Republic Of Iraq
Ministry Of Higher Education
And Scientific Research
University Of Baghdad
College Of Dentistry

Vitamin D And It's Role In Recurrent Aphthous Stomatitis Development

A Project Submitted to
The College of Dentistry, University of Baghdad
Department of Oral Diagnosis/ Oral Medicine Clinic
in Partial Fulfillment for the Bachelor of Dental Surgery

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2023 A.D. **1444 A.H.**

﴿ بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ ﴾

وَمَن يَتَّقِ اللَّهَ يَجْعَل لَّهُ مَخْرَجًا ﴿٢﴾ وَيَرْزُقْهُ مِنْ حَيْثُ لَا يَحْتَسِبُ ۚ وَمَن يَتَوَكَّلْ عَلَى اللَّهِ فَهُوَ حَسْبُهُ ۚ إِنَّ اللَّهَ بَالِغُ أَمْرِهِ ۚ قَدْ جَعَلَ اللَّهُ لِكُلِّ شَيْءٍ قَدْرًا ﴿٣﴾

﴿ صدَقَ الله العَظِيم ﴾

Certification of the Supervisor

I certify that this project entitled "**Vitamin D And It's Role In Recurrent Aphthous Stomatitis Development "** was prepared by the fifth-year student **Tabarak Yousif Ali** under my supervision at the College of Dentistry/University of Baghdad in partial fulfillment of the graduation requirements for the Bachelor Degree in Dentistry.

Supervisor's name: **Dr.Noor Saad Mohammed Ali**

Date: **2023**,**May**

Acknowledgment

My gratitude to **Dr. Raghad Abdulrazak** Dean of College of Dentistry\University of Baghdad

Dr. Bashar Hamed the Head of the Department of Oral Diagnosis and Medicine To all the professors and seniors in the Department

My special thanks to **Dr. Noor Saad** for her supervision,teaching, guiding, and help in this review.

Dedication

With love, I dedicate my graduation research:

To the source of my ambition, **My father** and the source of my inspiration, **My mother**, to **My Brothers And Sisters**... Without their presence, I would not have achieved any success.

To My Friends And Everyone who helped me achieve my goal

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Abstract

Background:

Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral mucosa diseases and the Etiology remains unclear.

Vitamin D is a steroid hormone and plays an important role in calcium metabolism but more recently, emerging evidence suggests that vitamin D plays an important role in immunity regulation.

In patients with recurrent aphthous stomatitis, the level of serum 25(OH)D is significantly lower than in healthy people of similar ages and genders, so recommend vitamin D supplementation as a supportive treatment.

The Aim of the present study:

To Review The Role Of Vitamin D In Recurrent Aphthous Stomatitis Development.

Conclusions:

The limited available evidence suggests that low levels of serum vitamin D might be a risk factor for RAS. However, more well‐designed studies are needed to further explore the potential association between vitamin D deficiency and RAS development.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral mucosa diseases. It affects 5% to 25% of the population, mostly women and in higher socioeconomic groups **(koybasi et al., 2006)** These idiopathic lesions are characterized by recurrent painful attacks **(Oztekin A & Oztekin C., 2018).**

The condition is chronic and usually self-limiting in immunocompetent patients, Etiology remains unclear, but local trauma, emotional stress, allergy, toxin exposure, poor oral hygiene, vitamin deficiency, and alterations in the oral flora are defined as risk factors **(Porter et al., 2000).**

The lesions are painful and their sizes range from 1 mm to a few centimeters in diameter, The lesion size is one of the diagnostic criteria used in classification which is divided into 3 categories: major, minor, and herpetiform **(Slebioda et al., 2016).**

Vitamin D is a steroid hormone and plays an important role in calcium metabolism, but more recently, emerging evidence suggests that vitamin D plays an important role in immunity regulation **(Nalbantoglu, 2019 ; Holick, 2007).**

Vitamin D receptor has been found in most of the immune cell types, including antigen-presenting cells, such as macrophages and dendritic cells, and T cells.

The immunomodulatory effect of this vitamin has raised an interest in its possible role in etiology immune-dependent entities. Also, vitamin D deficiency has been associated with some autoimmune diseases **(Disanto et al., 2012).**

As a regulator of mineral balance and bony tissue metabolism and a potent anti-inflammatory and immunomodulating agent, vitamin D can significantly affect oral cavity homeostasis. The role of vitamin D as a modifier of autoimmunologic conditions of the oral cavity is of considerable importance **(Krawiecka, 2017).**

There are only a few studies conducted in adult population to investigate the possible relationship of vitamin D and recurrent aphthous stomatitis **(Oztekin A & Oztekin C, 2018 ;Krawiecka, 2017; Bazrafshani, 2002).**

Aim Of The Study

To Review The Role Of Vitamin D In Recurrent Aphthous Stomatitis Development.

CHAPTER ONE
REVIEW OF LITERATURE

1.1 Recurrent Aphthous Stomatitis

1.1.1 Definition

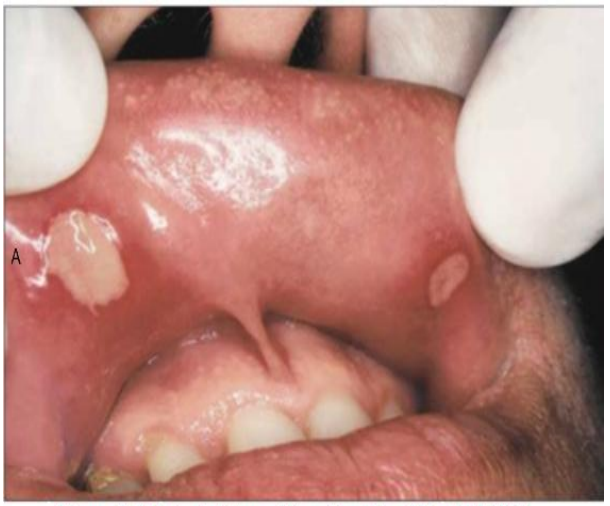

Figure (1-1) Major Aphthous Ulceration (Tarakji B et al.,2015)

Painful Oral Aphthous commonly referred to as aphthae, or canker sores, have been routinely appreciated by medical and dental professionals in otherwise healthy patients for thousands of years. They are the most common lesions of the oral mucosa in the general population **(femanio et al., 2007).**

The term aphthae is derived from the Greek word aphthi, which means "to set on fire" or "to inflame," and is thought to have been first used by the philosopher hippocrates to describe the pain associated with a common disorder of the mouth during his time (likely, aphthous stomatitis) **(Compilato et al., 2010).**

Local trauma, genetic factors, nutritional deficiencies, viral and bacterial infections, and immune or endocrine disturbances have all been implicated as etiological factors of frequent oral ulcerations. In a subset of patients, No etiology can be identified and a diagnosis of exclusion must be made; such cases are referred to as recurrent aphthous stomatitis (RAS).

