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The Role of Topical Vitamin D in Vitiligo: A Narrative Literature Review

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ABSTRACT

Vitamin D plays a role in the process of melanogenesis, namely increasing L-Dopa cells, inducing differentiation of immature melanocytes, and increasing melanocyte activity. The use of vitamin D in dermatology is in the treatment of vitiligo, psoriasis vulgaris, atopic dermatitis, verruca vulgaris, and alopecia. Vitiligo is an autoimmune disease of the skin in the form of depigmentation due to the destruction of melanocytes by T cells. The clinical manifestations of vitiligo are white macular lesions and no scale, asymptomatic, and symmetrical. Vitiligo can affect the patient's quality of life, so accurate therapy is needed. Standard therapy in vitiligo needs further research to find accurate therapy with minimal side effects. Topical vitamin D is a vitiligo therapy with minimal side effects. Several types of topical vitamin D with therapeutic effects in the field of dermatology are calcipotriol, calcitriol, tacalcitol, maxacalcitol, and hexafluoro-1,25 dihydroxyvitamin D3 with various dosages and preparations. The role of vitamin D in melanogenesis and immunomodulators as monotherapy or in combination with topical corticosteroids has been shown to be effective in the treatment of vitiligo. This literature review was on the role of topical vitamin D in the treatment of vitiligo.

1. Introduction

Vitamin D is a substance of the secosterol hormone group and is fat-soluble.^{1,2} Currently, vitamin D is known as an important prohormone substance in human organ systems. Vitamin D plays a role in the regulation of bone metabolism, regulates cell proliferation and differentiation, and is an immunomodulator.³ In the skin, vitamin D can increase tyrosinase activity and melanogenesis through nuclear hormone receptors. This receptor is called the vitamin D receptor (VDR). VDR levels were found to be elevated in vitiligo patients. Vitamin D exerts a significant effect on the activity of melanocytes and keratinocytes through various mechanisms. In

vitro studies prove that vitamin D3 can increase tyrosinase activity and melanogenesis so that it can help the repigmentation process.^{4,5} Some examples of vitamin D in use in dermatology are calcipotriol, calcitriol, tacalcitol, maxacalcitol, and hexafluoro-1,25 dihydroxyvitamin D3.⁶ Vitamin D and vitamin D analogues have anti-inflammatory effects and inhibit T cell proliferation and cytokine production, as well as reduce the capacity of monocytes to stimulate T cell proliferation and stimulating cytokine production from T cells.⁷ This is the basis for the use of vitamin D as an agent for vitiligo therapy. This literature review was on the role of topical vitamin D in the treatment of

vitiligo.

Vitiligo is an autoimmune disease of the skin in the form of depigmentation due to the destruction of melanocytes by T cells.^{2,8} The prevalence of vitiligo can be different in each population due to genetic and environmental differences. The prevalence of vitiligo is estimated to range from 0.5% to 1%.^{8,9} Vitiligo can occur at any age but usually occurs before the third decade. In most of the population, the lesions appear before the age of 20 years. Other studies suggest symptom onset occurs before the age of 12 years.⁸

Vitiligo is a multifactorial disease. Vitiligo is associated with genetic predisposition, autoimmune, and environmental factors. Melanocytes in vitiligo patients tend to be abnormal and more sensitive to changes in cellular processes, making it easier to produce reactive oxygen species (ROS). The accumulation of ROS will activate a protein cascade so that melanocytes initiate the release of danger signals, resulting in activation of the immune response. The immune response is mediated by T cells cluster of differentiation (CD) 8+. CD8+ cells will go to abnormal melanocytes to be destroyed.⁸

Manifestations of vitiligo are white macular lesions, no scales, and asymptomatic. There is an efflorescence of the lesions on examination using Wood's lamp. The distribution of the lesions is symmetrical and can begin in any area of the body. Depigmented macules in exposed areas of the skin can impair the patient's mental health. Various studies have shown that most vitiligo patients feel that they have received social stigma from the surrounding environment, have low self-confidence in their body condition, and suffer from mental problems. This can affect the patient's quality of life, so accurate therapy is needed. Some of the treatment options for vitiligo include topical corticosteroid therapy, topical calcineurin inhibitors, phototherapy and combination therapy, psychological interventions, depigmentation therapy, non-traditional therapy, and surgical therapy. There are still drawbacks to this therapy, such as side effects of long-term corticosteroid use, the risk of cancer in the long-term use of calcineurin inhibitors, limited

phototherapy facilities, and relatively expensive surgical therapy.⁸⁻¹⁰ This has caused a lot of research to be conducted to find other therapies with high efficacy and minimal side effects so as to increase the choice of therapy in the future.

