Review Article

The Relationship Between Iron and Zinc Deficiency and Aphthous Stomatitis: A Systematic Review and Meta-Analysis

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Abstract

Background: Recurrent aphthous stomatitis (RAS) is known as the most common ulcerative lesion in the oral mucosa. Aphthous has an unknown etiology and is considered a multifactorial disease. This study was conducted to investigate the relationship between iron and zinc deficiency and the occurrence of RAS.

Materials and Methods: This systematic review and metaanalysis was performed according to the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines. Data were obtained through an electronic search in international databases, including PubMed, Medline, Embase, ISI Web of Science, Scopus, Springer, ProQuest, ScienceDirect, Clinical Key, and Google Scholar, and domestic Persian databases, including SID, Magiran, and Iran Medex, until April 2021. New-castle Ottawa Scale (NOS) was used to determine the eligibility of studies by evaluating the title and summary of the articles and a partial evaluation of the full text. Comprehensive Metaanalysis (CMA) software was used for data analysis.

Results: Initially, a total of 1383 articles were retrieved, of which 941 were duplicate studies. Further, 384 studies were excluded after evaluation of the title and abstract, and 36 studies were excluded after considering the inclusion and exclusion criteria. Finally, 22 articles were included in the metaanalysis. The standardized mean difference value was –0.421 (–0.623--0.20) for iron factor, –0.309 (–0.463--0.154) for iron factor in men, –0.483 (–0.375--0373) for iron factor in women, and –0.955 (–0.282--1.628) for the zinc factor.

Conclusion: In general, the serum iron level (in general, in male and female patients separately) and the zinc serum level in patients with RAS were significantly lower than those of healthy people.

Keywords: Iron deficiency anemia, recurrent aphthous stomatitis, zinc deficiency

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Introduction

Recurrent aphthous stomatitis (RAS) is known as the most common ulcerative lesion in oral mucosa, which is divided into three categories, including minor, major, and herpetiform. It is characterized as a round to oval, painful, and low-depth ulcer with an erythematous margin covered with yellow-gray exudate. It is self-limiting and often affects nonkeratinized and nonmasticatory mucosa.[1] The exact etiology of aphthous is unknown, but it is considered a multifactorial disease. Factors such as age, gender, family history, stress, hormonal changes, microorganisms, local trauma, food allergies, systemic problems such as Behcet's syndrome, anemia, periodic neutropenia, as well as lack of blood and nutritional factors such as iron, folate, zinc, vitamin C, and calcium are known to be effective in causing aphthous stomatitis. Several studies have confirmed the deficiency of nutritional factors in patients

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with aphthous, and alternative therapies have been observed to be effective in reducing or limiting the recurrence of lesions so that hematologic screening is recommended for all patients with complex aphthous and persistent painful symptoms and patients with malabsorption and nutritional deficiencies.[2]

Iron is a rare element that is essential for the survival of cells. It is involved in hemoglobin, myoglobin, cytochromes, and enzyme synthesis. It is also essential for respiration, mitochondrial function, and energy production. The liver, where iron transport proteins are produced, has the largest nonfunctional iron store called ferritin or hemosiderin.[3,4] Low serum ferritin levels are a characteristic of absolute iron deficiency. The clinical signs and symptoms of iron deficiency anemia are limited and often overlooked, the most important of which is fatigue, which is nonspecific. Changes in epithelial cells such as dry mouth, atrophic glossitis, and hair loss are observed in long-term iron deficiency.[4-6]

Zinc is a rare element and one of the essential nutrients. It is the second scarcest metal element in the body after iron. The effect of zinc on a set of functions shows how a deficiency in nutrient uptake can lead to various diseases, and unlike iron, the body has no specific system for storing zinc.[7,8]

In a review and metaanalysis of 24 articles in 2012, Navabi *et al*.[9] reported the prevalent deficiency of ferritin, serum folate, erythrocyte folate, hemoglobin, serum iron, and vitamin B12 in patients with aphthous. Interventional studies have also indicated the amelioration of oral aphthous ulcers after iron administration.