The clinical picture of RAS is characterized by recurrent episodes of solitary or multiple painful ulcerations **(Preeti et al., 2011)** without an association with systemic diseases **(Jin et al., 2016).**

Three forms of RAS exist: minor (>70% of cases), major (10%), and herpetiform (10%). These subtypes differ in morphology, distribution, severity, and prognosis.

Despite their distinct characteristics, all forms of RAS have a significant impact on quality of life and interfere with activities of daily living **(Belenguer-Guallar et al., 2014).**

1.1.2 Epidemiology

The prevalence of RAS varies between 0.9 and 78% in different groups examined. In the US, for the period of 1988-1994 the prevalence was 0.89% in adults **(Shulman, 2004)** and 1.64% in children **(Shulman, 2004)**. In Iran (2005), Jordan (2008), India (2010-2012) and China (2013-2017) reported prevalence was 25.2% **(Davatchi et al., 2008)**, 70% **(Safadi, 2009)**, 21.7% **(Patil et al., 2014)** and 27.17% **(Wang et al; 2018)** respectively.

It frequently occurs among females more than men **(Pongissawaranunand et al., 1991),** It's onset appears to peak between 10 and 19 years of age **(Akintoye & Greenberg, 2014),** increases with increasing age. Besides, minor aphthous ulcers are responsible for more than 80% of cases **(Peretz et al.,1994).**

1.1.3 Etiology And Pathogenesis

The Etiology and Pathogenesis of RAS remain unclear, Multiple factors are associated with the establishment of this disease including a positive family history, food hypersensitivity, smoking cessation, psychological stress and immune disturbance **(Akintoye & Greenberg, 2014).**

However, for this evidence, there is often an absence of statistical risk analysis, Immune dysregulation linked to several triggers may facilitate the development of RAS, The roles of the immune system and inflammatory processes have been confirmed in recent large-scale bioinformatics analyses **(Rivera, 2017 ; Wu et al., 2017)** It is known that a Th1-type hyperimmune response favors the appearance of inflammatory reactions that precede ulceration **(Mimura et al., 2017).**

In addition, genetic risk factors can determine individual susceptibility to RAS; in particular, several DNA polymorphisms of the NOD-like receptor 3 **(Slezakova et al., 2018)**, toll-like

receptor 4 **(Karasneh et al., 2015)**, interleukin (IL)-6 **(Karakus et al.,2014),** E-selectin **(Alkhateeb et al., 2013)**, IL-1β and TNF-α genes **(Guimarães et al., 2007).**

However, despite the large number of factors examined, the underlying cause triggering the episodes of ulcers remains to be elucidated. Therefore, clinically, the emergence of new lesions cannot be avoided at present **(Slezakova et al., 2018).**

1.1.4 Predisposing and Environmental Factors

1.1.4.1 Hormonal changes

McCullough et al in 2007 reported that female patients with RAS relate the onset of their oral ulceration to their menstrual cycle, pregnancy, and dysmenorrhea. It has been reported that the RAS usually improves during pregnancy also RAS may be affected by the sex steroids **(Dolby, 1968)**.

1.1.4.2 Trauma

RAS patients often report aphthous ulcers at sites of trauma, particularly due to toothbrushing, or the site of a local anesthetic injection and dental treatment **(Kvam et al., 1987 ; Wray, 1981).**

1.1.4.3 Drugs

Boulinguez et al in 2000 reported that there is association between the use of some drugs such as (sodium hypochlorite – piroxicam – phenobarbital – phenindione - niflumic acid – nicorandil - gold salts - captopril) and RAS. Furthermore, the use of other drugs such as non-steroidal anti-inflammatory drugs (NSAIDs, e.g., pro-propionic acid, phenylacetic acid, and diclofenac) can stimulate the formation the oral ulcers very similar to RAS **(Healy et al., 1995).**

1.1.4.4 Food hypersensitivity

Some foods such as chocolate, coffee, peanuts, cereals, almonds, strawberries, cheese, tomatoes, and wheat flour (containing gluten) may be implicated in some patients **(Hay & Reade,1984 ; Eversole et al., 1982).**

Besu et al in 2009 reported that there is a strong association between high levels of serum anti-cow's milk proteins immunoglobulin A (IgA), IgG and IgE antibodies and clinical manifestations of recurrent aphthous ulcers.

1.1.4.5 Nutritional deficiency states

Nutritional markers associated with anemias (iron, serum ferritin) have been reported to be twice as common in RAS patients as in controls and up to 20% of RAS patients may have a nutritional deficiency **(Porter, 1988).** Nolan et al in 1991 found that 28.2% of patients with RAS had deficiencies of vitamins B1, B2, and or B6, They indicated that those patients could benefit from vitamin replacement therapy.

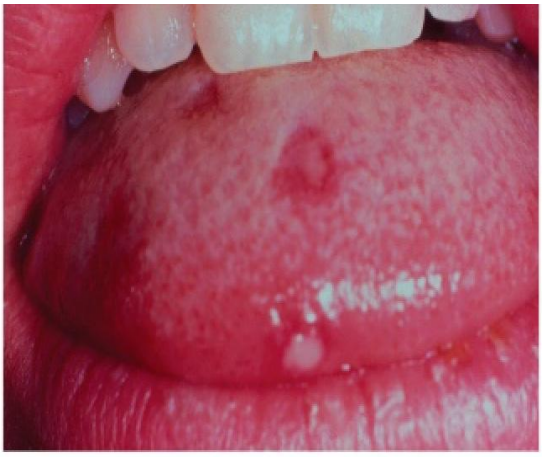

Figure (1-2) Iron Deficiency anemia with ulcers on the tongue (Glick etal., 2021).

