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The Prevalence of Recurrent Aphthous Ulceration and its Associated Factors Among The population of Makkah Holly City

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Abstract

Oral mucosa is a protective barrier against trauma, pathogens and carcinogens. It is affected by a variety of lesions and conditions, some of which are harmless, while others can have serious complication (Safadi, 2009). Due to the lack of previous research to assess the level of knowledge and understanding of prevalence among Makkah population, and its associated factors that might help in its management, this study aimed to estimate the prevalence of RAU among Makkah population, to assess the most common factors that are associated with RAU and to determine the population's knowledge and management of RAU. Furthermore, as we are still surviving the COVID-19 pandemic, this study also aimed to investigate the association of RAU with COVID-19 infection in our population before and now a days during COVID-19 pandemic.

Although our sample size aimed to be a minimum of 300 participants, 383 patients have participated in our study after providing a written consent for the voluntary participation. Our findings showed that the prevalence of RAU was 84.80% of the overall population; the onset of RAU in our samples seems to peak between the ages of 26 and 55 years before becoming less frequent with advancing age. The etiology of RAU lesions is unknown, but there are several factors that can be associated with RAU such as local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors have been proposed as associated factors. Our results also showed that RAU are experienced in both smokers and nonsmokers but nonsmokers are dominants.

Furthermore, 38.9% of participants did not relate the condition to eating certain types of food. While the remaining 61.1% reported; hot, spicy, sour, hard and cinnamon as trigger causes of RAU. Regarding hematinic deficiency reported that they had 28.2% decreased B12 vitamin and 35.6% hemoglobin, respectively.

RAU condition appearance in COVID 19 patients; reported as a result of neutrophil chemotaxis, stress, and immunosuppression that predisposed RAU. Our study reported a statistical significant association with COVID-19.

Introduction

Recurrent Aphthous Ulcers (RAU), also called canker sores, aphthae or stomatitis, is a common oral disease (Figure 1). The term aphthae is derived from a Greek word aphthi, which means "to set on fire" or "to inflame" and had been first used by the philosopher Hippocrates to describe the pain of these ulcers (Ship, 2000). RAU is described as recurrent, multiple, small, round, or oval ulcers with demarcated margins, a yellow or gray base, and a surrounding red halo (Scully, 2006).

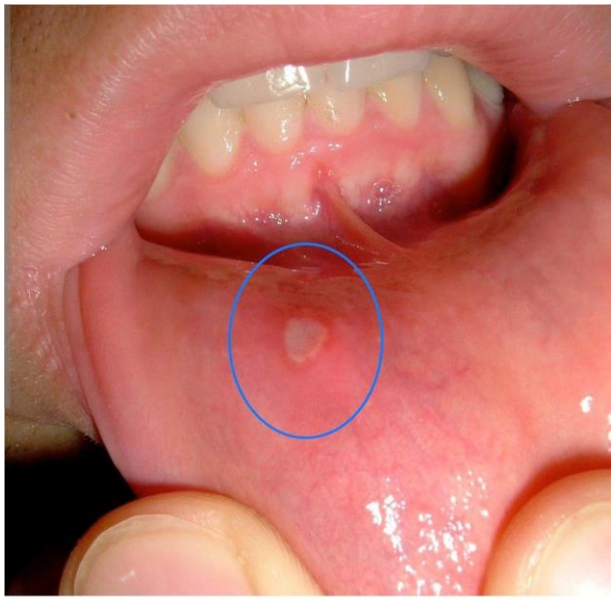

Figure:1 Recurrent Aphthous ulcer.

)https://commons.wikimedia.org/wiki/File;Apththe_Unterlippe.jpg(

The etiology of RAU is still unknown, however, RAU is classified as autoimmune disease (Jain et al., 2013). It is characterized by painful episodes of recurrent (single or multiple) ulcerations that are localized in the oral mucosa with red halo. Usually RAU start at early age before the age of 40 (Scully, 2006). RAU has three different clinical types; minor aphthous, major aphthous, and herpetiform ulcers (Natah al., 2004). The diagnosis of RAU is based on history and clinical examination (Chiang et al.,

2019). These ulcerative attacks, are associated with some factors such as stress, exposure to certain foods or drugs, topical trauma, blood deficiencies such as ferritin, folic acid, iron, vitamin B12, but it has an inverse association with smoking, and treated with either topical or systemic steroids (Belenguer-Guallar et al., 2014).

There is a study conducted on the Saudi population showed that the prevalence of RAU in Saudi dental adult patients reported as about 0.4% (AL-Mobeeriek & A, 2009). Since RAU is painful ulcer, affecting on taste, speak and eat/chew and there is no study was conducted specifically on Makkah population, current study aimed to;

- Estimate the prevalence of Recurrent aphthous ulcers among patients visiting Makkah dental clinics in PHCs and through online questionnaire to the remaining population, in period of time between April 2022- Jul 2022.
- Assess the most common factors that have an etiological, or associated with ulcers in Makkah population before and now a days during COVID-19 pandemic.
- Determine the population's knowledge about RAU and management of this condition.

Research problems

 Furthermore the reported RAU prevalence depended on the patient recall of the time of onset, duration and other details related to the lesion which might have occurred any time during the past year.

 As this study was cross-sectional, this will prevents us from making conclusions regarding what is known as risk factors. Risk markers or indicators are the only results which could be revealed.

 that sample was only from Makkah, and was not large to represent all Saudi people. Therefore, a larger sample including patients from all regions of KSA would be more representative.

 The compliance issues. When patient with a history of recurrent aphthous ulceration were asked to attend the clinic if aphthous ulcerations emerged in their mouth, they failed to comply for this request.

. The point prevalence measured from cross-sectional surveys can underestimate the actual prevalence of recurrent aphthous lesions since active lesions may be absent at the time of examination and the use of annual prevalence or life time prevalence may overcome this problem

The Aim of the study Is to

Find out the cause and prevalence of the Recurrent Aphthous Ulcersobjectives of the study

To Report the prevalence of Aphthous ulcer

To investigate the most common factors that play an etiologic/associated role in the pathogenesis of Aphthous ulcer in KSA adolescents.

To investigate the association of hematologic deficiencies in a representative sample in whom Aphthous ulcer is clinically diagnosed by the examiner.

Methods

Study design and study population

This is a cross-sectional survey-based study was conducted to assess the prevalence and the associated factors of RAU among Makkah population.

The sample size was aimed to be a minimum of 300 participants as calculated in recently published research conducted our target population (Alqathama et al., 2020). Briefly, they have calculated the sample size by using an online sample calculator (Raosoft). A single population proportion formula was used with a 95% confidence interval, 5% margin of error among 300 patients with type 2 diabetes in Makkah city (Alqathama et al., 2020).

In current study 383 patients have participated in our study after providing a written consent for the voluntary participation.

Inclusion Criteria& Exclusion Criteria

Inclusion Criteria

- People who live in Makkah and are 15-55-year-old.

Exclusion Criteria

- Young patients less than 15 years,
- Elderly more than 55

N.B: People who did not follow an inclusion criterion, excluded from the study.

Validation of the questionnaire.

The questionnaire of the study (see appendix 1 and 2), is adapted from a study conducted on children Jordanian population of a similar topic published by (Abu shoufa et al., 2012).

Data collection and analysis

Data collected via an online questionnaire that was shared through social media as well as paper questionnaire, which was filled by patients visiting the dental clinics in the primary health care centers (PHCC) in Holly Makkah city with cooperation of their team work.

Both paper and online data collected and analyzed by a professional statistician using SPSS Version 21

Literature Review

Definition of RAU:

Canker sores or aphthae are other words to call recurrent aphthous stomatitis or ulceration. Is a common inflammatory condition of unknown etiology. It recognized by its painful episode of recurrent ulcerations in the oral mucosa with red halo usually starting before 40 years of age (Scully, 2006).

The term aphthae is derived from a Greek word aphthi, which means “to set on fire” or “to inflame” and they have been first used by the philosopher hippocrates to describe RAU pain (Scully, 2006).

Types of RAU

Recurrent aphthous ulceration has three different clinical types: minor aphthous, major aphthous, and herpetiform ulcers (Natah al., 2004).

-1Minor RAU (MiRAU)

Miculiz's aphthae, is another name of minor aphthous which is the most common aphthous type. It affects about 80% patients and characterized with painful oval or round shallow ulcers, with uniform borders, and usually less than 10 mm in diameter. It also has a characteristic appearance as gray-white pseudomembrane surrounded by a thin red borders (Natah al., 2004).

