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Vitamin Deficiencies among Adult Patients with Recurrent Aphthous Stomatitis: A Systematic Review

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ABSTRACT
Recurrent aphthous stomatitis (RAS) is a common inflammatory condition of the oral mucosa characterized by recurrent, painful ulcerations that significantly impair quality of life. Although its etiology is multifactorial, nutritional factors, particularly vitamin deficiencies, have been proposed as potential contributors through their roles in immune regulation, epithelial integrity, and wound healing. Evidence regarding vitamin status in adults with RAS, however, remains inconsistent. This systematic review aimed to synthesize and critically evaluate available evidence on vitamin levels in adult patients with recurrent aphthous stomatitis. A comprehensive literature search was conducted in PubMed and Scopus for studies published between January 2015 and December 2025, following PRISMA 2020 guidelines. Eligible studies included adult participants (≥18 years) diagnosed with RAS and reported serum or salivary vitamin levels. Observational and interventional studies were considered. Data were extracted on study characteristics, vitamin assessment methods, and key findings, and were analyzed descriptively. Seven studies met the inclusion criteria. Vitamin D was the most frequently investigated micronutrient, followed by vitamin B12 and other hematinic parameters. Several studies reported lower vitamin D levels in patients with RAS compared with controls, while others found similarly high rates of deficiency in both groups. Associations between vitamin levels and clinical severity of RAS were generally weak, although vitamin D deficiency was linked to increased ulcer multiplicity in one study. Vitamin B12 deficiency was primarily observed in populations with concomitant iron deficiency anemia rather than in otherwise healthy adults with RAS. Current evidence suggests that vitamin deficiencies, particularly vitamin D, may function as modifying or aggravating factors in adult RAS rather than direct causal agents. Further high-quality studies are required to clarify their clinical relevance and therapeutic implications.

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most frequently occurring inflammatory disease in various region of the oral mucosa, in which recurrent episodes of painful and round or ovoid ulcers with halo area of erythema are present [1, 2]. Although common, with a considerable effect on the quality-of-life level; mainly through pain and troubles in eating or speaking [3, 4]; the etiology of RAS is still not entirely explained. At present, available evidence indicates that RAS is a multifactorial disorder associated with genetic susceptibility, immune dysfunction mediation, local trauma, food allergies, hormonal imbalance, psychological stress and nutritional factors [5].

Among the proposed etiological contributors, vitamin deficiencies have gained increasing attention due to their essential roles in epithelial integrity, immune modulation, and wound healing [6]. Vitamins such as B-complex vitamins, vitamin C, vitamin D, vitamin E, and vitamin A are known to influence oral mucosal health through their involvement in cell proliferation, collagen synthesis, antioxidant defense, and inflammatory regulation [6, 7]. Deficiencies in these micronutrients may impair mucosal barrier function and alter immune responses, potentially predisposing individuals to the development or recurrence of aphthous lesions [7].

Although RAS affects all age groups, the assessment of dietary risk factors varies between pediatrics and adult populations. Vitamin profile and status in children are heavily influenced by growth-related physiological demands, developmental dietary patterns, breastfeeding and supplemental feeding methods, and a higher prevalence of congenital defects or systemic disorders that impair nutrient absorption [8-11]. These factors may complicate the link between vitamin deficiencies and RAS, making it difficult to identify deficiency as an independent etiological cause. In contrast, vitamin status in adults more directly reflects long-term dietary consumption, lifestyle factors, and chronic systemic diseases [12], allowing for a more accurate assessment of the link between vitamin deficiencies and RAS.

Previous research in adult populations have found links between RAS and lower level of particular vitamins [13-15]. However, findings among research are still varied, with differences in study design, population characteristics, vitamin assessment methodologies, and the vitamins assessed. Furthermore, whereas many research concentrate on single nutrients, fewer have combined information from numerous vitamins, limiting comprehensive interpretation. The purpose of this systematic review is to compile and critically analyze existing evidence on vitamin deficits in people with recurrent aphthous stomatitis. By focusing on adult populations, this study aims to reduce age-related confounding factors and provide more clarity on the role of vitamin inadequacies in the pathophysiology and potential therapy of RAS.

METHOD

A comprehensive literature search was conducted using electronic databases, including PubMed and Scopus, to identify relevant studies published between January 2015 and

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December 2025. The search strategy combined the keywords “vitamin level,” “stomatitis,” and “oral ulcers,” with appropriate Boolean operators. This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Eligibility criteria were defined using the PICOS framework. The population of interest comprised adult patients (≥18 years) diagnosed with recurrent aphthous stomatitis. Studies reporting serum or salivary vitamin levels were included, with or without comparison to healthy control groups. Observational and interventional study designs were considered eligible. Studies that did not specify the age of the included participants were excluded. Literature reviews, books, editorials, letters, notes, short surveys, animal studies, pediatric studies, and articles without full-text availability were excluded.

