Association of Severity of Anemia and Depression Among Patients Presenting with Oral Ulceration

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Abstract

Objective: To determine the association of severity of anemia with depression among patients presenting with oral ulceration.

Methods: It was an observational study conducted at the department of oral medicine and diagnosis for the duration of one year. One sixty-one patients of age 20-50 years of either gender presenting with active aphthous stomatitis (burning sensation on NRS $\geq$2 and pain on NRS $\geq$3) from last 3-6 months were included in the study using non-probability consecutive sampling technique. All the patients were assessed for depression using Patient Health Questionnaire Depression Scale (PHQ-9) and anemia using CBC. PHQ-9 score $\geq$5 was deemed as depression positive and the hemoglobin (Hb) level less than 13 g/dL for men and less than 12 g/dL for women was deemed as anemia. Data regarding demographics along with characteristics of oral ulcerations were also noted on pre-designed proforma. SPSS version 23 was used to analyze data.

Results: Out of 161 patients with oral ulcers, depression was prevalent in 69%. About 37% of the patients were moderately anemic, 32% were severely anemic and 31% had mild anemia. The significant association was found between depression and severity of anemia "p=0.028". The factor such as age $\geq$35 years, female sex and multiple ulcer lesions among anemic and depressed patients were found statistically significant "p<0.05".

Conclusion: The study concluded that depression and anemia are significantly associated and can increase the incidence of oral ulceration.

Keywords: Oral ulcer, aphthous ulceration, recurrent aphthous stomatitis, depression, anemia, hemoglobin level.

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Introduction

The ulcerative and debilitating oral mucosal disorders of recurrent aphthous stomatitis or chronic aphthous ulceration[1] were estimated to affect up to 25% of the general population, primarily children and adults. In light of its wide-ranging acceptance for recurrent aphthous stomatitis in rehabilitation and medicine it is impossible to avoid the ulcers and most of the therapies are symptomatic[2-4]

Although precise pathogenesis and etiology remain unknown, certain determinants are considered crucial. Initiation is influenced by causes like diet, drugs, hematinic deficiencies, hypersensitivity, hormones, use of nicotine and psychological stress. There are sporadic reports of mutations and immunopathogens in addition to the local and systemic factors suggested[4].

Depression has been highlighted as a potential risk factor in recurrent aphthous stomatitis. Stress has been suggested to cause damage to oral soft

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tissues through parafunctional behaviors, such as chewing of the cheek or lips[2,5]. A recent study showed that the severity of depression and frequency of recurrent aphthous stomatitis episodes are not associated explicitly and suggested that psychological stress in patients prone to recurrent aphthous stomatitis, might happen to act as a triggering or influencing factor rather than an etiological factor.[4] In another study conducted in Pakistan showed 51.3% of the patients with recurrent aphthous stomatitis had positive history of stress[6].

Other potential risk factors for recurrent aphthous stomatitis is hematinic deficiencies (B12, folate, and iron usually causing nutritional anemia), which are frequent among newborns, infants, children, young adults, pregnant and menstruating females in developing nations[7,8]. Around 20% of hematinic deficiencies are observed in recurrent aphthous stomatitis. The non-complicated recurrent aphthous stomatitis may be linked to hematinic deficiency since latter causes atrophy of epithelial layer of oral cavity[7]. The thin oral epithelium makes it more prone to traumas and growth of bacterial exogenous antigens, hence a potential factor in recurrent aphthous stomatitis[7,9]. About 2.5 million Pakistanis are suffering from nutritional anemia and among them 11% are suffering from pernicious anemia which results in mucosal bleeding, oral ulceration and glossitis[8]. The association of stress is still not doubtless with recurrent aphthous stomatitis episodes. It is usually thought that the occurrence of chronic aphthous ulcers may cause severe psychological problems. Ulcer occurrence can be linked to elevated salivary cortisol levels and to reactive oxygen species in the saliva. Stressful situations may induce a temporary increase in the amount and function of leukocytes in salivary cortisol and/or immune control response in inflammation[10].

Literature has shown depression and anemia to be correlated with the beginning and recurrence of aphthous stomatitis[5,6,8-12] but the problem is that recent Pakistani data is falling short on this topic, along with the failure to implement the international data in our population. The potential reasons could be differences in socio-demographic, racial, eating and genetic factors.

The current study aims to determine the association between severity of anemia with depression among patients with oral ulceration and the rationale was to improve our local population by early detection of anemic patients affected by depression and providing behavioral-modification therapy and support which could lead to the better healing of oral ulcers. This study could definitely help improve the oral health status of our population and the dental community to look at the bigger scale.