MiRAU usually occurs on non-keratinized buccal, labial surface and the floor of the oral cavity, but rarely affects the keratinized gingiva, palate, or dorsum of the tongue. MiRAU is the most common form of childhood RAU. These lesions recur at different frequencies (every few years), do not leave scar and take one to two weeks to disappear (Natah al., 2004).

-2Major RAU (MaRAU)

It is also called "periadenitis mucosa necrotica recurrence" and affects 10% of RAU patients. They show similar legions appearance to the minor type, however, they are larger than 10 mm in diameter, and they occur as single or multiple lesion and very painful. MaRAU reported to be seen in the inside surface for the lips, soft palate, and fauces. Although they can affect any site inside the oral cavity, MaRAU takes for up to two months and often heals with scarring. Usually, their onset is after puberty (Natah et al., 2004).

-3Herpetiform (HuRAU)

It is characterized by multiple recurrent crops of small, painful ulcers; spread widely and may distributes all over the oral cavity. Up to 100 ulcers may be present at once, each is measuring 2-3 mm in diameter, although they tend to fuse, to produce large irregular ulcers. However, they heal without scar formation

within 7-10 days. Women are most affected with HuRAU and has a later age of onset than other types of RAU. They appear on both non-keratinized and keratinized mucosa unlike minor and major aphthae, which are limited to non-keratinized mucosa.

The hallmark of RAU is recurrence, and patients generally present with only one variant of the disease. However, two forms may coexist, or a change in clinical expression seen with time (Natah et al., 2004).

Classification of patients with RAU.

Patients can be classified characteristics as follows;

Type A: Brief episodes occurring few times yearly and its pain can be tolerated. Predisposing factors should be identified and controlled e.g. avoiding local trauma, using a soft toothbrush, providing brushing instructions. Also, it is advisable to avoid hard foods (e.g., hard toasted bread), all types of nuts (such as walnuts, hazelnuts etc.), chocolate, acid beverages or foods (such as fruit or citrus juices, tomato), salty foods, very spicy food (pepper, curry) and alcoholic and carbonated beverages (Slebioda & Bobkowska, 2019).

Type B: Episodes, which occur on monthly basis, lasts 3-10 days, with a pain that might causes the patient to modify habits of hygiene and diet. Predisposing factor of this type, which are identified as follow; (trauma, stress, diet, hygiene, etc.) should be commented with the patient and controlled (Slebioda & Bobkowska, 2019).

Type C: The episodes are very painful, with chronic aphthae. One lesion develops while the other heal, not responding to topical treatment. In such cases, systemic therapy can be suggested (Slebioda & Bobkowska, 2019).

Epidemiology of RAU

Twenty percent of the general population estimated to suffer from RAU at some time of life (He & Shao, 2021). In childhood, reported that RAU is the most common form of oral ulceration. Many studies showed that RAU is a disease of childhood (Zhengyang et al., 2005) and second decade is its peak of age. One third of school-age children may have a history of RAU. (Zhengyang et al., 2005). While some authors reported that the prevalence of RAU is about 17% while others stated it to be around 45% (Zhengyang et al., 2005). Thirteen to fourteen % of RAU lesions appear before the age of 10 years, 46% between 11 - 20 years and 24% of cases between 21 and 30 years (Zhengyang et al., 2005).

RAU etiopathogenesis is still lacking as they are multifactorial, with predisposing genetic and immunological changes factors aggravated by a range of environmental factors (Siml et al., 2018).

Factors Predisposing to RAU

Family and Heredity

Genetic factors are considered in RAU because of its recurrence and more than 42% of RAU patients, have reported RAU incidence in relatives (Natah, 2001). Furthermore, with a positive family history, patients develop RAU with severe attacks in younger age (Natah, 2001). If both parents experienced RAU conditions, incidence of having RAU is increased by 90% and 20% than that when neither parent developed RAU with high correlation of RAU twins patients. Variability in host susceptibility is different, dependent on environmental factors (Natah, 2001).

Studies on the association of RAU and the subtypes of the genetically determined human leukocyte antigen is linked to many genetic factors. For example, HLA subtypes is reported in RAU patients, but not its antigen (Natah, 2001).

Socioeconomic Status:

As a study reported by (Bessa et al., 2004), investigated the level of the socioeconomic factor in the presentation of RAU lesions the students of two schools with different socioeconomic levels. Nineteen% was the prevalence in the school with of a high level, 12% only was in the school low socioeconomic level. Also reported that, no significant association between the prevalence of RAU lesions and socioeconomic level (Bessa et al., 2004).

These lesions are less popular in black populations and can appear at any time of the year. Although with a slight predominance during spring and autumn (Zhengyang et al., 2005).

Food Hypersensitivity

Some foods cause ulcers initiation, such as gluten chocolate, nuts, cheese, azo dyes preservatives and flavoring agents (Swain et al., 2012). There are no association of RAU with the "3 commonly allergenic food items" i.e. tomatoes, strawberries and walnuts (Natah, 2001). An improvement of RAU conditions can be achieved by using gluten-free and gluten-supplemented diets, as demonstrated by a study that 5 out of 20 patients with- RAU (without celiac disease) experienced complete treatment of RAU when restrict their diet to gluten-free food (Scully & Felix, 2005). Some studies showed that no significant difference in the incidence of atopy among RAU patients compared with normal population, while others reported increased incidence of atopy in RAU patients (Natah, 2001).

Studies have shown a significant increase in the antibodies against cow's milk proteins in patients with minor RAU and in patients with other ulcerative lesions of the mouth. Furthermore, other studies have demonstrated that feeding newborn babies with cow milk may results in increased the risk of developing cow's milk intolerance. On the other hand, breastfeeding is associated with low incidence of RAU (Besu et al., 2009 and Maria & Gifrina, 2019).

Hematinic Deficiencies

Several studies have shown that RAU patients have decreased levels of iron, vitamin B12 and foliate found (Natah, 2001, Koybasi et al., 2006 and Chiang et al., 2019). These deficiencies of were present in about 20% of children aged 5-17 years with RAU (Natah, 2001).

Vitamin D levels

Studies have shown that vitamin D levels is decreased in RAU patients and vitamin D supplementation would help in the treatment of RAU (Oztekin et al., 2018).

In addition, it has been reported low level of vitamin D in People with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome. However, with replacement treatment reduce the typical PFAPA episodes and their duration (Oztekin et al., 2018).

Zinc Deficiency

Low levels of serum zinc are reported in patients with RAU, thus supplementation of Zinc sulphate is importance for RAU patients. On the other hand, normal serum copper level is reported in RAU patients (Natah, 2001). Serum calcium, magnesium and phosphorus found to show an increase in RAU, but not in a statistically significant manner (Koybasi et al., 2006).

Age and Sex

It is scientifically reported that 40% of children aged 15 years or less had a history of RAU and this prevalence increases with age (Natah, 2001).

In Swedish population, the onset age of RAU is 30 in 60-85% of patients (AlKassar et al., 2019).

No men developed RAU after the age of 50 whereas 10% of women had their first attack of ulceration between 50- 60. Also, female's children were slightly more predominant. But in age 2-80 male patients affected with RAU than more females in (Natah, 2001 & McCullough, 2007).

RAU and Hormonal Changes

About the association between RAU and menses, studies demonstrated that young women had recurring RAU at the onset of menstruation (Natah, 2001), McCullough, 2007 & Reza, 2018). While during pregnancy, complete reduction of RAU has been reported. However, increased RAU incidence has been shown in the puerperium (the period following childbirth). On the other hand, there is no association reported between RAU and menopause (Reza, 2018).

Environmental Factors

.Stress

An association of RAU and anxiety and stress was reported by Natah (2001) & Gallo et al., (2009) studies. It was described that higher level of psychological stress has been manifested among RAU patients (Gallo et al., 2009). Another study found that, rest can decrease RAU frequency (Reza, 2018). The high salivary serum cortisol concentrations and trait anxiety levels state in RAU, were significantly higher, than those in control group (Albanidou-Farmaki, 2008). Collectively these data conclude that stress increases the pathogenesis of RAU (Albanidou-Farmaki, 2008). Additionally, the likelihood of initiation of new RAU is increased three times in stressful life events among patients with history of RAU (Albanidou-Farmaki, 2008). Studies on the types of stress have shown that there is a significant association of mental stressors with RAU than physical stressors (Laura et al., 2012). However, this associated with RAU onset not duration (Laura et al., 2012). Other studies, on the other hand, didn't find an association between anxiety, depression, psychological life stress and recurrences of RAU (Swain et al., 2012). Especially in children within the age group of 15-16 years, there was no significant association could be found between stress and prevalence of RAU (Swain et al., 2012).

