Nutritional Status of Patient with Recurrent Aphthous Stomatitis: A Systematic Review of Observational Study

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Abstract

Recurrent aphthous stomatitis (RAS) is an oral mucosal disease, one of the predisposing factors for RAS is nutritional deficiency. Parameters of nutritional status included anthropometry, dietary assessment, and serological examination. The nutritional status of RAS sufferers has good macronutrients but low micronutrients.

The purpose of this study was to review the nutritional status of RAS patients worldwide and its relationship to the number of ulcers, diameter, severity, and frequency of RAS recurrence. The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines were used in structuring this systematic review. The PICO (population, intervention, comparison, outcome) and Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) were used. Of twelve research articles in this study, seven used the case-control method, four used a cross-sectional study, and 1 article used a retrospective study. All studies used blood samples, and 2 articles also used saliva samples.

This study found vitamin D, B12, and E deficiencies in RAS patients and no lack of folate, iron, zinc, and vitamins A and C. Vitamin D deficiency has a significant relationship with increasing ulcers. The nutritional status of patients with RAS showed a micronutrient deficiency and its relationship with increasing ulcers.

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Introduction

Recurrent aphthous stomatitis (RAS) is the most common oral mucosal disease in the community and is often referred to as ulcer.[1] This condition affects about 20% of the general population with an incidence of 5 to 50%.[2,3] The disease can occur in healthy individuals and without other systemic symptoms.[2,4] The condition is usually characterized by recurrent ulceration, a round or oval shape that has a reddish border on the periphery of the ulcer, and is covered by a yellowish-gray pseudomembrane in the middle.[5,6]

Increasing the ulcer duration and frequency will interfere the oral function, particularly in obtaining nutritional intake.[7] Apart from that, it is known that nutritional deficiency predisposes to RAS.[8] Nutrients are substances the body needs to carry out metabolic processes consisting of macronutrients (carbohydrates, protein, and fat) and micronutrients (vitamins, minerals, and water).[9] Nutritional status is a condition obtained from the balance of nutritional intake, which can be known through several parameters. The parameters were anthropometry, with the examination of body weight (BB) and height (TB); dietary assessment, using a food frequency questionnaire (FFQ), 24-hour recall, or food weighing; and biochemistry (serology). The nutritional intake was described as sufficient, insufficient, or excessive by certain standards.[9,10]

There was no research on RAS using comprehensive parameters and commonly only one parameter was used. Based on the Body Mass Index (BMI), the macronutrient status of RAS patients looks normal,[11] A study by Takci et al. showed no difference in BMI between RAS patients and controls of healthy individuals.[12] Even excess body mass index or decreased body weight are sometimes found in RAS

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patients.[13,14]Based on the Food frequency/Food frequency questionnaire (FFQ), it is known that patients with RAS have a habit of consuming eggs, milk, fruit, and vegetables and this condition leads to the macronutrient well fulfilled.[15] Meanwhile, a study by Du et al. found that some foods, such as lemon, pineapple, and vinegar, can indirectly cause RAS.[16] Study by Jelena et al. conducted a biochemical examination of RAS patients and found that the lipid profile was in a normal range while iron deficiency occurred.[13] Other studies by Takci et al. showed that fasting blood glucose levels in RAS patients were not different from controls.[12]

Anthropometric parameters and dietary assessment were still less used in RAS research. In contrast, biochemical and serological parameters were more widely used, showing a hematinic deficiency in RAS patients.[17] Hematinics are substances that form red blood cells, namely folate, iron, and vitamin B complex.[18] Susanto et al. also conducted research on vitamin B12 and vitamin D in patients with RAS. They found that there was an association between vitamin D and patients with RAS. The vitamin D level in RAS patients were lower than controls had low levels of vitamin D.[18] Therefore, this study aimed to review the published research articles on the determination of the nutritional status of patients with RAS and its relationship with the number of ulcers, diameter, severity, and frequency of recurrence. This review is expected to provide recommendations for RAS management in preventive, diagnosing, therapeutic interventions, and oral mucosal health.

