamin D supplementation resulted in an insignificant reduction in RA flares, defined by a DAS28 of >3.2 (risk difference−0.10, 95% CI:−0.21–0.00), although a high risk of bias was noted in one of the studies due to the open-label design [73,74]. It should, however, be noted that most of the individual studies included in these metaanalyses did not show a statistically significant benefit of vitamin D supplementation. This could be due to difference in patient characteristics, limited statistical power due to small sample size, and possibly the fact that the doses of vitamin D used in some studies were too low.

Inaddition,somestudieshavealsoshownthatgiving1,25(OH)2Dcanalsohelpimprove the outcomes of RA. In an open-labeled randomized clinical trial by Gopinath et al. [75], 59 RA patients who received 1,25(OH)2D3 along with disease-modifying anti-rheumatic drugs (DMARDs) and calcium demonstrated a significantly higher pain relief compared with the 62 patients receiving DMARDs and calcium alone. Another phase II clinical trial by Li et al. [76] gave 22-oxa-1,25(OH)2D3 or 1,25(OH)2D3 or placebo to 369 RA patients, and observed a significant reduction in swollen joints and improved Health Assessment Questionnaire Disease Activity Index scores in the groups receiving two active treatments compared with the placebo group. In summary, there is suggestive observational evidence that increasing vitamin D intake to raise serum 25(OH)D may reduce the risk of developing RA. However, there is no demonstration from a clinical trial that vitamin D supplementation can reduce the risk of incident RA. There is moderate evidence that vitamin D supplement or the oral administration of 1,25(OH)2D can mitigate the disease severity of RA. Further large-scale of randomized clinical trials are required before any form of vitamin D or 1,25(OH)2D can be recommended as an adjunctive treatment for RA inclinicalpractice.

Genome-wide association studies have identified hundreds of autoimmune risk genes, many shared across diseases. The challenge now is to use this genetic road map to better define the pathogenesis of the diseases and develop novel effective therapies and clinically useful biomarkers. The prevalence of many autoimmune diseases increases with distance from the equator in genetically similar populations in many countries. These associations have been attributed to reduced exposure to UV radiation, and consequent Vitamin D (Vit D) deficiency. This is supported by evidence of the importance of Vit D in immunomodulation.

Several recent lines of unrelated investigation provide further strong support for a key role of Vit D in the pathogenesis of autoimmune disorders. Two of the autoimmune-associated genes, *CYP27B1* and *CYP24A1*, control the availability of the ligand for the endogenous Vit D receptor (VDR), 1,25-dihydroxyvitamin D_3 (1,25D3): *CYP27B1* converts the precursor 25D3 to 1,25D3 and *CYP24A1* enhances catabolism of 1,25D3. These genes (*CYP27B1*/*CYP24A1*/*VDR*), singly or collectively, have been identified as risk factors in multiple autoimmune diseases. Second, Vit D supplementation has been found to be of therapeutic benefit in animal models of autoimmune disease, including in autoimmune encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis and systemic lupus erythematosus. Further, at a clinical level, higher serum Vit D levels are associated with reduced risk of autoimmune diseases and the function of regulatory T cells (Tregs) in patients has been shown to be proportional to serum 25D3 levels. As a result of these findings, Vit D has been considered a promising target pathway for therapeutic intervention and clinical trials have commenced (ahead of more detailed knowledge of the microenvironment in which Vit D immunomodActivation of VDR by 1,25D3 results in the liganded receptor binding to a large number of genes (the

VDR cistrome). We propose that a major mechanism by which VDR activation influences autoimmunity is through gene activation in immune cells of myeloid lineage, particularly antigen-presenting dendritic cells (DCs) with consequent activation of tolerizing states in the immune system, especially in DCs. We base this on several observations. VDR activation induces a tolerogenic phenotype in antigen-presenting cells, including DCs. Within immune cells, *CYP27B1* and *CYP24A1* are predominantly expressed in DCs (it seems likely T cells need an exogenous source of 1,25D3 since they have limited *CYP27B1* expression). In mouse models of autoimmune disease treatment with antigen-specific or generic tolerogenic DCs is remarkably successful. This has led to clinical trials in humans, with promising results, especially with autologous DCs. However, a major limitation is that DCs can be quite plastic, so that the choice of manipulation needs to be further informed by experimental data, and reliable quality control measurements of manipulation are needed. Given that the importance of Vit D in inducing and maintaining a tolerogenic DC phenotype is well established, identification of the molecular basis for this may lead to new tools to manipulate and assess DCs.

