The effectiveness of combination Vitamin D with phototherapy for vitiligo treatment

Putu Ayu Gadis Laksmitha Ksata Yadnya*, Putu Ayu Paramitha Saraswaty²

ABSTRACT

Vitiligo represents a pigmentary skin disorder that impacts the layers of the skin, characterized by the absence of pigmentary cells in the epidermis, which causes the body to develop white patches and macules. However, additional research is necessary to comprehensively grasp the mechanisms that can be obtained using vitamin D with phototherapy for vitiligo treatment. Current evidence indicates that vitamin D substantially influences keratinocytes and melanocytes' activities through various mechanisms. Therefore, this literature review was organized to assess the effectiveness of combining vitamin D with phototherapy for vitiligo treatment. A search was conducted across four electronic journal databases: Google Scholar, PubMed, Taylor & Francis, and ScienceDirect. Inclusion criteria involved studies with vitiligo respondents, explaining the effectiveness of combining vitamin D with phototherapy for vitiligo treatment and detailing the benefits or harms of using this combination in vitiligo patients. Only five studies met the specified criteria and are consequently considered deserving of further assessment. The combination of phototherapy and vitamin D is postulated to manage vitiligo effectively. Phototherapy enhances repigmentation, ensuring a harmonious color reconciliation with the innate skin tone. Simultaneously, Vitamin D assumes a pivotal role in modulating the activity of keratinocytes and melanocytes, operating through diverse mechanisms. Based on this article review, it can be concluded that phototherapy with vitamin D is more effective in treating vitiligo than phototherapy only.

Keywords: vitiligo, vitamin D, phototherapy, light therapy.


INTRODUCTION

Skin, the body's largest organ, covers the entire external surface and consists of three layers: the epidermis, dermis, and hypodermis. These layers differ significantly in anatomy and function.¹ These layers can be impacted by skin diseases such as vitiligo. The absence of pigmentary cells in the epidermis causes vitiligo, a pigmentary skin condition that manifests as white macules and patches on the body.² It is often associated with various autoimmune disorders, with thyroid abnormalities being the most common. Although the etiology of vitiligo remains unknown, several theories attempt to elucidate its pathogenesis. Vitiligo is believed to impact 0.5%-2% of the global population. Even though vitiligo is often disregarded as a cosmetic concern, it can have profound mental repercussions and substantially disrupt daily life. In 2011, a global consensus recognized and classified segmental vitiligo separately from other types of vitiligo. In vitiligo, there is a selective loss of melanocytes, leading to non-scaly, chalky-white macules.³

The clinical manifestations of vitiligo are characterized by the symmetrical distribution of white spots on the body, particularly in individuals with dark skin. The lesions appear as distinct, depigmented, or pearly white macules and patches with convex margins that might be oval, circular, or linear. They are centrifugally inflated and range in size from millimeters to centimeters. Trichrome, Quadrichrome, and Marginal Inflammatory vitiligo are notable clinical variations. One prominent clinical manifestation is the Koebner phenomenon, which is characterized by the progression of vitiligo at locations that are vulnerable to trauma, such as cuts, burns, or abrasions. First lesions usually appear on the hands, feet, forearms, and face, and they frequently have a perioral or periocular distribution.⁴⁵ In 2011, an international consensus established a classification for vitiligo, including nonsegmental vitiligo (NSV) and segmental vitiligo (SV). The pivotal decision to distinguish SV from other types of vitiligo was made due to its significant prognostic implications.⁶⁷

There are various interventions available for treating vitiligo, one of which is phototherapy. Phototherapy emerges as a pivotal and efficacious therapeutic modality in dermatology, exerting a profound influence on managing diverse skin disorders. This therapeutic approach precisely delivers non-ionizing radiation to the skin, specifically targeting the ultraviolet portion of the electromagnetic spectrum.⁸ Phototherapy has been employed for over 3000 years, with historical roots in sun exposure combined with extracts from Psoralea corylifolia and Ammi majus in ancient India and Egypt.⁹¹⁰ In generalized vitiligo, phototherapy, which includes PUVA and NB-UVB.
therapy, is the main line of treatment. On the other hand, topical medications and excimer laser therapy are frequently used to treat localized disease. Even while phototherapy works, it necessitates regular clinic visits and extensive treatment periods that can last months or years, occasionally producing less-than-ideal results.\(^{11}\)