Materials and methods

The Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines were used during the structuring of this systematic review. The PICO framework (population, intervention, comparison, and outcome) was used as follows: (1) population: patients with a diagnosis of RAS; (2) intervention: examination or determination of nutritional status in patients with RAS; (3) comparison: healthy individual group or control group; (4) outcome: nutritional status. The PubMed and ScienceDirect databases collected articles relevant to the research question. A search method using a boolean operator that combines the words "-OR" and "-AND" was used, with the keywords (micronutrient) OR (vitamin) OR (hematinic deficiency) AND (recurrent aphthous stomatitis) OR (recurrent aphthous ulcer). Additional articles were also searched manually by checking the reference list of articles obtained and if they were relevant to the research topic and of good quality. The inclusion criteria in this study were: articles published in the last ten years (2011-2021), in English, with a complete and accessible manuscript, articles with observational study designs, and following the research objectives. The screened articles then were assessed for eligibility using the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) to obtain articles with a low risk of bias and good quality.[19]

Results

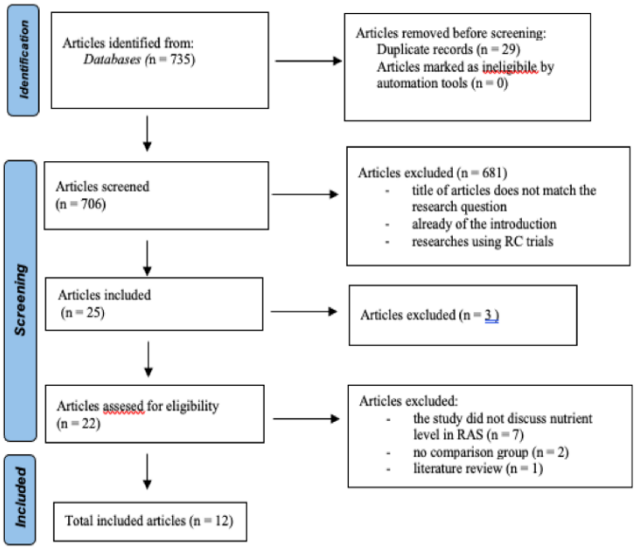

Figure 1. Flowchart strategy of searching articles.

Figure 1 shows the process of determining which articles will be reviewed qualitatively, 12 articles could be reviewed qualitatively because they were in accordance with by the purpose of the writing, met the inclusion requirements, and had good article quality. Table 1 showed that all of the included articles have a low risk of bias and have good article quality. The general characteristics of the articles to be analyzed are stated in Table 2. Five articles from Iran.[20-21] The most widely used research method is a case-control (n=7).[22,21,23,24-25] Overall, the number of study participants in

patients with RAS were 1087, while in the control group, there were 784 people. Seven articles examined the relationship between vitamin D levels and RAS.[20,26,21-27,28] The minor RAS type was the inclusion criteria in twelve research articles, and more than two types of RAS were included in three articles.[23,24,28]

No	Reference	Assesment Risk of Bias						Total Score	Result RoB	Conclusion
		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6			
1	Aynure oztekin *et al.*, 2018	1	1	1	0	1	1	5	Low	High quality
2	Burçin Nalbantoğlu *et al.*, 2020	1	1	1	0	1	1	5	Low	High quality
3	Ewa Krawiecka *et al.*, 2017	1	1	1	0	1	1	5	Low	High quality
4	Bahramian A *et al.*, 2018	1	1	1	0	1	1	5	Low	High quality
5	Shirzad A *et al.*, 2021	1	1	1	0	1	1	5	Low	High quality
6	Khabbazi *et al.*, 2015	1	1	1	0	1	1	5	Low	High quality
7	Suhail H. Amad *et al.*, 2019	1	1	1	0	1	1	5	Low	High quality
8	Zhe-Xuan Bao *et al.*, 2018	1	1	1	0	1	1	5	Low	High quality
9	Zuzanna Slebioda *et al.*, 2017	1	1	1	0	1	1	5	Low	High quality
10	Heidar Khademi *et al.*, 2014	1	1	1	0	1	0	4	Low	High quality
11	Xiao-Yan Li *et al.*, 2016	1	1	1	0	1	1	5	Low	High quality
12	Babaee *et al.*, 2016	1	1	1	0	1	1	5	Low	High quality
	Domain appraisal (%)	100	100	100	0	100	91.6	-	-	-

Table 1. Assessment of risk of bias in observational studies used the Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS).

***Description:** Item 1 = Selection of participants; Item 2 = Confounding variables; 3 = Intervention (exposure) measurement; Item 4 = Blinding of outcome assessment; Item 5 = Incomplete outcome data; Item 6 = Selective outcome reporting; 1 = Yes/available; 0 = No/not available; Total score 0 – 2 = high risk of bias; Total score 3 – 6 = low risk of bias.

