

# The Role of Vitamin D on the Wound Healing Process: A Case Series

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**Introduction:** Vitamin D is an essential steroid hormone that consists of two forms, namely vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), which can be obtained from exposure to sunlight, synthesis of vitamin D in the skin, food and dietary supplements. Prevalence of vitamin D deficiency in several countries including Indonesia is still high, while the role of vitamin D is very important including accelerating the wound healing process, increasing the immune system, anti-inflammatory, and anti-bacterial.

**Purpose:** This case report aims to find out the role of vitamin D in the wound-healing process in the oral mucosa.

**Case Reports:** Two men went to the Oral Disease Clinic with complaints of canker sores on the oral mucosa for more than a month accompanied by pain. Intra-oral condition in the first patient showed multiple ulcers with yellowish white base surrounded by erythematous areas, well-defined, irregular with a size of 1.5 × 1 cm and 1 × 0.5 cm on the right and left buccal mucosa, while intra-oral in the second patient, a single ulcer with a base was found yellowish colour surrounded by erythematous area, oval measuring 3x1 cm, clearly demarcated with induration.

**Results:** Laboratory examination of vitamin D in both patients showed decreased levels of vitamin D with values of 28.7 and 9.8 ng/mL.

**Conclusion:** Vitamin D supplementation has shown effectiveness in wound-healing processes in the oral mucosa.

**Keywords:** vitamin D, role, immune system, wound healing, mouth ulceration

## Introduction

Vitamin D is an essential steroid hormone consisting of two forms, namely vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) and can be obtained from exposure to sunlight, synthesis of vitamin D in the skin, food and supplements. These essential steroid hormones are fat soluble and have endocrine, paracrine and autocrine functions.<sup>1-6</sup> Vitamin D deficiency is frequently reported worldwide with a prevalence of around 1 billion people and around 50% of the global population has vitamin D insufficiency, therefore further research is needed to determine its effects on various human organs and systems. The prevalence of vitamin D deficiency in Europe, the United States and the Middle East has been reported to range from 20% to 90%. Countries such as Australia, India, Africa, South America, Turkey and Lebanon have been reported to have similar trends indicating that vitamin D deficiency is a problem for both developed and developing countries.<sup>3,5,7</sup> Indonesia has a fairly high vitamin D deficiency in women aged 50 years and over.<sup>7</sup>

Vitamin D plays a role in maintaining the homeostasis of various biological systems, such as accelerating wound healing, immune system (regulating the physiology of the immune response and reducing overregulation of T-cell responses), helping bone formation, skin (modulating the proliferation, differentiation, and apoptosis of keratinocytes as well as local immune responses), contributes to the regulation of the cardiovascular system, tumor suppressor properties by inhibiting cell proliferation and assisting differentiation and apoptosis, suppresses inflammatory reactions, antibacterial (induces the production of  $\beta$ -defensins and cathelicidins), kidney (increases calcium reabsorption), inhibits parathyroid hormone production, and intestine (increases calcium absorption).<sup>1,2,4,6,8-11</sup>

According to some studies, in patients with recurrent aphthous stomatitis, the serum level of 25(OH)D is significantly lower compared to healthy people of the same age and sex. Oztekin et al recommended vitamin D supplementation as a supportive treatment in patients with recurrent aphthous stomatitis, whereas Bakr et al reported that oral and topical vitamin D had a beneficial effect in reducing oral mucositis. Udeabor et al reported that more than 74% of patients with squamous cell carcinoma of the oral cavity showed decreased serum vitamin D levels compared to a control group without a history of cancer. A positive relationship between the risk of squamous cell carcinoma of the oral cavity and vitamin D deficiency, especially at levels below 25 ng/mL, can develop malignant neoplasms by 1.65-fold. Anand et al concluded that patients with squamous cell carcinoma of the oral cavity who received vitamin D3 at a dose of 1000 International Units (IU) per day for 3 months showed reduced side effects associated with chemotherapy and improved quality of life compared to patients who did not receive vitamin D3.<sup>3</sup>

This case report discusses the role and mechanism of vitamin D in the ulcer healing process.