Data extracted from the included studies comprised the author(s) and year of publication, article title, study population, vitamin assessment methods, and key findings. Extracted data were summarized in tabular form and analyzed descriptively.

RESULTS AND DISCUSSION

The study selection process is summarized in Figure 1. A total of 912 records were retrieved from PubMed and Scopus, of which 245 articles were considered potentially relevant and underwent full-text evaluation. After applying the inclusion and exclusion criteria, 7 studies were finally included in the review.

Table 1 provides the summary of the included studies. The included studies demonstrate heterogeneous associations between vitamin status and RAS in adults. Vitamin D was the most frequently investigated micronutrient, assessed in serum and saliva, followed by vitamin B12 and other hematinic parameters. Most investigations employed cross-sectional or case-control designs and included adult populations, with sample sizes ranging from 24 to 132 participants.

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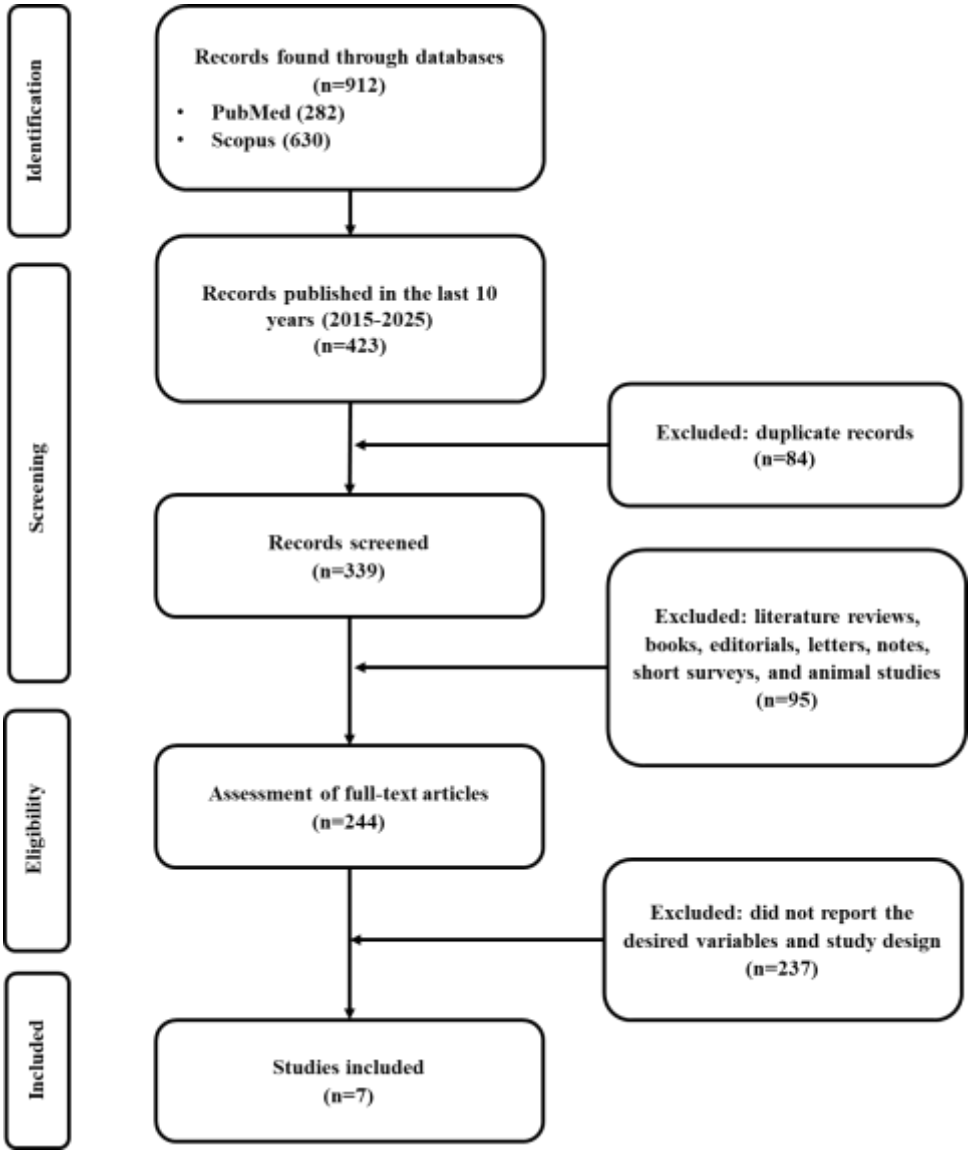

Figure 1. Study selection process using PRISMA guidelines

Five studies evaluated vitamin D status in adults with RAS using serum and/or salivary 25-hydroxyvitamin D [25(OH)D] measurements. While several studies reported significantly lower vitamin D levels in patients with RAS compared with healthy controls, others observed similarly high rates of vitamin D deficiency in both groups, reflecting its widespread prevalence in the general adult population [16]. Associations between vitamin deficiencies and clinical severity of RAS were generally weak, although one study identified a significant relationship between vitamin D deficiency and increased ulcer multiplicity [14].