No	Reference	Country	Study design	Objective	Sample size		Type of RAS		
					Cases	Controls	Mi	Ma	He
1	Aynure oztekin *et al.*, 2018	Turki	Cross-sectional	Investigating serum vitamin D levels	40	70	✓		
2	Burçin Nalbantoğlu *et al.*, 2020	Turki	Retrospective	Determine the vitamin D status in recurrent aphthous stomatitis in children.	72	70	✓		
3	Ewa Krawiecka *et al.*, 2017	Polandia	Case-control	Evaluate vitamin D status and severity of RAS	66	66	✓	✓	✓
4	Bahramian A *et al.*, 2018	Iran	Cross-sectional	Compare vitamin D levels in serum and saliva	26	26	✓		
5	Shirzad A *et al.*, 2021	Iran	Case-control	Evaluate and compare the serum levels of vitamin D between patients and controls	43	43	✓		
6	Khabbazi *et al.*, 2015	Iran	Cross-sectional	Investigating vitamin D levels and the severity of RAS	46	49	✓		
7	Suhail H. Amad *et al.*, 2019	Arab Saudi	Case-control	Investigating the relationship between the onset, severity of RAS, and vitamin D levels	52	52	✓	✓	
8	Zhe-Xuan Bao *et al.*, 2018	Cina	Case-control	Evaluate the relationship between a hematinic deficiency and RAS	517	187	✓		
9	Babaee *et al.*, 2015	Iran	Case-control	Compare salivary malondialdehyde levels, antioxidant capacity, hematinic in SAR	28	28	✓		
10	Heidar Khademi *et al.*, (2014)	Iran	Cross-sectional	Evaluate lipid peroxide enzymes in saliva and serum in patients with RAS	25	24	✓		
11	Xiao-Yan Li *et al.*, (2016)	Cina	Case-control	Compare serum levels of malondialdehyde, uric acid (UA), and vitamins C and E in RAS patients	97	97	✓		
12	Zuzanna Slebioda *et al.*, (2017)	Polandia	Case-control	Evaluate the relationship between serum zinc levels in patients with RAS	75	72	✓	✓	✓

Table 2. General characteristics of the included studies.

***Description:** minor (mi), major (ma), herpetiform (he). The total study participants were 1087 in patient RAS and 784 in the control group.

Table 3 shows the methods of determining vitamin levels and the examination results, five articles used the *enzyme-linked immunosorbent assay (ELISA)* method, and four used the *electrochemiluminescence (ECLA)* to determine micronutrient levels. Six articles examined vitamin D, and two other articles on vitamin B12 and serum vitamin E found that those vitamin levels were lower in patients with RAS, although not significant. Five articles discussed the correlation of RAS with diameter, healing time, and ulcer recurrences. There was a significant relationship between the number of ulcers with vitamin D (p = 0.027).

