Review Article

Relevance of Hematological Parameters in Patients with Recurrent Aphthous Stomatitis

Alberto Rodriguez-Archilla, Maria Brykova

Department of Stomatology, Oral Medicine Unit, Faculty of Dentistry, University of Granada, Granada, Spain

Abstract

Background: Recurrent aphthous stomatitis (RAS) continues to be a very common ulcerative disease of the oral mucosa, affecting approximately 20% of the general population. Hematinic deficiencies have been considered as a possible triggering factor, being iron, Vitamin B_{12}, or folic acid deficiencies two times more frequent in patients with RAS. **Objective:** The objective was to assess the hematological parameters as possible etiological factors of RAS. **Materials and Methods:** A PubMed search of articles on hematological parameters in RAS was conducted. From 93 articles published between 1954 and 2018 (64 with full-text availability), 45 were excluded for several reasons: studies without a control group (17), studies with no clinical data (12), and studies with nonusable data (16). Data were processed using the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For continuous outcomes, the estimates of effects of an intervention were expressed as mean differences using the inverse variance method, and for dichotomous outcomes, the estimates of effects of an intervention were expressed as odds ratio (OR) using Mantel-Haenszel method, both with 95% confidence intervals. **Results:** Nineteen studies of hematological parameters on RAS were included in this meta-analysis. RAS patients had a significantly higher risk of presenting low levels, together with lower concentrations, of hemoglobin (OR: 17.30), iron (OR: 6.67), folic acid (OR: 4.98), Vitamin B_{12} (OR: 3.99), ferritin (OR: 2.86), and higher levels of homocysteine (OR: 7.22). **Conclusion:** Hematological disturbances may be an etiological factor of RAS.

Keywords: Aphthous, folic acid, hemoglobin, iron, stomatitis, Vitamin B_{12}

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Introduction

Recurrent aphthous stomatitis (RAS) continues to be a very common ulcerative disease of the oral mucosa, affecting approximately 20% of the general population. Depending on the size of the lesions, three clinical forms of RAS have been described: minor aphthae (90% of cases), major aphthae (8%), and herpetiform ulcers (2%).[1] RAS is considered as a multifactorial process of unknown etiology, in which various triggering factors and an immunological disturbance are combined. Among its possible triggers are food allergy, oral mucosal trauma, hormonal changes, stress and anxiety, blood and/or nutritional deficiencies, family history, certain infectious agents, and various systemic diseases.[2]

Specifically, hematinic deficiencies (iron, Vitamin B_{12}, or folic acid) are twice as frequent in individuals with RAS compared to the control population.[3] In adult patients prone to develop RAS episodes, the existence of an underlying systemic disease, a connective tissue disease, a hematinic deficiency, or an immunodeficiency must be suspected.[4] The aim of this study was to analyze the role of hematological parameters as possible etiological factors of RAS.

Materials and Methods

A PubMed database search of articles on hematological parameters in RAS was made combining Medical Subjects Headings (MeSH) terms. The search terms were: "stomatitis, aphthous" (MeSH terms) AND ("iron" [MeSH terms] OR "folic acid" [MeSH terms] OR "Vitamin B_{12}" [MeSH terms] OR "ferritins" [MeSH terms] OR "hemoglobins" [MeSH terms] OR "homocysteine" [MeSH terms]). The initial search found 93 articles published between 1954 and 2018. The two inclusion

Address for correspondence: Prof. Alberto Rodriguez-Archilla, Faculty of Dentistry, University of Granada, Colegio Maximo, s/n. Campus de Cartuja, Granada 18071, Spain.
E-mail: alberodr@ugr.es

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criteria were: (a) articles with full-text availability (n = 64) and (b) studies that included, at least, one control group without RAS (n = 47). The exclusion criteria were: (a) studies without clinical data (n = 12) and (b) studies with irrelevant or nonusable data (n = 16). After the application of these criteria, 19 articles were analyzed in this meta-analysis [Figure 1].

Statistical analysis

The meta-analysis was performed with the RevMan 5.3 program (The Cochrane Collaboration, Oxford, UK). For dichotomous variables, the Mantel-Haenszel Chi-square odds ratio (OR) with 95% confidence interval (CI) was used. For continuous variables, the inverse of the variance for the mean difference (MD) with 95% CI was used. Heterogeneity was determined according to the Higgins statistic (I^2). The random-effects model was applied in cases of high heterogeneity. $P < 0.05$ was considered statistically significant.