Subjects And Methods

It was an observational study conducted in the Department of Oral Medicine and Diagnosis, for the duration of one year. The sample size was estimated by using open epi online sample size calculator and by taking statistics of depression as 28.6% among patients with recurrent aphthous stomatitis, absolute precision as 5% and 95% confidence level, the estimated sample size was 322 patients.

All patients of age 20-50 years of either gender presenting with oral ulceration/aphthous stomatitis (burning sensation of VAS $\geq$ 2 and pain score on VAS $\geq$ 3) from last 3-6 months were included in the study using non-probability consecutive sampling technique.

Exclusion Criteria were the patients who had any systemic disease such as neurological disorders, gastrointestinal diseases, Bechet's syndrome, pregnancy and lactating mothers, use of any antidepressants or any nutritional supplements.

After obtaining approval from ethical review committee data collection was initiated. Verbal and written informed consent was taken from all the eligible patients before enrollment in the study, Hemoglobin levels was checked for anemic patients with oral ulcers according to the graded anemic scale by the World Health Organization. The hemoglobin (Hb) level less than 13 g/dL for men and less than

12 g/dL for women were deemed as anemia. For severity of anemia; Hb level 10-12.9 g/dL for men and 10-11.9 g/dL for women was considered as "mild anemia", for both gender Hb level 7-9.9 g/dL is considered as 'Moderate Anemia' and Hb level<7g/dL was as "severe anemia".

Data regarding demographics along with characteristics of oral ulcerations was also noted on a pre-designed proforma. Oral ulceration in relation to pain was assessed according to that scale pain using the verbal numeric rating scale. The Numeric Rating Scale (NRS-11) is an 11-point scale for patient self-reporting of pain. The patient was asked to make three pain ratings, corresponding to current, best and worst pain experienced over the past 24 hours. The average of the 3 ratings was used to represent the patient's level of pain over the previous 24 hours.

The intensity of current, best, and worst pain levels over the past 24 hours on a scale was measured as: 0 (no pain) to 10 (worst pain imaginable)".0=No pain, 1-3=Mild Pain, 4-6=Moderate pain, 7-10=Severe Pain.

Anemic patients with oral ulcers were assessed for depression using Patient Health Questionnaire Depression Scale (PHQ-9) also. Each item of PHQ-9 was scored on a scale of 0-3 (0=not at all; 1=several days; 2=more than a week; 3=nearly every day). The PHQ-9 total score ranges from 0 to 27 (scores of 5-9 are classified as mild depression; 10-14 as moderate depression; 15-19 as moderately severe depression; ≥20 as severe depression).

SPSS version 23 was used to analyze data. Numeric variables were presented as mean and SD whereas categorical variables were presented as frequencies and percentages. Chi-square was applied to see the association between depression and severity of anemia. 'P-value ≤ 0.05' was taken as statistically significant.

Results

The mean age of the study sample was 35.12 ± 5.49 years ranging from 26 to 45 year. Majority of the patients were females (71.4%) and (28.6%) were males. About 102 patients had multiple oral lesions (63.4%) and 59 had single lesion (36.6%). The most frequent site of oral ulceration was buccal mucosa (n=88, 54.7%), followed by palate (n=63, 39.1%), tongue and gingiva (n=39, 24.2%).

Among 161 patients with aphthous stomatitis, 37% were moderately anemic, 32% were severely anemic and 31% had mild anemia. Fig 1. Out of 161, depression was prevalent in 69% of the patients. Fig 2. Patients who were suffering from depression, 35.1% were mild anemic, 39.6% were moderately anemic and 25.2% were severely anemic. The significant association was found between depression and severity of anemia "p=0.028". Fig 3.

About 55.9% of the patients were of age≤35 years, among them 28 patients had depression. On comparing depression with severity of anemia in this age group, majority of them were moderately to severely anemic and showed significant association with depression "p<0.05". Among males, depression and severity of anemia was not significantly associated "p>0.05", whereas among females depression showed significant association with severity of anemia "p<0.05" and majority of them had moderate to severe anemia. Among patients with single oral lesions no association was found between severity of anemia and depression "p>0.05", whereas among patients with multiple lesions statistically significant association was found between depression and severity of anemia "p<0.05" Table 1.

