

DENTINO
JURNAL KEDOKTERAN GIGI
Vol VIII. No 2. September 2023

**VITAMIN D DEFICIENCY AS A RISK FACTOR OF RECALCITRANT RECURRENT
 INTRAORAL HERPES (RIH)**

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ABSTRACT

Background: Recurrent Intraoral Herpes (RIH) is secondary infection due to Herpes Simplex Virus (HSV) which is latent and most often involves lips and oral cavity. RIH infection could be reactivated as triggered by various factors, such as stress, immunosuppressant, hormonal, sunlight exposure or vitamin D deficiency. **Objective:** To describe vitamin D deficiency as a risk factor of recalcitrant RIH. **Case:** A 22-year-old woman came to Oral Medicine Clinic of RSUP. Dr. Hasan Sadikin Bandung with complaints of recurrent stomatitis for two years. Her stomatitis was recalcitrant and recurred several times a month. Intraoral examination revealed ulcers with yellowish-white base surrounded by haloerytem on the right of buccal and tongue lateral and oropharynx. Immunoserology laboratory examination showed an increase of IgG HSV-1 value and vitamin D (25-OH) deficiency. **Case Management:** Patient was given Acyclovir 200mg 5 times daily for a week and Hyaluronic Acid 0.025% mouthwash as well as education to maintain an oral hygiene. Lesions were healed after 10 days therapy. However, 3 days later, lesion on the right buccal recurred with bigger size. Therapy was continued with additional administration of vitamin D and instructions to increase consumption of fruits, vegetables and to bask in the sun. Lesions of recalcitrant RIH were completely healed on the 5th visit or 45 days' therapy. **Conclusion:** Vitamin D plays a role in all of the body's defense mechanisms and could be given to reduce the high recurrence rate of RIH as vitamin D has a protective effect against viral infections, particularly against HSV.

Keywords: Deficiency Vitamin D, Herpes Infection, Recalcitrant, Recurrent Intraoral Herpes.

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INTRODUCTION

Recurrent Intraoral Herpes (RIH) is a secondary infection of latent Herpes Simplex Virus (HSV) which causes a variety of clinical disorders and most often involves lips and oral cavity.^{1,2} There are 2 types of HSV, namely HSV-1 and HSV-2 and both types are caused by a double-stranded DNA (Deoxyribose Nucleic Acid) virus which belongs to the Herpesviridae family.³ The main clinical difference between HSV-1 and HSV-2 is the location of infection: HSV-1 manifests more on the oral mucosa, pharynx and skin (waist up) while HSV-2 is more dominant in the genital area (waist down).^{4,5,6} Transmission of HSV infection is highly dependent on the close contact of secretions between susceptible seronegative individuals and individuals who secrete HSV seropositive and experience 4-7 day incubation.³ Based on the data from World Health Organization (WHO), in 2016, around 3.7 billion people or around 66.6% of the total world population aged between 0 to 49 years were infected by HSV-1 while 491.5 million of world population aged 15 to

49 years or equivalent 13.2% were infected by HSV-2.⁷

The first infection of HSV-1 is known as primary herpetic gingivostomatitis which most commonly occurs in childhood. Once infected, the virus is latent in peripheral nerve neurons. During latency period, the virus does not replicate and is not contagious. However, it could be re-activated at any time which is known as RIH and herpes labialis.⁶ RIH reactivation could be triggered by various factors, both internal and external factors, such as stress, fatigue, trauma, immunosuppression, hormonal disturbances, exposure to sunlight, cold weather, and vitamin D deficiency.^{2,8,9,10} Several recent studies have concluded that vitamin D has an important role in the regulation of the immune system. Vitamin D has several protective effects and potential to prevent infection or reactivation of the herpes virus.¹¹