A necessary fat-soluble steroidal hormone, vitamin D, is produced in the skin's outer layers when exposed to ultraviolet B radiation or can be consumed via foods like fish and mushrooms. Through a variety of ways, it has a substantial impact on how keratinocytes and melanocytes are modulated.\(^{12,13}\) Vitamin D and its metabolites have important roles in numerous physiological functions,\(^{14}\) including maintaining calcium balance, supporting bone mineralization, and serving as a treatment option for various skin disorders, including psoriasis and vitiligo.\(^{15,16}\)

Further research is imperative to comprehensively understand the mechanisms underlying the effectiveness of combining vitamin D with phototherapy for treating vitiligo. Existing evidence indicates that vitamin D significantly modulates the activity of keratinocytes and melanocytes through diverse mechanisms, offering a promising approach for vitiligo management and overall health enhancement. Despite numerous investigations into the effectiveness of standalone vitamin D treatment for vitiligo, research on the combined use of vitamin D and phototherapy is scarce. Consequently, this article review seeks to provide a more profound insight into the efficacy of amalgamating vitamin D with phototherapy for vitiligo treatment.

**METHODS**

We searched four electronic journal databases, Google Scholar, PubMed, Taylor & Francis, and ScienceDirect, to identify scientific articles addressing the effectiveness of combining vitamin D with phototherapy for vitiligo treatment. The criteria for selecting scientific articles as references for this literature review include the use of either the English or Indonesian language without timeframe restrictions. The inclusion criteria comprised studies involving respondents with vitiligo, describing the benefits or harms of using vitamin D combined with phototherapy in patients with vitiligo.

**RESULTS**

A collective of 488 studies was initially discovered through searches using designated keywords and their publication within the preceding ten years. A meticulous screening process was applied to these studies, incorporating predefined inclusion and exclusion criteria. As a result, only five studies met the specified criteria and are consequently considered deserving of further assessment. These comprise two randomized controlled trials (RCT) and three interventional prospective studies, as outlined in Table 1.

**Pathophysiology of Vitiligo**

Early evidence confirming the heredity of vitiligo was the discovery that the condition was more common in those directly related to those who already had it. While vitiligo affects about 1% of the general population, a patient’s sibling has a 6% chance of getting the condition, and an identical twin has a 23% chance. Furthermore, individuals with vitiligo and their family members exhibit an elevated susceptibility to other autoimmune disorders. Genome-wide association (GWA) studies were used to validate these initial findings by identifying several shared genetic variations among vitiligo patients.\(^{22,23,24}\)

One of the main factors in the pathophysiology of vitiligo is oxidative stress. Epidermal cells, encompassing melanocytes, endure continuous exposure to environmental stressors like UV radiation and diverse chemicals, resulting in an augmented generation of reactive oxygen species (ROS). Although healthy melanocytes proficiently counteract these stressors, those from individuals with vitiligo appear more susceptible. Melanocytes from perilesional vitiligo skin are particularly noteworthy for having abnormalities in their mitochondria and melanosome structure and a dilated endoplasmic reticulum (ER), signs of increased cellular stress. Patients with vitiligo also have increased epidermal H2O2 and decreased catalase levels, critical for protecting cells from oxidative damage.\(^{25,26,27}\)

The precise initiation events of vitiligo remain incompletely understood. Diverse studies suggest that a confluence of intrinsic deficiencies in melanocytes and exposure to particular environmental factors may be pivotal in disease onset. The melanogenesis process, wherein melanocytes generate melanin, encompasses multiple intricate steps. In this process, tyrosinase is essential to regulate melanin production by oxidizing a naturally occurring phenol, the amino acid tyrosine.\(^{28}\) Chemical phenols can be used as tyrosine analogs within melanocytes, according to in vitro research. Increased cellular stress levels are the result of it. Increased generation of reactive oxygen species (ROS) and the start of the unfolded protein response (UPR) could be signs of this stress, which would then trigger innate inflammation.\(^{22,29,30}\)

**The Utilization of Phototherapy in Vitiligo**

In dermatology, phototherapy is a well-known and effective therapeutic approach that significantly impacts the management of various skin conditions. It is purposefully applied to the skin for multiple dermatoses, mainly using the ultraviolet portion of the electromagnetic spectrum. This covers common spectrums, including UVA, UVA-1, PUVA, and UVB, which can also be represented as NB-UVB or BB-UVB.\(^{31,32}\) There are diverse variants of phototherapy, including lasers, photodynamic therapy (PDT), bath-PUVA, and extracorporeal photochemotherapy.