1.1.4.5 Stress

Gallo et al in 2009 reported that there was a higher level of psychological stress among RAS group patients when compared to the control group. Although the majority of research has been unable to validate the concept that stress plays an important role in the development of RAS.

1.1.4.6 Tobacco

Tobacco use is a risk factor for oral cancer, oral mucosal lesions and periodontal disease. The incidence of RAS was found to be lower in smokers than in non-smokers and clinical observation suggests that some smokers experience an increase in mouth ulcers upon

stopping smoking **(Mirbod & Ahing, 2000)** Patients who stop smoking often complain of RAS, A feature of interest is that RAS are infrequently seen in patients who smoke tobacco, The main explanation is that tobacco may increase keratinization of the oral mucosa, which in turn may render the mucosa less susceptible to ulceration **(McRobbie, 2004).**

Hill et al in 2010 describe a case of complex aphthosis which began within weeks of stopping smoking, After failing to respond to conventional agents, the patient was successfully treated with nicotine lozenges, They recommend considering the use of nicotine replacement therapy when conventional management has failed, particularly in ex-smokers.

All the predisposing and environmental factors mentioned above can be investigated and diagnosed from the general practitioners but the other environmental factors such as (infection factors) for both bacterial agents and viral agents , serology of RAS, and the systemic disease associated with RAS (celiac disease, Behcet's disease), and HIV associated with RAS should refer to the appropriate specialists because it is very difficult for general practitioners to diagnose and manage such those disease **(Tarakji et al., 2015).**

1.1.5 Clinical Presentation

RAS is known to be particularly painful **(TWu & Wang, 2017).** These idiopathic ulcerations are oval lesions of different sizes with clean edges surrounded by an erythematous halo. At the center of the ulceration, the necrotic fundus is covered with a yellow-white fibrinous exudate **(Schemel-Suárez et al., 2015).**

The ulcers typically present in the non-masticatory mucosa of the cheeks, lips, ventral and lateral surfaces of the tongue, non-attached gingiva and occasionally, the soft palate **(Cui, Bruce & Rogers., 2016).**RAS lesions are self-limiting (simple aphthosis), resolving within 1-2 weeks in the majority of patients **(Rogers, 1997).** In those affected by the disease, the

ulcers can compromise important daily functions, including nutrition, speech and oral hygiene **(Lalla et al., 2012)** affect quality of life **(Rajan et al., 2014).**

RAS occurs in three morphological presentations:

Minor RAS: Minor RAA is the most prevalent form and typically occurs in patients who are 5 to 19 years old. outbreaks are characterized by a few, superficial, round ulcerations that are <10mm and accompanied by a gray pseudomembrane and erythematous halo **(Yasui et al., 2010)** Minor aphthae are usually confined to the lips, tongue, and buccal mucosa **(Wallace et al., 2015).**

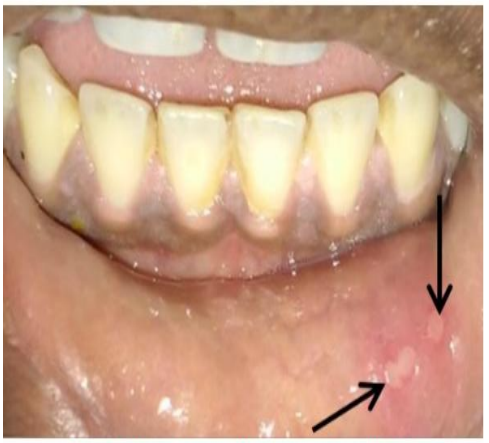

Figure (1-3) Minor Recurrent Aphthous Stomatitis (Black Arrow)
(Santosh Kumar et al.,2017)

Major RAS: Major ras has a wider distribution (commonly extending to the gingiva and pharyngeal mucosa), is larger in size (>10mm), and has a longer duration of outbreak, Minor aphthae typically resolve within 14 days of presentation whereas major aphthae may persist for over six weeks further, major aphthae pose a significant scarring risk as well **(Yasui et al., 2010).**

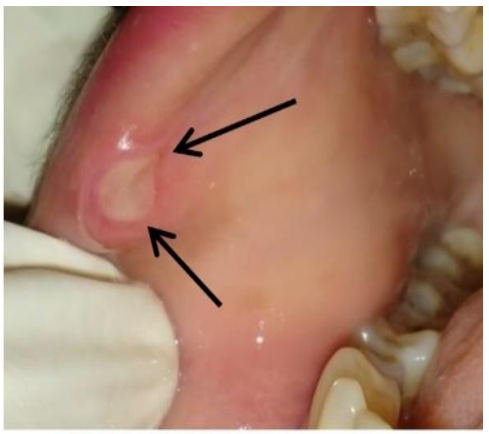

Figure (1-4)Major Recurrent Aphthous Stomatitis (Black Arrow)
(Santosh Kumar et al.,2017)

Herpetiform RAS: herpetiform RAS presents with dozens of small, deep ulcers that often coalesce and therefore present as large ulcers with an irregular contour, outbreaks are nonscarring and typically resolve within one month. Regardless of the subtype, RAS lesions can impair one's ability to effectively speak, swallow, and maintain dental hygiene **(Yasui et al., 2010).**

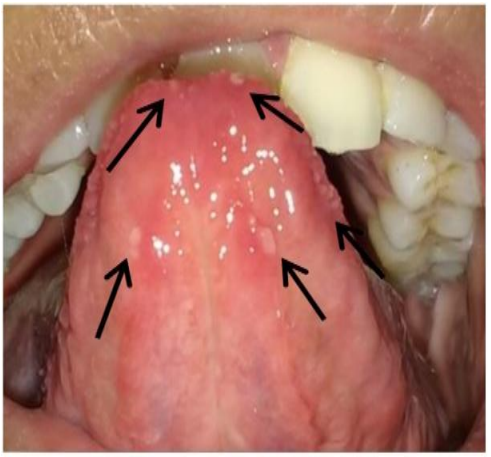

figure (1-5) Herpetiform Recurrent Aphthous Stomatitis (Black Arrow)
(Santosh Kumar et al.,2017)

Table 1. Clinical features of minor, major, and herpetiform recurrent aphthous stomatitis (RAS) (Adaptedw from Wallac et al., 2015).