Vitamin D does not only play an important role in the absorption of calcium and phosphate which are essential for bones and teeth health, but it also has potential immunomodulatory effects which

are related to the regulation of antimicrobial peptides (AMPs) which are good for protection against infections. Several studies have concluded that vitamin D has an antiviral effect that could induce gene expression of AMP namely cathelicidin in the form of LL-37 which functions to block viral entry so as to prevent infection and reactivation of viral. Study on HeLa cells concluded that cathelicidin has the ability to reduce HSV's viral titers and suppress T lymphocytes helper (Th)1 CD4+ and increase Th2 lymphocytes.^{6,10,12,13}

Infection and reactivation of HSV-1 caused a significant increase of m-RNA TLR2 activity as well as proinflammatory cytokines. Vitamin D3 which has been hydroxylated to form 1,25-hydroxyvitamin D3 or calcitriol was an agonist of vitamin D receptor (VDR) which could directly regulate genes and suppress proinflammatory cytokines. Study conducted by Kumar A. et al. in 2018 concluded that vitamin D supplementation to HeLa cells before being infected by HSV-1 was very effective in regulating titers of m-RNA TLR2.^{6,10,12,14} Vitamin D is a secosteroid that plays an active role in signalling pathways to regulate the adaptive immune system. This condition is characterized by the presence of active vitamin D receptors on macrophages, T lymphocytes and B lymphocytes which proves that vitamin D has a much bigger role than for skeletal muscle health.^{14,15} Nowadays, there are still a few studies that examine the important role of vitamin D in reducing the high rate of RIH recurrence. Therefore, this case report aims to describe the vitamin D deficiency as a risk factor for recalcitrant RIH.

CASE

A woman 22 years-old came to the Oral Medicine Clinic of RSUP. Dr. Hasan Sadikin Bandung with complaints of aches and pains due to canker sores on the inside of cheeks, tongue and throat causing difficulties to eat and talk. The patient had repeatedly experienced these symptoms for around 2 years. However, the patient had never been examined by a dentist or had never taken any medicines. Complaints of canker sores appeared and were sometimes preceded by fever, flu and headaches. The patient informed that canker sores recurred about 2 or 3 times a month with a very short healing time span about 2 to 3 days, there were no similar lesions on the other parts of the body. The patient also denied any history of allergies or family history of recurrent oral thrush.

Extraoral examination did not reveal any abnormalities in the lymph nodes however there was any an exfoliative lip. Intraoral examination revealed multiple ulcers, concave, yellowish-white in color, irregular borders, surrounded by

haloerythema areas on the buccal and lateral mucosa of the right tongue tooth region 44 to 45 and oropharynx with varying sizes ranging from 0.3 to 0.5 cm which felt painful and caries 47. [Figures 1A, B and C]. The patient was then referred for laboratory examination of 10 hematology parameters and Ig G anti HSV-1 immunoserology. The results showed that there was no abnormality to the hematological examination but the result of Ig G anti HSV-1 immunoserology test was reactive [Table 1] thus the diagnosis was established as RIH.



Figure 1. Oral manifestations of RIH at the first visit. Ulcerated lesions of the buccal and lateral mucosa of the right tongue and oropharynx (1A, 1B and 1C).

Table 1. Laboratory Result

| Investigations | Result | Normal |
|---------------------|------------------------|--|
| Hematology | | |
| • Hemoglobin | 13.7 | 12–16.5 gr/dL |
| • Erythrocyte | 4.46 | 3.80–5.20 10 ⁶ /μL |
| • Hematocrit | 37.8 | 35–47% |
| • MCV | 84.8 | 80-100 fL |
| • MCH | 28 | 26-34 pg/dL |
| • Eosinophil | 3 | 0-3% |
| • Basophil | 0 | 0-2% |
| • Rod neutrophil | 3 | 3-5% |
| • Lymphocyte | 35 | 18-45% |
| • Monocyte | 8 | 2-11% |
| Immunology | | |
| • IgG HSV1 | Positive > 100 | Negative: < 20 U/mL Borderline: 20-25 U/mL Positive: > 25 U/mL |
| Serology | | |
| • Vitamin D (25-OH) | Low 14.7 (Defisien cy) | 30-40 ng/mL or 75-100 nmol/L |

| | | |
|---------------------|-------------------------|---------------------------------------|
| • Vitamin D (25-OH) | 20.3 (Insuficie ncy) | 30-40 ng/mL or 75-100 nmol/L |
| • Vitamin D (25-OH) | 25,5 (Insuficie ncy) | 30-40 ng/mL or 75-100 nmol/L |

