ORIGINAL ARTICLE

SIGNIFICANCE OF IRON DEFICIENCY IN RECURRENT APHTHOUS STOMATITIS

[1]RABBIA SHABBIR, [2]AQSA MALIK, [3]RAHEELA YASMIN, [4]ATTEAYA ZAMAN, [5]YASIR IQBAL, [6]AMBREEN GUL, [7]AMENA RAHIM

ABSTRACT

The objective of study was to measure iron levels in patients of recurrent aphthous stomatitis and compare them with control.It was a case control study conducted in biochemistry department of Islamic International Medical College Rawalpindi from 15th March 2016 to 14 March 2017.The study included 140 subjects divided into two groups recurrent aphthous group and control. Recurrent aphthous group comprised of 70 patients with active lesion and 70 age and sex matched healthy controls were included in the control group. Recurrent aphthous stomatitis was diagnosed on the basis of history and clinical examination. Serum ferritin levels were measured by ELISA using Absorbance Microplate Reader, ELX 800, BioTek Instrument Inc. USA while serum iron and hemoglobin levels were measured by microlab 300.Based upon normal laboratory values, the iron levels were significantly low in RAS patients as compared to control.It was concluded that iron deficiency is related to recurrent aphthous stomatitis.

Key Words: *iron, ferritin, hemoglobin*

This article may be cited as: Shabbir R, Malik A, Yasmin R, Zaman A, Iqbal Y, Gul A, Rahim A. Significance of iron deficiency in recurrent aphthous stomatitis. Pak Oral Dent J 2021; 41(1):11-14.

INTRODUCTION

Aphthous is a Greek derivative word which means ulceration whose diagnosis and management is a common problem in dentistry.[1,2]Characteristics of Recurrent aphthous stomatitis (RAS) are ulcerations on the mucosa of oral cavity which may be single or multiple with a history of recurrence and having a shallow necrotic center with a covering of yellowish grey pseudomembrane encircled by raised margins and erythematous halo.[3]A patient with RAS experiences oral pain leading to discomfort from simple annoyance to pain during normal oral activities i-e chewing and swallowing.[4,5]Children are seemingly more affected as high as 39% and those with positive family history have more chance to develop RAS in comparison to others.[6]

These recurring ulcers are classified according to type, magnitude, quantity and healing time into minor RAS, major RAS and herpetiform ulcers.[7]Most commonly occurring RAS are of minor type and contribute to 80% of total cases.[8,9]It is a multifactorial disease with unknown exact etiology. Most likely factors that precipitate includes localized trauma, genetic predisposition and stress. Systemic diseases, nutritional deficiencies, food allergies, endocrine alterations and smoking cessation may also be considered as associated factors. Postulation is that the causative factors causeoxidative stress[10]but the exact cause of RAS is still not clear.[11]

In spite of extensive investigations, the exact etiology and pathogenesis of RAS has not been established. Hematological deficiencies have been proposed as possible etiologic factors but the presented data is still conflicting possibly because of difference in ethnicity, geography and diet.[12] In the absence of any complication Recurrent aphthous stomatitis can be linked with anemias as in hematinic deficiencies oral epithelium can be thinned out atrophied. Oral epithelium atrophy in turn makes it more prone to inures and provide favorable environment for bacterial antigen penetration,which is one of the factors involved in pathogenesis of RAS.[13]Hematological deficiency is prevalent in 18% to 28% of the general population[14] and estimated 1.3% people are anemic in Pakistan.[13] Approximately half of

[1] Dr Rabbia Shabbir, BDS, MPhil, Biochemistry Lecture, Department of Biochemistry HITCH-IMS Dental College, Taxilla Cantt Cell: 0336-5138978 Email: rabbia.shabbir@gmail.com
[2] Dr Aqsa Malik, MBBS, MPhil, Assistant Professor Biochemistry, Mohtarma Benazir Bhutto Shaheed Medical College, Mirpur AJK
[3] Dr Raheela Yasmin, MBBS, MPhil Biochemistry, Assistant Professor Biochemistry HITCH-IMS Taxila Cantt
[4] Dr Atteaya Zaman, MBBS, MPhil, MHPE Scholar, Assistant Professor Biochemistry FMDC Opposite Noori Hospital Islamabad
[5] Dr Yasir Iqbal, MBBS, FCPS, Associate Professor Opthalmology Watim Medical and Dental College, Rawat Rawalpindi
[6] Dr Ambreen Gul, MBBS, MPhil, MHPE, Associate Professor Biochemistry HITCH-Dental College Taxilla
[7] Prof Dr Amena Rahim, MBBS, FCPS Biochemistry, IMHPE, PGDE, PhD Scholar Professor Biochemistry Islamic International Medical College, Riphah University Islamabad

Received for Publication: Sep 2, 2019
First Revision: Oct 29, 2019
Second Revision: May 20, 2020
Approved: June 16, 2020

this incidence is caused by iron deficiency (IDA). IDA can be diagnosed via noninvasive methods, such as assessment of hemoglobin (Hgb), serum ferratin (sFer), serum iron (SI).

