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# Role of tumor necrosis factor-alpha in pathogenesis of recurrent aphthous stomatitis: A systematic review and meta-analysis

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**Review Article**

## Abstract

**BACKGROUND AND AIM:** Recurrent aphthous stomatitis (RAS) is a lesion of the oral cavity with an unknown etiology. Several studies have been performed on the role of tumor necrosis factor-alpha (TNF-α) in RAS. The main purpose of this paper was to review TNF-α level and its gene polymorphism in patients with RAS, the factors influencing the production of TNF-α, and its role in RAS development.

**METHODS:** In this review study, all articles containing English abstract were searched in the PubMed, Cochrane Library, and Scopus databases from January 2000 to December 2019. The searches were done using the Medical Subject Heading (MESH) terms and keywords of "recurrent aphthous stomatitis" or "recurrent aphthous ulcers" or "recurrent oral ulcers" and “tumor necrosis factor-alpha” or “TNF-α”. The data for gene polymorphism were analyzed using Comprehensive Meta-Analysis (CMA) software. Regarding the heterogeneity of studies, the random effects model was used. Cochran’s Q and $I^2$ tests were used to evaluate statistical heterogeneity between the studies.

**RESULTS:** Amongst the 619 articles obtained in the first stage of our search of database, 21 articles which were fitted to our study based on the entry/exit criteria were selected in the review. According to this meta-analysis, recessive model of TNF-α -308 G/A had protective effects for RAS [odds ratio (OR) = 0.392, 95% confidence interval (CI) = 0.145-1.061, P = 0.045].

**CONCLUSION:** The results showed the important role of TNF-α in RAS development. There are numerous factors involved in producing this cytokine. Identifying TNF-α production pathway and its effects in RAS formation is significant in developing new prevention and treatment methods.

**KEYWORDS:** Tumor Necrosis Factor-Alpha; Polymorphism, Single Nucleotide; Stomatitis; Aphthous

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Recurrent aphthous stomatitis (RAS) has been known as the most common oral lesions in which 10%-20% of the world's population is affected. RAS is characterized by repeated ulceration with defined borders, which might be single or multiple and very painful. The healing of these ulcers is slow compared to traumatic lesions.[1] Several parameters including allergies, genetic predisposition, effects of hormones and immune factors, blood disorders, infective agents, malnutrition, stress, and trauma are often considered in the RAS occurrence.[2-4] However, the cause of the condition is not yet known and no definitive medication is available for its treatment and treatment of the affected individuals consists of symptomatic modalities.

Evidence suggests that aphthous lesions are caused by abnormal expression of cytokines in the oral mucosa, leading to increased cellular

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immune response in the focal areas of the oral mucosa. These cytokines include interleukins (IL) 1, 6, and 10 and tumor necrosis factor-alpha (TNF-α). TNF-α is an essential cytokine produced by T lymphocytes and macrophages and is involved in the conversion of T lymphocytes to T helper 1 (Th1).[5]

Numerous studies have been performed to show the role of TNF-α in RAS. Some studies have examined TNF-α level in the tissues, saliva, and serum in RAS,[6-19] and some others have investigated the TNF-α gene polymorphism in RAS and contradictory results have been presented.[20-22] Other studies have examined the factors affecting the production of TNF-α and the mechanisms of RAS formation by this cytokine.[23-26] Due to the small volume of individual studies and other limitations, these studies have low statistical power and are poor in estimating disease risk. Also, due to inconsistent conclusions in this field, the aim of this study was to identify and comprehensively analyze all relevant clinical studies to investigate the levels of TNF-α in different samples, association of TNF-α gene polymorphism with RAS, production of TNF-α, and its role in the RAS creation. Identifying TNF-α production pathway and its effects on RAS formation is significant in developing new prevention and treatment methods.

## Methods

This systematic review study was accepted by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (ethical code: IR.TBZMED.VCR.REC.1398.167).

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting systematic reviews.[27] A focused question was produced according to the Participants, Intervention, Control, and Outcomes (PICO) principles.[28] The focused question for this review was "Is there an association between TNF-α and RAS?" In this review study, all articles containing English abstract were searched according to the relevant keywords in the PubMed, Cochrane Library, and Scopus databases from January 2000 to December 2019. The keywords were selected based on Medical Subject Heading (MeSH) terms. The studies were retrieved by searching the key terms of "recurrent aphthous stomatitis" or "recurrent aphthous ulcers" or "recurrent oral ulcers" and "tumor necrosis factor-alpha" or "TNF-α".