Topical vitamin D, such as calcipotriol, is often used in the treatment of vitiligo. Calcipotriol is often combined with topical corticosteroids. Case reports show that the effect of using calcipotriol and topical betamethasone dipropionate is more significant when used in combination than with monotherapy.¹¹ Meta-analysis studies of several randomized clinical trials (RCTs) have shown that combination therapy (narrowband-ultraviolet B) NB-UVB with topical vitamin D showed significant results compared to NB-UVB as monotherapy, but several other RCT studies did not show such results.¹² Research on the use of topical vitamin D as a therapeutic agent for vitiligo is still relatively small.

Topical vitamin D

Vitamin D is a fat-soluble substance of the secosterol hormone class. Vitamin D consists of two main forms, namely ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). Ergocalciferol (vitamin D₂) comes from plants, while cholecalciferol (vitamin D₃) comes from animals. The main source of vitamin D in humans comes from skin synthesis with the help of sunlight. Exposure to ultraviolet B (UVB) light to 7-dehydrocholesterol (7-DHC) will cause the formation of previtamin D₃ in the skin. Previtamin D₃ is an isothermal isomeric form of vitamin D₃.¹³ The synthesis of vitamin D depends on the intensity of ultraviolet (UV) radiation and depends on the season and altitude of the region. Melanin and sunscreen significantly reduce the production of vitamin D.³ The advantage of previtamin or vitamin D₃ is that it can be destroyed by sunlight, so it does not cause vitamin D poisoning.⁶

Vitamin D₃ is then bound by vitamin D binding protein (DBP) in the blood to be carried to the liver. In the liver, hydroxylation occurs to produce 25-hydroxyvitamin D₃ [25(OH)D₃] or calcidiol. This form

is the most abundant form in blood circulation, so it is used as a biomarker of vitamin D status. Substance $25(\text{OH})_2\text{D}_3$ will go to the kidneys and be filtered by the glomerulus. In the proximal tubule, $25(\text{OH})_2\text{D}_3$ is metabolized by the enzyme 25 hydroxyvitamin D-1- α -hydroxylase (CYP27B1) to $1,25(\text{OH})_2\text{D}_3$ or calcitriol, which is the active form of vitamin D regulated by serum calcium and phosphorus levels, parathyroid hormone, fibroblast growth factor, as well as vitamin D levels.¹³ Fibroblast growth factor causes transport of sodium-phosphate in kidney and small intestine cells and can suppress calcitriol synthesis. The efficiency of renal, intestinal, and phosphorus absorption of calcium is increased due to the effect of calcitriol. It also induces CYP24 enzyme expression. The enzyme will balance $25(\text{OH})_2\text{D}_3$ and calcitriol to calcitroic acid, which is biologically inactive and soluble in water.

Vitamin D can also be obtained from food or supplements. Some foods that contain vitamin D3 are fish meat and some types of mushrooms. Another form of vitamin D is vitamin D2. Vitamin D2 is mostly obtained from supplements. Vitamin D plays an important role in calcium and phosphate metabolism and bone formation. Vitamin D also plays a role in the immune system by reducing the activity of specific immune responses but increasing non-specific immune responses.⁷

Role of vitamin D in melanogenesis

Melanogenesis is the process by which melanocytes produce melanin. Melanocyte precursors are called melanoblasts. Melanoblasts are scattered in several organs of the body. In the skin, melanoblasts will develop into melanocytes and are found in the stratum basale of the epidermis and hair follicles. Melanocytes and keratinocytes form a unit for producing and distributing melanin. This unit is called the epidermal melanin unit.¹³ Melanin plays an important role in protecting human skin from the harmful effects of UV exposure. Exposure to UV light on the skin results in the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby causing skin abnormalities such as deoxyribonucleic acid (DNA)-