Criteria	Minor RAS	Major RAS	Herpetiform
Gender Predilection	Equal	Equal	Female
Morphology	Round Or Oval Lesions, Gray_ white Pseudomembranes Erythematous halo	Round Or Oval Lesions, Gray_ white Pseudomembranes Erythematous halo	Small, Deep Ulcers That Commonly Converge Irregular Contour
Distribution	Lips, Check, Tongue, Floor Of Mouth	Lips, Soft Palate, Pharynx	Lips, Check, Tongue, Floor Of Mouth, Gingiva
Number Of Ulcer	1-5	1-10	10-100
Size Of Ulcer	<10 mm	>10 mm	2-3mm
Prognosis	Lesions Resolve In 4-14 Days No Scarring	Lesions Persist >6 weeks High Risk Of Scarring	Lesions Resolve <30 Days Scarring Uncommon

1.1.6 Disease Phases

The disease sequence comprises the following stages: Premonition (24 h), comprising symptoms but no visible signs of disease; pre-ulcerative (between 18 h and 3 days), comprising erythema and mild edema; ulcerative (1-16 days), comprising active ulceration; healing (4-35 days) involving a decrease in symptoms and progressive healing; and remission, in which there is no evidence of ulcers **(Vucicevic Boras & Savage, 2007).**

The ulcerative and remission phases are those that can be evaluated with greater objectivity on dental examination, Disease recurrence is established with the appearance of new ulcers.

Disease severity can be determined based on the number, size and location of the lesions, pain, duration, ulcer-free periods **(Tappuni, 2013)** and the impact on patient quality of life **(Rajan, 2014 ; Brocklehurst, 2012).**

1.1.7 Diagnosis Of RAS

The correct diagnosis of RAS is dependent on a detailed and accurate clinical history and examination of the ulcers.

The important features to be noted when examining a patient with oral ulceration are shown in Table 2

Table 2:The Important features to be noted from general practitioners (Tarakji et al.,2015)

Important points in the history
Family history
Frequency of ulceration
Duration of ulceration
Number of ulcers
Site of ulcers (non-keratinized or keratinized)
Size and shape of ulcers
Associated medical conditions
Genital ulceration
Skin problems
Gastrointestinal disturbances
Drug history
Edge of ulcer
Base of ulcer
Surrounding tissue

Furthermore, the investigation tests for patients with persistent RAS are shown in Table 3:

Table 3 : The investigation tests for patients with persistent RAS (Tarakji et al. ,2015)

Hemoglobin and full blood count
ESR/CRP
Serum B12
Serum/red cell folate
Anti-gliadin and anti-endomysial autoantibodies
ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

Clinical assessment of an ulcer includes inspection and palpation, which complement each other. The base of the ulcer can be necrotic, granular purulent or covered with mucus.

The consistency of the base (soft, firm, or hard) and fixation to underlying structures can be evaluated by palpation. The edges of the ulcer can be straight or irregular and may feel hard in contrast to the surrounding tissue. This is the characteristic induration, associated with neoplastic infiltration. Another feature of a carcinoma is its rolled border. The tissue surrounding the ulcer may be white, speckled, erythematous, or normal in appearance. Patients with persistent RAS should have follow-up for underlying hematinic disorders, This includes a full blood count and measurement of inflammatory markers and hematinic (serum ferritin, serum B12, serum and red cell folate).

Screening for deficiencies of vitamin B complexes or zinc deficiencies is not routinely carried out but may be indicated in certain groups of patients. RAS associated with a systemic condition should be referred to the appropriate specialist for further investigations. If there is any suspicion of coeliac disease, either due to patient's history or evidence of malabsorption on routine testing then serological testing for appropriate IgA autoantibodies

should be carried out and patient is referred to a gastroenterologist for endoscopy and biopsy of the small intestine **(Tarakji et al., 2015).**

1.1.8 Differential diagnosis

Aphthous ulcerations (or RAS-like ulcerations) have an underlying systemic cause; therefore, they should be considered as a distinct medical condition **(Jin et al., 2016)**.

The differential diagnoses should be established with autoinflammatory syndromes, including periodic fever with adenitis, pharyngitis and aphthae (PFAPA) syndrome, Behçet's syndrome and Crohn's disease; and immunodeficiency states, including nutritional defects (such as celiac disease and other gastrointestinal disorders), immune defects (such as human immunodeficiency virus infection/acquired immune deficiency syndrome) and neutrophil defects (such as cyclic neutropenia) **(BMJ Best Practice, 2018)**, The term RAS should be used for ulceration present in the absence of systemic disease.

1.1.9 Management Of RAS

In mild cases with two or three small lesions, use of a protective emollient such as OrabaseTM often alleviates pain and facilitates healing. Pain relief of minor lesions can be effected with a topical anesthetic agent such as benzocaine or lidocaine.

In more severe cases, the use of a high‑potency topical steroid preparation, such as fluocinonide, betamethasone, or clobetasol, placed directly on the lesion, shortens healing time and reduces the size of the ulcers.

The steroid gel can be carefully applied directly to the lesion after meals and at bedtime two to three times a day or mixed with an adhesive such as Orabase prior to application.

Larger lesions can be treated by placing a gauze sponge containing the topical steroid on the ulcer and leaving it in place for 15–30 minutes to allow for longer contact of the medication.

Other topical preparations that have shown promise in decreasing the healing time of RAS lesions include use of chlorhexidine or a topical tetracycline such as doxycycline, which can be used either as a mouthrinse or applied as a paste directly to the lesions **(Fang et al., 2018)** Intralesional steroid injections can be used to treat large indolent major RAS lesions.

When patients with major aphthae or severe cases of multiple minor aphthae do not improve sufficiently with topical therapy, use of systemic therapy should be considered.
Drugs that have been reported to reduce the number of ulcers in selected cases of major aphthae include colchicine, pentoxifylline, dapsone, short bursts of systemic steroids and thalidomide **(Häyrinen‐Immonen et al., 1991 ; Wahba‐Yahav, 1995).**

1.2 Vitamin D

1.2.1 Definition

Vitamin D belongs to the group of fat-soluble secosteroid biomolecules, It is obtained in the body in two ways: alimentary (with food products and food additives intake) and through endogenous synthesis in the skin under UV radiation.