Local Trauma

Some patients with RAU are more likely to develop aphthae at sites of trauma compared to controls (Natah, 2001). It is suggested that this effect is mediated by histamine, a hypothesis also supported by similar work conducted in patients with Behcet's syndrome. However, the association of trauma from sharp foods, coarse tooth brushing and dental treatment and RAU is still unclear (Natah et al., 2004, Swain et al., 2012 & Koray & Tosun, 2019).

Some studies suggested that mechanical injuries of the oral mucosa might cause RAU ulceration. However, it was not clear if the mucosal sensitivity to mechanical injury, in RAU patients is due to their impaired wound repair, mobility of mast cells and histamine release (Koray & Tosun, 2019).

Smoking

Several reports documented the negative association between active smoking and the occurrence of RAU (Natah, 2001, Ciçek, 2004 & (McCullough, 2007). This negative association was also reported with the use of smokeless tobacco (Chewing tobacco and snuff) (Tuzun, 2000 & Natah et al., 2004).

It was reported that Nicotine prevent the development of RAU, by increasing mucosal keratinization, which protect it against trauma by unknown process (Sawair, 2010). A study reported that a regular dose with high levels of consumption of nico

Infectious Factors

Bacterial Agents

Studies reported no significant association of H pylori and RAU. On the contradictory, other reports have demonstrated that H. pylori was detected in RAU patient but has no association between RAU lesions and H pylori infection (Shimoyama, 2000).

High antibodies against streptococcal strains was found in RAU patients (Riggo et al., 2000) & (Natah, 2001).

Viral Agents

RAU is associated with different types of viruses, such as simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), epstein barr virus (EBV) and human herpes virus-6 (HHV-6) (Meyding-Lamadé & Strank, 2012). Except for adenoviruses in RAU which has no antibody response (Natah, 2001).

RAU patients have more IgM against cytomegalovirus and varicella-zoster virus (Natah, 2001). Human herpes virus-6 (HHV-6- DNA) detected in six of 21 RAU lesions by using PCR, whereas VZV-DNA and CMV-DNA not detected in any RAU samples (Natah et al., 2004) & (Ito et al., 2019).

Oral ulcers in RAU and/or Behçet's disease (BD) patients and VZV could not be can't be detected (Natah, 2001)

Human herpes virus-6 (HHV-6- DNA) detected in six of 21 RAU lesions by using PCR, whereas VZV-DNA and CMV-DNA not detected in any RAU samples (Natah et al., 2004) & (Ito et al., 2019).

Coronavirus Disease 2019 (COVID 19)

While recovering from COVID-19 pandemic, little is known about the association of COVID -19 and RAU. However, a studies showed that lesions like aphthous ulcerations in RAU Patients. That might related to the process of neutrophil chemotaxis, stress, and immunosuppression, which can cause this condition to, affects COVID-19 patients. In care guidelines has been reported, 21 laboratory-confirmed COVID-19 patients with RAU characteristics (Gizem& Erbas, 2022). COVID-19 can lead to respiratory failure linked to acute respiratory disease syndrome. A relationship of RAU and COVID-19 is unclear, the segment of the population affected by the most severe forms of COVID-19 is usually affected by arterial

hypertension and heart disease. There are many other research ideas that will allow us to conduct further studies next with the aim of better clarifying any therapeutic strategies to defeat COVID-19 and definitely RAU is playing a role for medical scientists (Ardes et al., (2020).

Diagnosis of RAU

The diagnosis of RAU based on the history and clinical criteria, RAU cannot be identified by the first attack without laboratory investigations, but a positive family history of the disease can help in the diagnosis (Scully et al., 2003)& (Scully & porter, 2008). Although the Etiology of RAU is unknown, history and physical examination can help in exploring any systemic secondary cause such as diarrhea in case of Crohn's disease or ulcerative colitis. For gluten-sensitivity, Malaise and malabsorption are associated (Scully & porter, 2008). Presences of ulcer in genital area, could lead to of Behçet's disease as a cause. Urethritis or pain or swelling of joint, could raise possibility of Reiter's syndrome. For HIV infection, history, examination and medications must be reviewed (Scully, 2006).

Toothpastes, containing sodium lauryl sulfate, may cause RAU; plus some studies advice for the usage of the product to stop RAU (Ozden & Selcuk, 2021). Very importantly, three weeks or more ulcer duration, needs careful evaluation for cancer and infection probability (Sunday& Akintoye, 2014). Cancers are suspected with (Scully& Felix, 2005) when swelling, a red or white lesion, leukoplakia and cervical lymphadenopathy are included, lichen planus, pemphigus, or pemphigoid, are suspended when chronic ulceration found (Sunday& Akintoye, 2014). Whenever, ulcers are not ovoid or round shape or clearly defined borders patients can be reassured (Natah., et al. 2004),(Scully, 2006)& (Sunday& Akintoye, 2014).

Treatment of RAU

Having the medical history and recognizing the associated factors, RAU can be controlled by deceased wrong habit, change the way of oral care, and control the diet, and then state the treatment of the choice; mouthwash or oral gel (Tarakji et al., 2015). Pain control can be subscribed especially for children (Anne et al., 2009) (Altnburg et al., 2014). It must be noticed that RAU will continue to recur until systemic cause or factors treated of decreased (Anne et al., 2009) (Altenburg et al., 2014).

Topical Agents

RAU can be treated topically, most of which are effective and safe but they are rinsed away from mucosa (Narah et al., 2004).

When the area is dry, topical agents are applied in a small amount and patient is asked to stop eating or drinking for at least 30 minutes after application (Natah et al., 2004).

Mouthwashes

Secondary bacterial infection is decrease by using (0.2%) chlorhexidine gluconate before meals. For pain relief, (Difflam) is used and for plaque management with tooth brushing trauma (Anne et al., 2009).

Chlorhexidine decreased the number of ulcers when used three times a day but other studies mentioned that it had no any effect on RAU (Natah et al. 2004).

For herpetiform ulceration, tetracycline is the product of choice, but not for young children because it causes intrinsic discoloration for dentine during its development when tetracycline is ingested (Anne et al., 2009)& (Vijayabala et al., 2013).

In (Abbasi et al., 2016). Amlexanox and Adcortyl reported as effective treatment for Aphthous ulcers by reducing lesions size and relieving pain.

Topical Steroids

Pain relief and shortening RAU duration, is achieved by a topical corticosteroid use, such as 2.5 mg hydrocortisone succinate (Corlan) drop when applied close to RAU or using of a coat paste containing 0.1% triamcinolone (carboxymethylcellulose). But this is not effective for sever type of RAU (Anne et al., 2009).

The inflammatory process associated with the formation of aphthae is limited by using a topical corticosteroid. Direct action of the corticosteroids on T-lymphocytes might occur and the response of effectors cells to precipitants of immunopathogenesis is altered (Natah et al., 2004) & (Liu et al., 2012).

Protective Pastes (Covering Agent)

Carboxy methylcellulose gel (Orabase) squibs with cotton swab or a clean finger before eating after drying the area but, this is difficult in young children for this thirty Albino Wister male rats were selected. Rats were sacrificed on three, six, twelfth day nanosponges used to apply the Benzydamine hydrochloride (Shaji & Vaswani, 2021).

Topical Analgesics

Topical analgesic gels containing lignocaine or salicylate applied to ulcers by a cotton swab, but this is difficult in young children. Benzydamine hydrochloride mouth washes are useful for older children with RAU before eating, and spray forms are for younger children (Sharma& Garg, 2018).

Systemic Agents

Systemic Steroids

In severe cases with constantly recurring ulcerations, topical treatment of RAU may not be enough. In these cases, systemic medications are better to use. Despite many medications tried over the last years, oral prednisolone is still the most popular one (Natah et al., 2004).