Due to contradictory studies about the role of hematological disorders towards development of Recurrent aphthous stomatitis i-e the role in RAS pathogenesis, this study was designed to determine whether iron deficiencies are present in RAS or not.

MATERIALS AND METHODS

This was a case-control study conducted in Biochemistry department of Islamic International Medical College, Rawalpindi with collaboration of dental outpatient department of Pakistan Ordinance Factories Hospital, Wah-Cantt in a period of one year from 15March 2016 to 14 March 2017.A formal approval was attained from the ethical review committee before the commencement of the study.

140 participants were selected by using convenient non-probability sampling technique and were divided into two groups, group I RAS patients (70) and group II control (70) after fulfilling the inclusion and exclusion criteria. Selection criteria for group I was patients of any age and gender having an active lesion of apthous ulcer with a history of recurring oral ulcer attack at least three times a year. For control it was healthy individuals without any history of aphthous stomatitis or any other systemic disease. RAS was diagnosed on the basis of history and clinical examination. Exclusion criteria was history of any oral lesion other than aphthous ulcers, any therapeutic regimen or iron supplementation, multivitamin, steroid or other immunomodulatory agents for past two months, pregnancy, lactation, smoking and alcohol use. Demographic information i-e age, gender, occupation and history of systemic disorders were recorded. To find out the type, size, number and location of ulcers the mucosa of oral cavity were thoroughly examined. With informed consent, venous blood of the participants in the study was collected and was transferred to the laboratory for assessment.

Serum ferritin levels were measured by ELISA using Absorbance Microplate Reader,ELX 800, BioTek InstrumentInc. USA while serum iron and hemoglobin levels were measured by microlab 300.The collected data was entered in the statistical package for social sciences (SPSS) version 21 for analysis. Gender was expressed as percentages and frequency whereas numerical variables like age, ferritin, Hb and iron levels were expressed as mean and standard deviation. Independent t –test was used to determine the significant difference of means between controls and patients. p values equal or less than 0.05 was considered as significant at 95% confidence interval.

RESULTS

One hundred and forty subjects were selected for the study and were divided two groups (group I RAS patients and group II control). Each group consisted of 70 participants

Group I (RAS) included 46 females (65.7%) and 24 males (34.2%) while group II (control) included 40 females (57.14 %) and 30 males (42.8%).Mean age of the RAS group was 28.76 ± 9.14 years and of control was 30.53± 6.9 years. The comparison of mean ages between the RAS group and control was not significant ($p > 0.05$). The age and gender distribution of the both group I and group II is shown in the table 1.

The difference of ferritin levels between aphthous group and control was significant $p< 0.005$ in 21-30 years age group and 31-40 years age group. When gender was compared there was a significant difference with p value < 0.05 for females

The mean hemoglobin levels in 21-30 years and 31-40 years age group of RAS group was significantly ($p<0.05$) lower than control. Among gender the difference in the mean Hb of RAS females was significant with p value <0.05 than mean of females of controls (table 3)

No significant difference was found while measuring serum iron levels ($p>0.05$) among different age groups (table 4). Minor RAS cases were seen in 67 patients (96%) whereas 3 patients (4%) suffered major recurrent aphthous stomatitis. Out of 70, 84 % had single ulcer, whereas 16% have multiple. RAS in sixty two patients (89%) were found on non-keratinized mucous membrane while on keratinized mucous membrane RAS were located in 5 patients (7%) whereas keratinized as well as non-keratinized mucous membranes were involved in 3 patients (4%).

DISCUSSION

Among the ulcerative and inflammatory diseases of oral mucosa the most common is recurrent aphthous stomatitis (RAS).[14] Despite extensive research, the pathogenesis of RAS remains unclear.[15] Numerous factors have been found to have a role in the etiology of RAS. Hematological parameters have been advocated as being the most significant factor for RAS .Therefore in present study hematological parameters in RAS

TABLE 1: DEMOGRAPHIC CHARACTERISTICS OF CONTROLS AND PATIENTS IN THE STUDY

	Group I (RAS) n=(70)	Group II (Control) n =(70)
Age(years)		
10-20 years	8(11.4%)	10 (14.2%)
21-30 years	35 (50%)	32 (45.7%)
31-40 years	27 (38.5%)	28 (40%)
Gender		
Male	24 (34.2%)	30 (42.8%)
Female	46 (65.7%)	40 (57.1%)