Worldwide vitamin D deficiency has increased interest in this compound and therefore further study is warranted of its effect on various human organs and systems **(Palacios et al., 2014 ; Holick et al., 2011).**

The most studied and effectively proven effects of vitamin D and its derivatives are the regulation of calcium phosphate metabolism and bone remodeling by enhancing intestinal absorption of calcium, increasing its reabsorption in the kidneys and decreasing urinary secretion.

In addition, the discovery of vitamin D receptors in many cells and organs, for example, macrophages, monocytes, dendritic cells, cells of the placenta, the parathyroid gland, prostate, osteoblasts, smooth muscle cells and epithelial cells of the gingival attachment contributed to the discovery of its "extra -osseous" effects **(McMahon et al., 2011 & Krawiec et al., 2018).**

A significant role of vitamin D has been proven in the immune processes, providing anti-inflammatory and antimicrobial effects, inhibiting cell proliferation and stimulating differentiation **(Ekaterina et al., 2021).**

1.2.2 Vitamin D Metabolism

There are two main native forms of vitamin D: vitamin D2 (ergocalciferol), which is contained in plants (yeast, mushrooms, crops) and enters the body only with food, and vitamin D3 (cholecalciferol), which is mostly synthesized in the skin from provitamin D3

(7-dehydrocholesterol) under the effects of sunlight, Another source of vitamin D3 is animals, such as wild salmon. Derivatives of vitamin D enter the extracellular matrix, and then bind to blood proteins in the bloodstream.

Both forms are inactive and undergo further transformation in the body. Initially, hydroxylation occurs in the liver under the action of 25-hydroxylase transforming to 25(OH)D (calcidiol), which is the main circulating form of vitamin D, This indicator is used to quantify the serum level of vitamin D in clinical practice, since its half-life is up to 3 weeks **(Mal'cev & Mansurova ., 2014).**

According to the Russian Endocrine Society Clinical Practice Guideline, A level of vitamin D of 21–29 ng/mL (525–725 nmol/liter) is considered as insufficient, A 25(OH)D level below 20 ng/mL (50 nmol/liter) is defined as deficiency and blood level above 30 ng/mL is interpreted as optimal **(Holick et al., 2011).**

The subsequent stage of vitamin D metabolism, catalyzed by 1-hydroxylase, occurs mainly in the kidneys and to a lesser extent in bone tissue, lungs, liver, parathyroid glands and keratinocytes.

The result of this process is the formation of the biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)2D or calcitriol), which is responsible for all the effects **(Mal'cev et al., 2014 ; Grygiel-Gorniak ; Puszczewicz, 2014).**

1.2.3 Vitamin D Mechanism Of Action

The mechanism of action of the active form of vitamin D is similar to that of other steroid hormones and is realized by its binding to the nuclear receptor **(Bikle, 2009)** 1,25(OH)2D is a high-affinity ligand for the vitamin D receptor (VDR), which is present not only in the intestines, bone tissue and kidneys main organs responsible for calcium phosphate metabolism but also in more than 38 different target organs **(Norman & Bouillon, 2010).**

Its binding leads to the formation of a hormone–receptor complex that modifies gene expression by linking its specific domain with the regulatory DNA sequence **(Adams et al., 2010).**

Thus, there is activation of the synthesis of some proteins (for example, calcium-binding protein, osteocalcin, osteopontin) and inhibition of others (proinflammatory cytokines: IL-6, IL-8) **(Adams et al., 2010 & Tang et al., 2013).**

The gene encoding the VDR is located in chromosome 12 in position 12q13.1, The gene allele variations of VDR are relatively common in the population, with some differences between people of diverse ethnic groups, The polymorphism of the VDR gene may play a key role in the course of tumor progress, decreasing bone density and increasing susceptibility to infections and autoimmune diseases, since it can influence the action of vitamin D on a cellular level including calcium metabolism, transcription, cellular divisions and the initiation of the immunologic response **(S´lebioda et al., 2016 ; Anand et al., 2017 ; Dragonas et al., 2020).**

A large number of studies have shown the correlation between low vitamin D levels and a number of different systemic diseases, i.e., diabetes mellitus, cardiovascular diseases (including coronary artery disease, congestive heart failure, valvular calcifications, stroke, arterial hypertension), autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, Crohn's disease), chronic kidney disease, and many others **(Lavie et al., 2011)**

Vitamin D's regulation of calcium phosphate metabolism and bone remodeling as well as it's anti-inflammatory and immunomodulatory effects (regulation cell proliferation and differentiation) can significantly affect the health of the oral cavity **(S´lebioda et al., 2016 ; Öztekin A & ÖztekinC, 2018 ; Antonova et al., 2019)**

A number of studies and reviews have demonstrated the association between low vitamin D levels and the course and frequency of recurrent aphthous stomatitis (RAS) **(Öztekin A & Öztekin C, 2018).**

1.2.4 Vitamin D Deficiency

Several high-risk groups for vitamin D deficiency have been identified including individuals who avoid sun exposure, having darkly pigmented skin, obese and those suffering from chronic kidney disease **(Ross et al., 2011).**

Serum 25- (OH)D concentration <50 nmol/L (< 20 ng/mL) has recently been defined as vitamin D deficiency **(Ross et al., 2011).**

Severe vitamin D deficiency is marked by a threshold <25 nmol/L (<10 ng/mL) and vitamin D insufficiency by concentration in the range 25–49 nmol/L (10–19 ng/mL) (Table 4) **(Holick et al., 2011).**

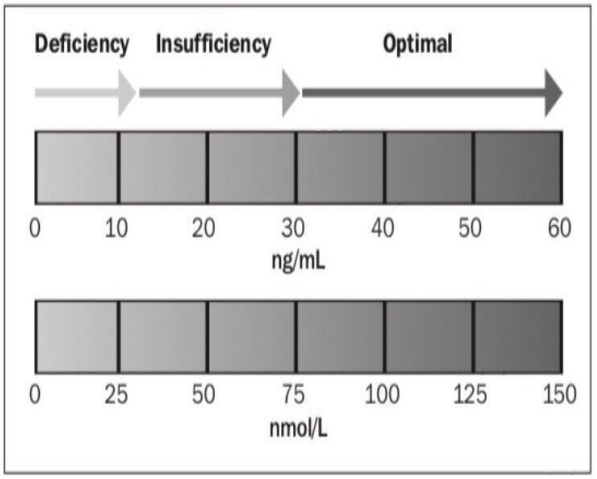

Figure (1-6) Schematic representation of vitamin D deficiency, insufficiency and optimal ranges (Basit;2013).