No	Reference	Methods	Vitamin and mineral levels(ng/mL)		Result
			Cases	Controls	
1	Oztekin *et al.*, 2018	ECLA	D : 11.00 ± 7.04	D : 16.4 ± 10.19	a. Lower in RAS patient (P=0.004) b. There was no correlation with diameter (p = 0.79), number (p = 0.651), healing time (p = 0.935)
2	Nalbantoğlu *et al.*, 2020	EIA	D : 16.4 ± 8.6	D : 23.1 ± 11.5	a. No correlation with number & severity (p = 0.76), recurrence (p = 0.65), healing time (p = 0.966) b. Lower in RAS patient (p = 0.002)
3	Krawiecka *et al.*, 2017	ECLA	D : 16.81 ± 8.45	D : 19.22±10.44	a. There is no correlation with severity (p=0.1517), number of ulcers (p=0.9151) b. There is no difference (p = 0.2073)
4	Bahramian A *et al.*, 2018	ECLA	D : 0.3307±0.1241 *saliva 0.1736±0.0801	D : 0.5089 ± 0.0930 *saliva 0.2079 ± 0.0631	a. Lower in RAS patient (p = 0.001) b. Salivary level difference was not significant (p = 0.09)
5	Shirzad A *et al.*, 2021	ELISA	D : 22.59 ± 16.06	D : 13.19 ±8.19	Lower in RAS patient (P=0.002)
6	Khabbazi *et al.*, 2015	ELISA	D : 0.121 ± 0.077	D : 0.274 ± 0.097	a. No correlation with duration (p = 0.690), number (p = 0.870), recurrence (p = 0.225) b. Lower in RAS patient (p = 0.0001)
7	Amad *et al.*, 2019	ECLA	D : 20.144 ± 9.84 Iron: 810 ± 304 B9 : 0.113 ± 0.292 B12 : 0.368 ± 0.208	D : 20.06 ± 10.76 Iron : 893 ± 292 B9 : 0.112 ± 0.0 5 B12 : 0.412 ± 0.192	a. There is no significant difference between the severity, diameter, number, and frequency of ulcers with hematinic variables b. Significant correlation between the number of ulcers and vitamin D deficiency (p= 0.027)
8	Bao *et al.*, 2018	AAK (VB12, Frt, VB9)	(236/517) B12 : < 0.18– 0.914 Folat : <4.0–18.7 Feritin : < 11.0–306.8	(52/187) B12 : < 0.18–0.914 Folat : <4.0–18.7 Feritin : < 11.0–306.8	a. Hematinic levels were lower in RAS patient (p = 0.001) b. There was no difference between feritin (p = 0.845) and folate (p = 0.343)
9	Babaee *et al.*, 2015	ELISA	Feritin :115.64 ± 107	Feritin : 55.42 ± 46.06	Higher in RAS patients (P = 0.008)
10	Khademi *et al.*, (2014)	ELISA	A : 700 ± 20 E : 12000 ± 350 C : 1090 ± 30 *saliva A : 570 ± 20 E : 11290 ± 40 C : 1060 ± 30	A : 650 ± 20 E : 12930 ± 540 C : 1120 ± 30 *saliva A : 550 ± 20 E : 10220 ± 50 C : 960 ± 30	No difference (p = 0.05)
11	Xiao *et al.*, (2016)	ELISA	E : 6770 ± 2500 C :14900 ± 2600	E : 9000 ± 1200 C :15900 ± 2400	a. Vitamin E levels were lower in RAS patients (p = 0.001). b. There was no difference in vitamin C (p = 0.894)
12	Slebioda *et al.*, (2017)	Spektrofotometer	*Zinc : 0.842 ± 0.1349*	*Zinc : 0.839 ± 0.10*	No difference (p = 0.7154)

Table 3. Vitamin and mineral levels.

***Description:** *electrochemiluminescence* (ECLA), *enzyme immunoassay* (EIA), *enzyme-linked immunosorbent assay* (ELISA).

Discussion

RAS is a multifactorial oral mucosal disease with unclear aetiology. Several developmental studies have linked the role of micronutrients to RAS.[29] Micronutrients function in the immune system in both adaptive and innate immune responses. An imbalance of these micronutrient intakes will cause changes and disorders in oral mucosal epithelial tissue.[30] Minor was the most commonly found type of RAS, with a percentage of 80 to 85%, and blood sample collection was the most common method carried out, as seen in Table 3.[27]

A total of 7 articles analyzed in this systematic revie w examined vitamin D levels in patients with RAS,[20,21,23,26-28,31,] two articles examined hematinic levels,[22,25] and two other articles discussed vitamins E and C.[32,33] Only 1 article examined zinc and vitamin A in patients with RAS.[32,24] Previous research on multivitamin deficiency in patients with RAS has often been associated with hematinic deficiencies, such as vitamin B12, folic acid, and iron.[34] However, our systematic review has shown that in the last ten years, we have found that vitamin D levels in patients with RAS appear to be lower than in controls. It is known that the vitamin D

receptor (VDR) and the vitamin D activating enzyme (1-α-hydroxylase) are expressed in many immune cells, such as T cells, macrophages, and dendritic cells.[27,35] These cells are found in the epithelial tissue of the human oral mucosa. Various diseases are also known due to vitamin D deficiency, such as multiple sclerosis, infectious diseases, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, thyroiditis, gastritis, autoimmune diseases, and obesity.[36] Some researchers have also found that autoimmune conditions predispose to RAS, and vitamin D affects autoimmune diseases.[37] The number of ulcers per episode in RAS patients with vitamin D deficiency increased fivefold.[23] Low levels of vitamin D in patients with RAS were associated with a receptor of vitamin D (VDR), the pro-inflammatory cytokine, and T helper 1.[38] T helper 1 induced the pro-inflammatory cytokines and made epithelial damage or ulcers.[39]

In this study, we did not find an association between a hematinic deficiency, severity, diameter, number, and frequency of ulcers in RAS patients. This shows a difference from the research study of Chen et al.[34] Basically, the function of vitamin B12 and folate were as metabolic co-enzymes which was carrying and activated a single carbon for the biosynthesis of purine and thymidylate nucleotides.[13,16]