CASE MANAGEMENT

Pharmacological therapy at the first visit was acyclovir 200 mg 5 times a day for 1 week, 0.025% hyaluronic acid mouthwash 3 times a day and instruction to apply a thin layer of 100% *petroleum jelly* 3 times a day. Non-pharmacological therapy provided was in the form of instructions and education to always maintain healthy teeth and mouth, get enough rest, eat high-protein foods and fruits.

At the second visit (a 7 days' follow-up), complaints of pain were decreased, the lesion size on the right buccal mucosa was reduced and lesions on the right of lateral tongue and oropharynx were healed. The patient informed that she routinely using the drugs given regularly. Again, at the second visit the patient was instructed to continue gargling with 0.025% hyaluronic acid 3 times a day and applying a thin layer of petroleum jelly 3 times a day [Figures 2A, B and C].



Figure 2. At the second visit (a 7 days' follow-up) the lesions were improved (2A) and healed (2B and 2C).

At the third visit or after 10 days of therapy, the lesion on the right buccal mucosa was completely healed. The Patient was still given instructions to always maintain the oral hygiene by brushing her teeth at least twice a day, getting enough rest and eating a balanced nutritious diet [Figures 3A, B and C].



Figure 3. The third visit showed healing of lesions on the buccal mucosa and right of tongue lateral including oropharynx (3A, 3B and 3C)

Three days after the third visit, the patient returned with complaints of new canker sores of a larger size in the same location i.e. on the right buccal mucosa, but without prodromal symptoms [Figure 4]. The patient admitted that she had carried out the instructions given, had enough rest and consumed foods of high protein and fruits. Anamnesis was deepened to look for risk factors behind the recalcitrant of RIH. Based on the anamnesis, it was known that the patient was rarely exposed to sunlight as the patient's daily activities and work are mostly done indoors. The patient works as an employee of a private bank in Bandung City. Thus, vitamin D deficiency was suspected as a predisposing risk factor for recalcitrant RIH.



Figure 4. Fourth visit during RIH recurrence. A single ulcerated lesion with a yellowish-white base, clearly demarcated, irregularly surrounded by erythematous and painful areas.

The patient was then referred for a vitamin D (25-OH) immunoserological test. The results showed that the patient's vitamin D (25-OH) level was 14.7 ng/mL, indicating that the patient had vitamin D deficiency. The patient was then treated with 0.025% hyaluronic acid mouthwash and additional supplementation of vitamin D 1,000 IU three times a day as well as instructions to consume foods of high protein and fruits containing vitamin D. A week after the consumption of vitamin D supplementation, the patient was instructed to routinely sunbathe in the morning sun between 09.00 a.m. to 10.00 a.m. for at least 5 to 15 minutes, 2 to 3 times a week. At the fifth visit the lesions were significantly healed [Figure 5].



Figure 5. The ulcerated lesion on the right buccal mucosa was healed and recurrence rate became rare after 30 days' therapy.

The patient was still educated to always bask in the morning sun. During the treatment period, the patient showed cooperative attitude to carry out the given instructions. Based on follow-up communication with the patient a few days after the fifth control, the patient informed that the recalcitrant canker sore was still recurred but over a long period of time. Patient was instructed to continue sunbathing in the morning sun three times a week and to check vitamin D levels every month for up to 6 months.

