Effects of Smoking on Recurrent Aphthous Stomatitis: Does Salivary Immunoglobulin-A play a Role?

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ABSTRACT

Patients who stop smoking often complain of aphthous (mouth) ulcers. This symptom is sometimes attributed to the use of smoking cessation medications, but little is known about it. After stopping smoking, some 40% of patients developed mouth ulcers, mostly in the first 2 weeks. The problem was generally mild, but 8% reported severe ulceration. The ulcers resolved within 4 weeks in 60% of patients affected. The ulcer ratings in patients using oral nicotine replacement products were higher than in those using patch, nasal spray or bupropion in the first week of abstinence but not afterward. Mouth ulcers were more prevalent in more dependent smokers, and the occurrence of ulcers correlated with other tobacco withdrawal symptoms. Our reviews confirm that mouth ulcers are a common result of stopping smoking, affecting two in five quitters. Patients should be reassured that the lesions are a result of stopping smoking and not a side-effect of smoking cessation medication.

Keywords: Immunoglobulin-A, Recurrent aphthous stomatitis, Saliva, Smoking cessation.

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INTRODUCTION

There are clinical and epidemiological evidences regarding the adverse effects of tobacco on oral health. Numerous studies have shown that tobacco use would lead to an increased incidence and severity of periodontal diseases and a higher rate of tooth loss. The adverse effects of cigarette smoking and other forms of tobacco are numerous and tobacco use has been associated with gingival, oral mucosa and dental alterations.1

Saliva is a complex and important body fluid which is very essential for oral health.3 Saliva is required for protecting the oral mucosa, teeth remineralization, digestion, taste sensation, pH balance and phonation. It includes a variety of electrolytes, peptides, glycoproteins, and lipids which have antimicrobial, antioxidant, tissue repair and buffering properties. Therefore, altered whole-mouth salivary flow rate (SFR) has an important role in the pathogenesis of oral and dental diseases. Saliva is the first biological fluid that is exposed to cigarette smoke, which contains numerous toxic compositions responsible for structural and functional changes in saliva.1

There are also several studies concerning the effect of chewing tobacco and smoking on salivary secretion. While some of these studies have shown an increase in SFR especially in short-term, no significant changes in tobacco user’s flow rate was reported as opposed to non-tobacco users.

The oral cavity is a moist environment which is kept at a relatively constant temperature (34–36°C) and a pH close to neutrality in most areas and thus supports the growth of a wide variety of microorganisms. However, the mouth must not be considered a uniform environment. There are several habitats in the oral cavity, each being characterized by different physicochemical factors and thus supporting the growth of a different microbial community. This is partly due to the great anatomical diversity of the oral cavity and the interrelationship between the different anatomic structures. The oral cavity possesses both hard (teeth) and soft (mucosa) tissues. The tooth can be described as a nonshedding hard surface that offers many different sites for colonization by bacteria below (subgingival) and above (supragingival) the gingival margin. In contrast, the oral mucosa is characterized by a continuous desquamation of its surface epithelial cells, which allows rapid elimination of adhering bacteria. The mucosa that covers the cheek, tongue, gingiva, palate, and floor of the mouth varies according to the anatomical site. The epithelium may be keratinized (palate) or nonkeratinized (gingival crevice). The tongue, with its papillary surface, provides sites of colonization that are protected from mechanical removal. The area between the junctional epithelium of the gingiva and teeth, referred to as the gingival crevice, also provides a unique colonization site that includes both hard and soft tissues.2

The indigenous microbiota plays an important role in health and diseases of the humans and animals. It
contributes to the development of the immune system and provides resistance to colonization by allochthonous or pathogenic microorganisms. It also constitutes a reservoir of potentially pathogenic bacteria that may infect host tissues. Oral diseases seem to appear after an imbalance among the indigenous microbiota, leading to the emergence of potentially pathogenic bacteria.3

The oral surfaces are also constantly bathed by two important physiological fluids, the saliva and the gingival crevicular fluid. These fluids are essential for the maintenance of the oral ecosystems by providing water, nutrients, adherence and antimicrobial factors. The supragingival environment is bathed by saliva, while the subgingival environment (gingival crevice) is bathed mainly by the gingival crevicular fluid. Saliva is a complex mixture that enters the oral cavity via the ducts of three pairs of major salivary glands, the parotid, the submandibular, and the sublingual, and the minor salivary glands. Saliva contains 99% water but also contains glycoproteins, proteins, hormones, vitamins, urea and several ions. The concentrations of these components will vary according to the salivary flow. Generally, a slight increase in the secretion rate leads to an increase in sodium, bicarbonate, and pH and a decrease in potassium, calcium, phosphate, chloride, urea and proteins. At higher secretion rates, the concentrations of sodium, calcium, chloride, bicarbonate, and proteins increase while the concentration of phosphate decreases. Saliva helps maintain tooth integrity by providing ions, such as calcium, phosphate, magnesium, and fluoride for the remineralization of tooth enamel.