Homocysteine changes into methionine through the remethylation process. When vitamin B12 or folate is deficient, homocysteine levels in plasma increase and cause arterioles thrombosis that supplies the epithelial cells of the oral mucosa, resulting in epithelial damage.[13,16] In addition, B12 deficiencies can affect DNA methylation of the IL6 gene, resulting in hypomethylation and an increase in IL6 levels in the inflammatory process in RAS.[13,16] Increased levels of IL6 can then increase the susceptibility of RAS patients.[40] In other hand, iron markers (ferritin) in RAS patients are also associated with an inflammatory process caused by pro-inflammatory cytokines and failure of gastrointestinal iron absorption.[22] Ferritin is a protein in which some minerals must be protected to prevent iron leakage. Iron serves to transport oxygen during iron deficiency, causes hypoxia of oral mucosal tissue, and leads to mucosal epithelial atrophy.[41]

An article discusses vitamin E levels in RAS patients compared to controls. Serum vitamin E levels in RAS patients were lower than in controls because vitamin E acts as a lipid antioxidant. Cellular membranes suppress lipid peroxidation when a deficiency of this vitamin causes many lipid electrons in the plasma membrane to be bound by free radicals, resulting in cell damage.[33,42] Vitamin E also plays a role in other oral diseases, such as periodontitis and leukoplakia. Vitamin E supplementation at a dose of 200 IU per day for two months can reduce attachment loss and the inflammatory effect on periodontal tissue.[43] Administration of 400 IU of vitamin E twice a week for 24 weeks to 43 leukoplakia patients gave 46% clinical and 21% histological effects.[44] Vitamin E supplementation is shown to dermatological diseases at a dose of 200-1200 IU per day depending on the illness,[45] whereas according to the study of Iqubal et al., consuming as much as 60-800 IU per day for oral health can help improve immune function.[44] Antioxidants are molecules that inhibit free radicals from forming oxidation reactions, preventing cell damage and death.[45] In carrying out its role, antioxidants will donate one of their electrons to neutralize free radicals.[45,46] Antioxidants that function to break the chain include Vitamin E (alpha-tocopherol), Vitamin C (ascorbic acid), and Vitamin A (beta carotene).[46] Vitamin E acts as an inhibitor of lipid peroxidation and prevents DNA damage in synergy with vitamin A to inhibit mutagenesis.[46] The role of vitamin C is to regenerate reduced vitamin E and enter the mitochondria to protect against oxidative injury.[45,46] Zinc acts as an immunomodulator by suppressing and inhibiting inflammatory cytokines.[17] When levels are low, it results in increased production of Th1 cells as one of the inflammatory cytokines.[17] Therefore, zinc deficiency has been associated with several diseases, such as atopic dermatitis and RAS.[17] The article on vitamin zinc screened in this study found no difference between RAS sufferers and controls. This is different from the study of Ozler et al. which found low zinc levels in patients with RAS in his study.[47] His research explains that zinc deficiency is one of the etiopathogeneses of RAS. A recent study by Halboub et al. conducted a meta-analysis of zinc supplementation as a treatment for RAS.[40] Zinc supplementation at a dose of 12-600 mg can reduce RAS recurrence

and pain and accelerate healing time.[40] Another treatment based on the results of this systematic review is supplementation of vitamin D, B12, vitamin E, and iron. Administration of vitamin D has an anti-inflammatory effect on maintaining oral health for an adult dose of 400 IU per day should be followed by sunbathing activities.[48] Volkov's study stated that vitamin B12 supplementation with a dose of 1000 mcg per day sublingually for six months can reduce the duration, several ulcers, and pain level.[49] Vitamin E supplementation for oral health at a dose of 60-1800IU per day.[44] Study Stoffel et al. recommend regularly giving iron at a dose of 150-200 mg daily.[50]

Research related to this thema in this review has only been carried out on two continents, Asia and Europe, and has not yet been carried out in Indonesia, so there is still an opportunity to conduct similar research in Indonesia or other continent. This research can be used as a basis for researching vitamin D and iron supplementation related to the occurrence of RAS. The limitations of this systematic review are that only two databases were used, namely PubMed and ScienceDirect, and limited the small number of filtered articles discussing vitamins A, C, E, and Zinc, in RAS patient.

Conclusions

The nutritional status of patients with RAS showed a micronutrient deficiency in several vitamins and minerals, including vitamin D, B12, serum vitamin E, and iron. There was a significant relationship between vitamin D and the number of ulcers. There is no significant difference between vitamins A, C, and zinc.

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Declaration of Interest

The authors report no conflict of interest.

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