damaged epidermal hyperplasia, collagen breakdown, and inflammation. Stem cell factor (SCF), adrenal noradrenaline, α -melanocyte-stimulating hormone (α -MSH), and Wnt hormone are involved in the physiological response of melanogenesis. These factors and hormones interact with c-Kit, adrenergic receptors, melanocortin 1 receptor (MC1R), and Wnt receptors. MC1R will regulate 3,5-cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA), increase cAMP-response element binding protein (CREB) and increase microphthalmia-associated transcription factor (MITF) in the nucleus. Increased MITF activates tyrosinase-related protein (TRP1) in the Golgi apparatus. The next process is the synthesis of blackish brown melanin, namely eumelanin, and yellowish red melanin, namely pheomelanin. TRP1 migrates to melanosomes to continue the synthesis process. The process of formation of eumelanin and pheomelanin consists of four stages. The stages start from tyrosine which is converted to dihydroxyphenylalanine (DOPA), then DOPAquinone, and then converted to DOPACHrome or cysteinylbenzothiazine. The formation of pheomelanin involves the coupling of glutathione or cysteine with DOPAquinone which is converted to cysteinylDOPA or glutathionylDOPA. The formation of eumelanin involves the conversion of DOPAquinone to L-3,4-dihydroxyphenylalanine (L-DOPA) or leukodopachrome without glutathione or cysteine.

Tyrosinase plays a role in the process of melanogenesis as well as regulates melanin production through the oxidation of the amino acid tyrosine. Tyrosine is a natural phenolic component in the human body. This explains why phenolic components can act as tyrosine analogs in melanocytes and increase cellular stress by increasing ROS production and triggering the unfolded protein response. The term unfolded protein response refers to a regulatory mechanism for increasing protein expression on endoplasmic reticulum function. This process keeps protein synthesis by the endoplasmic reticulum properly folded. Vitamin D increases tyrosinase activity and melanogenesis through the

vitamin D receptor (VDR). VDR levels were found to be elevated in vitiligo patients.^{4,5}

Research has shown that 1,25(OH)₂D₃ or calcitriol can increase L-3,4-dihydroxyphenylalanine-positive (DOPA) cells. Research by Watabe et al. proved that calcitriol could induce the expression of endothelin B receptors or also called endothelin receptor-B (EDNRB), in immature melanocyte cells. This causes the differentiation of immature melanocyte precursors, thereby accelerating the formation of melanin. In vivo studies, calcitriol causes the activation of melanocytes and keratinocytes. This process involves the elongation of the dendrites after exposure to UV radiation. Increased melanocyte activity causes tyrosinase activity to increase so that microphthalmia transcription factor (MITF) levels increase. This process causes the deposition of melanin in the epidermis. Previous research has proven that calcitriol has a protective function for melanocytes. These substances protect melanocytes from apoptosis by forming sphingosine-1-phosphate (S1P). The function of SIP is to inhibit ceramide as a pro-apoptotic precursor at the cellular level. Ceramide functions in the process of apoptosis and autophagy. The process of inhibiting the apoptotic precursors so that apoptosis in melanocytes can be inhibited.⁴

The role of vitamin D as an immunomodulator

Vitamin D can affect innate immunity and adaptive immunity through the regulation of receptors for T lymphocytes, B lymphocytes, macrophages, and dendritic cells. Calcipotriol is a synthetic analogue of vitamin D₃ with an immunomodulatory effect. The immunomodulatory effect is the ability to modify the immune system by increasing or decreasing the immune system response.⁵

Innate immunity is the body's first defense immune system in preventing infection. The role of vitamin D, namely calcitriol in innate immunity, is to increase the production of defensin β 2 and cathelicidin antimicrobial peptide (CAMP) by macrophages, monocytes, and keratinocytes so as to increase the microbial activity of these cells. Calcitriol also

enhances chemotaxis, autophagy, and phagolysosomal fusion in non-specific immune cells. In addition, calcitriol can also increase the function of physical defense, especially in epithelial cells.¹⁶

Adaptive immunity is the body's second defense immune system after innate immunity. The immune system is specific, and the memory system. The component of adaptive immunity consists of B cells and T cells. Both play a role in autoimmune reactions. Calcitriol is known to suppress the adaptive immune system through down-regulation of the response by T helper 1 (Th1) cells. Calcitriol inhibits the production of pro-inflammatory cytokines, such as interferon (IFN)- γ , interleukin-6 (IL-6), IL-2, and tumor necrosis factor- α (TNF- α). Calcitriol can also increase the activity of Th2 cells and regulatory T cells (Treg) and decrease the activity of Th17 cells. Th17 cells will produce IL-17. IL-17 plays an important role in the pathogenesis of several autoimmune diseases. Calcitriol prevents Nuclear Factor of Activated T-cells (NFAT) and Runt-related Transcription Factor 1 (RUNX1) from binding to the IL-17 promoter and inhibits RAR-related Orphan Receptor Gamma2 (ROR γ t). Both components are IL-17 transcription factors. The effect of vitamin D on helper T cell differentiation is mediated by the effect of helper T cells on dendritic cells. Dendritic cells are responsible for the differentiation of T cells into effector cells accompanied by a pro or anti-inflammatory cytokines. Dendritic cell modulation is very important in initiating and maintaining adaptive immune responses and self-tolerance. This process will stop autoreactive T cells. The effect of vitamin D on self-tolerance is the reason why vitamin D can be used as a topical therapy in autoimmune diseases.¹⁶