TABLE 2: DEMOGRAPHIC CHARACTERISTICS ACCORDING TO CONTROL'S AND PATIENT'S SERUM FERRITIN LEVELS

	Group I(RAS) (n= 70)	Group II(Control) (n = 70)	p-value
Age (years)	**Ferritin (ng/ml) Mean±S.D**	**Ferritin (ng/ml) Mean±S.D**	
10-20 years	27.68 ±10.3	34.59 ±21.5	0.387
21-30 years	25.02 ±15	38.0 ±15	0.002
31-40 years	23.8 ±12	35.67 ±15	0.004
Gender			
Male	38.3± 16.1	41.28± 9.9	0.44
Female	27.3± 14.2	40.18±17.6	0.00

TABLE 3: DEMOGRAPHIC CHARACTERISTICS ACCORDING TO CONTROL'S AND PATIENT'S HEMOGLOBIN LEVELS

	Group I (RAS) (n= 70)	Group II (Control) (n = 70)	p-value
Age (years)	**Hemoglobin (g/dl) Mean ± S.D**	**Hemoglobin (g/dl) Mean ± S.D**	
10-20 years	11.9±1.6	13.5±21	0.103
21-30 years	12.5 ±2.0	14.7 ±1.5	0.00
31-40 years	12.8 ±1.7	14.5 ±1.6	0.00
Gender			
Male	14.6±1.5	15.2± 1.0	0.11
Female	12.6±2.1	14.7±1.5	0.00

TABLE 4: DEMOGRAPHIC CHARACTERISTICS ACCORDING TO CONTROL'S AND PATIENT'S SERUM IRON LEVELS

	Group I (RAS) (n= 70)	Group II (Control) (n = 70)	p-value
Age (years)	**Iron (µg/dl) Mean±S.D**	**Iron (µg/dl) Mean±S.D**	
10-20 years	79.8 ± 8.6	83.25 ±8.9	0.419
21-30 years	68.0±10	72.98 ±28.18	0.09
31-40 years	78.57±11.4	81.8 ±14	0.521
Gender			
Male	80.54±10	82.34±10.3	0 .65
Female	78.8 ± 7.9	80.5±4.8	0.71

patients were determined.

Current study revealed that the mean age of RAS patients was 28.76 meaning that it was found to be around third decade. Literature reports the same.[8] In present study it was found that females are affected more with RAS as compared to males, that is in agreement with preceding work [8,16] but contrary to other studies.[17,12]This may be due to the fact that females are affected more from hormonal changes, pregnancy and are more predicted to psychological stress.

It was revealed in present study that most of RAS were minor in nature which is in agreement with other studies.[7,18] We also found that majority of the ulcers were located on the non-keatinized mucosa reason being that it is a movable structure and thus is more prone to trauma predisposing development of ulcers. These result correspond with the results of study conducted in Islamabad Dental Hospital.[7]

In Recurrent aphthous stomatitis patients hematological deficiencies were observed in larger percentage as compared to controls.[19]RAS patients having hematological deficiencies has been reported bya study[20] according to it 59% of these patients recovered when given replacement therapy whereas 28% showed significant improvement.

In this study low levels of hemoglobin and ferritin were found in RAS group as compared to controls. These findings are supported by other studies.[21]Due to low hemoglobin levels anemic patients have decreased oxygen carrying capacity which eventually results in

atrophy of oral mucosa and hence to ulceration. Similarly iron is a vital component for normal functioning and cellular growth of oral epithelial cells. It is also an important component of enzyme cytochrome oxidase which is essential for the normal epithelial maturation. When iron is deficient, cytochrome oxidase levels are reduced eventually causing epithelial atrophy making the oral mucosa at risk to the irritants. Furthermore iron deficiency causes inappropriate vascular channel formation resulting in reduced blood flow and atrophy.[22]

We are aware of the short comings of the study especially limited sample size and design of study i-e cross-sectional but we feel that it might be helpful in suggesting a causative relationship between RAS and hematological parameters. To establish new preventive and treatment options in recurrent aphthous stomatitis patients, further larger sample size comprising prospective work should be done in this direction.

CONCLUSION

Patients with recurrent aphthous stomatitis have more iron deficiencies than controls, so it was concluded from this study that iron deficiency is related to RAS.

REFERENCES

1 Preeti L, Magesh KT, Rajkumar K, Karthik R. Recurrent aphthous stomatitis. J Oral Maxillofac Pathol. 2011 ;15(3):252-256.

2 Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. J Oral Pathol Med. 2012 ;41(8):577-78.

3 Ranganath SP, Anuradha Pai. Is Optimal Management of Recurrent Aphthous Stomatitis Possible? A Reality Check. J Clin Diagn Res. 2016; 10(10):08-13.

