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PREVALENCE OF APHTHOUS AND APHTHOUS LIKE ULCERS AND THEIR RELATION TO PRECIPITATING FACTORS AMONG A SAMPLE OF EGYPTIAN POPULATION

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ABSTRACT

Introduction: Recurrent aphthous ulcer is one of the most common oral diseases worldwide. The prevalence ranges from 2% to 66% in different populations. Detection of the prevalence of oral ulcerations in the general population is very important as the ulcers have significant negative effects on the oral health, irrespective to the etiology. Moreover, many syndromes were known to be associated with recurrent aphthous ulcers.

Aim: the present study was performed to detect RAU prevalence among a sample of Egyptian population and to find out its incidence in relation to the precipitating factors.

Subjects & Methods: The present study was performed on a total of 4362 subjects, 1874 males and 2488 females. The subjects were recruited from the outpatient clinic of Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University. For patients with RAU, the diagnostic sheets were provided. Data obtained from the questionnaire was analyzed using software SPSS 16.0 for windows

Results: There were 50/4362 cases with aphthous ulcer giving a prevalence of 1.15%. Ten cases (20.0%) had major aphthous ulcer while 40 cases (80.0%) had minor aphthous ulcer and no herpetiform aphthous ulcers were reported.

Conclusions: The present study shed the light on the prevalence of recurrent aphthous ulcers and also pointed to the importance of a thorough history taking to identify the main risk factors of the ulceration and then to get the needed preventive measures.

KEY WORDS: Aphthous ulcer, Prevalence, precipitating factors.

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INTRODUCTION

The term "aphthous" was derived from the Greek word "aphtha" which means ulceration. ⁽¹⁾ Recurrent aphthous stomatitis (RAS = RAU) is defined as an inflammatory condition of unknown etiology which is characterized by painful recurrent, solitary or multiple ulcerations of the oral mucosa. ⁽²⁾ Recurrent aphthous ulcers are very common, affecting about 20% of the normal individuals. ⁽³⁾

Later on, **Shulman**, ⁽⁴⁾ reported that the prevalence of oral ulcers worldwide is about 4%, with aphthous ulcers being the most common, affecting about 25% of the population all over the world. It is one of the most common oral diseases worldwide. The prevalence ranges from 2% to 66% in different populations. ⁽⁵⁾

Detection of the prevalence of oral ulcerations in the general population is very important as the ulcers have significant negative effects on the oral health, irrespective to the etiology; moreover, ulcerations affect the quality of life. ⁽⁶⁾

It was reported that aphthous ulcers are more predominant in females. ^(7,8)

The onset is usually during early adolescence, and the condition often lasts for several years before it resolves.⁽⁹⁾

Regarding the pathogenesis of RAU; it primarily involves the activation of a cell-mediated immune response, mainly T lymphocytes, by which the production of tumor necrosis factor- α (TNF- α) and other cytokines induce epithelial cell death and ulceration. ⁽¹⁰⁾

The most common complain of patients suffering from RAU is pain that affects the life style of the patient as it leads to difficulty in speaking, eating, and swallowing. ⁽¹⁾ It was found that the process of oral ulceration causes a breach in the oral epithelium, which in turn exposes nerve endings in the underlying lamina propria, resulting in either pain or soreness, especially during eating spicy foods or citrus fruits. ⁽¹¹⁾

Clinically, it presents first in childhood or adolescence. ⁽¹⁾ Typical RAU lesions involve selflimiting, painful, clearly defined shallow round or oval ulcers, small in case of minor type and large in the major type, each with a shallow necrotic center. These ulcers are covered with a yellow-grayish pseudo-membrane; they are surrounded by minimal raised margins with erythematous halo representing superficial vasculitis and foci of extravasated erythrocytes located in the superficial layers of the lamina propria. ⁽¹²⁾

According to the clinical features, recurrent aphthous ulceration can be divided into three types: minor aphthae (Mikulicz'saphthae; MiRAS), major aphthae (Sutton's aphthae; MaRAS) and herpetiform aphthae (HeRAS). ⁽¹³⁾