Although the spectrum of genes regulated by VDR in B cells has been explored, and genes associated with autoimmune diseases are overrepresented in this spectrum, the potential role of VDR in DCs and other myeloid cells has yet to be characterized. For the reasons above, we believe these cells to be priority targets.

In this study we identify the VDR cistrome in myeloid (monocytes, inflammatory and tolerogenic DCs) immune cells and map it against genetic loci identified as risk factors for autoimmune states. We used chromatin immunoprecipitation and next generation sequencing

to identify the VDR-binding sites in monocytes and two types of in vitro differentiated DCs: inflammatory (stimulated with interferon gamma, DC1) and tolerogenic (stimulated with interferon beta, DC2). The phenotypes of these cells were demonstrated in an earlier study. Here we show that there are striking similarities in genomic locations of VDR-binding sites among the myeloid cell subsets, but also many which change dramatically with differentiation state. Differences are also seen in the spectrum of transcription factor (TF) recognition sequences co-located with the VDR peaks. Finally, latitude-dependent autoimmune disease (LAD) risk loci are overrepresented in the genomic vicinity of VDR peaks, pointing to a regulatory architecture that might be exploited for therapeutic purposes.

5.Conclusions

Vitamin D playsanessentialroleinnotonlymaintaininghealthymineralizedskeleton, but also modulating the innate and adaptive immune systems in a way that is thought to benefit as an adjunctive treatment for many immune-mediated diseases. A low level of 25(OH)Disassociatedwiththepresenceandseverityofmost,ifnotall,rheumaticdiseases, such as RA, SLE, SpA, and OA. However, the benefits of vitamin D supplement for thetreatmentandpreventionofthesediseasesarerelativelyunclarified,astheresultsfrom existingclinicaltrialsaremarkedlyinconsistent. Manyofthemaresmallinsamplesizeand likely underpowered; however, when those results were pooled in meta-analyses, there wereconceivablesignalsofthebenefitsofvitaminDfortheimprovementofdiseaseactivity, particularly for RA and SLE. It is also worth noting that, based on recent genomic studies on vitamin D, there might be inter-individual difference in responsiveness to vitamin D supplementation that need further investigations, suggesting that some individuals might be able to benefit from vitamin D more or less than others. Regardless of the evidence on the disease-specific benefits of vitamin D, it is advisable that patients with rheumatic disease with or without corticosteroid therapy should have sensible sunlight exposure and adequate vitamin D intake to maintain serum 25(OH)D level at least 30 ng/mL (75 nmol/L) in order to prevent osteomalacia, secondary osteoporosis, and fracture, and possibly 40–60 ng/mL (100–150 nmol/L) to achieve the maximal benefit from vitamin D

Recommendations

1- Serial measurement of Omentin-1, Fractalkine, and Migration inhibitory Factor should be done during and after a period of treatment with insulin sensitizing agent.

2- There should be an extended study of adipocytokines measurement in obesity and in related to cardiovascular disease.

3- Further studies on vitamin D, related with insulin resistance and the effect of vitamin D supplements on improving insulin sensitivity.

4-Study of arthritis patients for its differentials

Reference

1. Charoenngam,N.;Shirvani,A.;Holick,M.F.VitaminDforskeletalandnon-skeletalhealth: Whatweshouldknow. J.Clin. Orthop. Trauma 2019, 10, 1082–1093. [CrossRef]
2. Holick, M.F. Vitamin D Deficiency. N. Engl. J. Med. 2007, 357, 266–281. [CrossRef]
3. Nair, R.; Maseeh, A. Vitamin D: The “sunshine” vitamin. J. Pharmacol. Pharmacother. 2012, 3, 118–126. [CrossRef]
4. Pike, J.W.; Meyer, M.B.; Lee, S.-M.; Onal, M.; Benkusky, N.A. The vitamin D receptor: Contemporary genomic approaches reveal new basic and translational insights. J. Clin. Investig. 2017, 127, 1146–1154. [CrossRef]
5. Buckley, L.; Guyatt, G.; Fink, H.A.; Cannon, M.; Grossman, J.; Hansen, K.E.; Humphrey, M.B.; Lane, N.E.; Magrey, M.; Miller, M.; et al. 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. Arthritis Rheumatol. 2017, 69, 1521–1537. [CrossRef]
6. Charoenngam, N.; Holick, M.F. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients 2020, 12, 2097. [CrossRef] [PubMed]
7. Yang,C.Y.;Leung,P.S.C.;Adamopoulos,I.E.;Gershwin,M.E.TheimplicationofvitaminDand autoimmunity: Acomprehensive review. Clin. Rev. Allergy Immunol. 2013, 45, 217–226. [CrossRef] [PubMed]
8. Holick, M.F.; Binkley, N.C.; Bischoff-Ferrari, H.A.; Gordon, C.M.; Hanley, D.A.; Heaney, R.P.; Murad, M.H.; Weaver, C.M.; Endocrine, S. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. 2011, 96, 1911–1930. [CrossRef] [PubMed]