Phototherapy continues to be an extensively employed treatment modality for various skin diseases, including vitiligo.\(^{33,34}\) It has been determined that NB-UVB is better than PUVA for several reasons, including better repigmentation and a more skin-like color match. By maximizing the delivery of narrowband UVB radiation in the most beneficial UV spectrum segment, between 312 and 313 nm, NB-UVB offers a safer profile. Reducing the amount of UV radiation that is unnecessarily exposed significantly lowers the danger of severe burns or exposure to harmful UV ranges. Moreover, NB-UVB avoids the unfavorable side effects associated with psoralens usage in traditional PUVA therapy.\(^{35,36}\)
Photontherapy is still a safe, helpful treatment with a wide range of clinical uses.\textsuperscript{37} It treats vitiligo in two ways: by suppressing the immune system and by boosting melanocyte activity.\textsuperscript{10,38} Due to its effect that causes T-cell death, phototherapy is still a safe, helpful treatment with a wide range of clinical uses.\textsuperscript{37} It treats vitiligo in two ways: by suppressing the immune system and by boosting melanocyte activity.\textsuperscript{10,38} Due to its effect that causes T-cell death,

### Table 1. Summary of the effectiveness of combining vitamin D with phototherapy for vitiligo treatment

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design Study</th>
<th>Country</th>
<th>Sample</th>
<th>Age</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kullavanijaya and Lim, 2004.\textsuperscript{17}</td>
<td>Interventional prospective study</td>
<td>USA</td>
<td>20 patients with symmetrical vitiligo</td>
<td>17 – 68</td>
<td>Each patient received three sessions of narrowband ultraviolet B (NB-UVB) therapy weekly—an ointment containing calcipotriene-treated lesions on the patient's left side.</td>
<td>Seventeen patients completed the study. Eight patients, accounting for 35%, experienced significant repigmentation following 67-180 treatments. During 29–114 sessions, seventeen individuals showed noticeably better results with NB-UVB and calcipotriene treatment. Surprisingly, the disparities were still present in six individuals at the study's end. Notably, there were no recorded adverse consequences. In treating patients with vitiligo, topical calcipotriene combined with NB-UVB represents a feasible therapeutic approach that should be considered.</td>
</tr>
<tr>
<td>Goktas et al., 2006.\textsuperscript{18}</td>
<td>Interventional prospective study</td>
<td>Turkey</td>
<td>28 patients with generalized symmetric vitiligo</td>
<td>&gt; 15</td>
<td>Three times a week, each patient received NB-UVB treatment. Topical calcipotriol cream was applied to the lesions (right side of the body). The course of treatment was continued for a full six months.</td>
<td>The combination therapy group exhibited an average response rate of 51 ± 19.6%, while those on NB-UVB alone had a response rate of 39 ± 18.9%. These results imply that topical calcipotriol applied concurrently with NB-UVB improves its effectiveness in treating vitiligo. The outcome of the combination therapy is a decrease in the treatment period and cost. It also leads to early pigmentation with no side effects. Topical tacalcitol increases the improvement of repigmentation. It also increases the response rate in vitiligo patients than NB-UVB alone. In conclusion, using tacalcitol ointment and NB-UVB is an excellent alternative therapy for patients with generalized vitiligo.</td>
</tr>
<tr>
<td>Leone et al., RCT 2006.\textsuperscript{19}</td>
<td>RCT</td>
<td>Italy</td>
<td>32 individuals with symmetrical lesions and generalized vitiligo</td>
<td></td>
<td>Tacalcitol ointment was applied to the lesion daily. Participants also underwent NB-UVB phototherapy twice a week.</td>
<td></td>
</tr>
</tbody>
</table>
downregulation of inflammatory cytokines, and overexpression of interleukin 10, it is essential for stopping the active course of the disease. Additionally, it decreases the quantity of antigen-presenting epidermal Langerhans cells. Vitiligo can be treated with phototherapy by PUVA or UVB (NB-UVB, excimer laser, or lamp). The first phototherapy regimen to be used with good results was called PUVA; however, it has several drawbacks, such as phototoxic effects, nausea, and an increased risk of skin cancer. Moreover, it cannot be used on pregnant or young children. NB-UVB has proven to be a more effective treatment than PUVA and has fewer and milder side effects. Apart from the demonstrated benefits in treating vitiligo, NB-UVB phototherapy can potentially mitigate the harm from oxidative stress, which is thought to play a role in the illness's etiology. Consequently, NB-UVB is currently regarded as the gold standard of care and the most effective kind of phototherapy for vitiligo.  

