The role of oral vitamin D in several skin diseases

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Abstract

Vitamin D has many benefits for body and skin health. One of them is to regulate the immune system, both cellular and humoral. The pathogenesis of many skin diseases is associated with disturbance in regulation of cellular immune system. Research on the relationship between blood level of vitamin D and several diseases in dermatology is currently very advanced. Oral vitamin D is known to have many functions that play a role in the pathogenesis of several diseases of the skin. Therefore, its current use as a primary or supplemental therapy has been widely studied. Knowledge on various skin diseases with indication of oral vitamin D use is important to be understood, especially in association with some chronic diseases requiring long-term therapy. The effects of using oral vitamin D analogues are minimal, but hypervitaminosis D might cause uncomfortable symptoms for patients. Therefore, it is important to understand and regulate the amount of doses of oral vitamin D supplements prescribed.

Keywords: oral vitamin D, skin disease

Introduction

Vitamin D offers many therapeutic benefits in dermatology, both as monotherapy and combination with other medications. Vitamin D is available in topical, oral, and parenteral forms. Currently, topical vitamin D analogues have been widely used, in contrast with their oral and parenteral preparations.

This article will review the metabolism, role in dermatology, serum level dosage requirement, hypovitaminosis, and hypervitaminosis of vitamin D. Furthermore, several studies on benefits of oral vitamin D in skin diseases such as vitiligo, psoriasis, atopic dermatitis, urticaria, and melanoma will be discussed. Oral vitamin D can be considered as one of the therapeutic options.

Vitamin D metabolism

Vitamin D is a precursor of calcitriol involved in calcium homeostasis that can be obtained from food and produced by human body. Vitamin D from food is available in two forms, vitamin D2 (ergocalciferol) contained in plants and vitamin D3 (cholecalciferol) contained in animals.1,2 Vitamin D produced by human body is a result of synthesis in the skin and serves as the main source of vitamin D. The skin is also a target organ of its active metabolite. The synthesis process is influenced by skin color, age, clothing, indoor activity, sunscreen use, and geographical location according to latitude.2

Vitamin D synthesis

Synthesis of vitamin D in the skin begins with the conversion of 7-dehydrocholesterol (provitamin D3) to previtamin D by ultraviolet B.1 Previtamin D3 undergoes isomerization and changes form to vitamin D3. The formed vitamin is bound by vitamin D-binding protein (DBP) to enter the circulation. Some of the formed vitamin D3 in the skin is transported to the liver and metabolized by 25-hydroxylase (CYP27A1) enzyme to become 25(OH)D3 (calcidiol). Calcidiol is converted to
24,25(OH)2D3 by 24-hydroxylase (CYP24A1) and subsequently to 1,25(OH)2D3 (calcitriol) by 1-hydroxylase (CYP27B1) enzyme. Vitamin D obtained from food, either vitamin D2 or D3, will be absorbed by small intestinal cells through passive diffusion. The fastest absorption occurs in duodenum while largest absorption occurs in distal ileum. Vitamin D enters the circulation through lymphatic system, joining the chylomicrons and bound by DBP to be distributed to the liver and extra-hepatic tissues.

Most of vitamin D transported to the liver will undergo hydroxylation at the C-25 carbon by CYP27A1 to form calcidiol. Calcidiol is not stored inside the cells but directly released to circulation to be bound by DBP. Calcidiol will undergo hydroxylation at the C-1 carbon atom to form calcitriol in every cell of the body, particularly in extra renal tissues such as placenta, breast, lung, colon, prostate, and liver by CYP27B1 enzyme. This process takes place in renal proximal tubules. Formed calcitriol is the active metabolite of vitamin D that will subsequently exert its effect in cells with vitamin-D receptors (VDR).

**Vitamin D catabolism**

Catabolism is an important process for vitamin D inactivation and excretion. Hydroxylation at C-24 carbon atom can occur in calcidiol and calcitriol. This reaction is catalyzed by CYP24A1 enzyme. The enzyme has the largest activity in the kidney but is also found in other tissues with VDR. Calcitriol and 24,25(OH)2D3 will be converted to calcitroic acid. The end product of vitamin D catabolism will be excreted in stool and urine.