Pharmacodynamics of vitamin D

The main function of vitamin D was previously known to maintain bone structure through calcium and phosphorus homeostasis, but now it is known that vitamin D also functions in regulating cell proliferation, differentiation, apoptosis, and immune modulation. The performance of vitamin D is mediated

by VDR through interaction with the retinoid X receptor (RXR) to form a VDR-RXR heterodimeric complex.¹⁷ The VDR-RXR complex binds to deoxyribonucleic acid (DNA)-binding sites or vitamin D response elements. This can induce or suppress genes containing these elements.¹³

Apart from expressing VDR, keratinocytes can also synthesize vitamin D from the 7-DHC precursor to convert vitamin D into the active metabolite calcitriol.¹⁷ Vitamin D affects skin proliferation and differentiation directly or through interactions with calcium. Most of the in vitro studies have shown that the effect of vitamin D on keratinocyte proliferation and differentiation is dose-dependent. At low concentrations (10⁻⁹ M or less), calcitriol increases keratinocyte proliferation, whereas at high concentrations (10⁻⁸ M) inhibits proliferation and enhances differentiation. Calcitriol stimulates keratinocyte differentiation through increased synthesis of the structural components of involucrine, transglutaminase, loricrine, and cornified envelope filaggrin. The effect of vitamin D on keratinocyte differentiation is also mediated by increased intracellular calcium levels due to stimulation of calcium receptors, increased expression of phospholipase C- γ 1, and increased ceramide formation. Vitamin D also regulates keratinocyte differentiation through interaction with the VDR.¹³

A balance of keratinocyte proliferation and differentiation is necessary to maintain the epidermal barrier. Research by Hong et al. in 2010 proved that topical application of calcitriol could restore the permeability of the epidermal barrier. Vitamin D enhances cornified envelope structural protein synthesis. Calcitriol also regulates glycosphingolipid production for lipid barrier formation.¹⁸

Several studies have proven the role of vitamin D in modulating the immune system. The target of calcitriol is Th cells so that it can suppress proliferation and modulate Th cell production of cytokines. VDR expression in T and B cells only functions immunologically in active and proliferating cells, so it is suspected that there is an antiproliferative role of

calcitriol in T and B cells.¹⁹ Vitamin D inhibits T cells from producing IL-2 and IL-6 and inhibits TNF transcription, granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNA, cytotoxic T cells, and natural killer (NK) cell activity.¹⁷

Pharmacokinetics of vitamin D

Topical vitamin D administration has been started since 1985. One randomized controlled trial concluded that topical vitamin D could increase serum vitamin D levels.²⁰ Metabolism of topical vitamin D administration does not go through first-pass metabolism in the liver. The half-life of vitamin D₃ is between 36-72 hours. Vitamins are fat soluble, can enter adipocytes, and are stored in the subcutaneous and omentum.³

Indications and contraindications

The use of topical vitamin D has been approved by the Food and Drug Administration (FDA) in several skin diseases, such as psoriasis vulgaris. The use of topical vitamin D has begun to be used in skin diseases such as vitiligo, atopic dermatitis, skin diseases with keratinization disorders and acantholytic disorders, scleroderma conditions, papulosquamous and eczematous conditions, cutaneous neoplasms and dyskeratotic disorders, and verruca vulgaris.⁶

Calcipotriol is currently widely used for the treatment of psoriasis, congenital ichthyosis, palmoplantar keratoderma, keratosis pilaris, and Darier's disease. Calcipotriol is also used in the treatment of prurigo nodularis, morphea, and vitiligo.¹⁷ Calcipotriol should not be used on the face and skin folds as it causes irritation.²¹