Minor aphthae, also known as Mikulicz's aphthae, named for Johann von Mikulicz-Radecki, who was probably the first to describe the condition in late 19th century (1898), or mild aphthous ulcer, accounts for 75 -85% of all aphthous lesions. ⁽¹⁴⁾ Minor aphthous ulcers are mostly not larger than 8-10 mm and tend to heal within 10- 14 days (average 12 days) without scar formation. It involves every non keratinized mucosa of the oral cavity and is often observed in the labial mucosa, buccal mucosa, floor of the mouth, and on the ventral or border of the tongue. The labial mucosa was recorded as the most prevalent area. ⁽¹⁵⁾

The second type is the herpetiform which is characterized by recurrent crops of ulcers, 10 - 100 in number, involving the oral mucosa. The ulcers mostly have a diameter of 1-2 mm resembling herpetic lesion. ⁽¹⁶⁾

The third type is major aphthous ulcer which is larger in size, deep, crateriform, and may be accompanied by considerable induration; moreover, it characteristically heals with scar formation ⁽¹⁶⁾ The etiology of RAU had not been understood as reported by *Rogers in 1997* ⁽¹⁴⁾. Later on, both environmental and genetic factors emerged. It has been associated with a number of causes such as stress, trauma, nutritional deficiencies, allergy, genetic predisposition, hematologic and hormonal disorders or infection. ^(17, 18) None of these etiologies has been validated. Moreover, the precipitating factors for recurrent episodes in RAU patients were found to be diverse, thus it posed a challenge for the clinicians to identify the specific causes for this disease. ⁽¹⁹⁾ Furthermore, a wide spectrum of potential local and systemic factors was speculated by various researchers for the origin of RAU. ^(19, 20)

Many syndromes were known to be associated with recurrent aphthous ulcer, such as: Behcet's disease (BD), Fever Adenitis pharyngitis Apthous (FAPA), Mouth And Genital ulcers with Inflamed Cartilage (MAGIC syndrome), Imerslund-Grasbeck syndrome (IGS), Sweet's syndrome, also known as acute febrile neutrophilic dermatosis ⁽²¹⁾

There is no specific curative treatment available for RAU. After ruling out the systemic diseases, current conventional medications are usually used. The present conventional medications used for RAU are known to suppress the local immune response, relieve symptoms, and prevent the secondary infection. ⁽⁵⁾ Moreover, a variety of these medications are currently used for the management of RAU depending on its severity. ⁽²²⁾

The prevalence studies have role in determining the real reasons and enabling the assessment of the level of morbidity and the population "disease burden" for a non-fatal condition. Also, a great variation had been found regarding the prevalence of recurrent aphthous ulcers and aphthous like ulcers, therefore, the present study was performed to detect RAU prevalence among a sample of Egyptian population and to find out its incidence in relation to the precipitating factors.

Subjects and Methods:

The present study was performed on a total of 4362 subjects, 1874 males and 2488 females. The subjects were recruited from the outpatient clinic of Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University. The duration of the study was from March 2016 to March 2017.

The Participants were examined by the authors with participation of a team work of some of Oral Medicine department members. The examination included two major parts:

a) Interview of patient.

b) A comprehensive clinical examination

Detailed case history was recorded by trained professionals. The clinical examination of the oral cavity was done following the WHO guidelines, under artificial illumination on a dental chair, using a diagnostic set.

The oral cavity was divided into seven regions, examined thoroughly to avoid missing any lesion (the lips, cheek mucosa, floor of mouth, teeth and gingiva, hard palate, tongue and the retro-molar region).⁽²³⁾

The diagnosis of RAU was entirely based on history and clinical criteria mentioned by *Natah et al, in 2004.* ⁽¹⁷⁾

For patients with RAU, the diagnostic sheets were provided, they contained details about demographic characteristics, the history of recurrent oral ulcers, history of nature of the ulcers, history of association with any specific food intake, personal habits, history of previous treatment received, reasons for receiving/not receiving treatment, details of treatment received. Data obtained from the questionnaire was analyzed using software SPSS 16.0 for windows.

If any systemic abnormality was suspected referral to the internist for possible management was performed.



Fig. (1) A clinical photograph showing minor RAU in ventral surface of tongue



Fig. (2) A clinical photograph showing major RAU in labial mucosa

Statistical Analysis

Qualitative data were presented as frequencies (n) and percentages (%). Numerical data were presented as mean, median, standard deviation (SD), minimum and maximum values.