A protocol was used for establishment of the inclusion and exclusion criteria. The case-control studies or cohort trials that evaluated association between RAS and TNF-α were selected without restrictions of variants of RAS. To select the studies, all articles that were in English or abstracted in English were reviewed, and titles and abstracts were screened for relevance. Studies were excluded if they were review, case report, letter to editor, or animal studies. Also, studies involving participants with systemic disease and studies that examined the effect of different drugs on the RAS were excluded. Endnote X5 reference management software was used to organize study titles and abstracts and identify duplicates. A random effect model was also used to perform the meta-analysis.

The studies were checked by one author to extract all the relevant data. Another author reevaluated the data. Disagreements were resolved with the third author's discussion. Quality assessment of obtained articles was performed according to the checklist which was provided by the Joanna Briggs Institute (JBI).[29] Microsoft Excel (version 2010) was used to extract the characteristics of study. The details of the selected studies included the following: the name of the first author, publication year, country, design, sample size, and results.

The probability of each allele and genotype in the patient group was compared to the control group in the meta-analysis. Pooled odds ratios (ORs) were calculated for allelic model (G vs. A), homozygote model (AA vs. GG), heterozygote model (AG vs. GG), dominant model (AA + AG vs. GG), and recessive model (AA vs. AG + GG). Heterogeneity between studies was assessed

by Cochran's Q and $I^2$ tests, which expressed the percentage of variation between studies. $I^2$ values below 25% were considered as heterogeneity, 50% as moderate, and above 75% as high heterogeneity. Statistical analysis was performed using Comprehensive Meta-Analysis (CMA) software (version 3.0) and P-value less than 0.05 was considered as significant level.

## Results

In an initial research, 619 articles were identified through electronic database. After removing duplicated publications, 223 articles remained. Abstract of these studies were assessed for eligibility. Finally, 21 studies were evaluated. The flow chart for the identified articles is shown in figure 1. Of the 21 articles evaluated, 13 articles evaluated the TNF-α level in the different samples[6-12,14-19] and one article was about the amount of TNF-α-producing cells,[13] which are listed in table 1; 3 articles examined the polymorphism of the TNF-α gene in patients with RAS,[20-22] which are shown in table 2. As summarized in table 3, four articles evaluated the effect of different factors on the production of TNF-α and the mechanism of RAS creation by TNF-α.[23-26]

TNF-α -308 G/A was assessed in three trials with 201 cases and 240 controls.[20-22] As shown in figure 2, pooled results indicated that the correlation between the TNF-α -308 G/A polymorphism and RAS risk was statistically significant in the recessive model [OR = 0.392, 95% confidence interval (CI) = 0.145-1.061, P = 0.045], but not in any other models. According to this meta-analysis, recessive model of TNF-α -308 G/A has protective effects for RAS.

## Discussion

This study indicates that TNF-α has important effects on the RAS development. Numerous reports suggest that factors such as stress, hematinic deficiency, trauma, genetics, and cytokines can be effective in the formation of RAS.[3] TNF-α is a main pro-inflammatory cytokine that plays an important role in immune and inflammatory responses.[5] TNF-α actually shows important immune-modulatory activities and studies have shown its relationship with RAS. Thus, high levels of TNF-α have been reported in wound mucosa and peripheral blood of patients with aphthous ulcer.[16-19] High cytotoxic destruction of epithelial cells with TNF-α produced from peripheral blood mononuclear cells was shown in patients with aphthous ulcer.[16] In addition, RAS can be prevented by inhibitors of endogenous TNF-α synthesis such as thalidomide and pentoxifylline.[30]

