Review article

The Correlation between Iron Deficiency and Recurrent Aphthous Stomatitis: A Literature Review

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Abstract

Aphthous lesions of the oral mucosa are a very common symptom and can be seen in both family medicine practice, dental medicine practice, and dermatology or otorhinolaryngology clinics. Some patients develop a chronic recurrent condition, which is clinically known as recurrent aphthous stomatitis (RAS). These ulcers are round, clearly defined, and can be visible on the movable part of the oral mucosa, with variations in size. A prodromal symptom like the burning or stinging sensation can precede the appearance of lesions. The main reason why patients seek medical help is oropharyngeal pain with lack of appetite.

The exact etiopathogenesis of RAS remains unknown. Immune disorders, nutritional deficiencies, allergies, mechanical injuries, and even psychological disorders are being studied as potential causes of this condition. Some authors claim that iron deficiency may be a possible causative factor of RAS due to its role in DNA synthesis, mitochondrial function, and enzymatic activity. In iron deficiency, epithelial cells turn over more rapidly and produce an immature or atrophic mucosa. Such mucosa is vulnerable and can be a fertile soil for chronic inflammation and development of aphthae.

Finally, our goals were to describe the clinical aspects and etiology of RAS, as well as to determine whether RAS may be related to iron deficiency, in order to identify potential patients with iron deficiency in everyday work.

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Introduction

Recurrent aphthous stomatitis (RAS) is a frequent oral disorder characterized by multiple painful ulcers in the oral cavity and oropharynx. The prevalence of this condition in the general population is high and varies from 5% to 66%, with a mean of 20% (1). It can be seen in both family medicine practice, dental medicine practice, and dermatology or otorhinolaryngology clinics. We therefore wanted to describe the clinical aspects and etiology of RAS, as well as determine whether RAS may be related to iron deficiency, in order to identify potential patients with iron deficiency in everyday work.

Methods of literature search

We performed a literature search using PubMed and Google Scholar and we used the search filter with the following specific terms: recurrent aphthous stomatitis, aphthae, iron deficiency, and anemia, to find works published in the last twenty years, from 2000 until now. In searching these databases, we focused on meta-analyses, systematic reviews, randomized controlled trials, and landmark studies that have previously focused on similar topics (Table 1).

Table 1. Results of international research on hematinic deficiency in RAS

Author and year of study	Country	No. of subjects			Serum iron level (µg/dl)		Ferritin (ng/ml)		Hemoglobin (g/dl)		Anemia (N)
				ALL	M	W	M	W	M	W	
Slebioda et al. 2018	Poland	RAS	71	141	104.96	78.56	x		x		7
		C	70		115.85	102.43	x		x		1
Sun et al. 2014	Taiwan	RAS	273	546	96.8	83.9	x		14.1	12.8	57
		C	273		104.1	97.9	x		15.1	13.6	0
Piskin et al. 2001	Turkey	RAS	35	61	91.39	71.06	63.78	53.47	x		x
		C	26		84.23	75.31	59.74	67.73	x		x
Al-Amad et al. 2019	United Arab Emirates	RAS	52	104	81.0		x		14.0		13
		C	52		89.3		x		14.5		9
Koybasi et al. 2006	Turkey	RAS	34	64	67.82		x		13.53		x
		C	32		71.16		x		13.42		x
Babaee et al. 2015	Iran	RAS	28	56	x		115.64		12.87		x
		C	28		x		55.42		12.98		x
					LOW, number		LOW, number				
Lopez-Jornet et al. 2013	Spain	RAS	92	186	low (< 60 µg/dl) = 7		low (< 12 ng/ml) = 6		x		x
		C	94		low (< 60 µg/dl) = 2		low (< 12 ng/ml) = 5		x		x
Compilato et al. 2010	Italy	RAS	32	61	low (< 40 µg/dl) = 11		low (< 10 ng/ml) = 13		x		11
		C	29		low (< 40 µg/dl) = 2		low (< 10 ng/ml) = 0		x		2

C = control group, RAS = recurrent aphthous stomatitis, M = men, W = women, x = no data.

Classification of recurrent aphthous stomatitis

The onset of RAS is usually during childhood, with symptoms decreasing with age. The ulcers are round or oval and very painful. When looking closely at each aphtha, an erythematous lesion with a raised edge and inner necrosis covered with a yellow pseudomembrane can be seen. A

burning or stinging sensation can precede the appearance of erythematous macules and consequently very painful ulcers are formed (2).