At a concentration below 25 nmol/L (<10 ng/mL) adverse effects are observed in children and adults and increased bone resorption and an elevated risk for secondary hyperthyroidism are seen at concentration of 25–49 nmol/L (10–19 ng/mL).

A 25-(OH)D threshold of 75 nmol/L (30 ng/mL) is needed for optimal bone mineral density in younger (19–49 years) and middle-aged adults (>50 years) **(Bischoff-Ferrari et al., 2004).**

Increasing evidence suggests that 25-(OH)D serum concentration of 75–110 nmol/L (30–44 ng/mL) may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease and infectious disease (Fig.5) **(Forman et al., 2007 ; Pilz et al., 2009).**

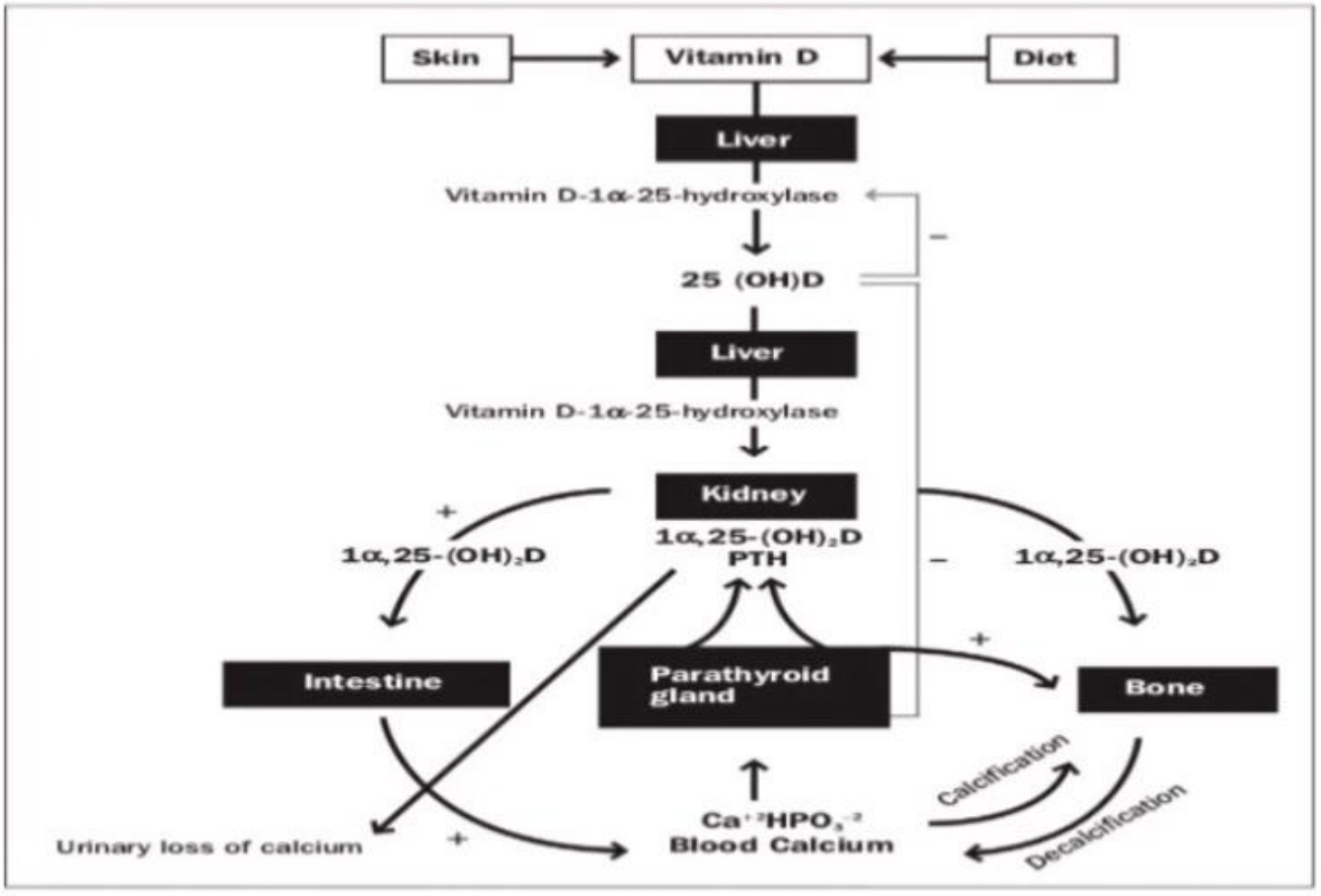

Figure (1-7) The physiological role of PTH in the maintenance of serum calcium level. Key target organs for PTH – bone, kidney and intestine – and their feedback interactions with calcium are shown (Basit;2013)

Table 4. Serum 25(OH)D concentration and its interpretation (Basit; 2013).

Classification	Serum 25(OH)D	Clinical Implications
Vitamin D deficiency	<50 nmol/L (<25 ng/mL)	Summarises concentrations in severe deficiency and insufficiency
Severe vitamin D deficiency	<25 nmol/L (<10 ng/mL)	Increased risk of rickets, osteomalacia, secondary hyperparathyroidism, myopathy, falls, fractures
Vitamin D insufficiency	<25–49 nmol/L (<10-19 ng/mL)	Increased risk of bone loss, secondary hyperparathyroidism
Adequate vitamin D threshold concentration	50 nmol/L (20 ng/mL)	Low risk for bone loss and secondary hyperparathyroidism, neutral effect on falls and fractures
Desirable vitamin D threshold concentration for fall and fracture reduction	75 nmol/L (30 ng/mL)	Optimal suppression of parathyroid hormone and bone loss,reduction of falls and fractures by about 20%.

