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Vitamin D and Vitiligo

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1. Introduction

Vitamin D is a steroid hormone with such pleiotropic effects as bone and calcium homeostasis, as well as immunomodulation, and it exerts its effects via the vitamin D receptor (VDR). Vitamin D can be obtained from food as vitamin D₃ (cholecalciferol), but is also synthesized in the keratinocytes in the epidermis from the precursor molecule 7-dehydrocholesterol (provitamin D₃) by ultraviolet B (UVB) radiation in sunlight to pre-vitamin D₃. Pre-vitamin D₃ then undergoes a spontaneous, temperature-dependent isomerization to vitamin D₃ (cholecalciferol), which enters the dermal capillaries. At this point, endogenous vitamin D₃ and exogenous dietary D₂ (ergocalciferol) undergo hydroxylation in the liver to 25-hydroxy Vitamin D (calcitriol). This molecule travels to the kidney where it is again hydroxylated to make mature vitamin D (1,25-dihydroxy Vitamin D, or 1,25(OH)₂D₃, which is also known as calcitriol) and 24,25-dihydroxyvitamin D. 1,25(OH)₂D₃ is the biologically active form of vitamin D, which regulates serum calcium and phosphate homeostasis. (Klaus Wolff 2008) Circulating 1,25(OH)₂D₃ has a very short half-life and is tightly regulated by parathyroid hormone. Fibroblast growth factor 23 (FGF23), which is produced in osteoblasts, is also important in regulating 1,25(OH)₂D₃ production in the kidney. (Jurutka, Bartik et al. 2007)

2. Vitamin D and autoimmune diseases

There is increasing evidence that vitamin D may have an immunoregulatory role in various autoimmune diseases. The mechanism by which vitamin D affects autoimmunity is unknown, but there is clear evidence of regulation of immune cells by vitamin D *in vitro*. (Adorini and Penna 2008; Cantorna, Yu et al. 2008) Vitamin D has multiple effects on innate and adaptive immune responses through its effects on T and B lymphocytes, macrophages, and dendritic cells (DC), all of which express the VDR. (Adorini and Penna 2008) High levels of 1,25(OH)₂D₃ inhibit dendritic cell maturation with lower expression of major histocompatibility complex (MHC) class II molecules, downregulation of costimulatory molecules that are required for antigen presentation, and lower production of proinflammatory cytokines such as interleukin (IL)-12. (van Etten and Mathieu 2005; Baeke, van Etten et al. 2008) In mouse models, 1,25(OH)₂D₃ drives the adaptive immune system from a T helper T_H1/T_H17 response toward a T_H2 and regulatory T-cell response, suggesting the potential beneficial effects of vitamin D on the inhibition of T_H1-mediated autoimmune

diseases in humans.(Daniel, Sartory et al. 2008) The immune system of VDR-deficient mice is grossly normal but shows increased susceptibility to autoimmune diseases such as inflammatory bowel disease and type 1 diabetes mellitus.(Bouillon, Carmeliet et al. 2008) In addition, $1,25(\text{OH})_2\text{D}_3$ may suppress autoimmune diseases by enhancing the production and function of regulatory T cells (Tregs), which are vital for preserving peripheral self-tolerance. $1,25(\text{OH})_2\text{D}_3$ plays a role in the activation of Tregs by DCs, by increasing the number of Tregs, and enhancing their secretion of IL-10, which inhibits the activation of T lymphocytes.(Loser, Mehling et al. 2006; Spach, Nashold et al. 2006) There is some evidence that vitamin D may play a regulatory role in autoantibody production by B cells, inhibiting the ongoing proliferation of activated B cells and inducing their apoptosis.(Chen, Sims et al. 2007) Several mechanisms have been proposed to explain the role for vitamin D insufficiency in the pathogenesis of autoimmune disorders.

There are also various reports of vitamin D deficiency associated with several autoimmune disorders, including inflammatory bowel disease, multiple sclerosis (MS), systemic lupus erythematosus (SLE), type 1 diabetes mellitus, and rheumatoid arthritis (RA).(Cantorna, Yu et al. 2008) Furthermore, vitamin D polymorphisms have also been associated with increased risk of multiple autoimmune diseases, including Hashimoto's thyroiditis, inflammatory bowel disease, Graves' disease, rheumatoid arthritis, SLE, primary biliary cirrhosis (PBC), autoimmune hepatitis, Addison's disease, vitiligo, celiac disease, type I diabetes mellitus and multiple sclerosis (MS).(Kriegel, Manson et al. 2011) Therefore, supplementation of vitamin D can possibly be used as a treatment in autoimmune disease. Vitamin D supplementation has been shown to be therapeutically effective in different experimental animal models, such as allergic encephalomyelitis, collagen-induced arthritis, type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis, and systemic lupus erythematosus.(Lemire and Archer 1991; Mathieu, Waer et al. 1994; Cantorna, Hayes et al. 1998; Cantorna, Munsick et al. 2000; Van Etten, Branisteanu et al. 2003) However, despite the *in vitro* and animal evidence for the promising effects of vitamin D to decrease systemic inflammation and prevent autoimmune disease in humans, these findings have been somewhat conflicting in humans.