9. Booth,D.R.;Ding,N.;Parnell,G.P.;Shahijanian,F.;Coulter,S.;Schibeci,S.D.;Atkins,A.R.;Stewart,G.J.;Evans,R.M.;Downes, M.; et al. Cistromic and genetic evidence that the vitamin D receptor mediates susceptibility to latitude-dependent autoimmune diseases. Genes Immun. 2016, 17, 213–219. [CrossRef
10. Hossein-nezhad, A.; Spira, A.; Holick, M.F. Influence of Vitamin D Status and Vitamin D3 Supplementation on Genome Wide Expression of White Blood Cells: A Randomized Double-Blind Clinical Trial. PLoS ONE 2013, 8, e58725. [CrossRef] [PubMed]
11. Hossein-nezhad, A.; Spira, A.; Holick, M.F. Influence of Vitamin D Status and Vitamin D3 Supplementation on Genome Wide Expression of White Blood Cells: A Randomized Double-Blind Clinical Trial. PLoS ONE 2013, 8, e58725. [CrossRef] [PubMed]
12. Adams, J.S.; Rafison, B.; Witzel, S.; Reyes, R.E.; Shieh, A.; Chun, R.; Zavala, K.; Hewison, M.; Liu, P.T. Regulation of the extrarenal CYP27B1-hydroxylase. J. Steroid Biochem. Mol. Biol. 2014, 144 (Pt A), 22–27. [CrossRef]
13. Jones, G.; Prosser, D.E.; Kaufmann, M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): Its important role in the degradation of vitamin D. Arch. Biochem. Biophys. 2012, 523, 9–18. [CrossRef]
14. Jones, G.; Prosser, D.E.; Kaufmann, M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): Its important role in the degradation of vitamin D. Arch. Biochem. Biophys. 2012, 523, 9–18. [CrossRef]
15. Bikle, D.D. Vitamin D and bone. Curr. Osteoporos. Rep. 2012, 10, 151–159. [CrossRef] [PubMed]
16. Takahashi,N.;Udagawa,N.;Suda,T.VitaminDendocrinesystemandosteoclasts. BonekeyRep. 2014,3,495. [CrossRef][PubMed]

17. Bikle, D.D. Vitamin D metabolism, mechanism of action, and clinical applications. Chem. Biol. 2014, 21, 319–329. [CrossRef]

18. Charoenngam, N.; Rujirachun, P.; Holick, M.F.; Ungprasert, P. Oral vitamin D3 supplementation increases serum fibroblast growth factor 23 concentration in vitamin D-deficient patients: A systematic review and meta-analysis. Osteoporos. Int. 2019, 30, 2183–2193. [CrossRef]

19. Holick, M.F. Resurrection of vitamin D deficiency and rickets. J. Clin. Investig. 2006, 116, 2062–2072. [CrossRef]

20. Martens, P.-J.; Gysemans, C.; Verstuyf, A.; Mathieu, C. Vitamin D's Effect on Immune Function. Nutrients 2020, 12, 1248. [CrossRef]

21. Adams, J.S.; Ren, S.; Liu, P.T.; Chun, R.F.; Lagishetty, V.; Gombart, A.F.; Borregaard, N.; Modlin, R.L.; Hewison, M. Vitamin d-directed rheostatic regulation of monocyte antibacterial responses. J. Immunol. 2009, 182, 4289–4295. [CrossRef]

22.. Verway, M.; Bouttier, M.; Wang, T.-T.; Carrier, M.; Calderon, M.; An, B.-S.; Devemy, E.; McIntosh, F.; Divangahi, M.; Behr, M.A.; et al. Vitamin D induces interleukin-1β expression: Paracrine macrophage epithelial signaling controls M. tuberculosis infection. PLoS Pathog. 2013, 9, e1003407. [CrossRef]

23.. Gombart, A.F. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol. 2009, 4, 1151–1165. [CrossRef]

24. Tebben, P.J.; Singh, R.J.; Kumar, R. Vitamin D-Mediated Hypercalcemia: Mechanisms, Diagnosis, and Treatment. Endocr. Rev. 2016, 37, 521–547. [CrossRef]