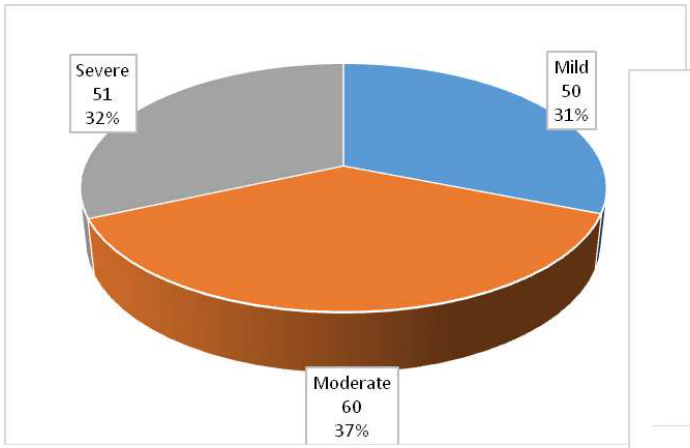

Fig 1. Frequency distribution of severity of anemia

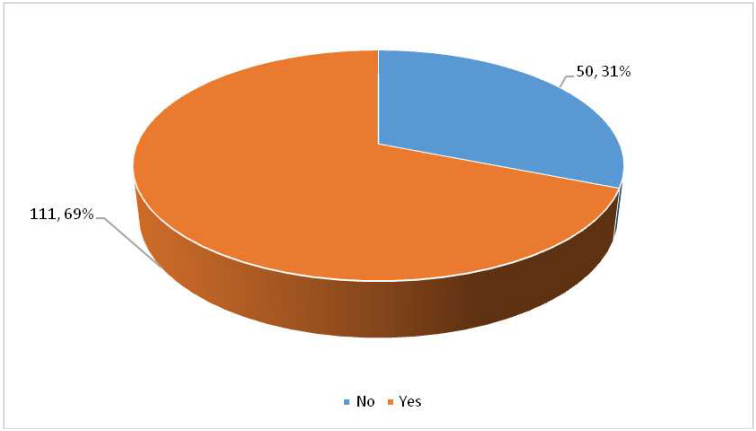

Fig 2. Frequency distribution of depression

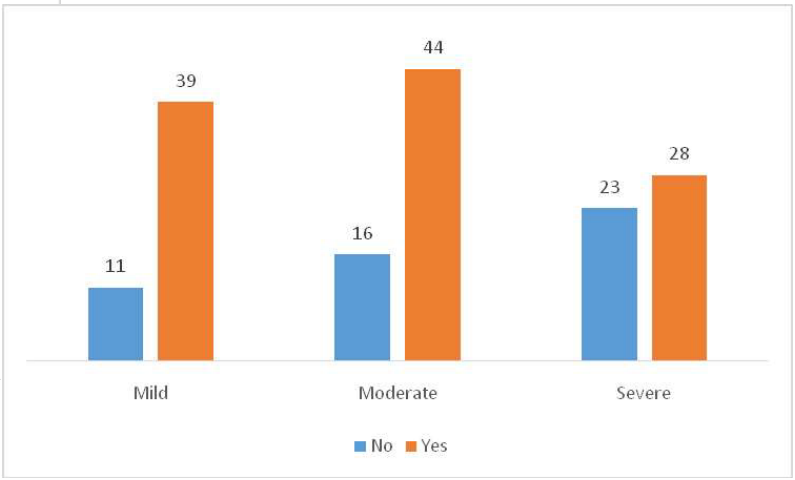

Fig 3. Comparison of severity of anemia and depression among patients with oral ulcers

Table 1. Comparison of severity of anemia and depression with respect to various factors

Variables	Severity of anemia	Depression		P-value
Age groups		Yes	No	
<35 years	Mild	25	11	0.446
	Moderate	8	0	
	Severe	16	11	
?35 years	Mild	14	0	0.002
	Moderate	36	16	
	Severe	12	12	
Gender				
Male	Mild	15	9	0.79
	Moderate	9	6	
	Severe	4	3	
Female	Mild	24	2	0.001
	Moderate	35	10	
	Severe	24	20	
Number of lesions				
Single	Mild	29	9	0.523
	Moderate	12	4	
	Severe	3	2	
Multiple	Mild	10	2	0.024
	Moderate	32	12	
	Severe	25	21	

Discussion

Recurrent Aphthous Stomatitis are single or multiple painful ulcerations that usually occur on non-keratinized mucosa of the oral cavity and appear as yellowish white ulcerations, surrounded by an erythematous halo. It affects 20% of the general population with a predilection for females, commonly seen in children and young adults, and after a time tends to decrease both in severity and frequency. The exact etiology of RECURRENT APHTHOUS STOMATITIS still remains unclear, and multiple factors have been considered in the exacerbation of RAS such as genetic predisposition, local trauma, allergy to certain food materials, vitamin deficiency, immunosuppression, smoking and psychiatric factors (stress and anxiety)[6]. Psychological stress is considered as a common provoking or trigger factor in the occurrence and progression of RAS, but little documentation has been presented to substantiate this widely held assumption[7-9]. This particular study was carried out to establish an association between RAS, stress, anxiety and depression by use of General Health Questionnaire, and Hospital anxiety and Depression scale.