Statistical analysis was performed with IBM[®] SPSS[®] Statistics Version 20 for Windows.

The present study included 4362 subjects; 2488 females (57.04%) and 1874 males (42.96%).

Prevalence of aphthous ulcer

There were 50/4362 cases with aphthous ulcer giving a prevalence of 1.15%. Ten cases (20.0%) had major aphthous ulcer while 40 cases (80.0%) had minor aphthous ulcer and no herpitiform aphthous ulcers were reported.



Fig. (3) Pie chart representing prevalence of aphthous ulcer

Demographic data of cases with aphthous ulcer

24 cases (48.0%) were males while 26 cases (52.0%) were females.

The mean \pm standard deviation values of age were 33.4 \pm 14.2 years old with a minimum of 12.5 years old and a maximum of 77.0 years old. The median age was 32.5 years old.

History and predisposing factors

Results of medical history and predisposing factors for cases with aphthous ulcer are presented in Tables (1, 2).

[®] IBM Corporation, NY, USA.

[®] SPSS, Inc., an IBM Company.

Medical history	n	%	Type of ulcer
Anemia	7	14.0	Minor and Major
Diabetes Mellitus	4	8.0	Minor and major
GIT disturbances	4	8.0	Minor and Major
Behcet's disease (history)	3	6.0	Minor
Cyclic neutropenia (history)	1	2.0	Minor
Epilepsy	1	2.0	Minor
Familial history	1	2.0	Minor
HCV	1	2.0	Minor
Hypertension	1	2.0	Minor
Reiter's syndrome (history)	1	2.0	Minor
Rheumatic fever	1	2.0	Minor
Medically free	26	52	Minor and major

TABLE (1) Descriptive statistics of medical history findings in cases with aphthous ulcer

TABLE (2) Descriptive statistics of predisposing factors in cases with aphthous ulcer

Predisposing factors	N	%	Type of ulcer
Stress	16	32.0	Minor and major
Smoking	3	6.0	Minor and major
Cheek biting	2	4.0	Minor
Alcohol	1	2.0	Major
Menstruation	1	2.0	Minor
Trauma	1	2.0	Minor
No predisposing factor revealed	26	52	Minor and major

Duration and frequency

The mean \pm standard deviation values of duration were 6.5 \pm 6.4 days with a minimum of 2 days and a maximum of 30 days. The median duration was 4 days.

For the minor aphthous ulcer type; the mean \pm standard deviation values of duration were 4.3 \pm 1.2 days with a minimum of 2 days and a maximum of 7 days.

While for the major aphthous ulcer type; the mean \pm standard deviation values of duration were 19.2 \pm 6.5 days with a minimum of 8 days and a maximum of 30 days.

The median frequency of occurrence was 3 times/year with a minimum of 1 time/year and a maximum of 11 times/year.

For the minor aphthous ulcer type, the median frequency of occurrence was 3 times/year with a minimum of 1 time/year and a maximum of 11 times/year.

While for the major aphthous ulcer type, the median frequency of occurrence was 1.2 times/year with a minimum of 1 time/year and a maximum of 2 times/year.

Site

The most affected site was the labial mucosa in 19 cases (38.0%) (all were minor type) followed by buccal mucosa in 16 cases (32.0%) (11 cases were of minor type, 5 cases were of major type). The tongue showed lower prevalence in 9 cases (18.0%) (7 cases were of minor type, 2 cases were of major type) followed by the floor of the mouth in 4 cases (8.0%) (were all of minor type) and hard palate in 3 cases (6.0%) (were all of major type). The least affected sites were the alveolar mucosa, soft palate and labial vestibule (1 case for each site representing 2.0 %) (all were of minor type). Four cases had RAU affecting more than one site.

Number of lesions

The median number of lesions in each patient was 2 lesions, with a minimum of 1 lesion and a maximum of 7 lesions.

All major apthous ulcers cases had single ulcer, while minor apthous ulcer cases showed variable number of ulcers.

Lymph node association

Seven cases, all were major type (14.0%) had lymph node association with the ulcer.