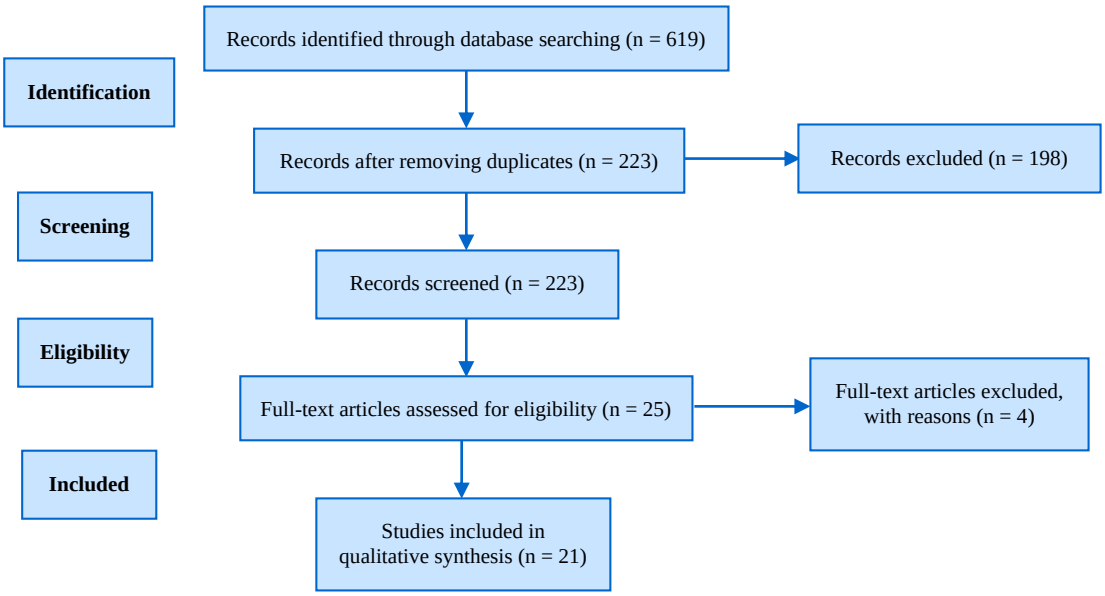


**Figure 1.** The flow chart of searching strategy based on PRISMA guidelines

**Table 1.** Articles evaluating the tumor necrosis factor-alpha (TNF-α) level in the different samples

| References | Study design | Country | Sample size | | Sample | Results |
|---|---|---|---|---|---|---|
| | | | RAS | Control | | |
| Wei[6] | Case-control | China | 14 | 14 | Saliva | The salivary TNF-α level in RAS group significantly increased compared with control group. |
| Hegde[7] | Case-control | India | 30 | 30 | Saliva | The salivary TNF-α level in RAS group significantly increased compared with control group. |
| Chaudhuri[8] | Case-control | India | 30 | 30 | Saliva | The salivary TNF-α level in RAS group significantly increased compared with control group. |
| Avci[9] | Case-control | Turkey | 25 | 25 | Serum | TNF-α level increased in the serum of the RAS group compared with those of the controls. |
| Eguia-del[10] | Case-control | Spain | 20 | 10 | Saliva | The salivary TNF-α level in RAS group significantly increased compared with control group. |
| Lewkowicz[11] | Case-control | Poland | 15 | 12 | Tissue | mRNA expression for TNF-α was significantly higher in RAS group compared with their tissue controls. |
| Borra[12] | Case-control | Brazil | 17 | 17 | Serum and saliva | No significant difference was observed in serum and salivary TNF-α between RAS and control groups. |
| Albanidou-Farmaki[13] | Case-control | Greece | 32 | 40 | Peripheral blood | No statistical difference was observed in the number of TNF-α-producing cells between RAS group and controls. |
| Dalghous[14] | Case-control | UK | 19 | 6 | Tissue | Expression for TNF-α was significantly higher in RAS compared with their tissue controls. |
| Boras[15] | Case-control | Croatia | 26 | 26 | Saliva | The salivary TNF-α level in RAS group significantly increased compared with control group. |
| Lewkowicz[16] | Case-control | Poland | 10 | 12 | Tissue | A higher level of TNF-α in PBMC of patients with RAS was observed. |
| Sun[17] | Case-control | Taiwan | 197 | 77 | Serum | TNF-α level increased in the serum of RAS group compared with those of the controls. |
| Yun-Qiu[18] | Case-control | China | 32 | 30 | Serum | TNF-α level increased in the serum compared with those of the controls. |
| Natah[19] | Case-control | Finland | 12 | 10 | Tissue | Expression for TNF-α was significantly higher in mononuclear inflammatory cells, mast cells, and vascular endothelial cells of RAS lesions compared with their tissue controls. |

RAS: Recurrent aphthous stomatitis; TNF-α: Tumor necrosis factor-alpha; mRNA: Messenger ribonucleic acid; PBMC: Peripheral blood mononuclear cell; UK: United Kingdom