There is a need to consider supportive treatment for children with severe aphthous ulceration, which fortunately is rare compared with less aggressive forms. Liquids advised maintain the fluid balance and having a rest is often helpful. Sugar free analgesics such as paracetamol elixir may be required and, if there, disturbed sleep, a sedative such as, promethazine, used as a short-term measure. If home supportive measures are not effective, hospital admission may be required for a short period, particularly if systemic steroids considered (Anne et al., 2009). Results remain not confirmed as systemic treatment for RAU. Which represented the poor ways of trials, drugs. Because of their complex in nature. Thalidomide for example, is an effective systemic drug, although it is not safe.

In patients with RAU, both enzymatic and nonenzymatic antioxidant defense systems are impaired, in another study. Results show that RAU causes peroxidation reactions in both plasma and erythrocytes. In addition, reported the supplementation with antioxidants such as selenium and ascorbic acid 26–28 may strengthen blood antioxidant defense and provide more benefit (Cimen et al., 2003)

Data obtained from studies show that in RAU, the relationship between free radical mechanism and RAU still needs to study in many respects (Cimen et al., 2003) & (Rezaei & Soltani, 2018).

The potential benefit of the drug weighed against potential side effects and the use of systemic drugs should be with great care (Cimen et al., 2003).

Low level laser technology (LLLT)

A study about using LLLT, to gain its properties including, its modulating action in the inflammatory processes, pain relief and restore functions showed that LLLT is effective in pain control and assists in healing of wounds. But still need for future studies in different parameters for the use of LLLT in RAU (Anand et al., 2013).

Natural Therapeutics

*Propolis

Which is flavonoid-containing food supplement, help healing RAU by their antimicrobial activity, freeradical-scavenging ability, activation of immune system. By the regular take of five hundred milligrams capsule of propolis, patients will have low RAU attack, and that improve their quality of life. If they avoid certain, trigger foods or activities (Samet, Laurent, & M, 2006).

**-Aloe Vera (A.V)

In a study evaluating the administration of A.V Gel on oral cavity of RAU patients, minor healing started (Atiba et al., 2011). A.V gel, is a plant have great anti-inflammatory and immuno-stimulation effects, which is of good in wound healing (Atiba et al., 2011). A.V. 2% oral gel decreased the pain score and size of wound, in a short healing period. By its ability to modulate the immunity, healing properties measured by RAU lesion size and decreases healing time to less than seven days (Atiba et al., 2011).

Results

The current study is the first study in Makkah to estimate the prevalence of RAU. It was a cross-sectional epidemiological survey.

Questionnaires filled 98.5 %, which is considered a high response rate.

The samples were targeted at City of Holly Makkah population 345 (86.25%). Throughout online survey (86.25%) and the remaining participants are those whom visited some dental clinics in the Makkah. In a point of time between Mar-April 2022.

1.Demographic and general information of the participants:

- A total of 383 people who fully answered the questionnaire (Table 1). Most of the participants were female (76.5%) and male were only (23.5%).
- The mean age of participants was 37.79 (11.3) years and 345 (86.25%) filled the questionnaire online, while the remaining at clinic during their routine dental visits.
- More than half of the participates were college graduates(64.7%) and non-smokers (86.4%). About 60.6% of the participants are healthy and don't take medicine at a daily basis.
- In a high percentage about 86.4% of participants which were nonsmokers, found to be more prevalent than smokers 13.6%. Lastly, the most used type of tooth brush by the participant was the medium brush (58.8%), followed by soft brush (37.4%) and finally coarse brush (3.7%). (Table 1)

		Mean (SD)	N	Valid N %
Do you agree to participate in the study?	Yes		383	98.5%
	No		6	1.5%
Age		37.7 (10.6)		
Age groups	Less than or equal to 25		41	13.5%
	26 - 40		151	49.8%
	41 - 55		99	32.7%
	More than 55		12	4.0%
Gender	Female		280	76.5%
	Male		86	23.5%
Educational level	Uneducated		0	0.0%
	Elementary		8	2.1%
	Medium		12	3.1%
	Secondary		76	19.9%
	College		247	64.7%
	Others		39	10.2%
Are you a smoker?	Yes		49	13.6%
	No		312	86.4%
The type of toothbrush you use	Soft brush		140	37.4%
	Middle brush		220	58.8%
	Coarse brush		14	3.7%
Do you take medicines on a daily basis for a long time?	Yes		69	39.4%
	No		106	60.6%

Table 1: Demographic and general information about study participants

2. Participants knowledge and experience of RAU

- More than 80% of the participants of this study have suffered from RAU, among which 61.7% have suffered from RAU during the past year (Table 2).
- Participants showed different incidences of RAU condition last year, some suffered from RAU twice (36%), once (31.5%), three times (15.7%), four times (5.1%) , five times (3.9%) or oven more. The mean age of RAU first incidence is 18.9 years old.
- The age of group of 11-20 years old showed highest percentage (48.5%) and the lowest percentage was shown by the age group of 30 or more age group.
- Our data also showed that RAU can run in families as 65.7% of participants who suffer from RAU reported that their family members also suffer from RAU(Table:2).

		N	Valid N %	Mean (SD)
Recurrent Aphthous Ulceration (RAU) is:	Bacterial infection	183	48.8%	
ulcers that appear inside the mouth or in	Biting the Tongue or cheek while eating	76	20.3%	
the area above the larynx, due to a break in the oral mucous membranes	I don't know	116	30.9%	
Have you previously suffered from RAU?	Yes	298	80.1%	
	No	74	19.9%	
During the past year, have you experienced RAU even once?	Yes	193	61.7%	
	No	120	38.3%	
If yes, how many times during the past year?	Once	56	31.5%	
	Twice	64	36.0%	
	Three times	28	15.7%	
	Four times	9	5.1%	
	Five times	7	3.9%	
	6 times	3	1.7%	
	More than 6 times	9	5.1%	
	Can't recall	2	1.1%	
Mean age of first ulcer experience?				18.9 (11.3)
How old were you when RAU started with you?	10 years or less	39	22.8%	
	11 - 20	83	48.5%	
	21 - 30	26	15.2%	
	More than 30	23	13.5%	
Do other members of your family suffer from RAU?	Yes	195	65.7%	
	No	102	34.3%	

Table 2: Perspective of study participants on personal experience with aphthous ulcer

3. Participants presentation of RAU and mode of Management.

- When we asked participants if they feel itching or any different feeling before or after the appearance of the RAU, about 50% reported the difference before and 50% after (Table 3).
- When participants were asked to rank the pain severity during RAU episodes on a scale of 0-10, 39 (14.6%) reported pain of 3 or less degrees, 142(53.2.0%) reported pain of 4-7 degrees and 86 (32.2%) reported pain of more than 7 degrees. Moreover, it is shown with participants who reported general fatigue during RAU episodes 37(43.0%), as shown in (Table 3).
- One third of participants reported that they are suffering from problems such are sores on the skin, itching or inflammation in the eyes, pain in the joints, and most of them reported GIT effect on RAU, while 34% of them reported the association with general fatigue (Table 3).
- Hematologic status in patients with RAU, 104 patients (35.6%%) were iron deficiency anemic and 83(28.2%) showed low serum vitamin B12(table 3).
- As the presented management modalities of RAU, 173 (61.6%) tolerate the ulcer with no medications, of those who treated RAU 94(33.5%) have used pain relievers and antibiotics and 64(22.8%) used local steroids (Table 3).