Side effects of vitamin D

Side effects of using topical vitamin D are skin irritation and dermatitis. The use of high doses may affect calcium homeostasis, making it contraindicated for patients with impaired calcium or bone metabolism.⁷ Metabolism of calcipotriol is relatively fast when used topically, so it is less likely to cause

hypercalcemia. At cumulative doses of less than 100 g/week, topical calcipotriol is safe to use. At doses of 300-360 g/week, hypercalcemia may develop but improves after three days of discontinuation of therapy. Irritation may occur in lesions and perilesional but will subside after discontinuation of therapy. The addition of corticosteroids as adjuvant therapy reduces the likelihood of irritation. Mild photosensitivity has been reported with the combined use of topical calcipotriol and UVB.¹⁷

Dosage and preparation

Several types of topical vitamin D in dermatology include calcitriol, calcipotriol, tacalcitol, maxacalcitol, and hexafluoro-1,25 dihydroxyvitamin D₃. Topical calcitriol is available as a 3 mcg/g ointment.²² The level of irritation is lower than calcipotriol, so it can be applied to the face and skin folds. Calcitriol tolerance is also better than calcipotriol. The maximum dose is 200 g/week with 35% body surface involvement. UVA, UVB, and NB-UVB significantly degrade calcitriol, so these drugs should be applied after radiation if used in conjunction with phototherapy.⁶

Calcipotriol is a synthetic analogue of calcitriol. Calcipotriol can bind to the VDR with a similar affinity to calcitriol.¹⁷ Calcipotriol is available as a 50 mcg/g cream or ointment and is applied 1-2 times a day. Calcipotriol is also available in the form of a solution of 50 mcg/mL and can be applied to the scalp or applied 1-2 times a day. The maximum dose of calcipotriol is 5 g/kg or 360 g/week. Hypercalcemia may occur if the dose is more than 100 g per week. The toxicity of calcipotriol is similar to that of vitamin D poisoning. Increased absorption of calcium and phosphate can cause hypercalcemia, hyperphosphatemia, parathyroid suppression, hypercalciuria, and hyperphosphatemia. Calcipotriol can be used long-term with a broad level of safety and is clinically proven effective. This drug is often used interchangeably with topical corticosteroids, such as calcipotriol, on weekdays and corticosteroids on weekends.⁶

Tacalcitol is available as an ointment or cream at 2 mcg/g, 4 mcg/g, and 20 mcg/g.²² This drug binds more strongly to high-affinity vitamin D receptors than calcitriol and affects skin inflammation, epidermal proliferation, and keratinocyte differentiation. The drug binds to plasma proteins, and its metabolites are excreted mainly in the urine and feces. Dosage once daily for ≥ 8 consecutive weeks. The efficacy and safety of tacalcitol have been proven in the literature. The combination of tacalcitol with NB-UVB phototherapy applied twice weekly in the treatment of vitiligo showed a synergistic effect by increasing c-Kit messenger ribonucleic acid (mRNA) in irradiated melanocytes. The lesions healed faster because the total UVB dose was reduced and showed excellent tolerability without phototoxic side effects.⁶

Maxacalcitol or oxacalcitriol is available as an ointment or lotion at 25 mcg/g.²² Hexafluoro-1,25 dihydroxyvitamin D₃ or F6-1,25(OH)₂D₃ is a new fluorinated derivative of calcitriol. Experimental research proves F6-1,25(OH)₂D₃ has ten times greater biological potential and long-lasting effect in inhibiting proliferation than calcitriol. The use of maxacalcitol did not increase blood or urine parameters and did not enter the circulation in large quantities so that it did not cause toxicity.⁶

Monitoring drug use

Laboratory tests on the use of topical vitamin D include total serum calcium, albumin-adjusted calcium, 24-hour urinary calcium, phosphorus, creatinine clearance, and urinary calcium-creatinine ratio.⁶ Topical calcitriol does not improve laboratory results for these parameters, so routine monitoring of serum calcium is not recommended. The examination is only recommended for certain medical conditions, such as in patients with a predisposition to hypercalcemia. If lab results show hypercalcemia on topical vitamin D, treatment should be discontinued until laboratory results return to normal.²³

Vitiligo

Vitiligo is an autoimmune disease with depigmentation disorders. Vitiligo manifestations in the form of white macules on the skin. Vitiligo can affect appearance, so it can have a negative impact on the quality of life and patient self-confidence. This also has an impact on the psychology of vitiligo patients due to societal stigma.²

Pathogenesis of vitiligo

Vitiligo is caused by various factors that influence each other. The initial triggering factors for vitiligo are unknown, but genetics and environmental factors are often suspected as triggering factors for vitiligo. These two things can trigger autoimmune disorders in skin melanocytes.^{2,24} Genetic factors are important factors in the course of vitiligo. Surveys show mothers with vitiligo have a 6% risk of children with the same condition. In twins with vitiligo in one child, the other child has a 23% risk of suffering from vitiligo within a certain time.