**Table 2.** Characteristics of studies included in the meta-analysis

| References | Study design | Genotyping method | Number | | | | | | Country |
|---|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | Total case (RAS group) | Mean age (year) | Control | Mean age (year) | |
| Sun[20] | Case-control | PCR | 22 | 20 | 42 | 46.70 | 86 | 43.90 | China |
| Guimaraes[21] | Case-control | PCR | 28 | 36 | 64 | 31.70 | 64 | 36.90 | Brazil |
| Bazrafshani[22] | Case-control | PCR | 33 | 62 | 95 | 37.33 | 90 | 37.33 | England |

PCR: Polymerase chain reaction; RAS: Recurrent aphthous stomatitis

**Table 3.** Articles evaluating the effect of different factors on the production of tumor necrosis factor-alpha (TNF-α) and effect of TNF-α on human oral keratinocytes (HOK)

| References | Study design | Country | Sample size | | Results |
|---|---|---|---|---|---|
| | | | RAS | Control | |
| Lewkowicz[23] | Case-control | Poland | 11 | 12 | $CD4^+CD25^+$ T regulatory cells are defective in function and quantity and are unable to inhibit TNF-α secretion. |
| Al-Samadi[24] | Case-control | Finland | 10 | 10 | TNF-α with IFNγ together increase TLR2 expression, but they did not do it alone.The effect of TNF-α on TLR4 expression was not statistically significant. |
| Al-Samadi[25] | Case-control | Finland | 8 | 7 | In acute phase, RAS epithelium BD2 (an antimicrobial peptide) was stained strongly. In HOK cell culture, BD2 increased by TNF-α and synergistically together with IL-17C. |
| Al-Samadi[26] | Case-control | Finland | 5 | 5 | In HOK cell culture, cells incubated with IL-17C produced more TNF-α than the group incubated without IL-17C. HOK in RAS lesions was stained strongly for IL-17C compered to control, that was associated with increased epithelial immunostaining of TNF-α. |

TNF-α: Tumor necrosis factor-alpha; IFNγ: Interferon-gamma; TLR: Toll-like receptor; RAS: Recurrent aphthous stomatitis; IL: Interleukin; BD: Beta defensin; HOK: Human oral keratinocytes

Effects of TNF-α were established to be associated with activation of a cascade of inflammatory events, enhancing expression of adhesion molecules and activation of neutrophils in addition to acting as a co-stimulator for T cell activation and antibody production.[31]