**Vitamin D role related to skin diseases**

**Keratinocyte proliferation and differentiation**

Keratinocyte is one of the cells expressing VDR, CYP27B1, and CYP24A1 enzymes. Calcitriol plays a role in keratinocyte regulation by inducing differentiation and limiting keratinocyte proliferation. VDR is present in all epidermal layers, particularly in basal layer and its activity is influenced by calcitriol level in the cells (Figure 1). Co-regulatory proteins such as SMRT, NCoR, SRC1, and NCoA2 also affect VDR activity. Failure in VDR and/or CYP27B1 enzyme function will result in excessive keratinocyte proliferation.

**Immune system regulation**

VDR is found in almost every cells in the immune system, including monocyte, macrophage, lymphocyte, mast cell, natural killer cell, and dendritic cell. Aside from having VDR, those cells also has CYP27B1 enzyme activity and therefore are able to synthesize and secrete calcitriol (Figure 2).

In natural immunity, toll-like receptor (TLR) on the antigen presenting cells (APC) surface is activated upon binding with antigenic component. This transmembrane receptor activation will induce VDR and CYP27B1 activity and propagate calcitriol production in cells. Calcitriol stimulates APC to produce anti-microbial peptides cathelicidin and defensin and increases phagocytic capacity of APC.

Calcitriol also plays a role in mast cell activation and produces interleukin 10 (IL-10) without causing degranulation. Calcitriol maintains mast cell stability and reduces histamine production. Generated IL-10 will inhibit the production of immunoglobulin E-dependent pro-inflammatory...
mediators. Mediators will reduce leukotriene C4 involved in eosinophil activation process.4

In adaptive immunity, CYP27B1 enzyme activity increases when T and B lymphocytes are activated. Calcitriol inhibits adaptive immune system by limiting proliferation and differentiation of B lymphocyte to plasma cell. Calcitriol inhibits proliferation and function of T helper-1 and T helper-17, but enhances T helper-2 and regulatory T cells. Furthermore, calcitriol also influences dendritic cell capacity by decreasing its ability in presenting antigen. Calcitriol’s effect in suppressing adaptive immune system is beneficial for several condition such as autoimmune diseases.6,7

Vitamin D serum level testing

Examination of plasma calcidiol is the most sensitive vitamin D level test. Calcidiol has a half-life of 19-31 days and demonstrates the level of vitamin D acquired from food and synthesized in the skin for several weeks to months. The Endocrine Society found the normal level of calcidiol to be 30-100 ng/mL, with insufficiency occurs at 21-29 mg/mL, and deficiency occurs under 20 ng/mL.1,2

Vitamin D requirement

According to Recommended Dietary Allowance (RDA), vitamin D requirement for newborns and infants under three months old is 400 International Unit (IU). Breast milk contains small amount of vitamin D and therefore breastfed infants are recommended to have adequate sun exposure. For infants older than three months old, vitamin D requirement is 400 IU to support growth and bone mineralization. For adults and people over the age of 70, vitamin D requirement is 600 IU and 800 IU, respectively. Adequate sun exposure as many as one minimal erythema dose on face, neck, and legs for 15 minutes will result in 7200 IU for each exposure.6 Adult population with high risk of vitamin D deficiency should consume 1000 IU of vitamin D daily to retain normal level in blood. Infants under one year old with vitamin D deficiency are recommended to receive 400 IU supplementation daily. Vitamin D requirement according to the Nutritional Adequacy (Angka Kecukupan Gizi) in Indonesia in 2013 is different from the one recommended by RDA, as shown in table 1.

Hypovitaminosis D

Hypovitaminosis D is a condition in which serum calcidiol level is below the normal range. Early symptoms are not specific and may be subjective, including weakness, fatigue, drowsiness, mood disorder, and immunodeficiency. More severe state leads to Rickettsia with osteoporosis, bone fracture, teeth and hair growth anomaly, as well as early closure of epiphyseal plate in children.