Clinically, RAS can be classified into three types: minor, major, and herpetiform. Small aphthous ulcers (minor RAS), which are smaller than 10 mm in diameter, appear in more than 80% of patients and heal without a scar in 7 to 14 days. The most commonly affected sites are buccal and labial mucosa. Large aphthous ulcers (major RAS), which are bigger than 10 mm, heal in 2 to 6 weeks and often leave scars (3). The soft palate, tonsillar fossa, and labial mucosa are frequently affected. Herpetiform RAS is rare and represents a condition in which a great number of small oral lesions is seen. The typical onset of herpetiform RAS is in adulthood and it resembles herpes simplex virus type 1 infection, which is usually seen on the gingiva and hard palate (1).

Etiology of recurrent aphthous stomatitis

Recurrent aphthous stomatitis is one of the recurrent ulcerative disorders of the oral cavity. The exact causative mechanism remains unclear, but experts agree on its multifactorial origin (4). Possible etiologic factors of RAS include dysregulation of the immune system, hematologic diseases, hypovitaminosis and mineral deficiencies, allergies, mechanical injuries, mental disorders, etc (5) (Figure 1).

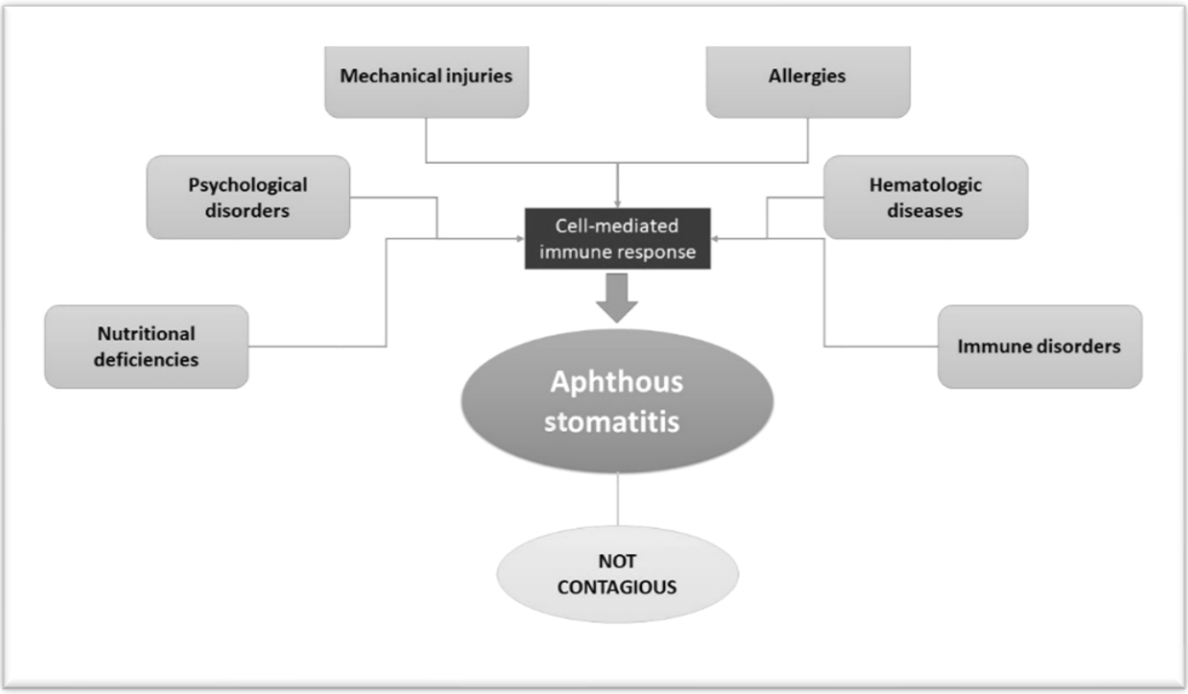

Figure 1. Etiology of recurrent aphthous stomatitis

Some studies suggest that local trauma may be the main cause of aphthae development, but only in susceptible individuals with a hereditary predisposition to the disease (6). Genetic predisposition plays a significant role in the development of RAS. The eruption of aphthae is more common in patients with positive family history. Likewise, it is followed by a severe clinical presentation (4). Guimaraes et al. examined whether DNA polymorphism related to the cytokine interleukin-1 beta (IL-1 β) may be associated with RAS. Their work showed a positive correlation and demonstrated how a genetic risk factor can determine susceptibility to the disease. Aberrant cytokine cascade induces an amplified cell-mediated immune response and activation of T-lymphocytes and phagocytes. These immune cells are directed

toward focal areas of the oral mucosa, resulting in ulceration (7).