		N	Valid N %	Mean (SD)
How long does it take for RAU to disappear from the mouth?	Less than 7 days	199	66.3%	
	7-14 days	93	31.0%	
	14-30 days	5	1.7%	
	More than a month	3	1.0%	
Before the appearance of the RAU, do you feel a slight itching or any different feeling in the area where the RAU appears?	Yes	127	44.1%	
	No	161	55.9%	
After the RAU disappears from the mouth, does it leave a trace or a scar?	Yes	31	10.7%	
	No	260	89.3%	
Mean rate of pain associated with the ulcer?				6.2 (2.4)
What is your estimate of the amount of pain associated with RAU out of 10 degrees (0 the lightest degree and 10 the most severe)?	3 or less	39	14.6%	
	4 - 7	142	53.2%	
	More than 7	86	32.2%	
In addition to RAU, do you suffer from problems in other areas (sores on the skin, itching or inflammation in the eyes, pain in the joints)?	Yes	84	28.4%	
	No	212	71.6%	
In addition to RAU, do you suffer from diseases in the digestive system, such as ulcerative colitis?	Yes	50	17.1%	
	No	243	82.9%	
In addition to RAU, do you suffer from general fatigue and pallor in your face?	Yes	100	34.0%	
	No	194	66.0%	
In addition to RAU, do you suffer from iron deficiency anemia?	Yes	104	35.6%	
	No	188	64.4%	
In addition to RAU, do you suffer from anemia due to vitamin B12 deficiency?	Yes	83	28.2%	
	No	211	71.8%	
What do you do when you develop RAU?	Tolerate the ulcer with no medications	173	61.6%	
	Pain relievers and antibiotics	94	33.5%	
	Local steroids (cortisone)	64	22.8%	

Table 3: Perspective of study participants on ulcer clinical presentation and modes of management

4. Perspective of study participants on ulcer associated conditions:

- Stress associated with RAU in 124(41.8%) of the participants, physical exhaustion 89(30%), medications 27(9.1%) and about 162(54.5%) not correlate the onset of aphthous ulcer in their mouth with any factors (Table 4)
- Effect of COVID 19 on the RAU nature, 192(88.5) reported no effect on RAU (Table 4).

- Eating certain types of food in association with RAU, 106(58.2%) reported with Sour food, hot food by 57(31.3%), spicy food by 84(46.2%), hard foods by 32 (17.6%), cinnamon and it's derivatives 11 (6.0%) (Table 4).
- Girls with menstruation36 (14.4%) correlated the occurrence of RAU to menstruation periods (Table 4).

		N	Valid N %
Do you notice that there is a correlation between the appearance of RAU and any of the following things?	Periods of psychological stress (exams, problems)	124	41.8%
	Periods of physical exhaustion	89	30.0%
	After taking a medication	27	9.1%
	There is no correlation	162	54.5%
Is the appearance of RAU associated with eating certain types of food?	Yes	182	61.1%
	No	116	38.9%
If the answer is yes, please specify the types?	Hot foods	57	31.3%
	Spicy foods such as peppers	84	46.2%
	Sour foods	106	58.2%
	Hard foods	32	17.6%
	Cinnamon and its derivatives	11	6.0%
Girls only. Have you noticed a link between the appearance of the RAU and the menstrual cycle?	Yes	36	14.4%
	No	214	85.6%
Have you contracted COVID-19?	Yes	137	47.4%
	No	152	52.6%
Was the infection with the virus associated with the emergence of RAU? And when?	Yes, the ulcer developed before COVID-19 infection	3	20.0%
	Yes, the ulcer developed after COVID-19 infection	10	66.7%
	No, they were not related	2	13.3%
What are the effects of COVID-19 infection on the ulcer?	Increased pain severity	7	3.2%
	Decreased pain severity	5	2.3%
	Increased ulcer duration	10	4.6%
	Decreased ulcer duration	3	1.4%
	No effect	192	88.5%

Table 4: Perspective of study participants on ulcer associated conditions

5: RAU associated factors.

- Non-smoker were the most participants who reported longest RAU duration in a trend association close to significant with P= 0.096(Table 5).
- Same trend association with RAU duration most of girls reported long duration of 7-14 days with p= 0.08(Table 5).

		How long does it take for RAU to disappear from the mouth?								
		< 7 days		7-14 days		14-30 days		> 30 days		p (X^2)
		N	N %	N	N %	N	N %	N	N %	
Are you a smoker?	Yes	17	9.3%	13	15.3%	2	40.0%	0	0.0%	**0.096 (6.3)**
	No	165	90.7%	72	84.7%	3	60.0%	3	100.0%	
Girls only. Have you noticed a link between the appearance of the RAU and the menstrual cycle?	Yes	19	9.5%	15	16.1%	2	40.0%	0	0.0%	**0.08 (6.7)**
	No	180	90.5%	78	83.9%	3	60.0%	3	100.0%	

Table 5(a): RAU associated factors.

6: RAU associated factors.

- Participants who reported long duration of RAU were those who reported about 50% of taking medications on daily basis.
- 34% of participants reported the association with general fatigue in a statistical significance with p= 0.023(Table 6).

		What is your estimate of the amount of pain associated with RAU out of 10 degrees?						
		3 or less		4 - 7		More than 7		p (X^2)
		N	N %	N	N %	N	N %	
	No	31	88.6%	113	85.0%	73	90.1%	
Do you take medicines on a daily basis for a long time?	Yes	5	27.8%	33	37.1%	24	46.2%	0.33 (2.2)
	No	13	72.2%	56	62.9%	28	53.8%	
Girls only. Have you noticed a link between the appearance of the RAU and the menstrual cycle?	Yes	3	7.7%	16	11.3%	14	16.3%	0.34 (2.2)
	No	36	92.3%	126	88.7%	72	83.7%	
Which types of food are associated with development of the ulcer?	Hot foods	7	30.4%	26	31.7%	17	30.9%	0.86 (5.4)
	Sour foods	11	47.8%	48	58.5%	34	61.8%	
	Hard foods	3	13.0%	12	14.6%	14	25.5%	
	Cinnamon and its derivatives	2	8.7%	4	4.9%	2	3.6%	
	No	31	81.6%	117	84.2%	71	83.5%	
In addition to RAU, do you suffer from general fatigue and pallor in your face?	Yes	13	33.3%	35	25.4%	37	43.0%	0.023* (7.7)
	No	26	66.7%	103	74.6%	49	57.0%	
	No	23	60.5%	106	76.3%	58	68.2%	

Table 6(b): RAU associated factors.

7. RAU associated factors.

About 50% of the Participants who suffered from RAU, were those were not contracted with COVID19; in a statistical significance value of P= <0.001.(Table7).

		Have you previously suffered from RAU?				
		No		Yes		p (X2)
		N	N %	N	N %	
Have you contracted COVID-19?	Yes	0	0.0%	129	43.3%	<0.001* (49.0)
	No	74	100.0%	169	56.7%	

Table 7©: RAU associated factors.

Discussion

1. Prevalence of RAU in Makkah population

A wide variation in the prevalence of RAU was reported by different studies in the literature. Leonardo (2010) reported prevalence of 78.67% in Brazil (Leonardo et al., 2010). In the USA, RAU prevalence is

0.89% (Chattopadhyay, 2011), about 2% of Swedish adults suffer from RAU as (AlKassar et al., 2019). Whereas in Turkey, (Çiçek, 2004) found that the prevalence of RAU in Turkish population, aged 10-50 years was 2.7%. RAU prevalence in Jordanian is 0.89% and that reported by (Shulman & M, 2004). Whereas Safadi (2009), reported 78% RAU in same Jordanian, but were dental adult patients (Safadi, 2009).

In Saudi Arabia the prevalence of RAU in Saudi dental adult patients reported as 0.4% (AL-Mobeeriek, 2009). For Makkah population, our study showed prevalence of 84.80% higher than the prevalence reported by (Souza et al., 2017) in Brazil with the prevalence of (24.9%). The annual prevalence reported by (Shulman, 2004) in Jordanian was 19.8%, close to prevalence reported by (Abu Shoufa et al., 2012) in the same country of (17.0%).

The variation may be related to different age groups, sample size, sampling method, type of sample, different lifestyle between different populations, and different inclusion criteria, for example, in (Majorana et al., (2010), the sample was limited to dental clinic attendees similar to those in (Safadi, 2009) & (AL-Mobeeriek, 2009).

2. Participants knowledge and experience of RAU

In this study, about 400 (98.5%) of participants reported that the amount of RAU related pain ranged (on a scale of 0-10) between 3 or less degrees, (14.6%) pain of 4-7 degrees (53.2.0%) reported and more than 7 degrees (32.2%) reported by 86 participants with p value (0.096) which is close to significant value. Females were higher than males in the prevalence of RAU, but not in a statistically significant manner (23.5%) males vs. 76.5% females .The higher prevalence of RAU in females is documented by reports in previous studies conducted on adult groups (Cicek et al., 2004). Plus, a study was conducted on a population aged 2-80 years reported a higher RAU in 10-30 years (McCullough et al., 2007). Another study reported in population aged 10 – 50 years by (Cicek et al., (2004), with higher prevalence on samples 10-30 years.