1.2.5 Prevalence of vitamin D deficiency

VDD has been historically defined and recently recommended by the Institute of Medicine (IOM) as a 25(OH)D of less than 0.8 IU. Vitamin D insufficiency has been defined as a 25(OH) D of 21–29 ng/mL **(Holick, 2007 ; Heaney, 2004)** Children and young and middle aged adults are at equally high risk for VDD and insufficiency worldwide. VDD is common in Australia, the Middle East, India, Africa, and South America **(Holick, 2007 ; Marwaha et**

al., 2005 ; Thacher et al., 2006) Pregnant and lactating women who take a prenatal vitamin and a calcium supplement with vitamin D remain at high risk for VDD **(Thacher et al., 2006 ; Bodnar et al., 2007)**.

1.2.6 Consequences of vitamin D deficiency

The major function of vitamin D is to provide and maintain adequate calcium and phosphorus in the body to facilitate optimal metabolic function. Low vitamin D levels have been associated with a range of disorders, The association of low vitamin D and bone diseases such as rickets and osteoporosis is well known **(Heaney, 2006 ; Heaney, 2005).**

A positive association between vitamin D level and low bone mass in Saudi men and women has been shown recently **(Sadat-Ali et al., 2011) .**

In addition, vitamin D deficiency impairs reproductive success **(Bodnar et al., 2010 ; Lewis et al., 2010)** and the ability to combat infections, in particular, tuberculosis, viral infections and influenza **(Ginde et al., 2009 ; Nnoaham & Clarke, 2008 ; Chesney, 2010)** It may precipitate or worsen autoimmune conditions **(Zhang et al., 2010 ; Blaney et al., 2005)** and increase the incidence of death associated with heart disease **(Semba et al., 2010 ; Drechsler et al., 2010)** stroke secondary to hypertension **(Pilz et al., 2011)** inflammatory bowel disease **(Levin et al., 2007)** muscle weakness and falls **(Bischoff-Ferrari et al., 2004 ; Pfeifer et al., 2002)** fractures **(Wimalawansa, 2011)** and cancers of the breast, colon and prostate **(Hisatake et al., 2001 ; Karlsson et al., 2010)** Several lines of evidence have shown that vitamin D reduces the risk of colorectal cancer **(Giovannucci et al ., 2005 ; Gorham et al., 2005)** other cancers that may be vitamin D-responsive include breast, lung, ovarian and prostate **(Giovannucci, 2005).**

Other disorders in which the role of vitamin D is being actively investigated are the autoimmune disorders such as multiple sclerosis (MS), type 1 diabetes mellitus and rheumatoid arthritis **(Hyppönen, 2010 ; Merlino et al., 2004).** The effect of vitamin D on asthma pathogenesis and control has also been extensively investigated **(Brehm et al., 2009 ; Litonjua et al., 2007)**.

1.2.7 Groups at risk of vitamin-D inadequacy

Obtaining sufficient vitamin D from natural food sources alone is difficult, Consumption of vitamin D-fortified foods and exposure to some sunlight are essential for maintaining a healthy vitamin D status, Dietary supplements might be required to meet the daily need for vitamin D in some groups of people **(Dietary Supplement Fact Sheet, 2011).**

1.2.7.1 Breastfed infants

Vitamin D requirements cannot ordinarily be met by human milk alone **(IOM, 2011 ; Picciano, 2001)** which provides <25 IU/L to 78 IU/L.**(Wagner & Greer, 2008)** Vitamin D content of human milk is related to the mother's vitamin D status; therefore mothers who supplement with high doses of vitamin D may have high levels of vitamin D in their milk **(Wagner & Greer., 2008).** American Association of Paediatricians (AAP) recommends that exclusively and partially breastfed infants must be supplemented with 400 IU of vitamin D per day **(Wagner & Greer., 2008 ; American Academy of Pediatrics Committee on Environmental Health, Ultraviolet light, 1999)** the recommended daily allowance for this nutrient during infancy.

1.2.7.2 Older adults

Older adults are at high risk of developing vitamin D insufficiency because of aging. Their skin cannot synthesize vitamin D as efficiently, they are likely to spend more time indoors, and they may have inadequate intakes of the vitamin **(IOM, 2011).**

1.2.7.3 People with limited sun exposure

Homebound individuals, women who wear long robes and head coverings for religious reasons and people with occupations that limit sun exposure are unlikely to obtain adequate vitamin D from sunlight **(Webb et al., 1988 ; Webb et al., 1990).**

The significance of the role that sunscreen may play in reducing vitamin D synthesis is still unclear. Intake of RDA levels of vitamin D from foods and/ or supplements will provide adequate amounts of this nutrient to these individuals **(IOM, 2011).**

1.2.7.4 People with dark skin

Larger amounts of the pigment melanin in the epidermal layer result in darker skin and reduce the skin's ability to produce vitamin D from sunlight, It is not sure that lower levels of 25(OH)D for persons with dark skin have significant health consequences. Intake of RDA levels of vitamin D from foods and/or supplements will provide adequate amounts of this nutrient to these individuals **(IOM, 2011).**

1.2.7.5 People with fat malabsorption

Vitamin D is fat soluble, therefore it requires some dietary fat in the gut for absorption, Individuals with reduced ability to absorb dietary fat might require vitamin D supplements **(Lo CW et al., 1985)** Fat malabsorption is associated with a variety of medical conditions including some forms of liver disease, cystic fibrosis, and Crohn's disease **(Holick, 2006)**.

1.2.7.6 People who are obese or who have undergone gastric bypass surgery

A BMI value of ≥30 is associated with lower serum 25(OH) D levels compared with non obese individuals. Obese people may need larger than usual intakes of vitamin D to achieve 25(OH)D levels comparable to those of normal weight **(IOM, 2011)** Greater amounts of subcutaneous fat sequester (captivate) more of the vitamin and alter its release into the circulation. Individuals who have undergone gastric bypass surgery may become vitamin D deficient over time without a sufficient intake of vitamin D from food or supplements, moreover part of the upper small intestine where vitamin D is absorbed is bypassed **(Malone, 2008 ; Compher et al., 2008).**

1.3 Vitamin D And It's Role In Recurrent Aphthous Stomatitis Development

Recurrent aphthous stomatitis (RAS) is a chronic mucosal disorder of the oral cavity, manifested in the presence of single painful erosions or ulcers of round or oval shape with necrosis in the center and hyperemia along the periphery.