In their cross-sectional study, Kalati *et al*.[10] measured the iron, ferritin, and serum zinc levels of 30 patients with recurrent oral aphthous but found no statistically significant relationship between the control group and the patients in any of the factors. Mojabi *et al*.[11] performed a study in 2003 in Qazvin to determine the ferritin, serum iron, and iron saturation capacity in 40 patients with RAS. They reported a significant difference between the control and patient groups in ferritin and iron levels. In the case--control study of Khademi *et al*.[12] in Isfahan on 44 patients with aphthous, the serum zinc level was measured by an atomic absorption spectrometer. There was a statistically significant difference in the mean zinc level between the patient and control groups.

The results of case--control studies conducted by Ozler *et al*. in Turkey in 2012, Ślebioda *et al*. in Poland in 2015, and Saravanan *et al*. in India in 2018 showed that hemoglobin and iron levels were significantly lower in the patient group.[13-15] In the case--control study of Bao *et al*.[16] on 156 patients with aphthous ulcers in China in 2015, the mean level of zinc was significantly lower in the patient group than in the control group.

Due to the contradictory results of the studies and the failure to include all articles in previous reviews, it is necessary to conduct a systematic review on the relationship between mean iron and zinc deficiency and RAS.

Materials and Methods

Searched databases

First, PubMed, Medline, and Embase databases, due to their comprehensiveness in the field of medical sciences, and then ISI Web of Science, Scopus, Springer, ProQuest, ScienceDirect, Clinical Key, and Google Scholar databases were searched using keywords In each database, specific strategies were used to find the published articles. Moreover, a manual search was used to check the references in each of the articles, for the unpublished sources, hand searching was done.

Search strategy

(A) Initial and rapid search of the subject and review of past articles and projects until April 2021

(B) Identifying the keywords related to the subject through existing thesauruses and MeSH as well as the keywords used in the text of the searched articles. The keywords used were such as aphthous, aphthous ulcer, aphthous stomatitis, OR "haematinic deficiency" OR "hematinic deficiency" OR "hematological deficiency", serum zinc level, and RAS following Medical Subject Headings (MeSH) and using the operators "AND" and "OR" in combination. Further, Persian databases, including SID, Magiran, and Iran Medex were searched using the keywords "recurrent oral aphthous", "iron deficiency anemia", and "zinc deficiency". The electronic search was done according to the patient/population, intervention, comparison, and outcomes (PICO) procedure.

Study selection and data collection

After performing an electronic search, to confirm the eligibility process, the studies of the two authors were screened independently in three phases. Phases 1 and 2: the titles and abstracts of the articles were reviewed to remove the articles that did not meet the inclusion criteria. Phase 3: the full texts of the articles were independently reviewed in detail by two reviewers to confirm all inclusion criteria. The authors extracted the data independently using a pre-standard data extraction form. Disagreements between the two authors were resolved through discussion or consultation with a third researcher [Figure 1].

Inclusion and exclusion criteria

The inclusion criteria were only case--control studies, human studies, studies whose abstracts and full texts were available, studies evaluating the mean serum iron or zinc levels, and studies RAS patient group. The exclusion criteria consisted of nonhuman studies, noncase--control studies, studies not reporting the desired statistical parameters such as mean iron and zinc levels and standard deviation, studies not evaluating the patient and control groups in terms of the presence of systemic diseases and other possible factors affecting the occurrence of aphthous ulcers, and low-quality studies.

Quality assessment of studies

The quality of the studies was measured based on the Newcastle-Ottawa Scale (NOS), which has three main

sections,[3] including the selection of study groups (0--4 stars), comparability of patient and control groups with control of relevant factors (0--2 stars), and exposure (0--3 stars).

The overall quality of studies was rated as high quality: 7 stars or more, medium quality: 4--6 stars, and low quality: 0--3 stars. The two researchers independently examined the quality and risk of bias of studies, and the disagreements between them were resolved through discussion or consultation with a third researcher [Tables 1 and 2].