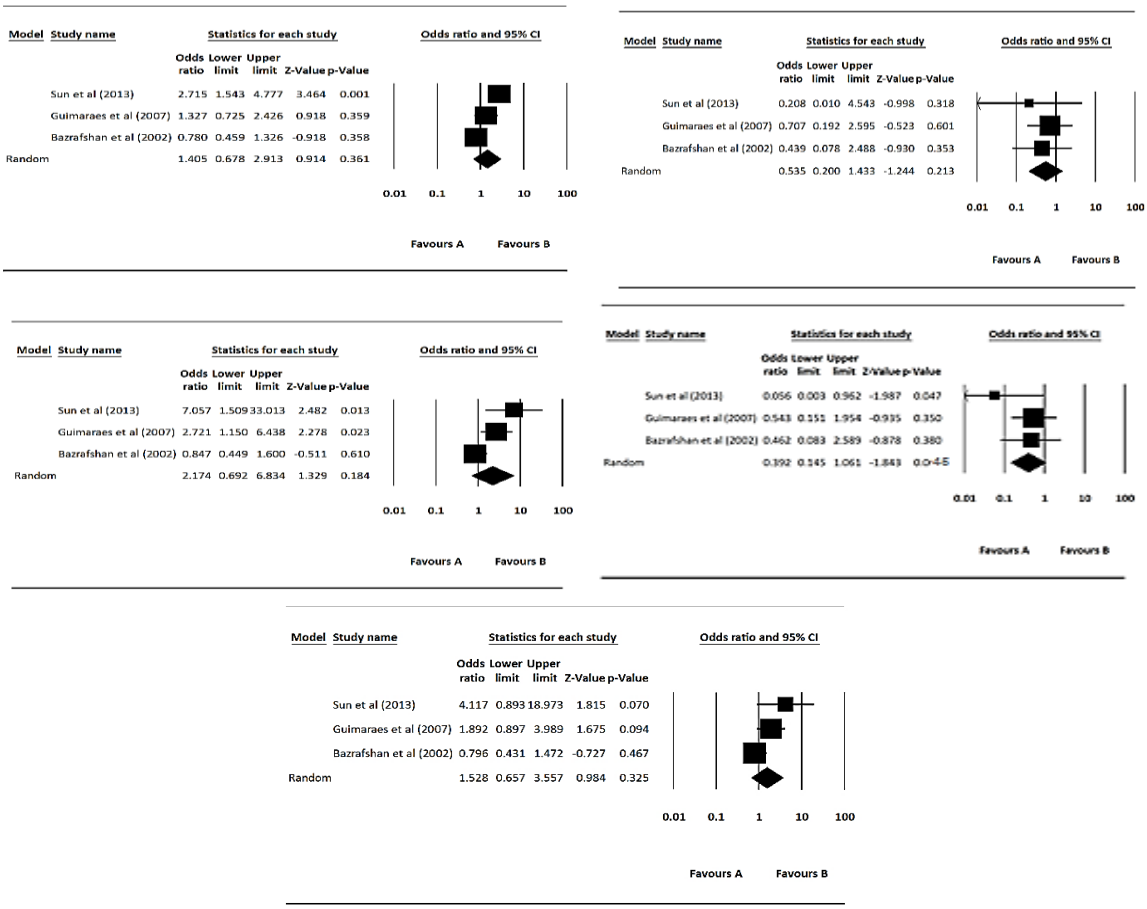


**Figure 2.** Forest plot of the tumor necrosis factor-alpha (TNF-α) -308 A/G polymorphism and recurrent aphthous stomatitis (RAS) susceptibility in A: allelic model (G vs. A), B: homozygote model (GG vs. AA), C: heterozygote model (AG vs. GG), D: recessive model (AA vs. AG + GG), E: dominant model (AA + AG vs. GG)
CI: Confidence interval

Different results were obtained in studies that examined TNF-α level. This difference may be partly due to patient differences, RAS subtypes, research methods, or sample size. Another important factor to consider is the interaction of genes and cytokines as well as the effect of gene polymorphism on cytokine production. In addition, none of the studies examined the effect of age and sex on TNF-α levels although these important factors should be considered in future studies. A remarkable point is that, in most studies, salivary TNF-α levels are higher in the RAS group than in healthy individuals, so it suggests that TNF-α may be a potential salivary marker for this disease. Considering two main advantages of easy access and non-invasive collection by intermediate-educated individuals, whole saliva is an affordable tool for monitoring recurrent diseases and screening systemic disorders.

The TNF-α gene is located on the chromosome 6 and several single nucleotide polymorphisms have been detected in its promoter region. Studies have indicated that a G-to-A mutation in the -308 promoter section is accompanied by an increase in TNF-α production.[32,33] Studies have also been conducted on the association between TNF-α gene polymorphism and susceptibility to aphthous ulcers. In some studies, a positive association was found between TNF polymorphism and susceptibility to aphthous ulcers;[20,21] and in other study, no association was found.[22] This discrepancy in studies in some comparative models and inconsistent conclusions may be attributed to several factors. First, these studies included people from different populations in different countries and could be the result of differences in the race of the individuals studied. Second, it may be the result of different etiologies of RAS. Third, some studies did not use Hardy-Weinberg equilibrium (HWE). Another reason may be related to the low statistical population of some studies. In this meta-analysis, no association was found between TNF-α -308 G/A single nucleotide polymorphism and overall RAS risk except in recessive model. Recessive model is likely to be protective against RAS when compared to other models.

Al-Samadi et al.[24-26] concluded that abnormal apoptosis of epithelial cells that progressed to necrosis, released the danger signals. Exposure of pathogen-specific receptors such as Toll-like receptor (TLR) to these danger signals increases the production of IL-17C and TNF-α and leads to inflammation and RAS.

Three limitations could be mentioned for the current study. First, sample size was limited for some groups. Second, our search was limited to articles with English abstract that may be considered language bias. Third, meta-analysis is a retrospective study in which methodological deficiencies of studies have remained.

## Conclusion

Numerous effective factors on the production of TNF-α have been reported in RAS. In addition, TNF-α can cause RAS lesions through its effect on keratinocyte cells. It is hoped that this review article raises our awareness about the effect of TNF-α on the etiopathogenesis of RAS and opens up new ways of preventing and treating.

## Conflict of Interests

Authors have no conflict of interest.

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