25. Szeles, L.; Keresztes, G.; Torocsik, D.; Balajthy, Z.; Krenacs, L.; Poliska, S.; Steinmeyer, A.; Zuegel, U.; Pruenster, M.; Rot, A.; et al. 1,25-dihydroxyvitamin D3 is an

autonomous regulator of the transcriptional changes leading to a tolerogenic dendritic cell phenotype. J. Immunol. 2009, 182, 2074–2083. [CrossRef] [PubMed]

26. Adorini, L.; Penna, G. Induction of tolerogenic dendritic cells by vitamin D receptor agonists. In Dendritic Cells; Lombardi, G., Riffo-Vasquez, Y., Eds.; Handbook of Experimental Pharmacology; Springer: Berlin, Germany, 2009; Volume 188. [CrossRef]

27. Piemonti,L.;Monti,P.;Sironi,M.;Fraticelli,P.;Leone,B.E.;DalCin,E.;Allavena,P.;DiCarlo,V .VitaminD3affectsdifferentiation, maturation, and function of human monocyte-derived dendritic cells. J. Immunol. 2000, 164, 4443–4451. [CrossRef] [PubMed]

28. Urry, Z.; Xystrakis, E.; Richards, D.F.; McDonald, J.; Sattar, Z.; Cousins, D.J.; Corrigan, C.J.; Hickman, E.; Brown, Z.; Hawrylowicz, C.M. Ligation of TLR9 induced on human IL-10-secreting Tregs by 1alpha,25-dihydroxyvitamin D3 abrogates regulatory function. J. Clin. Investig. 2009, 119, 387–398. [CrossRef]

29. Jeffery, L.E.; Burke, F.; Mura, M.; Zheng, Y.; Qureshi, O.S.; Hewison, M.; Walker, L.S.; Lammas, D.A.; Raza, K.; Sansom, D.M. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. J. Immunol. 2009, 183, 5458–5467. [CrossRef] [PubMed]

30. Dickie, L.J.; Church, L.D.; Coulthard, L.R.; Mathews, R.J.; Emery, P.; McDermott, M.F. Vitamin D3 down-regulates intracellular Toll-like receptor 9 expression and Toll-like receptor 9-induced IL-6 production in human monocytes. Rheumatology 2010, 49, 1466–1471. [CrossRef]

31. Lemire, J.M.; Archer, D.C.; Beck, L.; Spiegelberg, H.L. Immunosuppressive Actions of 1,25-Dihydroxyvitamin D3: Preferential Inhibition of Th1 Functions. J. Nutr. 1995, 125, 1704S–1708S. [CrossRef] [PubMed]

32. Boonstra, A.; Barrat, F.J.; Crain, C.; Heath, V.L.; Savelkoul, H.F.J.; O'Garra, A. 1α,25-Dihydroxyvitamin D3 Has a Direct Effect on Naive CD4; T Cells to Enhance the Development of Th2 Cells. J. Immunol. 2001, 167, 4974. [CrossRef]

33. Kongsbak, M.; Levring, T.B.; Geisler, C.; von Essen, M.R. The vitamin d receptor and T cell function. Front. Immunol. 2013, 4, 148. [CrossRef]

34. Eckard, A.R.; O'Riordan, M.A.; Rosebush, J.C.; Lee, S.T.; Habib, J.G.; Ruff, J.H.; Labbato, D.; Daniels, J.E.; Uribe-Leitz, M.; Tangpricha, V.; et al. Vitamin D supplementation decreases immune activation and exhaustion in HIV-1-infected youth. Antivir. Ther. 2018, 23, 315–324. [CrossRef] [PubMed]

35. Stallings, V.A.; Schall, J.I.; Hediger, M.L.; Zemel, B.S.; Tuluc, F.; Dougherty, K.A.; Samuel, J.L.; Rutstein, R.M. High-dose vitamin D3 supplementation in children and young adults with HIV: A randomized, placebo-controlled trial. Pediatr. Infect. Dis. J. 2015, 34, e32–e40. [CrossRef] [PubMed]

36. Lemire, J.M.; Adams, J.S.; Sakai, R.; Jordan, S.C. 1 alpha,25-dihydroxyvitamin D3 suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. J. Clin. Investig. 1984, 74, 657–661. [CrossRef]

37. Rolf, L.; Muris, A.-H.; Hupperts, R.; Damoiseaux, J. Illuminating vitamin D effects on B cells—The multiple sclerosis perspective. Immunology 2016, 147, 275–284. [CrossRef] [PubMed]