3. Most common associated factors as the Participant's Answers as follow;

1- Stressful life events increased the chance of RAU, with higher mental than physical stressors (Huling et al., 2012), all with regards to the Stratification not with duration of RAU (Huling et al., 2012). Psychological stress in RAU have a role in its manifestation Gallo et al., (2009). Our study showed that 41.8% of participants correlated the onset of RAU to a periods of stress. While Leonardo reported 10.5% (Leonardo et al., 2010). Other study by Souza et al., (2017) reported (24.9%) stress related RAU patients, Safadi (2009) reported 78 %of subjects experienced recurrent aphthous ulceration with association to stress in (50%) of participants (Safadi, 2009). Which was similar results with (McCullough et al., 2007). Cicek et al., (2004) reported 6.9% RAU patients linked there onset with the stress in the age of 10-50 years (Cicek et al., (2004).
2- Studies demonstrated that young women had recurring RAU at the onset of menstruation (Reza, 2018). According to that, we found in our participants with menstruation, (14.4%) correlated the occurrence of RAU to menstruation periods.
3- With Physical exhaustion (30%) was reported. But Safadi reported (68%) no association with tiredness (Safadi, 2009).
4- In regards to general fatigue (34%) associated to RAU with a statistical significance of p= 0.023 (7.7).
5- Long term use of medications may be associated with RAU as an answers of (9.1%). While about (54.5%) did not correlate the onset of aphthous ulcer in their mouth with any factors.
6- Our study showed that the onset of RAU was correlated with eating certain types of food, and that was shown in more than half of the samples reporting by (61.1%); in which (58.2%) correlated the attack of RAU after eating (sour food), (31.3%) correlated to hot food, (46.2%) mentioned that spicy food had an effective role in initiating ulcers with a value close to significant of p= 0.08 (6.7) which needs more researches on it to be proven. Similar to (Leonardo et al., 2010) which reported that (28.2%) the diet as an associated factor. While Safadi reported 85% no association with types of food ingested (Safadi, 2009).
7- Many reports documented that trauma from tooth brushing might play a role in triggering aphthous ulceration in some patients (Abu Shoufa et al., 2012). Our study showed (58.8%) using of medium toothbrush followed by (37.4%) soft brush type of tooth brush, finally coarse brush

(3.7%); which may cause trauma that initiates RAU. Leonardo reported (19.2%) trauma from tooth brush (Leonardo et al., 2010). Whereas, a significant relationship was found between RAU and tooth brushing by (Abu Shoufa et al., 2012).

8- Several reports documented the negative association between active smoking and the occurrence of RAU (Natah, 2001 and McCullough, 2007). We did not find relation between RAU and negative smoking with a trend value of p=0.096 (6.3). which needs further study to investigate an accurate result. In the literature, low prevalence of RAU in smokers reported by (McCullough et al., 2007) & (Leonardo et al., 2010); they reported that smoking was not associated with RAU in a statistical significance of (p>0.05). While Souza et al., (2017) reported that Smoking has protective effect on RAU.

9- With respect to family history, our data also showed that RAU can run in families; as 65.7% of participants who suffer from RAU reported that their family members also suffer from RAU. No statistical significant relation was noted between the RAU prevalence and family history of RAU. However, (65.7%) of participants having RAU reported that other family members have suffered from recurrent aphthous ulcerations. This finding is similar to Koybasi et al., (2006) & Compilato et al., (2010) results. McCullough (2007) reported 67% of samples 2-80 years have positive family history with statistical significance of (P<0.001) McCullough et al., (2007) & Eris et al., (2007) showed the same finding in 70.6% RAU with positive family history.

10- About 17.1% with gastrointestinal tract diseases, correlate the onset of aphthous ulcer in their mouths with GIT.

11- A studies showed that lesions might related to the process of neutrophil chemotaxis, stress, and immunosuppression can cause RAU. A statistically significant relation was noted between RAU incidence and Covid 19 with p= < 0.001* (49.0).

12- There are different conclusions about the link between RAU and the hematinic deficiencies as associated factors in development of RAU. A study reported a relation between B12 and RAU diagnosis but not in a statistically significant manner (Abu Shoufa et al., 2012). However, our data reported (35.6%) were anemic and (28.2%) showed low serum vitamin B12. In literature, another study showed that RAU is linked to iron deficiency anemia, but not in a statistical significance

(Koybasi et al., 2006). In a case control study conducted on a sample aged 10 – 66 years and found that 12 patients with RAU who had low B12 and RAU occurrence (Koybasi et al., 2006). Moreover, Piskin et al., (2002) screened 35 cases; and found that 8 of them have iron deficiency anemia with significant (p=0.005). And 61 RAU patients 5 of the cases with had B12 deficiency (Piskin et al., 2002). A study conducted on Jordanian population showed that 7% have low vitamin B12 and 4% have iron deficiency (safadi, 2009). On the other hand, Koybasi et al., (2006) did not find a significant correlation between RAU and hemoglobin. According to Burgan et al., 2006), 20 of RAU patients were anemic whereas 11 of RAU patients had iron deficiency anemia as reported by Compilato et al., (2010) reaching the level of significance.

4. Participants presentation of RAU and mode of Management.

Currently, the gold standard treatment is by management of the recognizing associated factors, eliminating bad habit, changing oral care habit, and correcting or to modify diet. After that, the use of topical therapy of corticosteroids in mouth wash or in oral gel are considered (Tarakji et al., 2005). Our study showed that more than half of participants tolerating their ulceration (61.6%) whereas (33.5%) of participants using pain relief and antibiotics and (22.8%) using Local Steroids. Other studies have reported similar finding in the patients managements of RAU episodes (Sawair, 2010).

Study Limitations

The reported RAU prevalence depended on the patients' recall of the time of initiation time of RAU did not answer by all participants, duration and other details related to the lesion which might have occurred anytime during the past year or life time. As this study was cross-sectional, this prevents us from making conclusions regarding what is known as associated Factors.

Future direction

Future efforts will be directed toward increase population's awareness about the prophylaxis dental visit which helps to explore, diagnose and treat RAU.

Result would be more reliable if the study is performed at dental clinics under full screening and laboratory investigations for all patients. Both symptomatic and asymptomatic; through a prophylaxis dental visit which will benefit in minimizing the duration of RAU episodes and/or pain severity.

Conclusion

Population prevalence studies were severely lacking for City of Holly Makkah, Saudi Arabia. Our sample size was aim to be a minimum of 300 participants. About 383 patients have participated in our study after providing a written consent for the voluntary participation.

Our findings showed that the prevalence of RAU was 84.80% of the overall population; with higher in females by 76.5% & in males by 23.5. The onset of RAU in our samples seems to peak between the ages of 26 and 55 years before becoming less frequent with advancing age. Our results also showed that RAU are experienced in both smokers (13.6%) and nonsmokers (86.4%) but nonsmokers are dominants. Furthermore, 38.9% of participants did not relate the condition to eating certain types of food. While the remaining 61.1% reported; hot, spicy, sour, hard and cinnamon as trigger causes of RAU. Regarding hematinic deficiency reported that they had 28.2% decreased B12 vitamin and 35.6% hemoglobin, respectively. The etiology of RAU lesions is unknown, but there are several factors that can be associated with RAU such as local, systemic, immunologic, genetic, allergic, nutritional, and microbial factors have been proposed as associated factors.