Results

Table 1 presents the main descriptive characteristics of the 19 studies considered in this meta-analysis.[5-23] The different hematological parameters assessed in patients with RAS and controls are shown in Table 2.

Regarding the iron, 11 studies[5-15] compared the presence of low iron levels (<50 μg/dL) in RAS patients versus control subjects without the disease. RAS patients were 6.67 times more likely to have low iron levels, with highly significant statistical differences (OR = 6.67, 95% CI: 2.37–18.77, $P < 0.001$). Six studies[8,11-13,15,16] analyzed the iron concentrations both in the RAS patients group and control group, observing lower iron concentrations of 11.75 μg/dL on average in RAS patients with respect to controls. After the statistical analysis, a highly significant association was observed (MD = −11.75, 95% CI: −15.76–−7.74, $P < 0.001$).

Fourteen studies[5-9,11-15,17-20] examined the presence of low levels of Vitamin B_{12} (<200 pg/mL) in patients with RAS with respect to controls subjects. RAS patients were 3.99-fold more likely to have low levels of Vitamin B_{12}, with a highly significant statistical relationship (OR = 3.99, 95% CI: 2.43–6.53, $P < 0.001$). Another seven studies[8,11-13,15,16,21] examined Vitamin B_{12} concentrations in both groups, RAS patients and controls. Vitamin B_{12} concentrations in RAS patients were lower in 31.35 pg/mL on average compared to controls. Statistical analysis showed significant differences (MD = −31.35, 95% CI: −55.75–−6.94, $P = 0.01$).

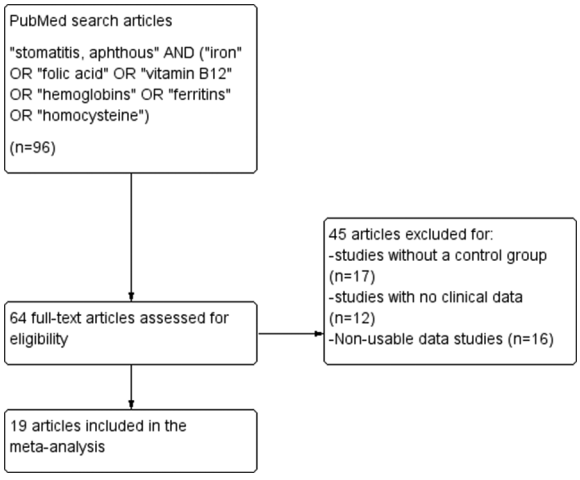

Figure 1: Study flow diagram

Fourteen studies[5,7-9,11,13-15,17-20,22,23] considered the low levels of folic acid (<6 ng/mL) in RAS patients and controls. Patients with RAS were 4.98 times more likely to present low levels of folic acid respect to controls, with a highly significant statistical association (OR = 4.98, 95% CI: 2.67–9.30. $P < 0.001$). Moreover, six studies[8,11,13,15,16,21] compared folic acid concentrations in both groups, finding folic acid concentrations lower in 0.95 ng/mL on average in RAS patients. After the statistical analysis, a very significant relationship was found (MD = −0.95, 95% CI: −1.53–−0.38, $P < 0.01$).

Six studies[8,12,13,15,18,19] assessed the low hemoglobin levels (<14 g/dL) in patients with RAS and controls without the disease. RAS patients were 17.30-fold more likely to have low hemoglobin levels, with very significant statistical differences (OR = 17.30, 95% CI: 2.27–131.79, $P < 0.01$). Respect to the mean hemoglobin concentrations in both study populations,[8,13,15,16] RAS patients had lower hemoglobin concentrations in 0.85 g/dL on average compared to controls. The statistical analysis showed a highly significant relationship (MD = −0.85, 95% CI: −1.21–−0.49, $P < 0.001$).

Eight studies[7,9,11,17-20,23] analyzed the levels of serum ferritin, finding lower levels (<15 ng/mL) in patients with RAS. These patients were 2.86 times more likely to have low ferritin levels than controls without the disease. The statistical association was highly significant (OR = 2.86, 95% CI: 1.97–4.14, $P < 0.001$). Three studies[11,16,23] investigated mean concentrations of serum ferritin in RAS patients and controls, although no statistically significant differences were found (MD = −14.57, 95% CI: −56.54–27.39, $P = 0.50$).