The etiology of this disease is still unknown, but dysregulation of the immune response is consider to be a risk factor along with genetic defects, local trauma, emotional stress, and vitamin deficiency **(Öztekin A & Öztekin C, 2018 ; Al-Maweri et al., 2020 ; Krawiecka et al., 2017)**

The significant role of vitamin D in the innate and acquired immune system, its ability to influence the synthesis of proinflammatory cytokines, and the presence of VDR on macrophages, dendritic cells, T- and B-lymphocytes, can explain the potential association with RAS **(Khammissa et al., 2018 ; Bahramian et al., 2018 ; Khabbazi et al., 2015).**

According to a few studies (Öztekin A & Öztekin C., 2018 ; Bahramian, 2018 ; Khabbazi22 et al., 2015 ; Zakeri, 2021) In patients with recurrent aphthous stomatitis, the level of serum 25(OH)D is significantly lower than in healthy people of similar ages and genders.

Thus, Ainure Oztekin & Joshkun Oztekin, 2018 recommend vitamin D supplementation as a supportive treatment in patients with recurrent aphthous stomatitis.

In the randomized clinical trial of Bakr Islam, 2021 a beneficial effect of topical oral vitamin D was demonstrated in its lowering of oral mucositis. However, in another study carried out by **Krawiecka et al., 2014** there was no significant difference in serum vitamin D levels.

In recurrent aphthous stomatitis pathology, the presence of chronic inflammation suggests an immunological basis, T-cell immunity plays an important role in the development of recurrent aphthous stomatitis. Accordingly, cluster of differentiation (CD)4 T lymphocytes

are more dominant in the early stage of aphthous stomatitis while CD8 T lymphocytes are dominant in the ulcerative stage **(Khabbazi et al., 2014).**

It has been shown that there is an increase in T helper 1 proinflammatory cytokines and a decrease in T helper 2 anti- inflammatory cytokines in the pathogenesis of recurrent aphthous stomatitis **(Buno et al., 1998 ; krawiecka et al., 2017).**

It has been shown that vitamin D plays a role in immune processes, has anti-inflammatory and antimicrobial effects, inhibits cell proliferation and stimulates differentiation **(Slebioda et al., 2016)**.

Vitamin D stimulates the innate immune response by increasing the differentiation of monocytes and the chemotactic and phagocytic effects of macrophages. It is emphasized that the effects of vitamin D on cell proliferation and differentiation can significantly affect oral cavity health **(Slebioda et al., 2016)**.

It has been shown that antimicrobial defensin and cathelicidin are synthesized through vitamin D receptors and have an antibacterial effect against oral pathogens by providing a nonspecific immune response **(Anbarcioglu et al., 2019)**.

Previous studies have shown that vitamin D decreases the release of T helper type 1 cytokines, increases the release of T helper type 2 cytokines and stimulates the formation of T regulatory lymphocytes by inhibiting the differentiation and maturation of dendritic cells **(Myszka et al., 2014 ; Hewison et al., 2012)**.

The important role of vitamin D in the innate and acquired immune system is its ability to influence the synthesis of proinflammatory cytokines And the presence of vitamin D receptors on macrophages, dendritic cells ,T- and B-lymphocytes may explain its potential relationship with recurrent aphthous stomatitis.

There is a significant difference in vitamin D levels between patients with recurrent aphthous stomatitis and the healthy control group and there is no correlation between vitamin D status and the severity of the disease.

There are only a few studies conducted in the adult population on the relationship between recurrent aphthous stomatitis and vitamin D **(Oztekin A & Oztekin C, 2018 ; Krawiecka et al., 2017 ; Khabbazi et al., 2015)** But the results are controversial.

Krawiecka et al in 2017 conducted a study in Poland and found no significant difference between patients with recurrent aphthous stomatitis and healthy individuals in terms of vitamin D levels.

Also, they found no correlation between vitamin D status and the severity of recurrent aphthous stomatitis.

Khabbazi et al in 2015 reported that vitamin D levels were significantly lower in the study group than the control group. Similarly, **Oztekin A and Oztekin C, 2018** found decreased levels in the serum of patients with recurrent aphthous stomatitis compared to healthy control patients. Also, **Bahramian et al in 2018** reported that the serum levels of vitamin D in patients with recurrent aphthous stomatitis were significantly less than that in healthy individuals.

Although there are only a few studies published on the vitamin D status in recurrent aphthous stomatitis, other studies have been reported on syndromes associated with aphthous stomatitis, such as Behçet disease and periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome.

Several studies reported significantly lower vitamin D levels in Behçet disease in comparison to healthy control groups **(Karatay et al., 2011 ; Faezi et al., 2014)** Similarly, several studies found the vitamin D levels to be significantly lower in patients with PFAPA than that in the controls **(Nalbantoglu et al., 2019 ; Stagi et al., 2014 ; Mahamid et al., 2013).**

The possible action of vitamin D as a modifying factor in recurrent aphthous stomatitis seemed to be worth considering because despite multicentered studies, relatively little is known about the etiopathogenesis of the disease.

The biologic effects of vitamin D including its modification of both the innate and acquired immune system and its influence on the cytokine profile suggest the potential role of this

hormone in the development of disease **(Krawiecka et al., 2017 ; Adorini, 2002)** Therefore, It can be concluded that the lower serum levels of vitamin D might be considered as a possible factor for inducing recurrent aphthous stomatitis, especially genetically susceptible patients.

However, it is not clear whether vitamin D deficiency is the cause or rather a consequence of the disease. So, even vitamin D replacement therapy will not cause significant adverse effects, recommending vitamin D as a supportive treatment option is controversial.

CHAPTER TWO
CONCLUSION

2.1 Conclusion

1. Recurrent Aphthous Stomatitis are the most common lesions of the oral mucosa in the general population.
2. The prevalence of RAS varies between 0.9 and 78% in different groups examined. Its onset appears to peak between 10 and 19 years of age and its frequency decreases with advancing age
3. RAS occurs in three morphological presentations : Minor, Major, Herpetiform .
4. Vitamin D belongs to the group of fat-soluble secosteroid biomolecules, It is obtained in the body in two ways: alimentary (with food products and food additives intake) and through endogenous synthesis in the skin under UV radiation.
5. A significant role of vitamin D has been proven in the immune processes, providing anti-inflammatory and antimicrobial effects, inhibiting cell proliferation, and stimulating differentiation.
6. In patients with recurrent aphthous stomatitis, the level of serum 25(OH)D is significantly lower than in healthy people of similar ages and genders.

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