Data analysis

Comprehensive Metaanalysis (CMA) software was used to analyze the data. After feeding the information of the articles into the CMA, the I^2 and Q-value tests were used to detect the heterogeneity of the studies. If the I^2 index was high, the random model was used, otherwise, the fixed model was used. Begg's and Egger's tests as well as the funnel plot were used to evaluate the dispersion bias. According to these test, the *P* value was reported 0.84085 that was not significant so there was no bias in the study.

Results

Study selection

In the initial search of international and domestic databases until April 2021, 1381 articles were retrieved. The manual search also yielded two articles. Of these, 941 articles were duplicates and excluded. After reviewing the title and abstract of the remaining 442 articles, 384 irrelevant articles were excluded. After the full-text analysis of the remaining 58 articles, 36 articles were excluded for reasons such as not reporting the mean or standard deviation of iron and zinc levels, failure to investigate diseases and systemic causes and other factors related to aphthous ulcers in patient and control groups, and studies other than case--control studies.

Descriptive results

Finally, 22 case--control studies (14 studies related to iron factor and 8 studies related to zinc factor) were included in the meta analysis.[4-22] The data extracted from the studies are shown in detail in Tables 2 and 3.

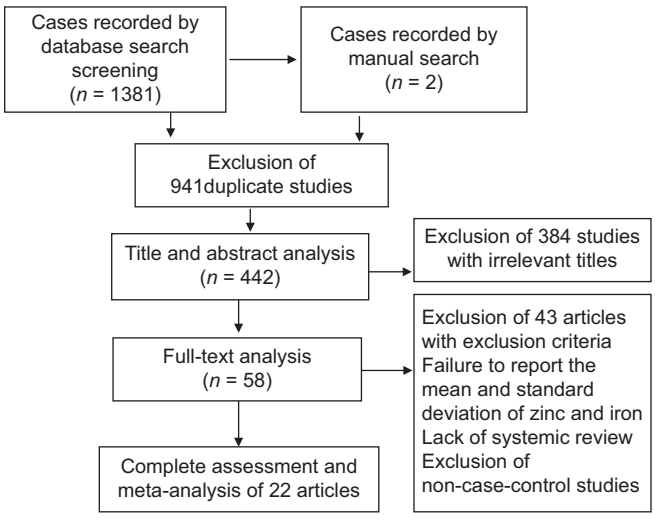

Figure 1: Steps to search and select the articles

Analytical results

The analyzed results have been demonstrated in Figures 2-5 and Tables 3 and 4.

Discussion

The present meta-analysis was performed to investigate iron and zinc deficiency in RAS patients. Most of the studies included in this metaanalysis showed that iron and zinc levels were significantly lower in patients with RAS than in the healthy group. Statistical analyses showed iron deficiency in both genders. Serum iron and zinc levels were significantly lower in RAS patients than in the control group, and serum iron levels were significantly lower in female and male patients with RAS than in the control group.

Iron is a rare element involved in hemoglobin and the synthesis of enzymes and is essential for many metabolic functions. Therefore, a deficiency of this factor can cause metabolic problems such as iron deficiency anemia, whose signs and symptoms are often disregarded.[5,17] Since nutritional factors are considered one of the causes of RAS,[1,2] low serum iron

Table 1: The quality of the studies was measured based NOS (Iron factor)

Study	Selection	Comparability	Exposure	Total score
Sun (2014)	***	*	**	6
Piskin (2002)	***	*	***	8
Sun (2016)	***		**	5
Che Wu (2016)	***	*	**	6
Slebioda (2018)	***		**	5
Shabbir (2021)	****		***	7
Babaee (2015)	***	**	**	7
Mojabi (2009)	***	*	**	6
Kalati (2009)	***	*	**	6
Koybosi (2006)	***		**	5
Al Ahmad (2019)	***	*	**	6
Saravanan (2021)	***		**	5
Kareem (2014)	***		**	5
Pickek (2012)	***		**	5