38. Chen, S.; Sims, G.P.; Chen, X.X.; Gu, Y.Y.; Chen, S.; Lipsky, P.E. Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. J. Immunol. 2007, 179, 1634–1647. [CrossRef] [PubMed]

39. Heine, G.; Niesner, U.; Chang, H.D.; Steinmeyer, A.; Zugel, U.; Zuberbier, T.; Radbruch, A.; Worm, M. 1,25-dihydroxyvitamin D(3) promotes IL-10 production in human B cells. Eur. J. Immunol. 2008, 38, 2210–2218. [CrossRef]

40. Shirakawa, A.K.; Nagakubo, D.; Hieshima, K.; Nakayama, T.; Jin, Z.; Yoshie, O. 1,25-dihydroxyvitamin D3 induces CCR10 expression in terminally differentiating human B cells. J. Immunol. 2008, 180, 2786–2795. [CrossRef]

41. Yamamoto, E.A.; Nguyen, J.K.; Liu, J.; Keller, E.; Campbell, N.; Zhang, C.J.; Smith, H.R.; Li, X.; Jorgensen, T.N. Low Levels of Vitamin D Promote Memory B Cells in Lupus. Nutrients 2020, 12, 291. [CrossRef]

42. Infante, M.; Ricordi, C.; Sanchez, J.; Clare-Salzler, M.J.; Padilla, N.; Fuenmayor, V.; Chavez, C.; Alvarez, A.; Baidal, D.; Alejandro, R.; et al. Influence of Vitamin D on Islet Autoimmunity and Beta-Cell Function in Type 1 Diabetes. Nutrients 2019, 11, 2185. [CrossRef] [PubMed]

43. Kennel, K.A.; Drake, M.T.; Hurley, D.L. Vitamin D deficiency in adults: When to test and how to treat. Mayo Clin. Proc. 2010, 85, 752–758. [CrossRef] [PubMed]

44. Schleithoff, S.S.; Zittermann, A.; Tenderich, G.; Berthold, H.K.; Stehle, P.; Koerfer, R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: A double-blind, randomized, placebo-controlled trial. Am. J.Clin. Nutr. 2006, 83, 754–759. [CrossRef] [PubMed]

45. Haddad Kashani, H.; Seyed Hosseini, E.; Nikzad, H.; Soleimani, A.; Soleimani, M.; Tamadon, M.R.; Keneshlou, F.; Asemi, Z. The Effects of Vitamin D Supplementation on Signaling Pathway of Inflammation and Oxidative Stress in Diabetic Hemodialysis: A Randomized, Double-Blind, Placebo-Controlled Trial. Front. Pharmacol. 2018, 9, 50. [CrossRef] [PubMed]

46. Shirvani, A.; Kalajian, T.A.; Song, A.; Holick, M.F. Disassociation of Vitamin D's Calcemic Activity and Non-calcemic Genomic Activity and Individual Responsiveness: A Randomized Controlled Double-Blind Clinical Trial. Sci. Rep. 2019, 9, 17685. [CrossRef] [PubMed]

47. Shirvani,A.;Kalajian,T.A.;Song,A.;Allen,R.;Charoenngam,N.;Lewanczuk,R.;Holick,M.F. VariableGenomicandMetabolomic Responses to Varying Doses of Vitamin D Supplementation. Anticancer Res. 2020, 40, 535–543. [CrossRef]

48. Carlberg,C.;Seuter,S.;deMello,V.D.;Schwab,U.;Voutilainen,S.;Pulkki,K.;Nurmi,T.;Virtanen,J.;Tuomainen,T.P.;Uusitupa, M. Primary vitamin D target genes allow a categorization of possible benefits of vitamin D(3) supplementation. PLoS ONE 2013, 8, e71042. [CrossRef]

49. Ross, A.C.; Manson, J.E.; Abrams, S.A.; Aloia, J.F.; Brannon, P.M.; Clinton, S.K.; Durazo-Arvizu, R.A.; Gallagher, J.C.; Gallo, R.L.; Jones, G.; et al. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: What dietetics practitioners need to know. J. Am. Diet. Assoc. 2011, 111, 524–527. [CrossRef]

50. Luxwolda, M.F.; Kuipers, R.S.; Kema, I.P.; van der Veer, E.; Dijck-Brouwer, D.A.; Muskiet, F.A. Vitamin D status indicators in indigenous populations in East Africa. Eur. J. Nutr. 2013, 52, 1115–1125. [CrossRef]