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Table 1. Summary of the included studies

Authors	Title	Sample Characteristics	Vitamin Assessment	Key Findings
Krawiecka, et al., 2017 [17]	Vitamin D status in recurrent aphthous stomatitis	Case-control study including 66 adult patients with RAS (mean age 34.2 years; range 19–63) and 66 healthy controls (mean age 32.1 years; range 20–65).	Serum 25-hydroxyvitamin D [25(OH)D] levels were measured using electrochemiluminescence binding assay. Vitamin D status was categorized as normal, insufficient, or deficient according to established serum cut-off values.	Mean serum vitamin D levels were below the normal range in both RAS patients and controls, with no significant difference between groups. The prevalence of vitamin D insufficiency and deficiency was high in both populations and did not differ significantly. No significant associations were observed between serum vitamin D levels and RAS severity, including clinical type, number of lesions, or recurrence frequency.
Bahramian, et al., 2018 [13]	Comparing Serum and Salivary Levels of Vitamin D in Patients with Recurrent Aphthous Stomatitis and Healthy Individuals	Cross-sectional study including 26 adults with RAS and 26 age- and sex-matched healthy controls. Participants were aged 18–60 years, with comparable mean ages and sex distribution between groups. RAS diagnosis was based on clinical history and examination.	Serum and salivary 25-hydroxyvitamin D [25(OH)D] levels were measured using electrochemiluminescence assays. Venous blood and unstimulated saliva samples were collected and analyzed under standardized laboratory conditions.	Mean serum vitamin D levels were significantly lower in patients with recurrent aphthous stomatitis compared with healthy controls. No significant difference was observed in salivary vitamin D levels between groups. A significant positive correlation was found between serum and salivary

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Authors	Title	Sample Characteristics	Vitamin Assessment	Key Findings
				vitamin D levels, suggesting salivary vitamin D reflects systemic vitamin D status.
Öztekin and Öztekin, 2018 [18]	Vitamin D levels in patients with recurrent aphthous stomatitis	Cross-sectional study including 40 adults with RAS and 70 healthy controls. Participants were ≥18 years old, with comparable age and sex distributions between groups. Only patients with minor aphthous lesions were included. Disease characteristics such as lesion number, size, frequency, and duration were recorded.	Serum 25-hydroxyvitamin D levels were measured using electrochemiluminescence binding assays from venous blood samples collected under standardized laboratory conditions.	Serum vitamin D levels were significantly lower in patients with recurrent aphthous stomatitis compared with healthy controls. No significant correlations were observed between serum vitamin D levels and clinical characteristics of aphthous lesions, including lesion diameter, number, or healing time.
Al-Amad and Hasan, 2020 [14]	Vitamin D and hematinic deficiencies in patients with recurrent aphthous stomatitis	Case-control study including 52 adults with recurrent aphthous stomatitis and 52 age- and sex-matched healthy controls (mean age: 34 vs 31 years; male-to-female ratio approximately 2:1; all participants ≥18 years).	Serum 25(OH) vitamin D, vitamin B12, folic acid, and iron were measured using automated laboratory assays; complete blood count and red cell indices were also evaluated.	Vitamin D deficiency was prevalent (53%) with no significant difference between RAS patients and controls. RAS patients had lower mean iron and vitamin B12 levels, but differences were not statistically significant. There were no patients with low level of folic acid. Vitamin D

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Authors	Title	Sample Characteristics	Vitamin Assessment	Key Findings
				deficiency was significantly associated with multiple ulcers (OR 4.98), indicating a role in disease severity rather than onset.
Susanto, et al., 2020 [19]	Serum vitamin B12 associated with vitamin D/25(OH)D in women with recurrent aphthous stomatitis	Cross-sectional study including 41 women aged 18–30 years diagnosed with RAS. Only patients with recent-onset minor aphthous ulcers and without systemic diseases, medication use, smoking habits, or other oral conditions were included.	Serum vitamin D [25(OH)D] levels were measured using electrochemiluminescence immunoassay (ECLIA), while serum vitamin B12 levels were assessed using chemiluminescent methods. Vitamin D deficiency was defined as serum 25(OH)D <20 ng/mL.	All participants exhibited vitamin D deficiency, while mean serum vitamin B12 levels were within the normal range. A significant positive correlation was observed between serum vitamin D and vitamin B12 levels. No significant associations were found between vitamin levels and clinical severity parameters of RAS, including ulcer size, number, or pain intensity.
Al-Hamdani and Yas, 2023 [20]	Serum and Salivary Vitamin B12 Levels among Iron Deficiency Anemia Patient with Recurrent Aphthous Stomatitis: An Analytical Cross-	Cross-sectional study including 75 adults aged 20–49 years, consisting of patients with iron deficiency anemia (IDA) with RAS (n = 25), IDA without RAS (n = 25), and clinically healthy controls (n = 25).	Serum and unstimulated salivary vitamin B12 levels were measured using enzyme-linked immunosorbent assay (ELISA).	Significant differences in both serum and salivary vitamin B12 levels were observed among the three groups ($p < 0.001$). The control group showed serum vitamin B12 levels within the normal range, whereas both IDA with RAS and IDA without