DISCUSSION

Recurrent aphthous ulceration represents a common inflammatory ulcerative condition that is encountered in daily dental practice. The prevalence rate of RAU in different areas of the world had shown considerable variation throughout different epidemiological studies. ⁽²⁴⁾

It is an important condition as it can be distressing and cause suffering and pain. Moreover, it interferes with normal life activities by affecting eating and swallowing. Studying the prevalence of recurrent aphthous ulceration is important as it gives insight into the proportion of people suffering from the condition as well as the possible causal factors. ⁽²⁵⁾

The present study was carried on to shed more light on the prevalence of RAU and aphthous- like ulcers among a sample of Egyptian population attending the Oral Medicine clinic in Faculty of Dentistry, Cairo University and to find out its incidence in relation to the precipitating factors.

The present study detected that there were 50/4362 cases with aphthous ulcer giving a prevalence of 1.15%.

The present result is very close to that detected by a study carried on a sample of South Indian Population, by *Hegde et al in 2015* ⁽²⁶⁾ which was 1.9%.On the same hand, the prevalence of oral aphthae was 4.5% in the study carried on a sample of population in Iran by Davatchi et al, 2008. (27)

The present finding was in accordance with a study conducted at Manipal in India, where prevalence RAU was reported as 2.1%.⁽²⁸⁾

On the other hand, these results are not in agreement with the study performed by *Patil et al*, 2014 ⁽²⁹⁾ who detected a prevalence of RAU to be 47.4%, which was higher than the previously mentioned studies. Also, 21.7% prevalence of RAU was detected by *Patil et al in 2014* in another study in the same year ⁽³⁰⁾, and in a study conducted in Iran the prevalence was 25.2 %. ⁽²⁷⁾

The study performed by *Muhaidat& Rodan in* 2013 ⁽⁶⁾ showed that the prevalence was 3%. This is also higher than other studies, they attributed this high incidence to that Jordanian people might be different from other populations regarding the genetic predisposition, level of stress and lifestyle.⁽³¹⁾

This great variation in the prevalence of RAU can be also attributed to the difference in the methodology of the study, the socio-economic level, and the professional level as explained by *Patil et al in 2014.* ⁽²⁹⁾ Also it could be attributed to the small sample size of the study (including patients attending oral medicine clinic, Cairo University) rather than sample collection at the diagnostic center.

Ten cases (20.0%) of the present study had major aphthous ulcers while 40 cases (80.0%) had minor aphthous ulcers, and no herpetiform aphthous ulcers were detected. These results are nearly similar to the previous studies conducted by many authors.^(24, 32, 33, 34)

Regarding the age; the mean \pm standard deviation values of age in the present study were 33.5 \pm 14.2 years old with a minimum of 12.5 years old and a maximum of 77.0 years old. The median age was 32.5 years old. These results are in agreement with *Crespo et al*, (2005) ⁽³⁵⁾, who reported that aphthous ulcer is a disease of childhood and youth, it is most prevalent between 10 and 30 years of age.

The present study detected that twenty-four cases (48.0%) were males while 26 cases (52.0%) were females which is consistent with the study of *Patil el al*, (2014) ⁽²⁹⁾ who detected that females (57.9%) were affected more frequently than males (42.1%). This was similar to the results of *Muhaidat and Rodan in 2013* ⁽⁶⁾ that also showed a female predominance. This could be attributed to that females are more liable to stress and emotional situations which can affect the immune response. Moreover, females seek medical examination more frequently than males. Also, hormonal changes during pregnancy and menstruation can play a role. ⁽³⁶⁾

On the same hand, the study performed by **Rao** et al, 2015 detected that females had higher RAU prevalence (67.7 %) compared to males (31.3%). Although they reported higher males affection (87%) as 69 males were affected among total number of 79 males, and the females showed less distribution (74%) of the studied females (145 females among 195 females). ⁽³⁷⁾

This is in accordance to a study reported by *Handa et al*, (2012) ⁽³⁸⁾ where females were more commonly affected than males. Also, the disease was more prevalent in females in the study of *Narang et al*, (2015). ⁽³⁹⁾

In respect to the number of lesions, the median number of lesions was 2 lesions with a minimum of 1 lesion and a maximum of 7 lesions. These results are consistent with the study carried on by *Nassaji and Ghorbani*, (2012). ⁽⁴⁰⁾