Iron in recurrent aphthous stomatitis

In some patients, the possible causative factors are vitamin and mineral insufficiency, such as lack of serum iron, folate, zinc, or vitamin B12, and their frequency is estimated at 5%–15% (8). Iron is a very important element in the human body. Hemoglobin, myoglobin, and a variety of enzymes contain the majority of the iron. The main storage of iron within the human body is the liver, where it is stored in the form of ferritin and hemosiderin. Transport of iron through the plasma is performed by the transport protein transferrin, which binds to its receptor when it reaches the tissue (9). When looking intracellularly, iron is essential for DNA replication, enzyme and mitochondrial action, and neurotransmitter function (10). When iron intake is too low to fulfill normal bodily demands or to satisfy a pathological deficit, stored iron is consumed, leading to a lack of available iron for hematopoiesis and erythropoiesis. Production of hemoglobin without adequate concentrations of iron culminates in hypochromic microcytic anemia (9). Moreover, a lack of iron will disrupt lymphocyte development and impair cytokine production, leading to decreased cellular immunity (11).

Cytochrome oxidase, the iron-dependent enzyme, is required for the development of epithelial cells (12). In iron deficiency, epithelial cells turn over more rapidly and produce an immature or atrophic mucosa (13). Such impaired mucosa is more sensitive and susceptible to a pathological process like ulcer development. In addition, lower oxygen levels in anemic patients mean lower oxygen levels in different tissue, as well as the mucosal epithelium of the oropharynx. Inadequate oxygen saturation contributes to the disintegration of cells, which provokes atrophic mucosa. Atrophic oral epithelium may be the cause of increased susceptibility to RAS development in anemic patients (14).

The influence of age-related changes on the immune system and development of recurrent aphthous stomatitis

Aging is related to a higher level of systemic inflammation and persistent activation of non-specific immune cells due to lifelong exposure to external antigens and raised stimulation with own antigens (15). Disbalance in the inflammatory response leads to a variety of common chronic diseases due to dysregulation of immune cells and lack of their self-limiting feature, although in the elderly, the driving mechanism is more complicated, considering the vast number of comorbidities (16, 17). Unfortunately, current understanding of the relationship between the physiological processes in aging and the development of age-related illnesses remains inconclusive, with a lack of standardized methodology to clinically evaluate the inflammation. Assessment of iron status is challenging when concomitant inflammation is present. Identifying how to optimally adjust conditions linked with chronic illnesses and how to select realistic target outcomes at various stages of disease progression is becoming increasingly difficult (18). Furthermore, difficulties in stress-induced physiological mechanisms result in a detrimental allostatic load, a cumulative burden of chronic stress and life events (20), eventually precipitating a negative stress response along with disease progression, especially in chronic medical conditions (19). Due to its association with endothelial dysfunction and chronic inflammation, it can be assumed that the frequency of RAS would be higher in the elderly, but this would be incorrect. The occurrence of RAS decreases with age, while its severity increases (21). However, there is no clear understanding of the pathophysiological mechanism. The first clinical presentation of aphthous lesions in the elderly can easily be a local sign of systemic disease, which is why the term “aphthous-like ulcers” is used (22).

Discussion

The effect of iron deficiency in the biology of RAS has been studied by various authors with inconclusive results (Table 1).

Koybasi et al. (23) examined the possible etiologic factors of RAS in a controlled prospective study by analyzing 34 patients with recurrent aphthous stomatitis and 32 healthy subjects. They identified some important predisposing factors, such as positive family history and vitamin B12 deficiency. Interestingly, their study showed that nonsmoking status is connected with a higher chance of aphthae development, which means that smoking can have a protective effect. This can be explained by increased keratinization of the oral cavity due to cigarette use. Finally, their results did not show a statistically significant correlation between iron, ferritin, hemoglobin and RAS. Piskin et al. (24) studied 35 patients with RAS and 26 control subjects. They found that patients with oral ulcers have iron, ferritin, and folic acid insufficiency more frequently, but that this is statistically irrelevant ($p > 0.05$). Vitamin B12 level was the only measured variable that showed significance ($p = 0.005$).

Al-Amad and Hasan (25) conducted a case-control study on 52 patients with stomatitis and 52 age-matched healthy subjects. Their results showed a high percentage of deficiencies in the overall study population. Low hemoglobin was seen in 22%, vitamin B12 deficiency in 15%, iron deficiency in 11%, and vitamin D deficiency surprisingly in 53% of the subjects, with no difference between the diseased and healthy cases. They pointed out that vitamin D deficiency makes ulcers more severe. Lopez-Jornet et al. (26) evaluated laboratory tests of 92 patients with RAS and 94 healthy controls. They measured the concentration of iron, ferritin, folic acid, and vitamin B12. Their results showed that the patients with RAS have hematinic deficiencies more often compared with healthy controls. However, this result was also statistically insignificant, with overall frequency of hematinic deficiencies in the RAS group amounting to 14.14% and in the control group to 6.39% ($p = 0.086$).