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Authors	Title	Sample Characteristics	Vitamin Assessment	Key Findings
	Sectional Study			RAS groups exhibited significantly reduced serum vitamin B12 levels. Salivary vitamin B12 levels were also significantly lower in both IDA groups compared with controls.
Pandiarajan, et al., 2025 [21]	Salivary Vitamin D3 As a Non-Invasive Biomarker in Recurrent Aphthous Stomatitis-A Case-Control Study	Case-control study including 24 adults aged 20–40 years, comprising 12 patients clinically diagnosed with recurrent aphthous stomatitis (RAS) and 12 age- and sex-matched healthy controls.	Salivary vitamin D_3 levels were measured using ELISA under standardized morning collection conditions.	Salivary vitamin D_3 concentrations were significantly lower in patients with RAS compared with healthy controls ($p = 0.001$). These findings suggest an association between reduced salivary vitamin D_3 levels and the presence of RAS.

Vitamin D exerts immunomodulatory effects through the vitamin D receptor, which is expressed on keratinocytes, dendritic cells, macrophages, and activated T lymphocytes [22]. Active vitamin D (1,25-dihydroxyvitamin D) downregulates Th1 and Th17 responses while promoting regulatory T cell (Treg) activity, thereby reducing excessive inflammatory reactions [22-25]. It also suppresses the production of pro-inflammatory cytokines such as TNF-α and enhances antimicrobial peptide synthesis, including cathelicidin and defensins, which contribute to mucosal defense [26-30].

In the context of RAS, vitamin D deficiency may lower the inflammatory threshold of the oral mucosa, leading to exaggerated immune responses to minor trauma or microbial stimuli [31, 32]. This mechanism provides a plausible explanation for findings in which vitamin D deficiency was associated with greater ulcer burden or multiplicity, rather than with disease onset. The observation that salivary vitamin D3 levels were reduced in some RAS patients further supports a potential local immunoregulatory role at the oral mucosal surface.

Vitamin B12 was evaluated in three studies, with heterogeneous findings. While severe deficiencies were evident in populations with iron deficiency anemia, vitamin B12 levels were generally normal in otherwise healthy adults with RAS. The observed correlation between

vitamin D and vitamin B12 in women with RAS suggests possible shared metabolic or nutritional pathways [33, 34], rather than a direct causal relationship with ulcer formation.

Vitamin B12 plays a critical role in DNA synthesis, epithelial cell turnover, and neural function [35, 36]. Deficiency may impair oral epithelial regeneration and increase mucosal vulnerability [35]. However, findings from the included studies, serum vitamin B12 levels were within normal ranges in most adult RAS populations, suggesting that isolated B12 deficiency is unlikely to be a primary etiologic factor. The association between reduced vitamin B12 levels and iron deficiency anemia observed in some studies indicates that systemic nutritional compromise, rather than RAS itself, may account for altered vitamin status.

Taken together, the available evidence supports a model in which vitamin deficiencies, particularly vitamin D, function as modifying or aggravating factors in RAS rather than direct causal agents. This may explain why supplementation appears to benefit certain patients clinically, despite inconsistent associations at the population level [37]. The emerging use of salivary biomarkers offers a biologically plausible and non-invasive approach to assessing local vitamin status; however, methodological variability and small sample sizes currently limit their interpretability.

CONCLUSION

Current evidence suggests that vitamin deficiencies, particularly vitamin D deficiency, may act as modifying factors that influence the severity of recurrent aphthous stomatitis rather than serving as primary causes. While low vitamin D levels were frequently observed in adults with RAS, similar deficiencies were also common in healthy controls, indicating a broader population issue. Findings on vitamin B12 were inconsistent and largely associated with underlying systemic or hematinic conditions. Overall, nutritional status appears to modulate immune responses and mucosal resilience in RAS, but further well-designed prospective and interventional studies are required to clarify causal relationships and clinical implications.

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