Genetic factors determine individual susceptibility and immune response to environmental exposures such as UV exposure, stress, and free radicals. Exposure to some of these agents will trigger neurohormonal activity, such as the release of catecholamines and other neuropeptides. Increased levels of neurotransmitters can be toxic to cells and trigger vasoconstriction of blood vessels so that cells will experience hypoxia. Both of these cause the production of reactive oxygen species (ROS) to increase. Furthermore, free radicals will trigger the process of apoptosis in melanocytes. Free radicals also act as antigens so that they have the potential to trigger an immune response. Immune response to antigens is one of the triggers for autoimmune vitiligo. Another theory states that UV exposure also triggers the production of ROS and an increase in the protein high-mobility group box 1 (HMGB1). Increased ROS and HMGB1 will cause activation of caspase enzymes resulting in apoptosis in melanocytes. The pathogenesis of vitiligo also involves the theory of melanocytorrhagy. Melanocytorrhagy is a

phenomenon where melanocytes are lost periodically over a long period of time. This theory explains that ROS and structural changes in melanocytes can cause an increase in tenascin. Tenascin is a component of the extracellular glycoprotein matrix with the effect of preventing the attachment of melanocytes to fibronectin. The increase in tenascin causes the adhesion between melanocytes and the basement membrane to be disturbed. This causes melanocytes to undergo a transepidermal elimination process. The term transepidermal elimination is the exit of skin components or foreign skin material to the exterior of the skin through the epidermis. Minor trauma is the main cause of transepidermal elimination. This causes melanocytes to decrease chronically so that the production of the melanin pigment is reduced.²

Patients with vitiligo are at risk for other autoimmune diseases such as autoimmune thyroiditis, type 1 diabetes mellitus, Addison's disease, and other autoimmune diseases. Several studies have shown that vitiligo patients have genetic variants that encode components of innate immunity and adaptive immunity. Genetic variations in innate immunity in vitiligo patients include NLR family pyrin domain containing 1 (NLRP1), interferon induced with helicase C domain 1 (IFIH1), Caspase-7, apoptosis-related cysteine peptidase (CASP7), C1q and TNF Related 6 (C1QTNF6), TIR-domain-containing adapter-inducing interferon- β (TRIF), while adaptive immunity includes forkhead box P3 (FOXP3), BTB Domain And CNC Homolog 2 (BACH2), CD80, CC Motif Chemokine Receptor 6 (CCR6), Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22), interleukin 2 receptor alpha deficiency (IL2R), α -Granzyme B (α -GZMB), human leukocyte antigen (HLA) class I and II.² Several studies have concluded defects in melanocytes, and Environmental factors play an important role in the onset of vitiligo.¹⁸⁻²⁰

Genetic variation in patients with vitiligo causes the locus in the gene to control innate immunity to be more susceptible. This causes abnormalities in regulating the transmission of components of innate immunity such as natural killer (NK) cells and the

release of pro-inflammatory proteins in response to cellular stress.²¹⁻²⁴ Molecular heat-shock protein (HSP) is one of the important pro-inflammatory proteins. The inducible HSP70 molecule (HSP70i) is one of the HSP molecules with unique characteristics because it can carry and present melanocyte-specific antigen T lymphocytes in lymphoid tissue, causing an immune response.²

Cytotoxic T lymphocytes play a role in melanocyte damage. Cytokine secretion due to the innate immune response causes T cells to be stimulated and localize melanocytes when experiencing cellular stress. Chemoattractant proteins in T cell migration are chemokines, IFN- γ and IFN- γ induced chemokines (CXCL9 and CLCX 10) expressed in large amounts in the skin of vitiligo patients. Both components play a role in disease progression.²

Oliver et al.'s research with factory workers research subjects showed vitiligo developed in the palm area first. The factory workers wear gloves containing phenolic components such as monobenzene. In addition to phenolics, chemicals from catechols such as hair dyes, adhesives, and skin are also associated with the pathogenesis of vitiligo.^{2,24}

Research has shown that melanocytes in vitiligo patients experience intrinsic defects, thereby reducing the capacity of cells to deal with cellular stress.