Compilato et al. (27) studied 32 adults with RAS and 29 healthy controls, measuring full blood count, hemoglobin, serum folate, vitamin B12, iron, and ferritin levels. Their study showed statistical significance between the observed groups, with overall deficiencies amounting to 56.2% in patients with RAS versus 7% in healthy age-matched individuals ($p < 0.0001$). When looking at anemia alone, 34.4% of diseased subjects had anemia, compared with 6.9% of healthy individuals. They implied that ulceration could anticipate the onset of anemia, which is why routine laboratory blood tests should be performed in patients with RAS to promptly diagnose hematinic deficiency and prevent more severe clinical manifestations caused by iron, folic acid, or vitamin B12 deficiency. Their study established a firm connection between positive family history and the onset and severity of symptoms. No significant differences were found in the body mass index in all observed groups. The second part of their research involved administering adequate replacement therapy for a month to patients with ulcers who had some hematinic deficiencies, after which they were re-evaluated in a 3-month follow-up period. Their results strictly classified two groups of people, one with total remission of ulceration in the oral cavity and another without remission. The variable by which they were divided was family history of RAS. People with negative family history completely recovered after replacement therapy, but in patients with positive family history, ulceration was present despite therapy. This fact emphasizes the importance of detailed case history examination and leads us to adequate therapeutic options for different patients with the same disease.

Sun et al. (14) piloted a 6-year study with 273 patients with RAS and the same number of controls. This was the longest study with the highest number of participants regarding this issue. They showed statistically significant differences between the observed groups, with lower mean hemoglobin in patients with RAS ($p < 0.001$) and lower iron levels for women in the diseased group ($p < 0.001$). Male subjects also had lower iron levels, but this was not statistically significant. In addition, there was no

distinction in the levels of vitamin B12 and serum folate between groups. However, when adjusted in hemoglobin, iron, vitamin B12, or folic acid deficiency groups by the World Health Organization criteria, patients with recurrent stomatitis had a significantly higher frequency of observed hematinic deficiencies (20.9%, 20.1%, 4.8%, 2.6%, respectively) than healthy control subjects ($p < 0.05$). Nevertheless, approximately 60% of people who suffer from recurrent aphthous stomatitis had blood test results within normal limits, which can be explained by genetic susceptibility and other possible causes, such as immunological, hormonal, and emotional factors.

Slebioda et al. (11) analyzed blood samples of 71 subjects with RAS and 70 individuals without the disease. They measured hemoglobin, hematocrit, mean corpuscular volume, red blood cell count, iron, and vitamin B12 levels. When comparing those two groups, hematinic deficiencies were more common in patients with aphthae. The mean serum iron levels were lower in the RAS group than in the control group (88.6 lg/dL vs. 105.88 lg/dL). However, there was no observed correlation between hematinic deficiencies and clinical presentation and the severity of aphthae in the tested sample. Therefore, these results may easily describe a confounding factor, and not the actual cause of the disease.

Babaee et al. (28) conducted a research about oxidative stress in 28 patients with RAS and the same number of healthy individuals. They compared markers of oxidative stress in the saliva and routine hematological tests in both groups. Salivary malondialdehyde is the main product of lipid peroxidation and it indicates oxidative stress. The oral cavity is the first entry point for outside pathogens, which is why saliva contains variant antioxidants to help fight infection. Their overall activity coincides with the total antioxidant capacity (TAC). When comparing the group with RAS and the healthy group, salivary malondialdehyde level was considerably higher ($p < 0.001$) and TAC level was significantly lower ($p < 0.042$). The imbalance between oxidants and antioxidants may cause many diseases of the oral mucosa. Several studies also acknowledge that tissue damage in patients with recurrent stomatitis is caused by disruption of the oxidant/antioxidant balance (29). According to hematological parameters, only the ferritin levels were significantly higher in RAS patients ($p < 0.008$). Ferritin is an indicator of the body's iron reserves and can expedite oxidative stress. Production of ferritin can initiate lipid peroxidation and the formation of reactive oxygen species (30). Therefore, high serum ferritin in RAS can be used as an inflammatory measure, comparable to c-reactive protein or erythrocyte sedimentation rate. Another hypothesis is that ferritin may be a protective attribute by making chelation with free iron during prolonged oxidative stress (28).

Conclusion

Numerous controlled studies analyzing the hematological status and iron levels of patients with recurrent aphthous stomatitis have been conducted. However, the methods, number of participants, including criteria, referent numbers, gender distribution, and other factors are not standardized. Therefore, the results remain inconclusive, with some authors reporting a strong connection between iron levels and the development of RAS, while others disagree. Nevertheless, routine hematological screening in patients with RAS may help reveal hidden nutritional deficiencies and prevent related systemic manifestations. Additional studies are required to improve comprehensive understanding and clarify the impact of serum iron levels on recurrent aphthous stomatitis.

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