The present study showed that the mean \pm standard deviation values of duration were 6.5 ± 6.4 days with a minimum of 2 days and a maximum of 30 days. The median duration was 4 days. These results are similar to the previous studies that reported that the duration of healing of the ulcer depends on its type where minor is known to heal within 10 to 14 days without scarring while major RAU persists for 6 weeks and heals with scarring

as reported by *Preeti et al*, (2015) and *Hegde et al*, (2015). ^(26, 41)

The median frequency of occurrence was found to be 3 times/year with a minimum of 1 time/year and a maximum of 11 times/year. These results are in agreement with *George and Joseph in (2016)*⁽⁴²⁾ who found that the frequency of the ulcers ranged between 2 to 12 times/ year

As regard to the site, the present study revealed that the mostly affected site was the labial mucosa in 19 cases (38.0%) followed by buccal mucosa in 16 cases (32.0%). The tongue showed lower prevalence in 9 cases (18.0%) followed by the floor of the mouth in 4 cases (8.0%) and hard palate in 3 cases (6.0%). The least affected sites were the alveolar mucosa, soft palate and labial vestibule (1 case for each site representing 2.0%).These results are nearly similar to the previous studies that detected that the lips, and bucccal mucosa are the mostly affected sites according to *George and Joseph in (2016).* ⁽⁴²⁾

Many predisposing factors are known to be related to RAU, one of these factors is stress which was detected in 32% of the studied cases, and this observation is similar to the study of *Shi et al*, (2015) ⁽⁴⁴⁾ and *Rao et al in* (2015) ⁽³⁷⁾ who detected that the mean stress scores of females were more when compared to males in their study, which is similar to the study conducted by *Singh et al*, (2013) ⁽⁴⁵⁾ this can be explained by the increased levels of salivary cortisol or reactive oxygen species in the saliva, which have been suggested as the initiator of the lesions as reported *by Farmaki et al*, (2008) and *Huling et al*, (2012).^(46,47)

Another explanation of the relationship between RAU and stress is that the psychological stress triggers the immunologic activity by increasing the number of leukocytes at the sites of inflammation; such pattern is commonly observed during the pathogenesis of aphthous ulcers. ⁽⁹⁾

Smoking was found to be associated with only 6% of the studied cases, moreover, two of the

smoker patients gave a notice of less frequency of the ulceration after starting smoking, and this observation is similar to *Abdullah*, (2013) ⁽⁴³⁾. This can be attributed to the negative association between oral ulceration and smoking (*Ussher et al*, 2003) ⁽⁴⁸⁾. Some investigators thought that smoking has protective effect on the oral mucosa and this protective effect is related to the increased keratinization of the oral mucosa in smokers as keratin layer acts as a mechanical and chemical barrier against trauma or microbes (*McRobbie et al*, 2004) ⁽⁴⁹⁾. Moreover, few researchers suggested that smokers may be less psychologically stressed than nonsmokers and that the psychological triggers may affect RAU development. ⁽¹⁾

On the same hand, multiple studies reported that mouth ulceration ranging from 13%-29% of quitters and have shown that mouth ulcers are less common in smokers than nonsmokers, which support the theory of the protective antibacterial effect of smoking.^(50,51)

The present study showed association between RAU and either cheek biting in 4% of the cases, or trauma in 2% of the cases, some researchers have speculated that anxiety due to stress could lead to parafunctional oral habits, such as lip and cheek biting, and that those physical traumas may play roles in initiation of the ulcerative process in susceptible individuals.⁽²⁵⁾

Another observation is that one (2%) of the studied cases gave history of alcohol intake, *Shim et al*, in (2012) ⁽⁵²⁾ recommended the avoidance of alcohol in patients of RAU, and this can be attributed to its irritating action.

Only one (2%) of the studied cases gave a history of association between RAU and luteal phase of menstrual cycle similarly to *Field and Allan*, (2003), *Balan et al*, (2012) and *Maheswaran* (2015)^{(53 54, 55),} thus relating the episodes of RAU to progesterone levels as suggested by *Scully et al*, (2003).⁽⁵⁶⁾ 14% of the studied cases suffered from anemia which is in agreement with *Healy et al*, (2004), *Burgan et al*, (2006) and *Khan et al*, (2013). ^(57,58,59) This may be attributed to the fact that adult women frequently encounter aphthae or histories of aphthae because they have high predisposition to become anaemic as reported by *UNICEF*, (2002). ⁽⁶⁰⁾

In the present study, 8% of the patients gave history of diabetes mellitus, **Bangash et al**, $(2012)^{(61)}$ reported that recurrent aphthous stomatitis, has been detected in people with diabetes mellitus.