51. Dudenkov, D.V.; Mara, K.C.; Petterson, T.M.; Maxson, J.A.; Thacher, T.D. Serum 25-Hydroxyvitamin D Values and Risk of All-Cause and Cause-Specific Mortality: A Population-Based Cohort Study. Mayo Clin. Proc. 2018, 93, 721–730. [CrossRef]
52. Amrein, K.; Quraishi, S.A.; Litonjua, A.A.; Gibbons, F.K.; Pieber, T.R.; Camargo, C.A., Jr.; Giovannucci, E.; Christopher, K.B. Evidence for a U-Shaped Relationship Between Prehospital Vitamin D Status and Mortality: A Cohort Study. J. Clin. Endocrinol. Metab. 2014, 99, 1461–1469. [CrossRef]
53. Aleksova, A.; Beltrami, A.P.; Belfiore, R.; Barbati, G.; Di Nucci, M.; Scapol, S.; De Paris, V.; Carriere, C.; Sinagra, G. U-shaped relationship between vitamin D levels and long-term outcome in large cohort of survivors of acute myocardial infarction. Int. J. Cardiol. 2016, 223, 962–966. [CrossRef] [PubMed]
54. Hossein-nezhad, A.; Holick, M.F. Vitamin D for health: A global perspective. Mayo Clin. Proc. 2013, 88, 720–755. [CrossRef]
55. Dowdy, J.C.; Sayre, R.M.; Holick, M.F. Holick's rule and vitamin D from sunlight. J. Steroid Biochem. Mol. Biol. 2010, 121, 328–330. [CrossRef] [PubMed]
56. Wacker,M.;Holick,M.F.SunlightandVitaminD:Aglobalperspectiveforhealth. Dermatoendocrinology2013,5,51–108. [CrossRef] [PubMed]
57. Force, U.S.P.S.T. Screening for Vitamin D Deficiency in Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2021, 325, 1436–1442. [CrossRef]
58. Myasoedova, E.; Crowson, C.S.; Kremers, H.M.; Therneau, T.M.; Gabriel, S.E. Is the incidence of rheumatoid arthritis rising?: Results from Olmsted County, Minnesota, 1955–2007. Arthritis Rheum. 2010, 62, 1576–1582. [CrossRef]

59. Schulze-Koops, H.; Kalden, J.R. The balance of Th1/Th2 cytokines in rheumatoid arthritis. Best Pract. Res. Clin. Rheumatol. 2001, 15, 677–691. [CrossRef]

60. Paradowska-Gorycka, A.; Wajda, A.; Romanowska-Próchnicka, K.; Walczuk, E.; Kuca-Warnawin, E.; Kmiolek, T.; Stypinska, B.; Rzeszotarska, E.; Majewski, D.; Jagodzinski, P.P.; et al. Th17/Treg-Related Transcriptional Factor Expression and Cytokine Profile in Patients with Rheumatoid Arthritis. Front. Immunol. 2020, 11, 3189. [CrossRef]

61. Zhang, L.; Li, Y.-g.; Li, Y.-h.; Qi, L.; Liu, X.-g.; Yuan, C.-z.; Hu, N.-w.; Ma, D.-x.; Li, Z.-f.; Yang, Q.; et al. Increased Frequencies of Th22 Cells as well as Th17 Cells in the Peripheral Blood of Patients with Ankylosing Spondylitis and Rheumatoid Arthritis. PLoS ONE 2012, 7, e31000. [CrossRef]

62. Aho, K.; Heliovaara, M. Risk factors for rheumatoid arthritis. Ann. Med. 2004, 36, 242–251. [CrossRef]

63. Aslam, M.M.; John, P.; Bhatti, A.; Jahangir, S.; Kamboh, M.I. Vitamin D as a Principal Factor in Mediating Rheumatoid ArthritisDerived Immune Response. Biomed. Res. Int. 2019, 2019, 3494937. [CrossRef]

64. Bagheri-Hosseinabadi, Z.; Imani, D.; Yousefi, H.; Abbasifard, M. Vitamin D receptor (VDR) gene polymorphism and risk of rheumatoid arthritis (RA): Systematic review and meta-analysis. Clin. Rheumatol. 2020, 39, 3555–3569. [CrossRef]

65. Rozmus, D.; Ciesielska, A.; Plominski, J.; Grzybowski, R.; Fiedorowicz, E.; Kordulewska, N.; Savelkoul, H.; Kostyra, E.; Cieslinska, A. Vitamin D Binding Protein (VDBP) and Its Gene Polymorphisms-The Risk of Malignant Tumors and Other Diseases. Int. J. Mol. Sci. 2020, 21, 7822. [CrossRef]