RAU condition appearance in COVID-19 patients; reported as a result of neutrophil chemotaxis, stress, and immunosuppression that predisposed RAU. In our study, a statistically significant relation was noted between RAU incidence & Covid-19 with p= < 0.001* (49.0)

References

1. Abbasi, F ., Raoof, M., Khatami, R ., Shadman, N & Borjian-Boroojeni .(2016) . Effectiveness of Amlexanox and Adcortyl for the treatment of recurrent aphthous ulcers .*J Clin Exp Dent*, 368
2. Abiko, Y., Paudel,D., Matsuoka,H., Yamazaki, Y., Koga,C., Kitagawa,Y et al . (2022) psychostomatology: The psychostomatic status and approaches for the management of patients with inflammatory and oral mucosal diseases .*Jornal of oral and maxillofacfial surgery, medicine and pathology*.
3. Abushofa, N., Safadi R., & AlBatanyeh, O. (2012).Recurrent Aphthous Ulceration in a sample of Jordanian children and adolescents .*JUST*.
4. Anne Fleld, E., Brookes, V ., William, R .& Tyldesley.(2009) .Recurrednt Aqhthous Ulceration in Children . *International Journal of Pediatric Dentistry*.
5. Azka,S., Zergham & Acharya, U. (2021) Cyclic neutropenia .*National Library of Medicine*.
6. Atiba, A., Nishimura, M., Kasinuma, S ., Hiraoka, T., Goryo, M & Shimada, Y . (2011) Aloe vera oral administration accelerates acute radiation-delayed wound healing by stimulating transforming growth factor production .*Am J Surg*.Anand, V., Gulagi, M., Govila, V., & Anand, B .(2013) Low level laser therapy in the treatment of aphthous ulcer .*Indian J Dent Res*, 267
7. .AlKassar, Wz., Alhadi,Y., Alshamahy, H., &AlHazmyM .(2019) .The Association of Elevated serum IgE and Xerostomia with Recurrent aphthous stomatitis .*Dentistry and oral health*.
8. Alqathama, A., Alluhiabi, G ., Baghdadi, H., Alijahani, L ., Khan, S., Jabal, S et al.,(2020) .Herbal medicine from the perspective of type ll diabetic patients and

physicians: what is therelationship? *BMC complementvary medicine and therapies*, 65

9. .Altenburg, El-Haj, N., Micheli, C., & Zouboul , CC . (2014) The treatment of chronic recurrent oral aphthous ulcers .*Dtsch Arztebl Int*, 665
10.. Alrashdan, .MS., M & AlKhade,M .(2017)Psychological factors in oral mucosal and orofacial pain condithions .*Eur J Dent*, 548-552.
11. Barron,RW.(2001) Treatment strategies for recurrent aphthous ulcers .*Am J Health-syst pharm*, 41-50
12. Bazrafshani & Reza, M.(2018) the genetic basis of human oral imflammatory disease.Belenguer-Guallar, Y Jimenez-Soriano, & A Claramunt-Lozano .(2014) Treatment of recurrent aphthous stomatitis. A literature review .*J Clin Exp Dent*, 168.
13. Bankvall,M., Sjoberg,F., Gala,G., Wold,A., Jontell,M. & Ostman.S. (2014) The oral microbiota of patients with recurrent aphthous stomatitis .*J Oral Microlbiol.*
14. Bell ., J (2005) .Amlexanox for the treatment of recurrent aphthous ulcers .*Clin Drug Investig*, 66-555.
15. Besu, I .,Jankovic, Magdu, IU. , Konic-Ristic, A& Juranic, Z .(2009) Humoral immunity to cow's milk proteint and glindin within the etiology of recurrent aphthous ulcers ?*Oral Diseases*.
16. Bulur, I& Onder, M .(2017) .Behcet disease: New aspects .*Clin Dermatol*, 34-421
17. Bijelic, B ., Matic, IZ., Besu, I ., Jankovic, L., Marusic, S& Anderjevic., S. (2019) Celiac disease-specific and inflammatory bowel disease-related

antibodies in patients with r ecurrent aphthous stomatitis . *Immunobiology*, 75-79.

18. BN,N., Zabihi,E., Mohseni,S & Akbar Moghadamnia,A. (2012)Evaluation of the theraputic effect of Aloe vera gel on minor recurrent aphthous stoomatitis.
19. Bucci,P. (2006) Oral Aphthous Ulcers And Dental Defects In Children with Coeliac Disease .*Acta Paediatrica*.
20. Brignadllo-Petersen .R. (2019) Patient who seek professional treatment of recurrent aphthous stomatitis probably have an increased risk of having head and neck cancer and othertypes of cancer .*J Am Den tAssoc*, 24.
21. Canker Sores(2007) *The AAOM Web Writing Group*.aprevalence of recurrent aphthous ulceration experience in patients attending primary dental speciality in Sulimani City(2013) *Journal of Clinical and Expeimental*, 89-94.
22. Chattopadhyay, A., BDS, MDS, FFPH, MPH, & CPH.(2011) Recurrent Aphthous stomatitis .*Otolangol Clin N*
23. Cimen, B ., Kaya, G., Eskandari, U ., Turesen, G ., Ikizoglu, U & Atik.(2003) Oxidant/antioxidant Status in patients with recurrent aphthous stomatitis . *Clinical and Experimental Dermatology*
24. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review(2014) *Agrch Immunol Ther Exp*, 15-205.
25. Cheng, C ., Malahias, T ., Brar, P ., Teresa, M., Peter& Green, HR .(2010)The Association Between Celiac Diseas, Dental Enamel Defects and Aphthous Ulcers In aUnited States .*J Clin Gastroenterol*.

26. Chiang, CP ., Wang, YP. & Sun, A .(2019) .Recurrent aphthous stomatitis-Etiology, serum autoantibodies, anemia, hematinin deficincies and management . *J Formos Med Assoc*, 1279-1289.
27. Garioch, J., Ketola, I. & Savilahti, E .(2002) .Inflammatory Cytokines in Small Intestinal Mucos of Patients with potential Celiac Diseas .*Clinical & Experimental Immunology*, 94-101.
28. Gallo, CB., Mimura, MAM., & Sugaya, NN .(2009) .Psychological stress and recurrent aphthous stomatitis .*Clinics*, 645-647.
29. GrimsuxX., Leducq, S., Goupille,P., Aubourg,A., Miquelestorena-Standley, E.& Samimi .(M.)2018) Aphthous mouth ulcers as an initial manifestation of secukinumab-induced inflammatory bowel disease .*Ann Dermatol Venereol*, 676-682
30. Gizem, S., &Erbas .(2022) COVID-19-related oral mucosa lesions among confirmed SARS-CoV-2 patient: systemic review .*Int J Dermatol*.
31. Hello, M., Barbarot, S., Bastuji-Garin, Revuz, J. & Chosidow., O . (2010) .Use of thalidimidefor sever recurrent aphthous stomatitis:a multicenter cohort analysis .*Medicine*, 82-176
32. Ito,no, s., Sawada,A., Sakai, K., Katok, Y. &Muro .(2019) .Recurrent Aphthous Stomatitis caused by cytomrgalovirus, herpes simplex virus and candida species in a kidney transplant recipient:- A case report .*Science Direct*, 993-997
33. Jain,M., Kasetty, S., Sridhara,S., Jain,N., Khan,& S., Desai, A.) .(2013) . Poptosis and its significance in oral diseases: An Update .*Jornal of oral diseases*, 11.
34. Koray, M. & Tosun,.T. (2019) .*Oral mucosal trauma and injuries*.

35. Kim,Yi. Choi,YS., Baek,KJ., Yoon,SH., Park, HK. &Choi,Y .(2016) Mucosal and salivary microbiota associated with recurrent aphthous stomatitis .*BMC Microbiol*, 1-10.
36. Kaur, S & Chhabra,M. (2020).Recent advancement in mouth ulcers treatment . *Int J Pharm Biol Sci*, 14.
37. Koybasi,S., Parlak, A., Serin, E., Yilmaz, F., & Serin, D (2006) Recurrant aphthous stomatitis: investigation of possible etiologic factor .*American Journal of otolaryngology*, 229-232.
38. Kerr, AR.& Ship, JA .(2003) .Managenent strategies for HIV-associated aphthous stomatitis .*AM J Clin Dermatol*, 80-669.
39. Lankarani,KB., Sivandzadeh, GR. & Hassanpour.,S. (2013) .Oral manifestation in inflammatory bowel disease: a review .*World J Gastroenterol*.
40. Latour, I., Ortega-Quijano, D., Fernandez-Guarino, M. & Torrelo, A . (2019) .Sever recurrent aphthous stomatitis treated with adalimumab: a case report in teenage patient .7-986.
41. Laura, B., Huling, B., Baccaglini, L., Choquette, L ., Richard, S., Feinn et al . (2013) .Effect of stressful life events on the onset and duration of recurrent Aphthous Stomatitis .*Jornal of Oral Pthology & Medicine*.
42. Leonardo, Li., Digo,DI., Afrnaldo, Jrrll., Fabiola,Alll., Veronica, Rll&VBruno.,V. (2010) .Prevalence and risk factors for the development of recurrent aphthous stomatitis .*Rev. Cir. traumatol. buco-maxilo-fac.*
43. Lrhman, JS& Rogers,lll .(2016) .Acute ulcers .*Clin Dermatol*, 4-470

44. Liu, C., Zhou, Z., Liu, G., Wang Q., Chen, J. & Wang, L. (2012) Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration .*Am J Med*, 292-301

45. Marchini, L., Compos, M., Silva,A., Paulino, L & Nobrega,F. (.2007) .Bacterial diversity on aphthous ulcers .*Oral Microbiol Immunol*.