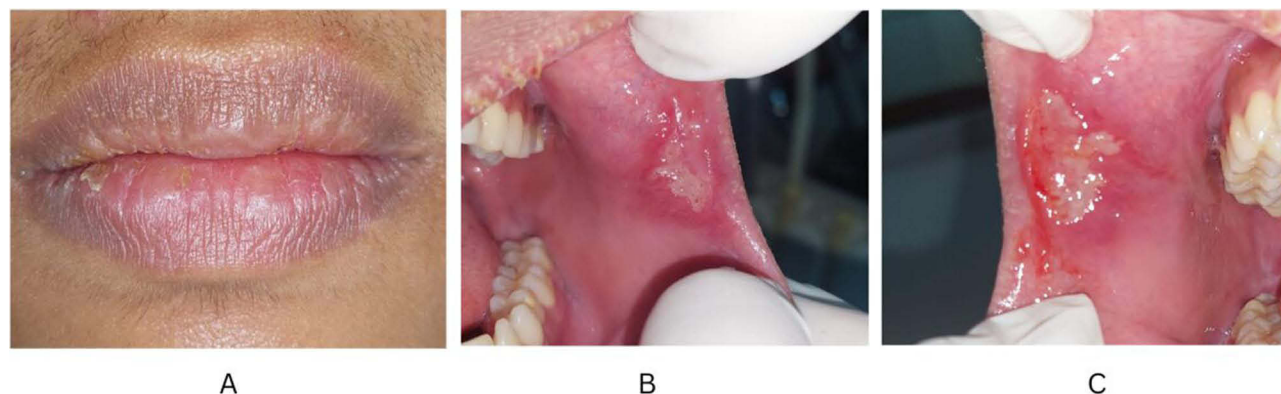
## Case Reports

In the first case, an 18-year-old male patient came to the oral disease clinic with complaints of canker sores that did not heal for one month. Recurrent canker sores recur but heals within a week. History of smoking, fever and systemic diseases were denied and consuming mineral water per day. The drugs that the patient has been taking for more than a month are betadine gargle and policresulen.

The results of extra-oral examination showed dry, exfoliative lips and intra-oral examination found an ulcer with a white base surrounded by erythema, well-defined border, irregular with a size of  $1 \times 0.5$  cm, and pain in the left buccal mucosa, then another ulcer was found with a white base surrounded by erythema, well-defined border, irregular, with a size of  $1.5 \times 1$  cm, and pain in the right buccal mucosa (Figure 1). Based on clinical examination, the patient was diagnosed with major type of recurrent aphthous stomatitis (RAS) with the results of laboratory investigations reporting that the patient had vitamin D insufficiency (Table 1).

In the pharmacological treatment, the patient is given hyaluronic acid mouthwash 3 times 10 mL a day before eating, after one hour then smearing triamcinolone acetonide in oral base 0.1% on canker sores 3 times a day, smearing a thin vaseline album on the lips 3 times a day and drink a multivitamin with a vitamin D level of 400 IU once a day, while for non-pharmacological therapy consume 2 liters of mineral water per day, fruits and vegetables. The oral cavity lesions resolved after 3 weeks of therapy (Figure 2). Vitamin D 25-OH levels after therapy showed normal values (Table 1).

In the second patient, a 68-year-old male patient came to the oral disease clinic with complaints of canker sores on the lower labial mucosa since three months ago. History of fever, diabetes mellitus, hypertension, and drug allergy was denied, while smoking habit was admitted by the patient. The drugs that have been consumed by patients to cure canker sores are betadine gargle.



**Figure 1** Clinical features at the first visit; (a) Dry and exfoliative lips; (b) another ulcer with a white base surrounded by erythematous areas, clear boundaries, irregular with a size of  $1 \times 0.5$  cm, sore on the left buccal mucosa; (c) Right buccal mucosa.