### The Effectiveness of Combination Vitamin D with Phototherapy

According to the reviewed article, phototherapy with vitamin D is more effective than phototherapy alone in treating vitiligo. The main way that vitamin D helps the establishment of a well-structured epidermal barrier is by encouraging the differentiation and maturation of keratinocytes. Consequently, this preserves the skin's integrity and speeds up the vitiligo patient's repigmentation process. Furthermore, vitamin D has immunomodulatory effects by reducing overreactions from the immune system that could lead to the loss of melanocytes in vitiligo. Additionally, it increases melanin pigment synthesis in melanocytes, which helps pigmentation of areas of the skin that have lost pigment. 

Vitamin D plays a role in controlling the release of several cytokines and growth factors that support melanocyte survival and proliferation. It has been demonstrated that vitiligo-affected skin has aberrant calcium absorption in keratinocytes and melanocytes and elevated thioredoxin levels. This abnormal absorption of calcium can inhibit melanogenesis by reducing tyrosinase activity. 

In the studies discussed in this review article, one of the vitamin D compounds used is calcipotriol, which is a synthetic derivative of calcitriol or vitamin D. The presence of defective calcium transport systems in vitiligous melanocytes and keratinocytes can impact tyrosinase activity, ultimately inhibiting melanin formation. Another vitamin D also used is taclecal, a synthetic vitamin D3 combined with NBUVB to enhance repigmentation, reduce total UV radiation exposure, and minimize side effects like erythema and irritation. Vitamin D3 analogs bind to the vitamin D receptor (VDR), eliciting their effects through genomic and nongenomic pathways. In the context of vitiligo, the nongenomic mechanism holds particular significance. Vitamin D3 enhances intracellular calcium concentration by hydrolyzing phosphatidylinositol phosphate. The elevation in intracellular calcium levels governs diverse cellular functions, encompassing the proliferation and differentiation of keratinocytes and melanocytes, induction of melanogenesis, and augmentation of tyrosinase activity. Additionally, it downregulates the skin infiltration of effector CD4+ T cells in vivo, thereby inhibiting T-cell activation.

Despite the potential benefits of combining vitamin D with phototherapy in treating vitiligo, there are several limitations to consider in the existing research. A research gap, shown by the insufficient number of references available, has limited our ability to draw a definitive conclusion. Additionally, the available studies vary in methodology. Furthermore, the study periods were relatively short, making comparing and generalizing the findings challenging. Overall, the available evidence suggests the effectiveness of combining vitamin D with phototherapy for vitiligo treatment. Therefore, further studies are needed to overcome these limitations and provide a more comprehensive understanding.
CONCLUSION

In summary, phototherapy alone does not seem to be as helpful in treating vitiligo as vitamin D combined with it does. This combination decreases the cumulative doses of NB-UVB radiation, speeds up the process of skin repigmentation, and increases the amount of skin repigmentation. Current data indicates that combining vitamin D with phototherapy may help vitiligo patients’ condition more than phototherapy alone, despite the lack of studies on this combination’s efficacy in treating the condition. The effects of vitamin D3 on intracellular calcium concentration and its regulatory function in several cellular processes bolster its possible advantages in treating vitiligo. More carefully planned research is necessary to overcome current obstacles and offer a more thorough understanding of this treatment method.

CONFLICT OF INTEREST

No competing interests were declared.

FUNDING

The author(s) received no financial support for this article’s research, authorship, and publication.

AUTHOR CONTRIBUTION

All of the authors equally contributed to preparing this article until the article was published.

REFERENCES


