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Review Article

REVIEW OF THE RELATIONSHIP BETWEEN VITAMIN D AND VITILIGO

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ABSTRACT

Vitamin D, is a steroid that plays endocrine, paracrine and autocrine functions; obtained by cutaneous photo exposure to ultra violet and diet, or supplements; its greatest importance form is Vitamin D_3.Vitamin D deficiency is linked to many diseases such as Vitiligo disease and almost of autoimmune disease as diabetes (type 1 or latent autoimmune diabetics). In this Review, we discuss the important role of Vitamin D with Vitiligo disease. Vitamin D and its receptor found to have been assured the immunoregulation through down-regulating T-helper1 immune responses with proinflammatory cytokine, Inhibiting the B-cells differentiation, T-lymphocytes proliferation and immunoglobulin secretion;. However, Vitamin D has photo-protective and antioxidant effects by the blockage of DNA (Deoxyribonucleic acid) damage factor of in mitochondria. Moreover its induced the proliferation of epidermis and increased the level of dihydroxyphenylalanine-positive melanocytes. The conclusion can be drawn that Vitamin D has the propensity ensure the repigmentation to restoring skin color in a patient with vitiligo disease.

INTRODUCTION

Vitamin D (calciferol), is a steroid that plays endocrine, paracrine and autocrine functions [1]. The major forms is 1α,25-dihydroxy vitamin D3 (1,25(OH) 2D3, calcitriol) the most active vitamin D metabolite in the organism and a pleiotropic hormone with ample regulatory actions [2]. Vitamin D regulates calcium homeostasis and is vital for bone health [3].

Table1 Vitamin D Content of Various Foods [15]

Food	IUs per serving*
Swordfish, cooked, 3 ounces	566
Salmon (sockeye) cooked, 3 ounces	477
Tuna, canned in water, drained, 3 ounces	154
Milk, vitamin fortified, 1 cup	115-124
Margarine, fortified, 1 tablespoon	60
Egg yolk, 1 large	41
Cereal, fortified with 10% of the daily value of vitamin D, 1 cup	40
*IUs = International Units	

It's obtained from three sources; sunlight, vitamin D supplements and diet, or dietary supplements include fatty fish(salmon, mackerel, sardines, cod liver oil), cheese, mushroom, milk and egg yolk [4].(Table 1)

However, the important source of vitamin D for most humans is casual in the skin from 7-dehydrocholesterol following exposure to ultra violet B (UVB) radiation with wavelength 290 to 320 nm [5], leads conversion of provitamin D (7-dehydrochole-sterol,7-D HC) to previtamin D in the skin by exposure to UVB radiation; because a whole body exposure to UVB radiation inducing the light pink color of the minimal erythema dose for 15-20 min is able to induce the production of up to 250l g vitamin D (10,000 IU) [6]. The previtamin D isomerized by body heat to form vitamin D_3 then in the blood vitamin D is bound mainly to a vitamin D-binding protein, although a small fraction is bound to albumin in a cytochrome P450-like enzyme mediated reaction, vitamin D transported by the blood to the liver, hydroxylated and converted in 25-hydroxyvitamin D [25(OH) D] the most abundant circulating form, which is biologically inactive. In the kidneys, the

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formation of the active form of vitamin D,1,25-dihydroxyvitamin D[1,25(OH)2D] is tightly regulated by the parathyroid hormone (PTH). The additional hydroxylation in the cells of the convulated proximal tubule of the kidneys, originating 1.25-dihydroxy vitamin D [1.25(OH)2D3], the biologically active form is the final step in the production of the hormone [7]. Therefore, many of the body's tissues contain vitamin D receptors, consequently vitamin D is important for many bodily functions. More recently, it was found that 1,25-dihydroxyvitamin D can be produced in tissue and cells, decoupling partly the production of 1,25-dihydroxyvitamin D and its effects from the renal functions and PTH.(Fig 1)