Table 2: The quality of the studies was measured based NOS (Zinc factor)

Study	Selection	Comparability	Exposure	Total score
Kalati (2009)	***	*	***	7
Arora (2002)	**		**	4
Ozler (2014)	***	*	**	6
Ozturk (2013)	***	*	**	6
Slebioda (2017)	***		***	6
Bao (2016)	***	*	**	7
Tamer (2019)	***	*	**	6
Khademi (2006)	**		**	4

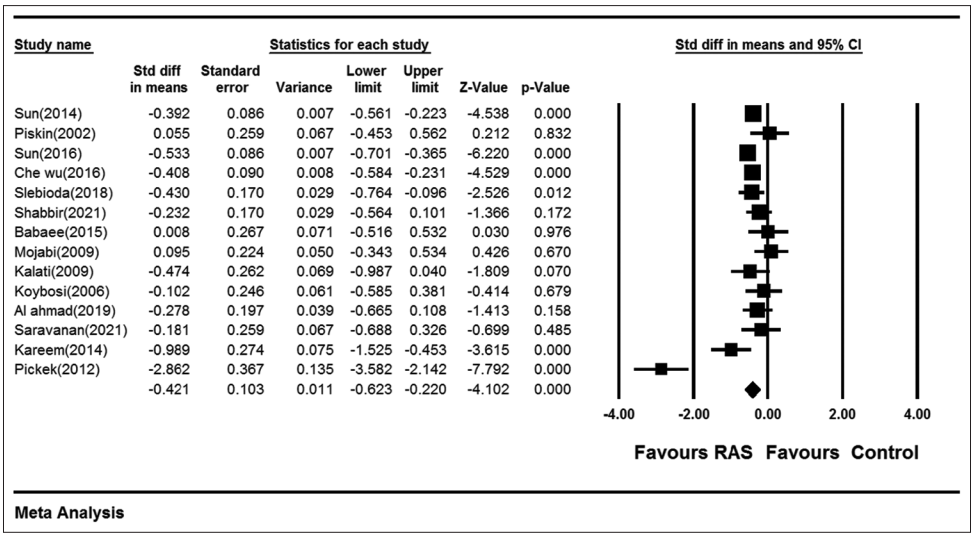

Figure 2: Accumulation chart of standardized mean difference of serum iron levels between RAS patients and healthy individuals based on random model. The midpoint of each line shows an estimate of the standardized mean difference, the lines show 95% confidence in each study. The rhombus sign indicates the standardized mean difference for all studies

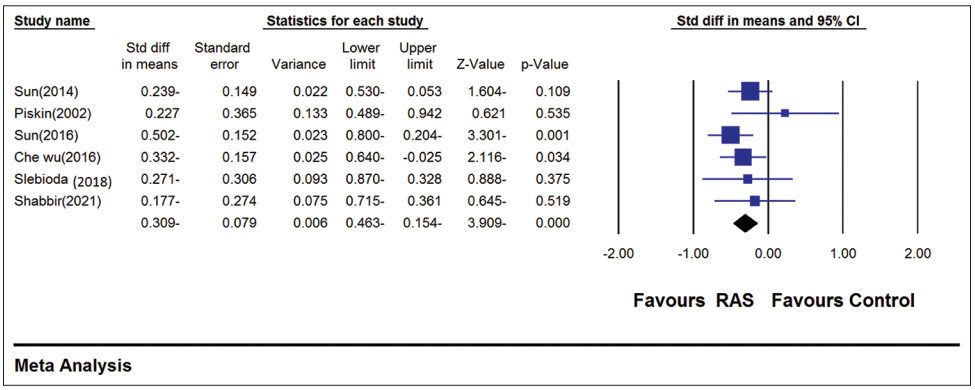

Figure 3: Accumulation chart of standardized mean difference of serum iron level between RAS patients and healthy individuals based on fixed model. The midpoint of each line shows an estimate of standardized mean difference, the lines show 95% confidence in each study. The rhombus sign indicates the standardized mean difference for all studies