66. Lee, Y.H.; Bae, S.C. Vitamin D level in rheumatoid arthritis and its correlation with the disease activity: A meta-analysis. Clin. Exp. Rheumatol. 2016, 34, 827–833. 67. Merlino, L.A.; Curtis, J.; Mikuls, T.R.; Cerhan, J.R.; Criswell, L.A.; Saag, K.G.; Iowa Women's Health, S. Vitamin D intake is inversely associated with rheumatoid arthritis: Results from the Iowa Women's Health Study. Arthritis Rheum. 2004, 50, 72–77. [CrossRef]
67. Arkema, E.V.; Hart, J.E.; Bertrand, K.A.; Laden, F.; Grodstein, F.; Rosner, B.A.; Karlson, E.W.; Costenbader, K.H. Exposure to ultraviolet-B and risk of developing rheumatoid arthritis among women in the Nurses' Health Study. Ann. Rheum. Dis. 2013, 72, 506–511. [CrossRef]
68. Arkema, E.V.; Hart, J.E.; Bertrand, K.A.; Laden, F.; Grodstein, F.; Rosner, B.A.; Karlson, E.W.; Costenbader, K.H. Exposure to ultraviolet-B and risk of developing rheumatoid arthritis among women in the Nurses' Health Study. Ann. Rheum. Dis. 2013, 72, 506–511. [CrossRef
69. Staples, J.A.; Ponsonby, A.-L.; Lim, L.L.Y.; McMichael, A.J. Ecologic analysis of some immune-related disorders, including type 1 diabetes,inAustralia: Latitude,regionalultravioletradiation,anddiseaseprevalence. Environ. HealthPerspect. 2003,111,518–523. [CrossRef]
70. Vieira, V.M.; Hart, J.E.; Webster, T.F.; Weinberg, J.; Puett, R.; Laden, F.; Costenbader, K.H.; Karlson, E.W. Association between residences in U.S. northern latitudes and rheumatoid arthritis: A spatial analysis of the Nurses' Health Study. Environ. Health Perspect. 2010, 118, 957–961. [CrossRef] [PubMed]
71. Hajjaj-Hassouni, N.; Mawani, N.; Allali, F.; Rkain, H.; Hassouni, K.; Hmamouchi, I.; Dougados, M. Evaluation of Vitamin D Status in Rheumatoid Arthritis and Its

Association with Disease Activity across 15 Countries: “The COMORA Study”. Int. J. Rheumatol. 2017, 2017, 5491676. [CrossRef]

72. Guan, Y.; Hao, Y.; Guan, Y.; Bu, H.; Wang, H. The Effect of Vitamin D Supplementation on Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis. Front. Med. 2020, 7, 596007. [CrossRef]

73. Nguyen, Y.; Sigaux, J.; Letarouilly, J.-G.; Sanchez, P.; Czernichow, S.; Flipo, R.-M.; Soubrier, M.; Semerano, L.; Seror, R.; Sellam, J.; et al. Efficacy of Oral Vitamin Supplementation in Inflammatory Rheumatic Disorders: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 2020, 13, 107. [CrossRef]

74. Yang, J.; Liu, L.; Zhang, Q.; Li, M.; Wang, J. Effect of vitamin D on the recurrence rate of rheumatoid arthritis. Exp. Ther. Med. 2015, 10, 1812–1816. [CrossRef]

75. Gopinath, K.; Danda, D. Supplementation of 1,25 dihydroxy vitamin D3 in patients with treatment naive early rheumatoid arthritis: A randomised controlled trial. Int. J. Rheum. Dis. 2011, 14, 332–339. [CrossRef]