DISCUSSION

This case report describes the impact of vitamin D deficiency as a risk factor of recalcitrant RIH. RIH is a form of secondary infection of HSV-1 and HSV-2 which generally appears in an oral cavity.^{16,17,18} After primary infection, the virus moves to sensory ganglion via axons and then settles in dorsal ganglia, especially in the trigeminal nerve ganglion and there is a chance of reactivation.^{2,6,16,17,18}

Based on the anamnesis of the patient, it is known that canker sores often recurred. This condition led to suspicion of anemia to the patient and a history of fever prior the appearance of canker sores was suspected of involvement of a viral infection, in particular of the HSV-1 virus. Thus, at the initial visit the patient was advised to carry out hematology laboratory of 10 parameters and also Ig G anti HSV-1 immunoserology tests. The results of the hematological test showed a normal condition however the results of the Ig G anti HSV-1 immunoserological test was reactive with values of > 100 U/mL (**Table 1**). Therefore, the diagnosis was established as RIH.

After infected, HSV could be reactivated at any time through anterograde axonal flow to the site where the primary infection occurred.^{17,18} Virus reactivation could be caused by various factors such as physical and emotional stress, fever, fatigue, excessive exposure to ultraviolet light, hormonal imbalance or if the host has decreased immunity.² Based on the anamnesis of the patient, it is known that canker sores appear 2 to 3 times a month with a short healing period. The high rate of recurrence of RIH as a result of decreased immunity due to

vitamin D deficiency whereas based on the anamnesis, the patient in this case was rarely exposed to the morning sunlight as she works in a closed room with working hours from morning to evening on daily and also lacked consumption of foods containing vitamin D. The result of the patient's vitamin D (25-OH) immunoserological test was 14.7 ng/mL (table 1), which means that the patient has a vitamin D deficiency.

Vitamin D is a fat-soluble steroid hormone derived from 7-dehydrocholesterol. Vitamin D is synthesized endogenously by the skin after exposure to sunlight. However, it can also be obtained through food intake and supplements. After absorption in the intestine, vitamin D is metabolized in the liver and kidneys to produce 25-hydroxyvitamin D [25 (OH) D] consisting of 25 (OH) D2 and 25 (OH) D3. Vitamin 25 (OH) D is known as calcidol and is further converted to 1,25-dihydroxyvitamin D [1,25 (OH) 2D which is known as calcitriol.^{14,19}

The correlation between vitamin D and the immune system began since the discovery of vitamin D receptors (VDR) and CYP27B1 in almost all immune cells including T and B lymphocytes, neutrophils, macrophages and dendritic cells.^{11,14} Liang Yu Lin et al. recently observed several studies and concluded that vitamin D deficiency is closely associated with an increased risk of infection or reactivation of the HSV. Vitamin D supplementation could reduce HSV viral load and m-RNA expression in HSV-infected cells.^{11,14}

Another study concluded that vitamin D has potential immunomodulatory effects related to the regulation of antimicrobial peptides (AMP). Vitamin D induces the expression of a gene from AMP called cathelicidin which could reduce HSV-1 virus titers and plays a role in increasing innate and adaptive immune responses in dealing with viral, bacterial and inflammatory infections.^{11,14,19,20} In cases of viral infections, the innate immune system is a first line mechanism of defense in which the processes are dependent on vitamin D through the activation of epithelial and immune cells, such as macrophages and neutrophils.⁶

The natural source of vitamin D for humans is direct exposure to sunlight so that a lack of outdoor activities or working indoors for a long period of time can be one of the triggers of vitamin D deficiency in the body. Modern society in general and women in particular, currently tend to avoid a direct exposure to sunlight by using sunscreen. If vitamin D is obtained naturally, it is relatively small, this condition can increase the risk of infections, especially those caused by viruses.^{14,20}

Therapy for oral lesions from the Oral Medicine Department was 0.025% Hyaluronic Acid mouthwash, 200mg Acyclovir tablets, vitamin D

supplementation and petroleum jelly. 0.025% Hyaluronic Acid mouthwash was given 3 x 10ml, as symptomatic therapy to relieve pain complaints as the drug has anti-inflammatory action. The anti-inflammatory action mechanism of Hyaluronic acid is to reduce the production of TNF- α pro-inflammatory cytokines, mediate a number of growth factors and recruit inflammatory cells so that they could accelerate the healing process and reduce pain.²¹ The first-line antiviral therapy for RIH was Acyclovir 200 mg tablets which were to prevent viral DNA synthesis by inhibiting DNA polymerase through Thymidine Kinase (TK). Acyclovir enters infected cells and is converted to acyclovir monophosphate (ACV-MP), and then ACV-MP is converted to acyclovir diphosphate (ACV-DP) and acyclovir triphosphate (ACV-TP). Acyclovir triphosphate is the active part of acyclovir which functions to thwart viral replication by inhibiting and damaging the viral DNA chain.²² *Petroleum jelly* administration was intended to moisturize the lips with a mechanism to delay water evaporation so as to prevent dry lips.²³