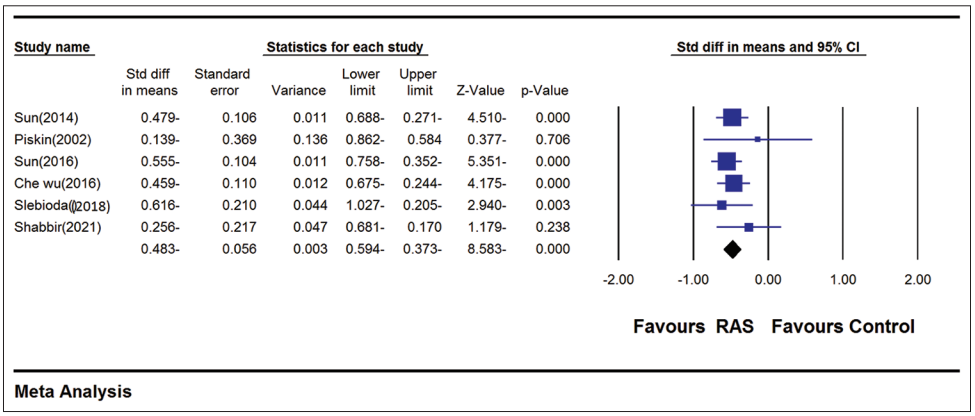

Figure 4: Accumulation chart of standardized mean difference of serum iron level between RAS female patients and healthy individuals based on fixed model. The midpoint of each line shows an estimate of standardized mean difference, the lines show 95% confidence in each study. The rhombus sign indicates the standardized mean difference for all studies

level is considered to have a role in the occurrence of aphthous. Various studies have also reported a relationship between iron deficiency and RAS. However, some studies have indicated no significant relationship between iron deficiency and RAS.

Table 3: Specifications of studies included in the meta-analysis (iron factor)

Author (s)/year/country	Type of study	Participants (age/gender)		Assessment method	Outcome
Sun (2014) Taiwan	Case-control	RAS n: 273 m: 91 f: 182 Age: 52.2±16.8	Control n: 273 m: 91 f: 182 Age: 53.1±14.7		Only female patients with RAS had significantly lower iron levels
Piskin (2002) Turkey	Case-control	RAS n: 35 m: 18 Age: m: 34.44±11.55 f: 36.29±7.86	Control n: 26 m: 13 Age: m: 34.69±10.5 f: 35.77±9.7	Colorimetric method	No significant difference
Sun (2016) Taiwan	Case-control	RAS n: 240 m: 78 f: 162 Age: 50.9±16.3	Control n: 342 m: 104 f: 238 Age: 52.7±14.7		Significantly lower iron levels in RAS patients
Che Wu (2016) Taiwan	Case-control	RAS n: 195 m: 67 f: 128 Age: 50.4±15.6	Control n: 355 m: 106 f: 249 Age: 53.1±14.7		Significantly lower iron levels in RAS patients
Slebioda (2018) Poland	Case-control	RAS n: 71 m: 27 f: 44 Age: 36.8	Control n: 70 m: 18 f: 52 Age: 34.3	Colorimetric Ferrozine-based assay	Significantly lower iron levels in RAS patients (but in the normal range)
Shabbir (2021) Pakistan	Case-control	RAS n: 70 m: 24 f: 46 Age: 10-40	Control n: 70 m: 30 f: 40 Age: 10-40	Microlab300	No significant difference
Babaee (2015) Iran	Case-control	RAS n: 28 m: 15 f: 13 Age: 34.7±15.18	Control n: 28 m: 13 f: 15 Age: 32.03±11.3	Standard laboratory kit	No significant difference
Mojabi (2009) Iran	Case-control	RAS n: 40 m: 21 f: 19 Age: NA	Control n: 40 m: 20 f: 20 Age: NA		No significant difference
Kalati (2009) Iran	Case-control	RAS n: 30 m: 13 f: 17 Age: 29±7.3	Control n: 30 m: 13 f: 17 Age: 33±9.8	Iran Zist-Shimi kit	No significant difference
Koybosi (2006) Turkey	Case-control	RAS n: 34 m: 17 f: 17 Age: 36.7	Control n: 32 m: 13 f: 19 Age: 34.3		No significant difference
Al-Ahmad (2019) UAE	Case-control	RAS n: 52 m: 32 f: 20 Age: 34	Control n: 52 m: 32 f: 20 Age: 31 Control	Fully automated colorimetric/ spectrophotometric assay	RAS patients had a lower mean of serum iron but not statistically significant