Local immune factors may play a role in protection against oral diseases and these defences may be related to 6 immunoglobulin (Ig) A and G subclass responses. Immunoglobulins are proteins of the animal origin endowed with known antibody activity and for certain other proteins related to them by chemical structure. Immunoglobulins are synthesized by plasma cells and to some extent by lymphocytes also. All antibodies are immunoglobulins, but all immunoglobulins may not be antibodies. Immunoglobulins constitute 20 to 25% of the total serum proteins.2

Five distinct classes of immunoglobulin molecules are recognized in higher mammals, namely IgG, IgA, IgM, IgD and IgE.3 The immunoglobulins responsible for the protection are IgA and IgG.4 Secretory IgA (SlgA) constitutes the predominant immunoglobulin isotype in secretions, including saliva. It is considered to be the first line of defense of the host against pathogens, which colonize or invade surfaces bathed by external secretions.5

Immunoglobulin-A is the primary protective antibody at mucosal surfaces. Immunoglobulin-A is produced by plasma cells in the minor salivary glands. Secretory IgA can traverse mucosal membranes; in this way, it helps to prevent the entry of infectious microorganisms.4 Several factors may influence the IgA levels in serum as well as in secretions. The secretion rate is an important factor. An increase in the secretion rate is accompanied by a decrease in concentration of SlgA in saliva. Another factor is cigarette smoking, which has been reported to decrease SlgA concentrations.6 Smoking has been shown to affect T-cell subsets, natural killer cells, and serum immunoglobulin concentrations.7 Decrease of SlgA may be due to an influence on the salivary gland cells responsible for the completion of the SlgA or on the cells of immunologic system involved in the production of the IgA molecules.8

Many studies were performed relating the physiology of IgA secretion occurrence of recurrent aphthous stomatitis (RAS).9 Recurrent aphthous ulceration (RAU) is a common oral disease appearing usually on nonkeratinized oral mucosa, especially on the tongue, vestibulum, palate and buccal mucosa. Recurrent aphthous stomatitis is one of the most common oral lesions seen by dentists.10 Recurrent aphthous stomatitis affects approximately 20% of general population, but when specific ethnic or socioeconomic groups are studied, the incidence ranges from 5 to 50%.11 The most common presentations are minor recurrent aphthous ulcers: round, painful ulcers up to 10 mm in diameter that heal within 10 to 14 days without scarring. Major ulcers are larger than 10 mm in diameter, and can last for several weeks and frequently scar. The etiology of RAS may be immunological one. Increased circulating levels of antibody against oral mucous membrane may be found in affected individuals. These increased antibody levels may be due to an immunologic cross-reaction between oral epithelium and indigenous microorganisms or the exposure, by ulceration, of previously sequestered, hidden antigens setting up cycles of recurrent disease. Thus, there will be increased IgA levels in RAS patients.12

**INTERRELATIONSHIP OF SMOKING AND INCIDENCES OF RECURRENT APHTHOUS STOMATITIS**

In the early 1960s, it was reported that aphthous ulceration was relieved by the resumption of cigarette smoking (Brookman,1960; Dorsey, 1963), and in a 1970 population study, Shapiro et al (1970) showed a negative correlation between self-reported smoking histories and RAS. This was confirmed in a further study by Axell in 1985 (Axell and Henricsson 1985). Smokeless tobacco has also been noted to have a negative correlation with RAS (Grady et al 1992). These studies, relying on self-reporting of
tobacco habits, have shown that there appears to be a negative epidemiological association between smoking and aphthous stomatitis.

Significant differences in the prevalence of RAS in the group who were cigarette smokers were related to the dose and duration of the smoking habit. The ‘protective effect’ of tobacco on RAS was only noticed when persons were heavy smokers or smoked for longer periods of time. Of course this lower prevalence of RAS in the heavy smokers should not encourage smokers who suffer from RAS to increase their consumption. Data upon the ‘protective effect’ of smoking on RAS are controversial particularly with respect to a possible underlying mechanism. Some researchers thought that this protective effect is related to the increased keratinization of the oral mucosa in smokers and that this keratin layer acts as a mechanical and chemical barrier against trauma or microbes. In contrast, some have hypothesized that nicotine may be the responsible agent for the reduction in RAS prevalence rate in smokers. Nicotine has been shown to affect the immune response in inflammatory conditions by inducing the production of adrenal steroids through the hypothalamus-pituitary-adrenal axis and reducing the production of tumor necrosis factor-α (TNF-α) and interleukins 1 and 6 through its direct effect on macrophages. Some investigators support the belief that nicotine may act as protector of the oral mucosa in the patients with RAS while subjects who quit smoking often complain of RAS and resumption of smoking results in the faster resolution of RAS. In addition, those who quit smoking are less likely to develop RAS, if they use nicotine replacement therapy (NRT) as compared to those who do not use NRT. Few investigators suggested that smokers may be less psychologically stressed than non-smokers and that some psychological trigger might affect RAS development.13