Finally, four studies[8,13,15,21] investigated blood homocysteine in RAS patients versus controls. About 8.6% of RAS patients (61/708) and 1.3% of controls (13/970) had high homocysteine levels (>10.4 μmol/L). Patients with RAS were 7.22-fold more likely to have high homocysteine levels, with a highly significant statistical relationship (OR = 7.22, 95% CI: 3.90–13.38, $P < 0.001$). In contrast, when homocysteine concentrations were compared in both population groups, there were no statistically significant differences (MD = −0.02, 95% CI: −0.11–0.08, $P = 0.74$).

Discussion

In the present meta-analysis on the possible influence of different hematological parameters on RAS, data from 19 studies were included.

In this study, RAS patients had 6.67 times more likely than controls to have low iron levels (<50 μg/dL) with statistically

Table 1: Descriptive characteristics of included articles

First author	Year	Country	Study groups	Hematological parameter assessed	Remarks
Barnadas *et al*.[5]	1997	Spain	80 RAS patients 29 controls	Iron, folic acid, and Vitamin B_{12}	Hematinic deficiencies: 26.2% RAS patients 13.2% controls
Challacombe *et al*.[6]	1977	UK	193 RAS patients 100 controls	Iron, folic acid, and Vitamin B_{12}	Hematinic deficiencies: 25.9% RAS patients 7% controls
Compilato *et al*.[7]	2010	Italy	32 RAS patients 29 controls	Iron, folic acid, and Vitamin B_{12}	Hematinic deficiencies: 56.2% RAS patients 7% controls
Lin *et al*.[8]	2017	Taiwan	240 RAS patients 342 controls	Iron, folic acid, Vitamin B_{12}, hemoglobin, and homocysteine	Hematinic deficiencies: 16.4% RAS patients 0.9% controls
Lopez-Jornet *et al*.[9]	2014	Spain	92 RAS patients 94 controls	Iron, folic acid, Vitamin B_{12}, and hemoglobin	Hematinic deficiencies: 14.4% RAS patients 6.4% controls
Olson *et al*.[10]	1982	USA	90 RAS patients 23 controls	Iron, folic acid, and Vitamin B_{12}	Hematinic deficiencies: 3.3% RAS patients 0% controls
Piskin *et al*.[11]	2002	Turkey	35 RAS patients 26 controls	Iron, folic acid, Vitamin B_{12}, and ferritin	Hematinic deficiencies: 22.8% RAS patients 3.8% controls
Ślebioda *et al*.[12]	2018	Poland	71 RAS patients 70 controls	Iron and Vitamin B_{12}	Hematinic deficiencies: 16.9% RAS patients 5.0% controls
Sun *et al*.[13]	2015	Taiwan	273 RAS patients 273 controls	Iron, folic acid, Vitamin B_{12}, and homocysteine	Hematinic deficiencies: 11.2% RAS patients 1.1% controls
Wray *et al*.[14]	1975	UK	130 RAS patients 130 controls	Iron, folic acid, and Vitamin B_{12}	Hematinic deficiencies: 17.7% RAS patients 8.5% controls
Wu *et al*.[15]	2016	Taiwan	195 RAS patients 355 controls	Iron, folic acid, Vitamin B_{12}, hemoglobin, and homocysteine	Hematinic deficiencies: 11.7% RAS patients 2.0% controls
Koybasi *et al*.[16]	2006	Turkey	34 RAS patients 32 controls	Iron, folic acid, and Vitamin B_{12}	Hematinic deficiencies: 35.2% RAS patients 0% controls
Bao *et al*.[17]	2018	China	517 RAS patients 187 controls	Folic acid, Vitamin B_{12}, and ferritin	Hematinic deficiencies: 45.6% RAS patients 27.8% controls
Burgan *et al*.[18]	2006	Jordan	517 RAS patients 187 controls	Folic acid, Vitamin B_{12}, hemoglobin, and ferritin	Hematinic deficiencies: 15.6% RAS patients 8.2% controls
Khan *et al*.[19]	2013	Pakistan	60 RAS patients 60 controls	Folic acid, Vitamin B_{12}, hemoglobin, and ferritin	Hematinic deficiencies: 46.6% RAS patients 20.1% controls
Porter *et al*.[20]	1988	UK	69 RAS patients 75 controls	Folic acid, Vitamin B_{12}, and ferritin	Hematinic deficiencies: 6.0% RAS patients 3.2% controls
Gönül *et al*.[21]	2009	Turkey	47 RAS patients 69 controls	Folic acid, Vitamin B_{12}, and homocysteine	No significant differences between two groups
Thongprasom *et al*.[22]	2002	Thailand	23 RAS patients 19 controls	Folic acid, Vitamin B_{12}, and hemoglobin	Hematinic deficiencies: 21.7% RAS patients 0% controls
Challacombe *et al*.[23]	1983	UK	105 RAS patients 78 controls	Ferritin	Hematinic deficiency: 8.0% RAS patients 3.0% controls