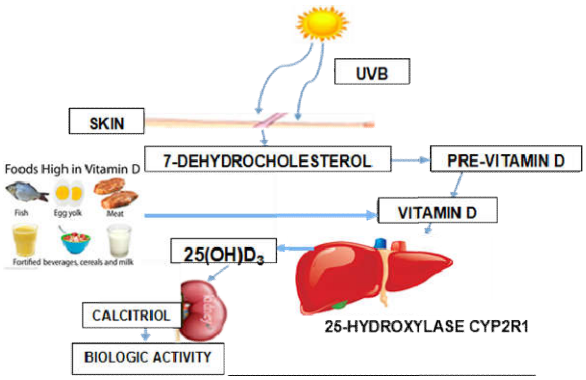

Fig 1. Vitamin D synthesis

Physiopathology of Vitamin D

Much of the vitamin D produced in the skin is taken up and used by other systems of the body; modulates the transcription of cell cycle proteins, that decrease cell proliferation and increase cell differentiation of a number of specialised cells of the body after the activation of vitamin D receptors(VDR).Vitamin D has a specific level, 50 nmol/L has been widely used to define 25(OH)D sufficiency, while some studies have used 37.5 nmol/L as the lowest level of sufficiency [8]. In addition, Chronic vitamin D deficiency may have serious adverse consequences, including increased risk of hypertension, multiple sclerosis, cancers of the colon, prostate, breast, and ovary, type 1 diabetes, bacterial infection, auto immune diseases, osteoarthritis, periodontal disease, increased risk of non alcoholic steatohepatitis in adults with non-alcoholic fatty liver disease [9], furthermore new research suggests that the high doses of Vitamin D may reduce HIV progression [10]. Otherwise most of patients of Vitiligo not having enough of a specified quantity of vitamin D <30-15 ng/mL; and this lack of 25(OH) D increasing Fitzpatrick phototype which assures the sun damage in the skin. Li K et al., found the relationship between the high level of 25(OH) D and VDR BsmI-B allele, the ApaI-A allele, and the TaqI-t allele that decreased risk for vitiligo [11, 12]; as well, vitamin D_3 promotes melanogenesis via augmentation of microphthalmia transcription factor (MITF) and an increased amount of tyrosinase in B16 melanoma cells [13, 14],and also elevated melanin content level in human melanocytes [15]. Mounting evidence indicates that vitamin D and its receptor (VDR) play key roles in the pathogenesis of human diseases mainly in Vitiligo diseases [16]; this knowledge may explain the actions of Vitamin D in the skin. In the present study, we reviewed the role and mechanisms of Vitamin D, largely in the treatment of Vitiligo disease.

Vitiligo Disease

Vitiligo is the most frequent disorder of pigmentation in the skin, displayed by the acute destruction of melanocytes in the skin and precipitate the inhibition of melanogenesis factors. The epidemiology of Vitiligo in the world approximately 1% to 2% of the world population and 0.38% for Caucasians in the United States and Northern Europe, 8.8% in Delhi India, and affects 0.19% of the population in China; Both sexes are equally affected , without liking of black or white race and may occur at any age [17,18]. Multiple hypotheses have been suggested as potential triggers that cause vitiligo and includes three main factors: genetic (heredity), environmental such as sunburn, autoimmune causes; being, Lamont *et al* 1981., attenuated the hypopigmentation in the Smyth chicken, after removing T cell activity with cyclosporine A [19]. Further, we found that in patients suffering from Vitiligo disease had lower levels of IFNγ (Interferon gamma), GM-CSF (Granulocyte-macrophage colony-stimulating factor), bFGF (Basic fibroblast growth factor) and SCF (Stem cell factor), and a significantly higher expression of IL-6, IL-2 and TNF-alpha was detected [20,21] ; and also caused by oxidation stress, inasmuch as H_2O_2 turn in to reduce the activity site of catalase that It's a very important enzyme in protecting the cell from oxidative damage by reactive oxygen species (ROS) [22]. Recently, these causes of Vitiligo lead us to study and answer this question; how Vitamin D regulates melanogenesis in the skin and assure the repigmentation of Vitiligo?

Immune System and Vitamin D

Immune system is a network of cells, tissues and organs that work together to defend the body against attacks by "foreign" invaders and protects against disease. Within the skin, Vitamin D and its receptors help form an impermeable barrier and promote an innate immune response against foreign microbes [23]. The active metabolite of Vitamin D, 1,25(OH) 2 D 3 also can suppress autoimmune diseases, Du T *et al*., demonstrated that, Cytokine production by monocytes from both normal controls and from patients with autoimmune diabetes (type 1 or latent autoimmune diabetics) is significantly diminished by vitamin D [24];as though its role in immunoregulation has led to the concept of a dual function as both as an important secosteroid hormone for the regulation of body calcium homeostasis and as an essential organic compound that has been shown to have a crucial effect on the immune responses [25]. Besides, many immunologic cells (B cells, T cells and antigen presenting cells) are capable of synthesizing the active Vitamin D metabolite may act in a paracrine or autocrine manner in an immune environmenent [26]. Likewise the effects of Vitamin D on human adaptive immune cells demonstrated an expression of the nuclear VDR as well as Vitamin D-activating enzymes in both T- and B-cells [27], provoke down-regulating Th1 immune responses, lowering proliferation of B-cells and blocks B cell differentiation and immunoglobulin secretion; and also suppresses T-cell or T-lymphocytes proliferation [28,29,30]; that play a central role in cell mediated immunity, and promotes stimulation of T regulatory cells. Yong Zhang *et al* 2012., revealed that 30-50 ng/ml of Vitamin D significantly inhibits the lipopolysaccharide which induce the inflammatory responses [31,32] and inhibitited the expression of IL-6, IL-8, TNF-alpha, and INF-gamma; thereby, 1,25(OH) D inhibits ICAM-1 (Intercellular Adhesion Molecule