Contd...

Table 3: Contd...

Author (s)/year/country	Type of study	Participants (age/gender)		Assessment method	Outcome
Saravanan (2021) India	Case-control	RAS n: 30 m: 19 f: 11 Age: 26.5±8.78	Control n: 30 m: 15 f: 15 Age: 26.3±11.07	Colorimetric method (Ferrimat kit)	No significant difference
Kareem (2014) Iraq	Case-control	RAS n: 30 m: 15 f: 15 Age: 40±14	Control n: 30 m: 16 f: 14 Age: 36±11	Direct method BIOLABO reagents (Ferene)	Significantly lower serum iron levels in RAS patients
Picek (2012) Croatia	Case-control	RAS n: 30 m: 10 f: 20 Age: 36.27±15.3	Control n: 30 m: 10 f: 20 Age: 29.83±9.08	Spectrophotometric method	No significant difference

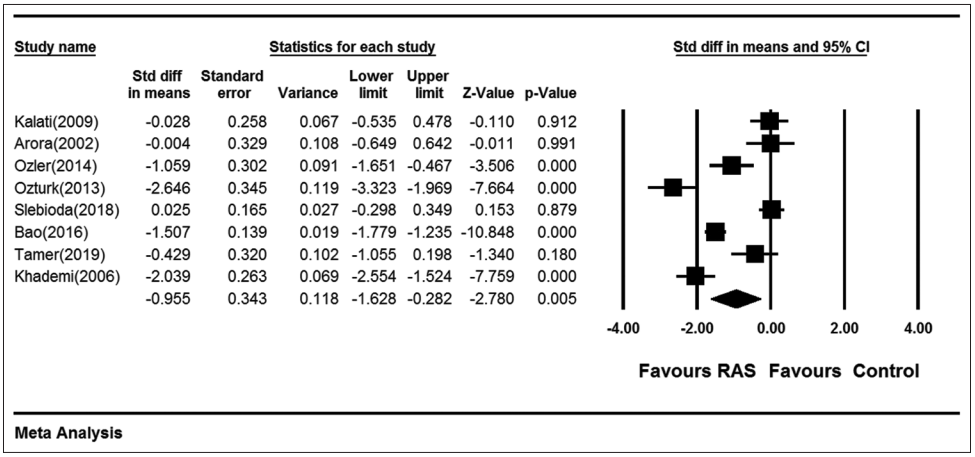

Figure 5: Accumulation chart of standardized mean difference of serum zinc level between RAS patients and healthy individuals based on random model. The midpoint of each line shows an estimate of standardized mean difference, the lines show 95% confidence in each study. The rhombus sign indicates the standardized mean difference for all studies

Studies by Sun (2016) and Che-wu (2016) have reported an association between iron deficiency and aphthous ulcers.[18,19]

Since iron is an important micronutrient, and since iron deficiency anemia is one of the world's public health problems and the most common cause of anemia in the world, depletion of iron sources in the body can lead to epithelial atrophy, oral ulcers, and RAS. Iron deficiency affects ferritin synthesis and reduces ferritin transfer to mRNA.[5,6,17,20]

The results of the metaanalysis showed the importance of iron deficiency in RAS. Multiple aphthous ulcers may be a sign of iron deficiency and anemia, which can cause numerous systemic problems in patients. However, it has not been addressed, and its related symptoms have been ignored. On the other hand, iron deficiency and oral ulcers are important to be screened, and in people who frequently experience these oral ulcers, iron replacement therapies or the addition of iron-rich substances to the diet will help to improve the patients' quality of life. Further, despite the higher prevalence of iron deficiency anemia in women, this study indicated that male patients with aphthous also had lower serum iron levels than the healthy group, so screening for serum iron levels, regardless of gender, is recommended.