Recurrent aphthous stomatitis influences up to 20 percent of general population with predominance among females, most seen in adolescents followed by young adults however after some period, its frequency and severity tend to reduce. The exact cause of recurrent aphthous stomatitis is not yet clear and several potential factors such as genetic predisposition, allergy to certain food products, local trauma, vitamin deficiency, hematological deficiencies, immunosuppression, psychiatric disorders, and smoking have been associated with the exacerbation of recurrent aphthous stomatitis[13,14]. Psychological stress and anemia are considered in the incidence and development of recurrent aphthous stomatitis as a reciprocal cause or triggering factor, but little evidence has been provided to support this widely held belief[15-17]. Hence, the present study was conducted to assess an association between severity of anemia and depression among patients presenting oral ulceration.

The prevalence of recurrent aphthous stomatitis differs from 5-60 percent and depend upon the target group which have been investigated[18]. A study in India revealed that majority of the patients were females (56.3%) and 43.7% were males who suffered from recurrent aphthous stomatitis and gender-wise difference in frequency of oral ulceration was statistically significant ($p<0.05$)[19]. In another study by Queiroz et al. found among 68 cases of recurrent aphthous stomatitis , 59% were females and 41% were males.[20] In the present research, similar results have been observed majority of the patients with oral ulceration were females (71.4%) as compared to males. Lakdawala et al. also found in Karachi that 80% of the patients with apthous ulcers were females[21]. This high frequency of females can be elucidated by the fact that females pursue more medical attention than males[20]. One of the predisposing factors for oral ulceration may also be the predisposition of women because the hormone is unique to women and because the hormone changes are rare for males[22].

We found buccal mucosa as the common site of ulceration followed by palate, tongue and gingiva whereas Lakdawala et al. found lip (32%) as the most common site of ulceration followed by cheeks (27.05%) and palate (27.05%) respectively[21]. Ojo et al. in a study conducted at Nigeria observed the most frequent site for recurrent aphthous stomatitis as gingiva.[18] Further research showed among children, the high frequency of recurrent aphthous stomatitis was observed on gingivitis. Hence, the oral ulceration site can be exaggerated by age.[23]

In Pakistan, almost 2.5 million people suffer from nutritive anemia and 11% suffer from pernicious anaemia, which culminated in oral ulcers, mucous glossitis and bleeding[24]. In a Pakistani study, it has been observed that (58.3%) had low anemia among patients presenting with oral ulceration, whereas frequency of low anemia was significantly high among males as compared to females[8]. In current research, majority of the patients had moderate anemia (37%), followed by severe and mild anemia respectively.

The association of stress is still not certain with recurrent aphthous stomatitis episodes. It is usually thought that the occurrence of chronic aphthous ulcers may cause severe psychological problems. Ulcer occurrence can be linked to elevated salivary cortisol levels and to reactive oxygen in the

saliva. Stressful situations may induce a temporary increase in the amount and function of leukocytes in salivary cortisol and/or immune control response in inflammation[17]. Hence, in the present study (69%) of the patients with oral ulceration had depression. In an Indian study, mean depression score was higher among patients with oral ulceration 5.20 ± 2.66 as compared to controls 3.96 ± 2.93. This results show that patients with oral ulceration had higher levels of depression as compared to controls[17]. Aslam et al. in their research also found high prevalence of depression among oral ulceration (51.3%).[6]

Depression frequency commonly combined with physical/systematic diseases, indicates similar underlying pathophysiological mechanisms (e.g., brain adaptation and inflammatory system)[24]. In patients with depression the high incidence of anemia in relation to the general population was found[25]. A study by Abbasi et al. also found correlation between depression and aphthous ulceration and between iron deficiency anemia and aphthous ulceration "p<0.05"[26]. In dissonance, some researches showed no association between levels of Hb and depression[27].

We also found substantial association in current research between anemia severity and depression "p<0.05" in patients with oral ulcers. Based on the results of our research, depression and anemia may play an important role in the oral ulceration incidence. Rate and extent of oral ulceration can also be increased by other variables, such as age ≤35 years, female sex and numerous ulcer lesions among anemic and depressed patients. In a study by Abdullah et al. found (43.3%) of the patients had oral ulceration associated with stress however only (5.31%) of the oral ulceration were anemic. They also found the most affected age group by oral ulceration was 20-29 years (36%) followed by 30-39 year old (30%) and predominance among female gender (32%)[28].

Cross sectional design and small sample size are the limitations of study. It is recommended that further studies should be conducted on the topic with larger sample size so that more beneficial results will be obtained.

Conclusion

The study concluded that depression and anemia are significantly correlated and can increased the incidence of oral ulceration. Therefore, proper stress-management interventions and diagnosis and treatment of anemia should be done in order to reduce aphthous stomatitis occurrence and episodes.

Conflict of Interest

Authors have no conflict of interest and no grant/funding from any organization

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