Moreover, aphthous ulcers which heal within one week, however, in diabetics the healing process is disturbed and ulcers may persist for longer period. ⁽⁶²⁾ This can be explained by the poor cleansing action of saliva as the diabetic patient mostly suffers from hypo-salivation. Also, the components of saliva are altered in diabetics. Actually, saliva in diabetics contains less glutathione and melatonin that are known to function as scavengers for the free radicals than that in healthy individuals. ⁽⁶³⁾

Diabetic patients are also known to produce more free radicals at the wound during elevated blood-sugar and hypo-oxidation conditions than healthy non-diabetic individuals.⁽⁶⁴⁾

6% of the studied cases suffered from gastrointestinal disturbances which is consistent with Abdullah, (2013) (43). Previous studies remarked the association of the lesion in some individuals with systemic conditions such as gastrointestinal disease. (63) Moreover, Elsheikh and Mahfouz in (2005) ⁽⁶⁶⁾ found that *H pylori* DNA was detected in 67% of patients in whom the ulcers were strictly limited to the lymphoid tissues, but in only 10% of patients in whom the ulcers were randomly distributed in the oral cavity and pharynx. These results support the suggestion of the possible etiologic role for H pylori in recurrent aphthous ulcers. On the other hand, some studies did not support the assumption that H pylori could be involved in RAU development. Unfortunately, those studies showed overall controversial results; the incidence of *H pylori* DNA in oral aphthous ulcers varied from 4.5% to 38.9%, and in none of them was this incidence rate significant compared with their controls. $^{(67, 68)}$

In the present study, 6% of the patients gave a history of Behcet's disease which is more than the prevalence detected in the study of *Patil et al*, 2014 (1.6%).⁽²⁹⁾ It was reported that aphthous like ulcer is the most frequent manifestation of Behcet's disease and it thought to be induced by the circulating immune complexes that lead to vasculitis of the small and medium sized blood vessels.^(53,69)

In the present study, 2% of the cases showed cyclic neutropenia, similarly, *Neville et al*, (2008) ⁽⁷⁰⁾ reported that aphthous-like ulceration occurs in conditions that involve systemic immuno-dysregulation, such as cyclic neutropenia and human immunodeficiency virus infection. In cyclic neutropenia, more severe oral ulceration occurs during periods of severe immuno-dysregulation. Moreover, resolution of the underlying neutropenia prevents the cycle of ulceration.

The present study found out 2% of the cases had epilepsy, to authors' knowledge, no previous studies reported cases of RAU in epileptic patients; however, *Ettore* in (2007) ⁽⁷¹⁾ reported that RAU is one of the clinical manifestations of epilepsy.

2% of the studied cases suffered from hypertension, this observation is similar to *Mimura*, (2009). ⁽⁷²⁾

The present study detected that 2% of the studied cases were HCV patients, where one of the cases that had major aphthous ulcer, was suffering from HCV, to authors' knowledge no previous studies showed association between HCV and RAU, although, Major aphthae can be associated with other viruses such as human immune-deficiency virus (HIV) infection as reported by *Shetty*, (2005).⁽⁷³⁾

In 2% of the studied cases, familial history was detected which is consistent with the study of

Abdullah, (2013)⁽⁴³⁾. This could be supported by various associations of HLA antigens with RAU that have been reported. These associations vary with specific racial and ethnic origins.⁽⁴⁰⁾

Moreover, 2% of the studied cases gave a history of Reiter's syndrome; which is considered an example of the systemic conditions associated with aphthous-like ulceration as reported by *Brocklehurst* et al, (2012).⁽⁷⁴⁾

2% of the studied cases gave a history of rheumatic fever, to the authors' knowledge no previous studies showed association between rheumatic fever and RAU.

Finally, it should be noted that the present study showed the prevalence of RAU in the patients attending the oral medicine department who complained of oral lesions, not on the total patients attending the diagnostic center; moreover, no children younger than 12 years old were included in the study, therefore it may not show the real prevalence among the Egyptians. Another limitation of the present study is the recurrent nature of the ulcer so that many patients do not seek medical advice for the treatment of the ulcers.

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