Table 1. Vitamin D requirement according to the Nutritional Adequacy (Angka Kecukupan Gizi) in Indonesia9

<table>
<thead>
<tr>
<th>Age group</th>
<th>IU requirement (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>200 (5)</td>
</tr>
<tr>
<td>7-11 months</td>
<td>200 (5)</td>
</tr>
<tr>
<td>1-18 years</td>
<td>600 (15)</td>
</tr>
<tr>
<td>19-50 years</td>
<td>600 (15)</td>
</tr>
<tr>
<td>51-70 years</td>
<td>600 (15)</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>600 (15)</td>
</tr>
</tbody>
</table>

Hypervitaminosis D

Excessive intake of vitamin D is associated with increasing calcidiol level in circulation. Symptoms of toxicity are not specific and may include dizziness, vomiting, appetite loss, constipation, weakness, and weight loss.1,2 In hypervitaminosis D, intestinal calcium absorption increases and bone calcium resorption occurs, causing hypercalcemia, decreasing level of parathyroid hormone and glomerular filtration rate, leading to calcium homeostasis disturbance.1 Increased calcium and phosphate level in the long term will cause calcinosis and calcium phosphate deposition in kidneys, heart, lungs, and blood vessels.1,2 Hypercalciuria will induce calcium and phosphate precipitation in kidney tubules and form stones.2

Benefits of oral vitamin D administration in dermatology

Vitiligo

Mechanism of vitamin D role in vitiligo is demonstrated in immune system regulation, particularly in T helper cells as previously mentioned. There were two studies during the past five years that reported successful treatment using oral vitamin D administration in vitiligo.

In 2013, Danilo et al.10 conducted an open-label study in sixteen vitiligo patients aged 18 years old and above in Sao Paulo Brazil. In this study, 35,000 IU oral vitamin D3 was administered daily for six months and demonstrated satisfactory
result. Patient evaluation was performed using documentations before and after therapy. Lesion size was calculated using quartile grading scale. This study found 32% patients had up to 75% repigmentation, 32% had 50% repigmentation, and the remaining number had up to 25% repigmentation.

In addition to adult population, oral vitamin D can also be administered in pediatric population with vitiligo. A study conducted by Chris and presented in The 9th Joint Meeting of Pediatric Endocrinology in 2013 in Italy found that oral vitamin D3 administration combined with topical corticosteroid significantly reduced lesion size. This study was performed for six months in 30 children aged ten years in average who had never had any treatment before. This study compared the combination of topical corticosteroid with oral vitamin D and topical corticosteroid alone. The result showed lesion size reduction from 66.1 cm² to 48.0 cm² in case group, compared to increased lesion size from 34.8 cm² to 53.5 cm² in control group. Unfortunately, this study has not been published and the dose of oral vitamin D is yet to be confirmed.

Psoriasis

In psoriasis, keratinocyte proliferation occurs in a very high rate. The current therapy aims to control the process. The role of vitamin D in this condition is to limit keratinocyte proliferation.

Perez et al. conducted a study in 1996 in 85 psoriasis patients receiving 400 IU of oral vitamin D3 every evening with an increasing dose of 400 IU every two weeks for 36 months. Evaluation was performed monthly by calculating psoriasis area severity index (PASI) score before and after the therapy. This study found 88% patients improved, 26.5% had total remission, 26.3% had partial remission, and 25.3% only had little remission.

In 2013, Danilo et al. conducted an open-label study in patients with psoriasis, administering oral vitamin D3 with dose of 35,000 IU daily for six months. This study was performed in two dermatology clinics in Sao Paulo Brazil to nine patients over the age of 18. Patients evaluation involved PASI score calculation before and after the therapy. The study found all patients had significant lesion improvement. Statistical data analysis showed a negative correlation between calcidiol level and PASI score in psoriasis patients. The higher the calcidiol level, the smaller the patient’s PASI score; this demonstrates clinical improvement of psoriatic lesion with oral vitamin D administration.

Atopic dermatitis

Some studies on oral vitamin D administration in atopic dermatitis still give controversial results. There are differences in concluding whether blood vitamin D level is associated with atopic dermatitis lesion severity. Factors contributing to such result remain studied.

Amestejani et al. in 2012 conducted a randomized, double-blind, placebo-controlled trial in 60 children divided into two groups. In case group, oral vitamin D3 with dose of 1,600 IU was administered for sixty days. Lesion severity was assessed using scoring atopic dermatitis (SCORAD) and three item severity score before and after therapy. The result showed significant improvement in lesion severity in case group while placebo group did not show any improvement.