1) that plays an important role in Vitiligo disease [33]. Further, Vitamin D and VDR inhibits dendritic cells differentiation and maturation with preservation of an immature phenotype as evidenced by a decreased expression of MHC class II molecules, co-stimulatory molecules and IL12.1,25(OH) 2 D3 also asssure the suppressive effect on the nuclear factor-*K*B (NF-kB) signalling pathway has been observed in T-cells, monocytes or macrophages [34].(Fig 2)

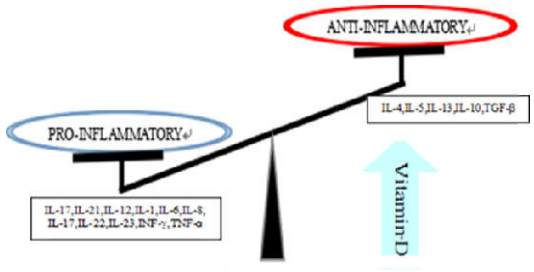

Fig 2. Regulation of cytokine by vitamin D

These effects of Vitamin D sweep away in lower level of (IL-17, IL-21) and the monocyte production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12 and TNFα, with increased production of anti-inflammatory cytokines such as IL-10 [35]. Also Vitamin D_3 and VDR affect the Wnt signaling through direct interaction with β-catenin, and attenuating growth in colon cancer cells [36].The immuno-modulatory effects of Vitamin D are summarized in Table 2.Therewith, Linker-Israeli *et al* 2001., showed that the treatment with Vitamin D significantly inhibited the production of anti-double stranded DNA antibodies [37].

It has also been found that assure the functionality of melanocyte cooperating with cytokines endothelin-3 (ET-3) and the activity of the SCF/c-Kit system, which is an important growth factor for melanocytes viability and maturation [38]. (Table 2.)

Antioxidant and Photoprotective Activities of Vitamin D

Photoprotection is a kind of mechanisms to block photoinhibition and oxidative stress to avoid UV photodamage to the skin and prevent DNA damage induced by ultraviolet (UV) light. Vitamin D has photoprotective effects that increases the pigmentation and all melanogenesis factors in the melanocytes and by its antiapoptotic effect through the blocking of cytochrome C released from mitochondria and consequently reduce free radical damage to the human body [39]; Hanada K *et al*, also showed the existence of the most favorable level of $1,25(OH)_2D_3$ for reducing photodamage in humans [40].On the other hand, Vitamin D provides protection against oxidative DNA damage as produce a variety of antioxidants against molecular damage from reactive oxygen species (ROS) , ensures the decreasing of (41%, $p<0.05$) ROS and helps repair damaged DNA [41];while 800 I.U. of Vitamin D was push to lower level of oxidative DNA damage in colon epithelium of humans and in lymphocytes reduced the level till 50□70% of endogenous oxidants. In addition H. Dorota Halicka *et al*., observed after treatment of 1,25-dihydroxyvitamin D3 (1,25-VD) on mitogenically stimulated human lymphocytes, pulmonary carcinoma A549 and lymphoblastoid TK6 cells discovered the reduction level of constitutive expression of phosphorylation of histone H2AX on Ser139 (γH2AX) and Ataxia Telangiectasia mutated protein kinase-Ser1981 phosphorylation ($ATM\text{-}S1981^P$); which are the