Smokers have been shown to have lower SlgA levels than non-smokers (Barton JR et al 1990; Evans et al 2000), while non-smokers and ex-smokers have been shown to have similar levels of SlgA (Barton JR et al 1990), suggesting that the immunosuppressive effects of smoking are reversed following smoking cessation.14 Natah found that elevated levels of serum IgA and IgG were present in patients with RAU, and that salivary IgA did not differ in patients with RAU compared to the control group. Guven also found elevated levels of serum IgA and IgM in patients with RAU. However, the author did not find any changes in serum IgG levels. Porter et al described IgG subclass levels in the serum of patients with minor oral aphthous stomatitis, and concluded that there is no evidence to suggest that changes in IgG subclass are present in patients with RAU. In that study, patients did not have active lesions of the oral mucosa. A more recent study by Vincente et al suggested that low serum levels of IgG2 in patients with acute ulcers might play an important role in the pathogenesis of RAU. The same authors also reported that serum IgG subclass level as well as total IgA may undergo changes which are dependant on different periods of activity and quiescence of the disease. Ben-Aryeh et al found that salivary IgA and serum IgA and IgG in patients with either dormant or acute RAU were within the physiologic range for healthy people. Authors found lowered serum IgA in patients with acute RAU. Bennet and Reade found that salivary IgA in patients with minor aphthous ulceration undependable of stage disease showed no deviation from the control group. Both in patients with minor and major RAU, during acute phase, remission and in controls salivary flow rate was within normal ranges and we can conclude that the quantity of saliva is unchanged in patients with RAU.

Similarly, we found that mean levels of SlgA in saliva were significantly decreased in tobacco smokers either with or without dental caries when compared with non-smokers. Moreover, smokers with dental caries had lower concentrations of salivary SlgA compared to caries-free smokers.15 Some investigators have shown that smoking influences the salivary Ig content as well as systemic responses to antigens encountered in nasal and respiratory mucosa.15

Another study observed a striking and reproducible influence of cigarette smoking on salivary Ig in healthy smokers, found reduced concentration of IgA in pure parotid saliva, compared with nonsmokers, and showed that smokers had a dose dependent and probably reversible humoral mucosal immunodeficiency, as reflected either directly or otherwise by salivary IgA concentrations. The decrease in salivary IgA in tobacco smokers can be explained on the basis of immunosuppressive effects of combustion products of tobacco. Secondly, smoking markedly increases the flow rate of saliva leading to increased calcium levels in the oral cavity during smoking. However, an earlier study reported a level of salivary IgA reduced by 56% after physiologic stimulation and its authors opined that these findings indicated that a considerable portion of salivary IgA is produced locally, depending on selective transport and the release from the local storage sites.16

Increased IgG levels in acute RAU patients implies the possible importance of IgG1–4 subclasses in acute RAU together with intense response to possible microbial etiologic factor. During the remission period, IgG2–3 remained increased whereas IgG1 and IgG4 returned to the values seen in healthy controls. Certainly, IgG
subclass levels play a role during the period of disease activity and quiescence, and might support the role for an infective causative agent in the development of RAU.

Healthy smokers had significantly lower salivary IgA concentrations, and higher salivary IgM, when compared with non-smokers. There was no influence of smoking on salivary IgG concentration. There was a strong inverse correlation between salivary IgA concentration and the number of cigarettes currently smoked daily (10–60); however, no such relationship existed for salivary IgG or IgM concentrations.17

CONCLUSION

In the oral cavity, indigenous bacteria are often associated with many major oral diseases. These diseases seem to appear following an imbalance in the oral resident microbiota, leading to the emergence of potentially pathogenic bacteria. To define the process involved in such diseases, it is necessary to understand the ecology of the oral cavity and to identify the factors responsible for the transition of the oral microbiota from a commensal to a pathogenic relationship with the host. The regulatory forces influencing the oral ecosystem can be divided into three major categories: host related, microbe related, and external factors. Among host factors, SlgA constitutes the main specific immune defense mechanism in saliva and may play an important role in the homeostasis of the oral microbiota. Naturally, occurring SlgA antibodies that are reactive against a variety of indigenous bacteria are detectable in saliva. These antibodies may control the oral microbiota by reducing the adherence of bacteria to the oral mucosa and teeth. It is thought that protection against bacterial etiologic agents of oral diseases could be conferred by the induction of SlgA antibodies via the stimulation of the mucosal immune system. However, elucidation of the role of the SlgA immune system in controlling the oral indigenous microbiota is a prerequisite for the development of effective vaccines against these diseases. The role of SlgA antibodies in the acquisition and the regulation of the indigenous microbiota is still controversial. Data upon the ‘protective effect’ of smoking on RAS are controversial particularly with respect to a possible underlying mechanism. Some researchers thought that this protective effect is related to the increased keratinization of the oral mucosa in smokers and that this keratin layer acts as a mechanical and chemical barrier against trauma or microbes. In contrast, some have hypothesized that nicotine may be the responsible agent for the reduction in RAS prevalence rate in smokers. Nicotine has been shown to affect the immune response in inflammatory conditions by inducing the production of adrenal steroids through the hypothalamus-pituitary-adrenal axis and reducing the production of tumor necrosis factor-α (TNF-α) and interleukins 1 and 6 through its direct effect on macrophages.

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