The patient was also given 1,000 IU vitamin D supplementation therapy three times a day. Vitamin D supplementation was intended to help increase vitamin D levels so that it could increase body immunity which was able to prevent reactivation of the HSV-1 virus and reduce regulation titers of HSV-1 viral mRNA and DNA by suppressing viral load through mechanical activation of the innate and adaptive immune systems so as to prevent recalcitrance and recurrence of the viral infection.^{11,14} The patient was also educated to always maintain oral hygiene by brushing her teeth at least 2 times a day, consuming foods containing high vitamin D and actively basking in the morning for 2 to 3 times a week. RIH recurrence rate to the patient in this case report became rare after 30 days' therapy. Comprehensive treatment with additional of vitamin D supplementation and instruction for sunbathing under morning sunlight showed reduction of recalcitrance and recurrence of RIH.

Based on the follow-up communication a few weeks after the fifth visit, the patient informed that the canker sores were still recurring in a longtime span of 15 to 20 days. This condition was better than before being treated with vitamin D, where recurrences occurred between 2 to 3 days. The patient was instructed to return for a control visit if canker sores reappear dan tetap dianjurkan untuk rutin melakukan kegiatan berjemur di pagi hari. After 8 weeks of therapy, the patient was referred again for a re-examination of vitamin D (25-OH) level where the result of the patient's vitamin D (25-OH) level was 20.3 ng/mL and categorized as insufficient (**Table 1**).

The patient's limited time makes it difficult for the patient to control and evaluate on vitamin D therapy for the next 6 months after therapy. The patient informed that there was a change in the RIH recurrence rate between before and after being given vitamin D therapy whereas the RIH recurrence rate became low. Patient was monitored and given instructions to actively engage in sunbathing activities in the morning, consume vitamin D 1000IU 2 times a day and carry out a routine vitamin D level assessment every 4 weeks until the patient's vitamin D level is in the sufficiency category. The assessment results of the patient's vitamin D level after 12 weeks therapy was 25.5 ng/mL (**Table 1**) and patient informed that currently RIH recurrences occur once a month. Patient was satisfied with the therapy provided as the healing process of the lesions was faster and the recurrence time was quite long.

Patient has approved and written the informed consent for the publication including for taking clinical photos. The limitation of this case report is that anamnesis was not carried out to other risk factors which can trigger RIH other than vitamin D deficiency such as stress, fatigue and others. The challenge in managing the patient's recalcitrant RIH in this case was the difficulty of identifying risk factors for recalcitrant RIH, given the many risk factors that could trigger this infection. Quick and precise identification of precipitating factors could reduce RIH recurrence rates. Asymptomatic RIH infection often causes a misdiagnosis so that RIH could be diagnosed as Recurrent Aphthous Stomatitis (RAS), Cocksakie Virus Infection or Erythema Multiforme.

Vitamin D plays a role in all of the body's defense mechanisms, both innate and adaptive immune systems in producing antimicrobial peptides, suppressing inflammation and self-tolerance. Vitamin D deficiency could reduce the body's immunity which can trigger the reactivation of the HSV-1 virus. In addition to giving acyclovir, the supplementation of vitamin D and optimizing sun exposure are factors that must be considered in preventing and reducing the high recurrence of RIH due to vitamin D deficiency. We would like to thank the patient and his family who kindly participated in this study. This study was approved by the Oral Medicine Department, Faculty of Dentistry, Padjadjaran University. The authors declare that they have no conflicts of interest.

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