Table 2 Immunomodulatory effects of 1,25 (OH) 2 D3

Immunomodulatory effects of 1,25(OH) 2 D3			
	MACROPHAGE		**DENDRITIC CELL**
MONOCYTE:	-Autocrine, intracrine and paracrine effects -Stimulates the differentiation of monocytic precursors in mature cells -Stimulates PGE2production -Stimulates 'oxidative burst' -Enhances chemotaxis and phagocytosis -Regulates the expression of CD14 (co-receptor of TLR4) -Induces hypo-responsiveness to PAMPs -Alters the TLR9-dependent production of IL-6 --Decreases TNF-α, IL-1, IL-6 and IL-23 production. -Induces defensins and cathelicidin -Regulates iNOS expression (contradictory data)		-Suppresses antigen presentation to T cells -Regulates negatively DCs differentiation, maturation, and immunostimulatory capacity -Decreases CD1a, CD83 maturation -Decreases T-cell stimulation -Decreases IL-6, IL-12, and IL-23 synthesis 1,25(OH)2 D3+ LPS generates tolerogenic DCs -Upregulates CD152 -Indirect Th1 response inhibition -Impairs IFN-γ production -Display antigen unspecific suppressor activity. -Effect on IL-10 production (Controversial data) -Inhibits NF-κ B family transcription factors activation and expression
KERATINOCYTES and MYELOID CELLS [30]	Major regulator of AMPs like antimicrobial peptides cathelicidins and defensins		
LYMPHOCYTE	T-LYMPHOCYTE	T-reg lymphocyte	B LYMPHOCYTE
	-Increases VDR levels -Regulates T cell development and migratory function. -Suppresses effector T cell activation -Induces regulatory T cells -Decreases Th1 cells proliferation -Inhibits chemokines and chemokine receptors -Inhibits production IL-2, IFN-γ , TNF-α and IL-5 -Enhances TGF-b 1 and IL-4 transcripts -Increases Th-2 cells function -Inhibits T cell surface expression of CLA -Regulates Th17 cells and decreases IL-17expression	-Increases the suppressive activity and pansion of antigen-specific Treg cells -Inhibits the lineage commitment of Th17 cells -Decreases IL-2 levels	-Inhibits NF-κ B -Regulates VDR expression -Up-regulates CYP24A1 Decreases CDK4, CDK6 and cyclin D -Mediates death of proliferating B cells -Inhibits plasma cells differentiation and reduces Ig-secreting cells and Ig production
Source:	Vitamin D3:a helpful immuno-modulator, Immunology, 134, 123–139		

Severe factors provoke DNA replication stress through the production of oxidative metabolism [42,43]

Epidermal Differentiation

Vitamin D, 1, 25 dihydroxyvitamin D3, stimulates differentiation in epidermal keratinocytes through interaction with the vitamin D receptor (VDR). Nathaniel P., demonstrated that VDR, DRIP (VDR- interacting protein) and SRC (steroid receptor coactivator), are all required for promotion of both early and late keratinocyte differentiation [44]. As, the deficient in VDR reduced levels of protein epidermal cells and loss of keratohyaline granules or the stratum granulosum of the epidermis [45, 46]. Therefore, the level of DOPA-positive melanocytes increased with interactive effect of UVB-light after treatment of 100 µg of vitamin D3 on the surface of the epidermis mice for few days [47]. (Fig 3)

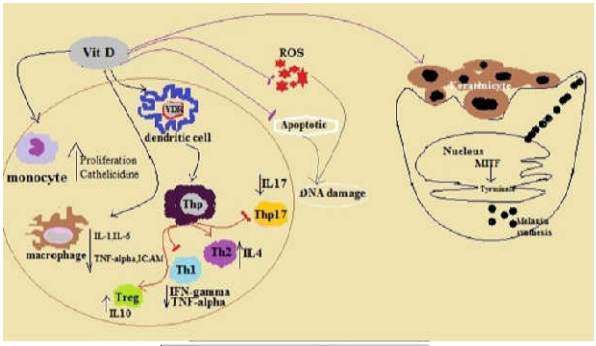

Fig 3. Illustration the influences of vitamin D

CONCLUSION

Relationship of Vitamin D with Vitiligo had been discussed. It have been clearly shown that Vitamin D and its receptor found to have assured the immune-regulation through down-regulation of Th1 immune responses with pro-inflammatory cytokines, Inhibiting the B-cells differentiation, T-lymphocytes proliferation and immunoglobulin secretion. These potential effects of vitamin D which induces differentiation and inhibits proliferation of various normal and cancer cells. The immuno-modulatory effects of vitamin D showed that the treatment with vitamin D significantly inhibited the production of anti-double stranded DNA antibodies. Vitamin D also has photoprotective effects that increase the pigmentation and all melanogenesis factors in the melanocytes and by its anti-apoptotic effect through the blocking of cytochrome C released from mitochondria and consequently reduce free radical damage to the human body. On the other hand, Vitamin D provides protection against oxidative DNA damage, ensures the decreasing of ROS and helps repair damaged DNA. Vitamin D also stimulates differentiation of epidermal keratinocytes through interaction with the VDR.

So, in conclusion it can be drawn that Vitamin D has the propensity to ensure the repigmentation to restoring skin color in a patient with Vitiligo and protect the melanocyte from any kind of damage.

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