In 2013, a study by Hatta et al. compared oral vitamin D administration in adult population with atopic dermatitis. This was a double-blind randomized controlled study on sixty subjects divided into two groups. In this study, cathelicidin level was measured in regards to its role in the pathogenesis of atopic dermatitis. The case group had vitamin D3 with dose of 4,000 IU daily for three weeks and control group had placebo. The study found correlation between increased vitamin D level with cathelicidin level in skin lesion, but no correlation between healthy skin of patients without atopic dermatitis and healthy skin of patients with atopic dermatitis. There was no correlation between the severity of atopic dermatitis lesion and blood vitamin D level. Atopic dermatitis lesion severity was assessed using Rajka-Langeland score.

A cross-sectional study conducted in Children’s Hospital of Wisconsin in 2013 by Chiu et al. evaluated 94 children aged 1-18 years with atopic dermatitis. Evaluation of lesion severity was performed using SCORAD system. The study found no correlation between vitamin D level and atopic dermatitis lesion severity.

In 2013, Camargo et al. conducted a randomized, double-blind, placebo-controlled study in 104 children aged nine years on average with atopic dermatitis lesion during winter in Boston. The subjects received oral vitamin D3 with dose of 1,000 IU daily for a month. Lesion severity was assessed using the eczema area and severity index (EASI) before and after therapy. The study found significant improvement in EASI score in all subjects.
Urticaria

Oral vitamin D therapy in urticaria provides the benefit of a significant symptom improvement. A retrospective case series presented in 2011 by Goetz reported 50,000 IU of vitamin D administration as an adjunctive therapy in urticaria. Therapy was given every week for twelve weeks in 57 patients. The study found 70% patients had total lesion improvement that started to occur at the fourth week of therapy.

Similar to previous studies, a double-blind prospective study in Nebraska in 2014 by Rorie et al. found symptoms improvement following oral vitamin D3 administration. The study was performed in 42 patients with chronic urticaria who previously had received therapy consisting of cetirizine, ranitidine, or montelukast for twelve weeks. The first group received a dose of 600 IU and the second group received 4,000 IU daily for twelve weeks. Urticarial lesion severity was assessed using urticaria activity score before the study, at the first and sixth weeks, and at the end of the study. The study found 40% symptom improvement in the second group but no improvement in the first group.

The role of vitamin D in immune system is also beneficial for physical urticaria due to various causes. Administration of vitamin D for several months can improve the existing symptoms. A case report by Varney and Warner in 2014 showed five cases of urticaria in allergy and immunology clinic of St. Helier Hospital receiving oral vitamin D3 with dose of 2,000-5,000 IU daily for 2-4 months that demonstrated significant symptoms improvement. Difference in age, ethnicity, and previous therapy did not influence the result. Patients were followed-up and various recurrence rates were found in 2-48 months later.

In the same year, Boonpiyathad et al. conducted a case-control prospective study in sixty patients with chronic spontaneous urticaria in allergy clinic of Phramongkutklao Hospital Bangkok. The patients had received therapy consisting of 10 mg cetirizine twice daily, 10 mg loratadine twice daily, 5 mg levocetirizine twice daily, 5 mg desloratadine twice daily, or 180 mg fexofenadine twice daily. Patients with vitamin D level <30 ng/mL received oral vitamin D. Previous study had used oral vitamin D3, while this study used oral vitamin D2 with dose of 20,000 IU daily for six weeks. Severity was evaluated using urticaria activity score. This study found correlation between the level of vitamin D and the severity of urticarial lesion.

Conclusion

Vitamin D and its analogues offer benefits for management of various skin diseases. Several studies demonstrated correlation between skin diseases and patients’ vitamin D level. Limited number of studies on vitamin D as a primary or adjunctive therapy for those diseases contributes to its limited use. Standardization of vitamin D dose administered is necessary, but since not all vitamin D supplementation gives clinical improvement, further studies are warranted.

References

10. Danilo C, Finamor, Rita S, Luiz C, Neves, Gutierrez, et al. A pilot study assessing the effect of prolonged administration of high daily doses of vitamin D on the clinical course of