Various cells in the epidermal layer, including melanocytes, are often exposed to environmental stressors such as UV radiation and harmful chemicals that can cause increased ROS production. In general, melanocytes are able to reduce these components. Melanocytes in vitiligo patients are more susceptible to damage from exposure to stressors. This can be proven by microscopic examination of the skin of vitiligo patients. Melanocytes at the periphery of skin lesions of vitiligo patients show enlargement of the endoplasmic reticulum and abnormalities in mitochondria and melanosome structure. This indicates an increase in cellular stress. H₂O₂ levels at the cellular level also increased, while levels of the enzyme catalase decreased. The enzyme catalase functions to protect cells against damage caused by free radicals. This causes the cells to be susceptible to damage.²

Manifestations of vitiligo are white macular lesions, no scaling, and asymptomatic with efflorescence at the edges of the lesions on examination using Wood's lamp. The distribution of the lesions is symmetrical and can begin in any area of the body. Lesions also appear on the mucous membranes of the mouth and nose. In the hair, the color changes to white or gray (Figure 1).⁸



Figure 1. Clinical features of vitiligo.⁸

Management of vitiligo

Treatment for vitiligo includes topical therapy, phototherapy, depigmentation therapy, non-traditional therapy, surgical therapy, and psychological therapy.⁸ Topical agents in the treatment of vitiligo other than vitamin D are corticosteroids and calcineurin inhibitors. The advantage of using topical corticosteroids is that they are easy to use and less expensive. Side effects of topical corticosteroids include skin atrophy, telangiectasia, hypertrichosis, acneiform eruptions, and striae.^{8,25}

Topical calcineurin inhibitors are considered safer than topical corticosteroids. Topical calcineurin inhibitors can be applied to the face and around the face. Long-term use of topical calcineurin inhibitors increases the risk of developing malignancy.^{8,25}

The use of topical vitamin D as a therapeutic agent for vitiligo

Therapy in vitiligo patients is often a problem for patients. This is because vitiligo therapy requires a long period of time, and the progressivity of the results of therapy is relatively slow. Topical corticosteroids are the gold standard therapeutic agents for the treatment of vitiligo, but there are various side effects of long-term topical corticosteroid therapy.¹¹ The use of vitamin D in the treatment of vitiligo is common, but research on its effectiveness, efficacy, safety, and optimum dosage is still very limited. Various studies have proven satisfactory results in the use of calcipotriene. This proves that topical vitamin D has an optimal therapeutic effect on skin repair in vitiligo patients.¹¹

The research by Zahoor et al. proved that the use of topical 0.005% calcipotriol monotherapy compared to the use of topical 0.05% betamethasone dipropionate monotherapy showed optimal results. Both agents are quite effective when used as monotherapy. The use of betamethasone with a pulse dose of 5 mg for 2 days a week showed a decrease in the distribution of lesions by 89%. The use of calcipotriol monotherapy showed a 52% reduction in

the lesion area. This proves that topical vitamin D has an effect on the initiation of the repigmentation process.¹¹

Several cases report high effectiveness of calcipotriol and betamethasone dipropionate when used in combination. The combination of calcipotriol with topical corticosteroids is the best treatment option.¹¹ In the RCT study of Ronghua et al. comparisons were made of the use of NB-UVB therapy as monotherapy, a combination of NB-UVB with topical calcineurin inhibitors, and a combination of NB-UVB with topical vitamin D analogues showed different results. Two RCT studies proved excellent results, both in combination therapy using NB-UVB and topical calcineurin inhibitors and NB-UVB as monotherapy. Significant results can also be seen in combination therapy with topical vitamin D analogues using either tacalcitol or calcipotriol. Several studies have failed to show a significant comparison between NB-UVB as monotherapy or in combination with topical vitamin D. Several other sources prove that the addition of vitamin D to NB-UVB therapy does not provide optimal results. These differences in results should be studied further.¹²

2. Conclusion

The role of vitamin D in melanogenesis is to accelerate the formation of melanin. The role of vitamin D as an immunomodulator is to increase the non-specific immune system but suppress the specific immune system, namely Th cells. Through these two roles, vitamin D in the topical application has proven to be effective in the treatment of vitiligo, either in monotherapy or in combination with topical corticosteroids.

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