**Table 1** Laboratory Examination of Levels of Vitamin D 25-OH

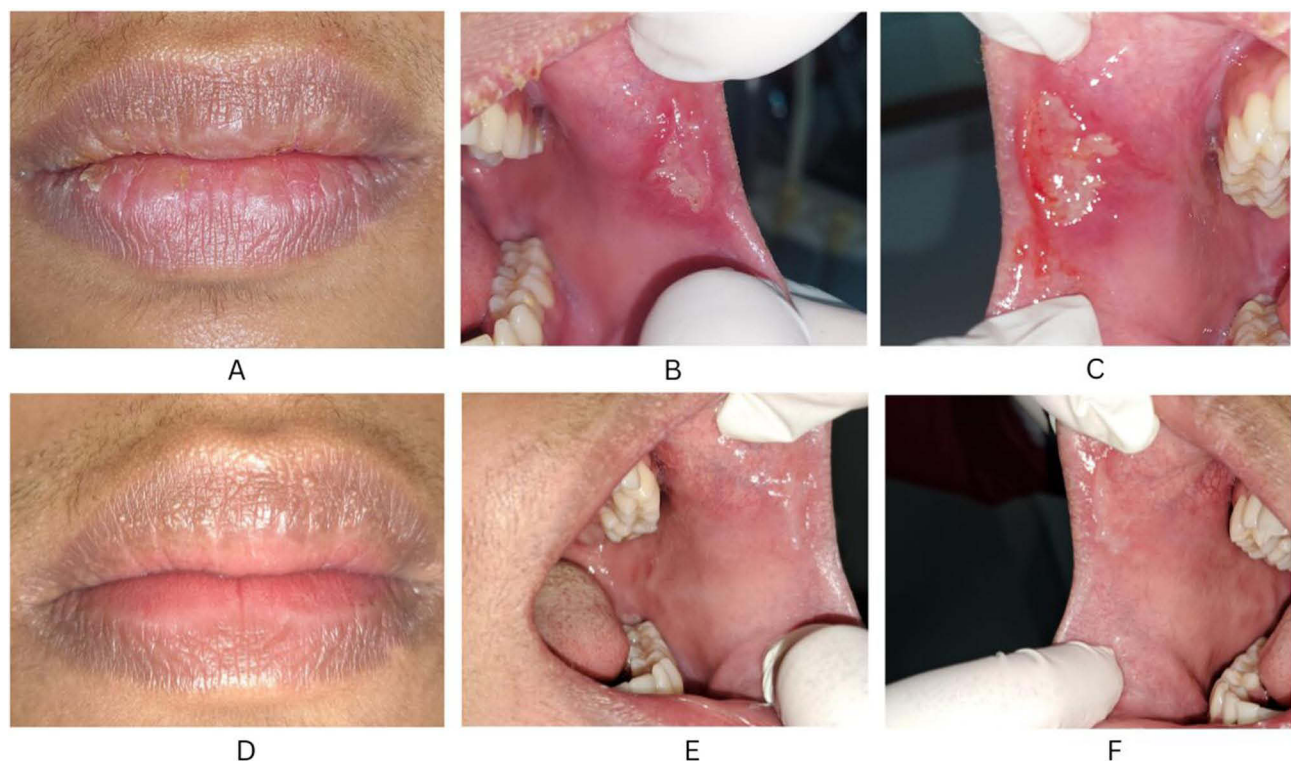
No.	Diagnosis	Vitamin D Levels Before Therapy	Vitamin D Levels After Therapy	Normal value	Intra-Oral
1	Major type SAR	28.7 ng/mL	30 ng/mL	30 ng/mL	White base surrounded by erythema, well-defined border, irregular with a size of 1×0.5 cm on the left mucosa and 1.5×1 cm on the right buccal mucosa
2	TUGSE	9.8 ng/mL	21 ng/mL	30 ng/mL	Single ulcer with yellowish base surrounded by erythematous area, oval, well-defined border with induration and pain et tooth region 43

The results of intra-oral examination found a single ulcer with a yellowish base surrounded by an area of erythema, oval, well-defined border with induration and pain in tooth region 43 (**Figure 3**). Based on examination and clinical picture, the patient was diagnosed with traumatic ulcerative granuloma with stromal eosinophilia (TUGSE) and by laboratory investigations the patient was diagnosed with vitamin D deficiency (**Table 1**).

Pharmacological management of the patient consisted of giving triamcinolone acetonide in oral base 0.1% to canker sores 3x a day, applying a thin layer of vaseline album to the lips 3x a day and taking a multivitamin with vitamin D levels of 400 IU once a day. Patients are also advised to consume 2 liters of mineral water per day, fruits and vegetables. Factors causing trauma are referred to the dental conservation department for treatment. Oral cavity ulcers improved about 3 weeks after therapy and were not accompanied by pain (**Figure 3**). Vitamin D 25-OH levels increased after therapy (**Table 1**).

## Discussion

Recurrent aphthous stomatitis (RAS) is a chronic oral mucosal disorder manifested by a single erosion or ulcer accompanied by a round or oval sore with necrosis in the center and hyperemia along the periphery. The etiology of

**Figure 2** (a–c) Ulcer before treatment; (d–f). Oral cavity lesions resolved 3 weeks later (after treatment).



**Figure 3** (a) Single ulcer with a yellowish base surrounded by erythematous areas, oval, well-defined margins with induration and pain; (b) lesion improved at about 3 weeks of therapy.