RAS=Recurrent aphthous stomatitis; Controls=Individuals without RAS

Table 2: Different hematological parameters in recurrent aphthous stomatitis patients and controls

Hematological parameter (measurement units)	Study references	Outcome	Statistic	95% CI	I^2 (%)	*P*
Iron (μg/dL)						
Low levels (<50)	[5-15]	RAS patients	OR: 6.67	2.37-18.77	79	<0.001*
Concentrations	[8,11-13,15,16]	↓ RAS patients	MD: −11.75	−15.76-−7.74	38	<0.001*
Vitamin B_{12} (pg/mL)						
Low levels (<200)	[5-9,11-15,17-20]	RAS patients	OR: 3.99	2.43-6.53	34	<0.001*
Concentrations	[8,11-13,15,16,21]	↓ RAS patients	MD: −31.35	−55.75-−6.94	44	0.01*
Folic acid (ng/mL)						
Low levels (<6)	[5,7-9,11,13-15,17-20,22,23]	RAS patients	OR: 4.98	2.67-9.30	34	<0.001*
Concentrations	[8,11,13,15,16,21]	↓ RAS patients	MD: −0.95	−1.53-−0.38	26	<0.01*
Hemoglobin (g/dL)						
Low levels (<14)	[8,12,13,15,18,19]	RAS patients	OR: 17.30	2.27-131.79	92	<0.01*
Concentrations	[8,13,15,16]	↓ RAS patients	MD: −0.85	−1.21-−0.49	90	<0.001*
Ferritin (ng/mL)						
Low levels (<15)	[7,9,11,17-20,23]	RAS patients	OR: 2.86	1.97-4.14	13	<0.001*
Concentrations	[11,16,23]	↓ RAS patients	MD: −14.57	−56.54-27.39	88	0.50
Homocysteine (μmol/L)						
High levels (>10.4)	[8,13,15]	RAS patients	OR: 7.22	3.90-13.38	0	<0.001*
Concentrations	[8,13,15,21]	↓ RAS patients	MD: −0.02	−0.11-0.08	8	0.74

*Statistically significant. RAS=Recurrent aphthous stomatitis; OR=Odds ratio; MD=Mean difference; 95% CI=95% confidence interval; I^2 (%)=Higgins statistic for heterogeneity (percentage); ↓=Lower concentrations

significant differences ($P < 0.001$). The 11 studies[5-15] that considered this parameter also found low iron levels in RAS patients. Similarly, patients with RAS had significantly lower iron concentrations (11.75 μg/dL lower on average) compared to controls ($P < 0.001$). Of the six studies[8,11-13,15,16] that analyzed these iron mean concentrations, only one of them[11] found lower iron concentrations in the controls, although without a significant relationship. Iron deficiency is responsible for anemia in which the decrease in the number of erythrocytes results in less oxygen transport to tissues, including the oral mucosa. This lack of oxygen affects the differentiation and maturation of the epithelial cells causing the atrophy of the oral mucosa. This atrophy increases tissue susceptibility favoring antigenic exposure and the development of a cytotoxic immunological response that could lead to RAS.[13]