3. Association between vitamin D and vitiligo

Vitiligo, an autoimmune pigmentary disorder, is characterized by the aberrant loss of functional melanocytes from involved epidermis. The association of vitiligo with autoimmune conditions is well-established. Vitiligo is commonly associated with thyroid disorders and abnormalities, particularly Hashimoto's thyroiditis and Grave's disease, type I diabetes mellitus, and Sjögren's syndrome.(Sehgal, Rege et al. 1976; Niepomniszcze and Amad 2001; Montes, Pfister et al. 2003; Adorini and Penna 2008) Low levels of vitamin D have also been associated with autoimmune diseases, including rheumatoid arthritis, type I diabetes mellitus, and multiple sclerosis.(Adorini and Penna 2008) However, little is known about the association of vitiligo and reduced vitamin D levels.

Silverberg *et al.* reported that patients with vitiligo who have low levels of vitamin D were at higher risk for secondary forms of autoimmunity and that insufficient vitamin D levels were associated with increasing Fitzpatrick phototype.(Silverberg, Silverberg et al. 2010) They suggested that monitoring vitamin D levels in patients with vitiligo may identify individuals at greater risk for secondary autoimmune diatheses. However, there is no reliable evidence that vitamin D supplementation can treat or prevent vitiligo.

4. Effect of topical vitamin D on vitiligo

In recent years, topical vitamin D analogues, particularly calcipotriol and tacalcitol, have been used as monotherapy or in combination with phototherapy for the treatment of vitiligo. Even if their exact mechanism of actions were unclear, vitamin D analogues have two different effects on vitiligo in terms of immune function and melanocytes. Vitamin D ligands are designed to target the local immune response in vitiligo, acting specifically on T cell activation, mainly by inhibiting the transition of T cells from the early-to-late G₁ period in interphase and by inhibiting the expression of several pro-inflammatory cytokines genes, such as those encoding tumor necrosis factor-alpha (TNF-α) and interferon gamma (IFN-γ). Vitamin D₃ compounds are known to influence melanocyte maturation and differentiation and also to up-regulate melanogenesis through pathways activated by specific ligand receptors, such as the endothelin receptor and the proto-oncogene c-kit (mast/stem cell growth factor receptor [SCFR]).(Birlea, Costin et al. 2008)

At the molecular level, the addition of vitamin D compounds to a vitiligo treatment regimen along with different forms of UV and glucocorticoids can halt disease progression in vitiligo by immunosuppression and possibly induce repigmentation by activating melanocyte precursors and the promotion of melanogenic pathways.(Birlea, Costin et al. 2009)

However, the true effects of vitamin D analogues on vitiligo remain controversial (Table 1). Some studies have reported a good response or even an augmented response to them over conventional vitiligo therapies, whereas other studies have reported no response to or only limited effects of vitamin D analogues.(Leone, Pacifico et al. 2006; Lu-yan, Wen-wen et al. 2006; Goldinger, Dummer et al. 2007; Rodriguez-Martin, Garcia Bustinduy et al. 2009) One of the authors (SHO) published a prospective study which showed that the use of high concentration tacalcitol had a limited effect as either monotherapy or as part of combination therapy with excimer laser in the treatment of vitiligo.(Oh, Kim et al. 2011)

Treatment	Type of Vitamin D	Study design	Results	Effect	References
Tacalcitol ointment (4µg/g)+ 30min sunlight daily vs placebo + sunlight	Tacalcitol	Randomized, double-blinded, placebo-controlled	Placebo+heliotherapy: 1/31 Tacalcitol+heliotherapy: 0/32 >75% repigmentaton after 4 months	No	(Rodriguez-Martin, Garcia Bustinduy et al. 2009)
NB-UVB vs NB-UVB+ tacalcitol (4µg/g)	Tacalcitol	Randomized, investigator blinded, controlled, left-right trial	NB-UVB: 0/32 NB-UVB+tacalcitol: 16/32 (50%) >80% repigmentation after 6 months	Yes	(Leone, Pacifico et al. 2006)
Excimer light once weekly+ placebo vs excimer light+tacalcitol (2µg/g)	Tacalcitol	Randomized, double-blinded, placebo-controlled, left-right trial	MEL+placebo: 2/35 (5.7%) MEL+tacalcitol: 9/32 (25.7%) >75% repigmentation after 12 treatments (3 months)	Yes	(Lu-yan, Wen-wen et al. 2006)