the disease is unknown, but dysregulation of the immune response is considered a risk factor, along with genetic defects, local trauma, emotional stress, and vitamin deficiencies.<sup>3</sup> TUGSE (traumatic ulcerative granuloma with stromal eosinophilia) is a rare chronic reactive benign lesion with unclear nature, etiology, and pathogenesis. Still, it is often associated with trauma and self-healing of the oral mucosa. Viruses, poisons, and bites are considered to be harmful agents. Repeated trauma triggers a local immune response that causes changes in tissue antigens or can introduce toxins, microorganisms, endogenous degradation products, or foreign proteins into the tissue. The tongue is the most frequently affected site. However, other sites are also involved, including the buccal and vestibular mucosa, the palatal mucosa, the retromolar area, the gingiva, and the floor of the mouth. TUGSE often manifests as ulcers with raised edges and hardened with a yellowish fibrin base that presents asymptomatic or mild to severe pain. Histological examination reveals a marked ulcerative lesion with a granulomatous, sometimes jigsaw-like appearance with a diffuse polymorphic inflammatory infiltrate of histiocytes, predominantly activated T lymphocytes, and eosinophils, which often extend to the submucosa, deeper muscle fibers and salivary glands.<sup>12,13</sup>

Ulcerations in this case report are RAS major and TUGSE, which experience delays in healing. The first patient was diagnosed with major RAS for one month, and the second patient had TUGSE, which did not heal for three months; then, laboratory investigations were carried out with the results of decreased vitamin D levels with values of 28.7 and 9.8 ng/mL. A 25(OH)D value of 20 ng/mL indicates vitamin D deficiency, while values ranging from 21 to 29 ng/mL indicate vitamin D insufficiency, and a value of 30 ng/mL or 75 nmol/L indicates normal levels.<sup>1,8</sup> The best clinical results from vitamin D supplementation can be provided with daily doses rather than weekly or monthly because daily doses produce serum and tissue concentrations.<sup>8</sup>

Vitamin D helps heal wounds by binding with the vitamin D receptor (VDR) through calcitriol. It regulates the transcription downstream in different target cells by stimulating the production of mitogenic growth factors and receptors like platelet-derived growth factor (PDGF), epidermal growth factor receptors (EGFR), and keratinocyte growth factor receptor (KGFR). These effects are partially mediated by calcitriol-induced keratinocytes. In cultures of keratinocytes treated with calcitriol, the levels of antiproliferative transforming growth factor- $\beta$  (TGF- $\beta$ ) are observed to rise, which suggests that the epidermal overgrowth during the proliferative phase is inhibited. The anti-inflammatory properties of vitamin D are considered to have an antiproliferative effect on skin and mucosal regeneration with suppression of monocytes and inflammation mediated by Langerhans cells. It also decreases keratinocytes expressed from pro-inflammatory cytokines IL-1 $\alpha$ , IL-6, and IL-8 in response to vitamin D3. Vitamin D weakens adaptive immunity and enhances innate immune responses. Calcitriol directly induces the expression of several pairs of antimicrobial peptides, including cathelicidin and defensin  $\beta$ 2, and can recognize microbial toll-like receptor 2 (TLR2) and the cofactor of CD14. These collective activities provide an immunoprotective effect against the colonization of pathogenic organisms.<sup>14</sup>



In addition to administering anti-inflammatory drugs, coating agents, and other therapies for ulcers, a multivitamin regimen is recommended for this case due to the various vitamins and minerals, such as vitamins A, C, E, K, B1, B2, B5, and zinc, which play a role in the wound healing process.<sup>14,15</sup> Another recommendation to further reduce inflammation and speed up healing is mouthwash therapy containing hyaluronic acid and triamcinolone acetonide in an oral base of 0.1%. Hyaluronic acid (HA) is a glycosaminoglycan that has polysaccharides consisting of disaccharide units consisting of N-acetylglucosamine and D-glucuronic acid. Hyaluronic acid (HA) is known to have various biological effects, including cell differentiation, embryological development, inflammation, wound healing, and viscoelasticity, among others.<sup>16</sup> Additionally, triamcinolone acetonide in an oral base of 0.1% is a medium-acting glucocorticoid and a moderate-to-high potency corticosteroid derived from fluorinated prednisolone. The use of corticosteroids can reduce the signs and symptoms of inflammation in the oral cavity, skin diseases, asthma, and allergic rhinitis.<sup>17</sup> Vaseline album is a lip protector, so the lips do not dry and peel.<sup>18</sup> The non-pharmacological therapy is to drink 2 liters of mineral water daily and consume a balanced nutritious diet, fruits and vegetables. Further studies are required to prove its efficacy in general population. They have approved and written the informed consent of case details and all images for the publication of this report. The institution has also approved the publication of this case report.

## Conclusion

Vitamin D supplementation has shown effectiveness in wound-healing processes in the oral mucosa.

## Disclosure

The authors report no conflicts of interest in this work.

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