الاستنتاجات

يلعب فيتامين د دورًا أساسيًا ليس فقط في الحفاظ على هيكل عظمي معدني صحي، ولكن أيضًا في تعديل أجهزة المناعة الفطرية والتكيفية بطريقة يُعتقد أنها تستفيد كعلاج مساعد للعديد من الأمراض التي تنتقل عن طريق بوجود وشدة معظم، إن لم يكن كل، الأمراض الروماتيزمية، مثل D(OH)المناعة. يرتبط المستوى المنخفض لـ 25 ومع ذلك، فإن فوائد مكملات فيتامين د لعلاج هذه الأمراض والوقاية منها غير .OA، وSPA، وSLE، وRA واضحة نسبيًا، حيث أن نتائج التجارب السريرية الحالية غير متسقة بشكل ملحوظ. والعديد منها صغير الحجم في العينة ومن المحتمل أن يكون ضعيفًا؛ ومع ذلك، عندما تم تجميع هذه النتائج في التحليلات التلوية، كانت هناك إشارات يمكن تصورها عن فوائد فيتامين د لتحسين نشاط المرض، خاصة بالنسبة لالتهاب المفاصل الروماتويدي ومرض الذئبة الحمراء. ومن الجدير بالذكر أيضًا أنه بناءً على الدراسات الجينومية الحديثة حول فيتامين د، قد يكون هناك اختلاف بين الأفراد في الاستجابة لمكملات فيتامين د التي تحتاج إلى مزيد من التحقيقات، مما يشير إلى أن بعض الأفراد قد يكونون قادرين على الاستفادة من فيتامين د أكثر أو أقل من آحرون. بغض النظر عن الأدلة على فوائد فيتامين د الخاصة بالمرض، فمن المستحسن أن المرضى الذين يعانون من أمراض الروماتيزم مع أو بدون علاج بالكورتيكوستيرويد يجب أن يتعرضوا لأشعة الشمس بشكل معقول وتناول كمية كافية من فيتامين د للحفاظ على في المصل لا يقل عن 30 نانوغرام. / مل (75 نانومول / لتر) من أجل منع تلين العظام D (OH) مستوى 25 وهشاشة العظام الثانوية والكسور، وربما 40-60 نانوجرام / مل (100-150 نانومول / لتر) لتحقيق أقصى فائدة من فيتامين د لصحة

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

كلية الحلة الجامعة

قسم الفزياء الطبية

العلاقة بين نقص فيتامين والتهاب المفاصل الروماتيدي

بحث مقدم الى مجلس كلية الحلة الجامعة
وهو جزء من متطلبات الحصول على درجة البكالوريوس في الفيزياء الطبية

مقدم من
محمد حيدر جابر
علي حسين كاظم
سيف عبد الحسن عباس
زينب موسى كاظم
زهراء رعد فضل
دنيا احمد عوده

يشرف عليها
د.أحمد سلام عبود

2024 1445

الاهداء

الحمد الله الذي ملاء السموات والأرض ومابينها نشكره سبحانه وتعالى عله منحه لنا نعمة العقل ولأمل والصبر والصلاة والسلام على أشرف المرسلين وبعده بكل حب اهدي بحث تخرجي إلى من قال بهما الرحمان وأحفض لهما جناح الذل من الرحمه وقل رب أرحمهما كما ربياني صغير

إلى من جعل الله الجنه تحت أقدامها إلى من حملتني وهن على وهن ومن كافحة من أجل وصولي إلى هذا اليوم وأحتضنني قلبها قبل يدها وسهلت لي الشدائد بدعائها إلى القلب الحنون وسر قوتي ونجاحي جنتي : أمي

إلى الذي زين أسمي بأجمل الالقاب ومن دعمني بلا حدود أعطاني بلامقابل إلى من علمني أن الدنيا كفاح سلاحها العلم والمعرفه داعمي الأول في مسيرتي وسندي وقوتي وملاذي بعد الله فخري وأعتزازي : أبي

كل من أمدوني بالقوه والتوجيه وآمنو بي ودعموني لأ صل الى ما أنا علية الآن لكل أخ وأخت

واخيرا من قال أنا لها "نالها" وأنا لها أن ابت رغما عنها اتيت بها وما كنت لافعل هذا لو لا توفيق من الله.

الشكر والعرفان

قال تعالى

(وَمَن يَشْكُرْ فَإِنَّمَا يَشْكُرُ لِنَفْسِهِۦ)

{لقمان :12}

وقال رسوله الكريم (ص)

(من لم يشكر الناس؛ لم يشكر الله عز وجل)

للنجاحات اناس يقدرون معناه والابداع أناس يحصدونه لذا نقدر جهودك المضنيه فأنت أهل للشكر والتقدير فوجب علينا تقديرك ولك منا كل الثناء والتقدير وأخص بالذكر استاذنا المشرف الفاضل دكتور احمد سلام عبود لما بذله معنا من وقت وجهد

ونتوجه ايضا بأصدق عبارات الشكر والامتنان الى عمادة كلية الحلة الجامعة والى قسم الفيزياء الطبية لكم منا كل الشكر والتقدير

واخيرا اختمها ب انار الله دروبكم كما انرتم دروب الكثير