With respect to Vitamin B_{12}, in the present study, RAS patients had 3.99-fold more likely of having low levels of this vitamin compared to controls. After the statistical analysis, highly significant differences were found ($P < 0.001$). Thirteen studies[6-9,11-15,17-20] coincided in finding low Vitamin B_{12} levels (<200 pg/mL) in patients with RAS; meanwhile, a single study observed low levels in the controls.[5] Similarly, RAS patients had Vitamin B_{12} concentrations lower in 31.35 pg/mL on average in contrast to those in controls with a statistically significant relationship ($P = 0.01$). Only one of the seven studies[8,11-13,15,16,21] that evaluated these concentrations found higher Vitamin B_{12} concentrations in patients with RAS.[21] Vitamin B_{12} deficiency, either separately or in combination with other deficiencies of the Vitamin B complex, can be a possible precipitating factor for RAS. Vitamin B_{12} plays an important role in the synthesis of DNA and cell division of epithelial cells, and its deficiency may result in atrophy of the oral epithelium. In addition, according to some studies, replacement therapy with Vitamin B_{12} produces a clinical improvement in RAS patients, reducing the frequency, and severity of oral aphthous ulcers.[13]

The possible relationship between folic acid and RAS was also investigated. A greater number of RAS patients had low levels (<6 ng/mL) of folic acid, in line with findings of 14 studies.[5,7-9,11,13-15,17-20,22,23] In fact, RAS patients were 4.98 times more likely than controls to have low levels of folic acid with a highly significant statistical association ($P < 0.001$).

Six studies[8,11,13,15,16,21] also investigated folic acid concentrations in patients with RAS and in controls. Patients showed lower folic acid concentrations (0.95 ng/mL lower on average) compared to controls with very significant statistical differences ($P = 0.001$). Only one study[16] did not find lower folic acid concentrations in RAS patients, although these results could be conditioned by the characteristics of the population included in that study. Folic acid deficiency also induces oral mucosa atrophy and increases the inflammation, situations that favor the appearance of oral aphthae.[13] As in the case of Vitamin B_{12}, folic acid replacement therapy has shown an improvement in patients with RAS.[18]

When analyzing hemoglobin, RAS patients had 17.30 times more likely of having low hemoglobin levels (<14 g/dL) compared with controls. After the statistical analysis, a very significant relationship was observed ($P < 0.01$). Six studies[8,12,13,15,18,19] coincided in finding low levels of hemoglobin in RAS patients. Likewise, lower hemoglobin concentrations in 0.85 g/dL on average were found in patients with RAS, with a highly significant statistical association ($P < 0.001$) in consonance with the results of three studies.[8,13,15] The lack of hemoglobin reduces the capacity of the blood to transport oxygen to the oral tissues, inducing epithelial atrophy that increases the risk of developing RAS lesions.[13]

Of the eight studies[7,9,11,17-20,23] that investigated the ferritin levels, all of them found low ferritin levels (<15 ng/mL) in RAS patients with respect to the control subjects. Patients with RAS were 2.86-fold more likely to have low ferritin levels, with a highly significant statistical relationship ($P < 0.001$). Nevertheless, when ferritin concentrations were analyzed both RAS patients and controls, no statistically significant differences were found ($P = 0.50$).

There is a direct relationship between iron and ferritin levels, the decrease of ferritin has the same biological effect on tissues as iron deficiency.[19] In RAS patients, it seems that other factors such as age or sex influence ferritin levels. Hence, serum ferritin deficiency is more common in young women with RAS.[17]

Finally, four studies[8,13,15,21] assessed the possible influence of homocysteine on RAS. Patients with RAS had 7.22-fold more likely to have high homocysteine levels (>10.4 µmol/L) compared to controls, with a highly significant statistical association ($P < 0.001$). However, in the case of blood homocysteine concentrations, no statistically significant differences ($P = 0.74$) were observed between RAS patients and controls. The increase in blood homocysteine levels can cause oxidative cell stress and endothelial damage.[13] In patients with RAS, Vitamin B_{12} deficiency increases the levels of homocysteine that induces the thrombosis of the blood capillaries which supply the oral tissues, favoring the breakdown of the epithelial integrity, and the development of aphthous ulcers.[8]

The high heterogeneity of some studies considered in this meta-analysis and the methodological differences among the different studies could be a potential source of bias, compelling to interpret the findings with caution.

Conclusion

In this meta-analysis, RAS patients were more likely to have significantly lower levels of hemoglobin (OR: 17.30 and MD: −0.85 g/dL), iron (OR: 6.67 and MD: −11.75 µg/dL), folic acid (OR: 4.98 and MD: −0.95 ng/mL), Vitamin B_{12} (OR: 3.99 and MD: −31.35 pg/mL), and ferritin (OR: 2.86). In contrast, these patients had higher homocysteine values (OR: 7.22).

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Conflicts of interest

There are no conflicts of interest.

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