46. Maria, M., Sherlin & Jifrina,J .(2019) .Dietary habits leading to Recurrent Aphthous Ulcers-A survay .*Research Journal of Pharmacy and Technology*.

47. KPD, DNSVR, Koppal, S ., Byatnal,AR., Rukmangada,& T., Byatnal.AA. (2014) . Effecacy of rebamipide and levamisole in the treatment of patients with recurrent aphthous ulcer- a comparative study .*J Clin Diagn Res*, 22-119

48. Magalhaes, R., Biral,A., Pancoto,J., Donadi, E., Mendes-Jurnior,C., Magna,L et al .(2010) .Human leukocyte antigen (HLA)and single nucleotide polymorphisms(SNPs)tumor necrosis factor (TNF)-alpha-238 and -308 as genetic markers of susceptibility to psoriasis and severty of the disease in long-term follow-up Brazilian study . *Int. J. Deratol*, 1133-1140

49. Minhas, S., Sajjad,A., Kashif,M. ,Taj, F ., AlWaddani, H & ZKhurshid ,Z. (2019). Oral ulcers presentation in systemic diseases: An Update .*Open Access Maced J Med Sci*, 33-41.

50. Meyding-Lamade, U & Strank, C .(2012) Herpesvirus Infictions of The Central Nervous System In Immunocompromised Patients .*Ther Adv Neural Disord*, pages 279-296

51. Natah,S.(20011)Recurrent Aphthous Ulceration Immuno-pathological aspect . *Helsinki*.

52. Ozdedn, H. & Selcunk, A .(.2021) Is there a role of toothpaste in the development of recurrent aphthous atomatitis? A prospective controlled clinical trial with skin patch testing .*Oral Medicine*.
53. Oztekin, S., &Oztekin,C. (2018) Vitamin D level in patient with recurrent aphthous stomatitis .*BMC*, 186.
54. Okoh, M. & Ikechukwu,O. .(2019) Presentation of recurrent aphthous ulcer among patients in a tertiary hospital .*Afr J Oral Health Sci*, 2-8
55. Paleri,V., Staines,K., Sloan, P., Douglas, A., & Wilson,J. (2010) .Evaluation of oral ulceration in primary care .*Brit Med J*,26-39
56. Patil,S., Reddy, SN., Maheshwari, S., Shruthi, D. & Doni,B. (.2014) Prevalence of recurrent aphthous ulceration in the Indian Population .*J Clin Exp Dent*, **36.**
57. Pittock,S., Drumm,B., Fleming, P., Mc Dermott,M., Imrie,C. & Flint.S. (2001) The oral cavity in crohn's disease .*J Pedi*Dermats71-767
58. Philip, R & Cohen(.2007) Sweet's Syndrome- acomprehensive review of an acute febrile neutrophilic dermatosis .*Orphanet J Rare Disease*.
59. Queiroz, S., Silva, M., & Silveira,E. (2018) .Recurrent aphthous Ulceration: an epidemiological study of etiological factors, treatment and differential diagnosis. *An Bras Dermatol*, 341-346.
60. Rezaaei, F& . Soltani, T. (2018) .Evaluation and comparison of total antioxidant capacity of saliva between patients with Recurrent Aphthous Stomatitis and healthy subjects .*National Library of Medicine*, 303-309
61. Rivera, C., Munoz, A ., Puentes, C. & Aguayol, E. .(2021) Risk factors for Recurrent Aphthous Stomatitis: A systemic Review .*Prep*Scully, c.(2006). Aphthous Ulceration .*New Eng J Med*, 72-165

62. Riggo,MP., Lennon, A., & Wary, D (.2000) Detection of helicobacter pylori DNA in recurrent aphthous stomatitis tissue by PCR .*J Oral Pathol Med*.
63. Safadi,R. (2009) .Prevalence of recurrent aphthous ulceration in Jordanian deental patients .*BMC Oral Health*.
64. Saikaly, S., Saikaly, T.& Saikaly, L .(2018) Recurrent Aphthous Ulceration: a review of potential causes and novel treatment .*Journal of Dermatological Treatment*, 542-552
65. Samet,N., Laurent, C., Srinivas, M.,Susarla & Naama .(2006)The effect of bee propolis on recurrent aphthous stomatisis: a pilot study .*samet-Rubinsteen*.
66. Staines, K. & Greenwood,M. (2015) .Aphthous ulcers (recurrent .(*BMJ Clin Evid*, 26.
67. Scully, C ., Gorsky, M. & Lozada-Nur, F.(2003) .The Diagnosis and Management of recurrent aphthius stomatitis .*The Journal of the American Dental Association*.
68. Scully, C & Felix, D .(2005) .Oral Medicine-Updated for the dental practitionerAphthous and othercommon ulcers .*British dental journal*.
69. Swain,N., Poonja, L. & Penkar, Y (2012) Etiological Factors of Recurrent Aphthous Stomatitis:A Common Perplexity .*Journal of Contemporary Dentistry*.
70. Sunday,O., & Akintoye,MS. (.2014) Recurrent Aphthous Atomatitis .281-297
71. Shaji, J & . Vaswani, TH.(2021) .Effect of Benzydamine Hydrochloride loaded Nanosponge formulations against mouth ulcers in Albino Wistar Rats .*Res J Of Pharm Technol*, 90-986

72. Shimizu, J., Kubota, T., Takada, E., Takai, K., Fujiwara, N. & Arimitsu., N . (2016) Bifidobacteria abundance-featured gut microbiota compositional chyange in patients with Behcet's disease .*PLOS One*.
73. Ship, JA., Chavez, EM., Doerr, PA., Henson, BS, & Sarmadi, M.(2000) . Recurrent aphthous stomatitis .*Quintessence Int*, 112-295.
74. Sharma, D&. Garg., R .(2018) .A comprehensive review on Aphthous stomatitis, its types, management and treatmentavailable .*Journal of Developing Drugs*.
75. Slebioda, Z. &.Bobkowska,B. (2019) Systemic and enviromental risk factors for recurrent aphthous stomatitis in a polish cohort of patients .*National Library of Medicine*, 196-201.
76. Shirzaiy, M., Sarabadani, J., & Damle.SV. (2019) .Recurrent Aphthous stomatitis and related factors Among 12-17-years-old students in Zahedan, Irantists in the city of bandar AB .*J Res Dentomaxillofac* Sseis, 1-5,
77. Souza, P., Alegre, S., &Duquia,R. .(2017) Recurrent aphthous stomatitis in 18-years-old adolescents-prevalence and associated factors: A population-based srudy .*Anais Brasilerios de Dermatologia*, 626-629
78. Tarakji, B ., Gszal, G., AlMaweri, SA., Azzeghaiby, SN& . Alaizari., N (2015) . Guideline for the diagnosis and treatment of recurrent aphthous stomatitis for dental practitioners .*J Int Oral Health*, 74.
79. Thornhill, MH., Baccaglini,L., Theaker, E. & Pemberton,MN. (2007) A randomized, double-blind, placebo-controlled trial of pentoxifyline for the treatment of recurrent aphthous stomatitis .*Arch Dermatol*.

80. Vanoni, F ., Caorsi, R., Aeby, S., Cochard, M ., Anton, J ., Berg, S et al .(2018) . Towards a new set of classification criteria for PFAPA Syndrome .*Pediatric Rheumatol Online J,* 60.
81. Vijayabala, GS ., Kalappanavar, AN ., Annigeri, RG., R Sudarshan, & SS Shettar.(2013) .Single application of topical doxycycline hyclate in the management of recurrent aphthous stomatitis .*Oral Surg Oral Med Oral Pathol Oral Radiol*, 440- 6
82. Wang, H., He, F., Xu, c ., Fang, C& . Peng., J. (2018) .Clinical analysis for oral mucosal diseasein 21972 cases .*Zhong Nan Da Xue Xue Bao Yi Xie Ban*, 779-783
83. Zhengyang, Zhiixing, Guanqun, He.،Yongsheng, & Shao,T. (20211) Altered oral microbiota composition associated with Recurrent aphthous stomatitis in young females .*National Library of Medicine*.

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