4 Dudding T, Haworth S, Lind PA, Sathirapongsasuti JF, Tung JY, Mitchell R, Colodro-Conde L, Medland SE, Gordon S, Elsworth B, Paternoster L. Genome wide analysis for mouth ulcers identifies associations at immune regulatory loci. Nat Commun. 2019 ;10(1):1-2.

5 Edgar NR, Saleh D, Miller RA. Recurrent aphthous stomatitis: a review.J Clin Aesthet Dermatol. 2017;10(3):26-36.

6 Akintoye SO, Greenberg MS. Recurrent aphthous stomatitis. Dent Clin N Am. 2014 ;58(2):281-97.

7 Maqbool S, Fatima N, Siddiqi KM, Jamal M, Baig MZ, Noor S, Hameed S. Frequency and pattern of recurrent apthous ulcers in patients reporting to oral medicine and diagnosis department of islamabad dental hospital. Pak Oral Dent J. 2019 ;39(1):30-33.

8 Lakdawala YA, Masood S, Gulzar I, Batool F, Arshad R. Frequency of apthous ulcers: a study. Pak Oral Dent J. 2017; 37(3): 419-21.

9 Y□ld□r□myan N, Özalp Ö, □at□r S, Altay MA, Sindel A. Recurrent Aphthous Stomatitis as a Result of Zinc Deficiency. Oral Health Prev Dent. 2019;17(5):465-68.

10 Polat C, Düzer S, Ayy□ld□z H, Seç S, Aksoy N, Sakall□o□lu Ö, Akyi□it A, Çetiner H. Association Between Anxiety, Depression, and Salivary Cortisol Levels in Patients with Recurrent Aphthous Stomatitis. Turk Arch Otorhinolaryngol. 2018 ;56(3):166.

11 Tarakji B, Gazal G, Al-Maweri SA, Azzeghaiby SN, Alaizari N. Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners. J Int Oral Health.2015 ;7(5):74-80.

12 Bao ZX, Shi J, Yang XW, Liu LX. Hematinic de□ciencies in patients with recurrent aphthous stomatitis: variations by gender and age. Med Oral Patol Oral Cir Bucal. 2018 ;23(2):e161.

13 Khan NF, Saeed M, Chaudhary S, Khan NF. Haematological parameters and recurrent aphthous stomatitis. J Coll Physicians Surg Pak. 2013;23(2):124-27.

14 Babaee N, Hosseinkazemi H, Pouramir M, Baboli OK, Salehi M, Khadir F, Bijani A, Mehryari M. Salivary oxidant/antioxidant status and hematological parameters in patients with recurrent aphthous stomatitis. Caspian J Intern Med 2016;7(1):13.

15 Ajmal M, Ibrahim L, Mohammed N, Al-Qarni H. Prevalence and psychological stress in recurrent aphthous stomatitis among female dental students in Saudi Arabia. Clujul Medical. 2018;91(2):216.

16 Natah SS, Konttinen YT, Enattah NS, Ashammakhi N, Sharkey KA, Häyrinen-Immonen R. Recurrent aphthous ulcers today: a review of the growing knowledge.Int J Oral Maxillofac Surg.2004;33(3):221-34.

17 Shahzad M, Moosa Y, Ahmad F, Farooq S. Prevalence of oral diseases: a study done on world oral health day. Pak Oral Dental J. 2015; 35(3):483-84.

18 □lebioda Z, Krawiecka E, Szponar E, Dorocka-Bobkowska B. Evaluation of serum zinc levels in patients with recurrent aphthous stomatitis (RAS). BMC oral health. 2017;17(1):158.

19 Sun A, Chang JY, Chiang CP. Blood examination is necessary for oral mucosal disease patients. J Formos Med Assoc. 2016;115:1-2.

20 Burgan SZ, Sawair FA, Amarin ZO. Hematologic status in patients with recurrent aphthous stomatitis in Jordan. Saudi Med J. 2006;27(3):381-84.

21 Tamer F, Avc□ E. Decreased serum ferritin and vitamin D levels in patients with recurrent aphthous stomatitisDermatol Online J. 2019;10(3).

22 Shruthi L, Pushparaja S, Bhavna P. Role of Copper and Iron Deficiencies in Pathogenesis of Recurrent Aphthous Ulcer. Int Res J Pharm. 2013;4(5):219.

CONTRIBUTIONS BY AUTHORS

1 Rabbia Shabbir:	Study concept, data collection and manuscript writing
2 Aqsa Malik:	Data interpretation and statistical analysis
3 Raheela Yasmin:	Critical review of manuscript
4 Atteaya Zaman:	Data analysis
5 Yasir Iqbal:	Manuscript writing and literature reivew
6 Ambreen Gul:	Proof reading
7 Amena Rahim:	Research supervision