Treatment	Type of Vitamin D	Study design	Results	Effect	References
Untreated vs calcipotriol	Calcipotriol	Prospective, left/right comparative, open study	3/24: partial response Of 3 patients showing response 1: 5% repigmentation (only treated area) 2: 20% repigmentation (both treated and untreated areas) 3: 30% repigmentation (treated), 10% repigmentation (untreated)	No	(Chiaverini, Passeron et al. 2002)
Betamethasone vs 0.005% calcipotriol vs betamethasone/calcipotriol	Calcipotriol	Randomized, non-placebo controlled study	All groups: no patients >75% repigmentation Betamethasone: 2/15, Calcipotriol: 1/15, Betamethasone/calcipotriol: 4/15 50-75% repigmentation Time to repigmentation was faster in combination treatment	No (alone) Yes (combination)	(Kumaran, Kaur et al. 2006)
NB-UVB thrice weekly vs NB-UVB+ calcipotriol (0.05%)	Calcipotriol	Randomized, non-placebo controlled study	NB-UVB: 10/24 (41.67%) NB-UVB + calcipotriol: 6/13 (46.2%) 50-100% repigmentation after 30 treatments (10weeks)	No	(Arca, Tastan et al. 2006)
PUVA+placebo vs PUVA+ calcipotriol (0.05mg/g-0.005%)	Calcipotriol	Randomized, double-blinded, placebo-controlled, left-right trial	PUVA+placebo: 30.07±1.34 treatments PUVA+calcipotriol: 27.4±1.47 treatments (time to complete repigmentation)	Yes	(Ermis, Alpsoy et al. 2001)

Treatment	Type of Vitamin D	Study design	Results	Effect	References
PUVASol+ placebo vs PUVASol+calci potriol (50µg/g-0.005%)	Calcipotriol	Randomized, double-blinded, placebo-controlled, left-right trial	PUVASol+placebo: 9/17 (52.9%) PUVASol+calcipotriol: 13/17 (76.5%) >75% repigmentation after 18 months	Yes	(Parsad, Saini et al. 1998)
Excimer laser thrice week vs excimer laser +calcipotriol (0.005%)	Calcipotriol	Randomized, single-blinded, left-right trial	Excimer: 22% Excimer +calcipotriol: 23% mean repigmentation after 8 weeks	No	(Goldinger, Dummer et al. 2007)
Excimer laser twice a week vs excimer laser +high concentration of tacalcitol	High concentration of tacalcitol	Randomized, single-blinded, left-right trial	Excimer vs Excimer + tacalcitol: no significant difference	No	(Oh, Kim et al. 2011)

µg/g: microgram/gram, vs: versus, NB-UVB: narrowband ultraviolet B, MEL: monochromatic excimer light, PUVA: psoralen and ultraviolet A, mg/g: milligram/ gram, PUVASol: psoralen and sun exposure

Table 1. Randomized, controlled studies regarding the effect of vitamin D on the treatment of vitiligo

Vitamin D analogues as monotherapy are less effective than topical corticosteroids in vitiligo, although there is some evidence of an additive effect with combining the two. (Hossani-Madani and Halder 2011) There is no convincing evidence to suggest that topical vitamin D analogues in combination with phototherapy, *i.e.*, narrowband UVB (NB-UVB), psoralen and ultraviolet A (PUVA), or 308 nanometer (nm) excimer laser, are superior to phototherapy alone. Gawkrödger *et al.* recommended that topical vitamin D analogues in combination with NB-UVB or PUVA therapy should not be used in the treatment of vitiligo.(Gawkrödger, Ormerod et al. 2008)

5. Conclusion

Vitiligo is generally considered to be an autoimmune disorder. There is preliminary evidence that vitamin D deficiency could be causally related to a variety of autoimmune diseases. There have been some reports showing good responses to topical vitamin D analogues alone or as part of combination treatment with phototherapy. However, future studies are required to evaluate the relationship of serum vitamin D levels and vitiligo, as well as to elucidate the effects of vitamin D in vitiligo. The utility of topical vitamin D agents in the treatment of vitiligo also needs to be substantiated.

6. References

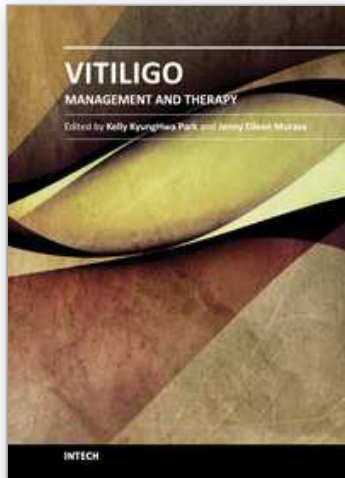
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