Zinc, as the second scarcest element in the body after iron, has an important effect on the health and function of the cells, especially the regulation of the immune system. Unlike iron, the body has no specific system for storing zinc; therefore, zinc deficiency is very likely to occur, especially in people with poor diets, and is considered one of the nutritional factors associated with RAS. Numerous studies have reported an association between low serum zinc levels and the incidence of RAS, while some other studies have reported no significant relationship.[7,8] Ozler (2014) and Ozturk (2013) reported an association between RAS and serum zinc deficiency.[13,21]

Zinc is an essential nutrient that plays an important role in the structure of many proteins and cellular functions, especially

Table 4: Studies included in the meta-analysis (zinc factor)

Author (s)/year/country	Type of study	Participants (age/gender)		Assessment	Outcome
Kalati (2009) Iran	Case-control	RAS n: 30 m: 13 f: 17 Age: 29±7.3	Control n: 30 m: 13 f: 17 Age: 33±9.8	Randox kit	No significant difference
Arora (2002) India	Case-control	RAS n: 15	Control n: 24	Thermo Jarral Ash atomic absorption emission spectrophotometer	No significant difference
Ozler (2014) Turkey	Case-control	RAS n: 25 m: 48% f: 52% Age: 31.5±7.17	Control n: 25 m: 52% f: 48% Age: 32.04±7.34	Flame atomic absorption spectrophotometry (FAAS)	Significantly lower serum zinc levels in RAS patients
Ozturk (2013) Turkey	Case-control	RAS n: 33	Control n: 30	Flame and furnace atomic absorption spectrophotometer	Significantly lower serum zinc level in RAS patients
Slebioda (2017) Poland	Case-control	RAS n: 75 m: 29 f: 46 Age: 35.08±16.9	Control n: 72 m: 19 f: 53 Age: 32.2±14.3	Flame Atomic Absorption Spectroscopy (FAAS)	No significant difference
Bao (2016) China	Case-control	RAS n: 156 m: 38.5% f: 61.5% Age: 51.57±16.39	Control n: 115 m: 37.4% f: 62.6% Age: 53.1±15.59	Colorimetric method zinc assay kit	Significantly lower serum zinc levels in RAS patients
Tamer (2019) Turkey	Case-control	RAS n: 20 m: 5 f: 15 Age: 34±12.3	Control n: 20 m: 6 f: 14 Age: 33.9±13.4		Lower zinc levels in the RAS group, but no statistically significant difference
Khademi (2006) Iran	Case-control	RAS n: 44 m: 14 f: 30 Age: NA	Control n: 44 m: 14 f: 30 Age: NA	Atomic absorption spectrometer	Significantly lower serum zinc level in RAS patients

in the body's immunological reactions. Although the exact etiology of RAS is unknown, several immune mediators are thought to play a role in RAS. The role of zinc deficiency in the incidence of RAS may be due to the ability of this element to stimulate the production of interleukin-1, interleukin-6, and TNF-α. The production of cytokines is impaired due to zinc deficiency, and also the early stages of aphthous ulcers are in response to cytokine disorder.[1,13,21,22]

Therefore, owing to zinc deficiency in patients with RAS, zinc replacement therapies can help reduce the severity and frequency of RAS. This factor should be considered in patients with RAS who have a diet with zinc deficiency and are vegetarians or consume a small amount of red meat. Hence, alternative zinc therapies should be suggested and prescribed periodically and regularly.

Conclusion

In general, serum iron and zinc levels are significantly lower in patients with RAS than in healthy individuals.

Limition

There was problem accessing some databases and full text article

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Conflicts of interest

There are no conflicts of interest.

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