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## **ТИББИЁТДА ЯНГИ КУН НОВЫЙ ДЕНЬ В МЕДИЦИНЕ NEW DAY IN MEDICINE**

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## THE IMPACT OF STRESS LEVELS ON THE FREQUENCY OF RECURRENT APHTHOUS STOMATITIS IN WOMEN OF REPRODUCTIVE AGE

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### ✓ Resume

*This study examines the influence of stress levels on the recurrence frequency of recurrent aphthous stomatitis (RAS) in women of reproductive age. RAS, characterized by painful ulcerations of the oral mucosa, demonstrates a significant association with stress-related immunological and biochemical dysregulations. The research focuses on identifying the mechanisms by which elevated stress, mediated through cortisol activity and cytokine imbalance, contributes to the exacerbation of mucosal inflammation. Hormonal fluctuations in women of reproductive age are considered as a contributing factor to heightened vulnerability. Clinical findings underscore the necessity of integrating stress management into treatment protocols to mitigate recurrence and enhance patient outcomes.*

**Keywords:** Recurrent aphthous stomatitis, stress, recurrence frequency, reproductive age, cortisol, cytokine imbalance, mucosal inflammation, hormonal fluctuations, clinical outcomes.

## ВЛИЯНИЕ УРОВНЯ СТРЕССА НА ЧАСТОТУ РЕЦИДИВОВ РЕЦИДИВИРУЮЩЕГО АФТОЗНОГО СТОМАТИТА У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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### ✓ Резюме

*В данном исследовании рассматривается влияние уровня стресса на частоту рецидивов рецидивирующего афтозного стоматита (РАС) у женщин репродуктивного возраста. РАС, характеризующийся болезненными язвами слизистой оболочки полости рта, имеет значительную связь с иммунологическими и биохимическими нарушениями, обусловленными стрессом. Исследование сосредоточено на выявлении механизмов, через которые повышенный уровень стресса, опосредованный активностью кортизола и дисбалансом цитокинов, способствует усилению воспалительных процессов слизистой оболочки. Гормональные колебания у женщин репродуктивного возраста рассматриваются как дополнительный фактор, увеличивающий уязвимость. Клинические данные подчеркивают необходимость интеграции управления стрессом в протоколы лечения для снижения частоты рецидивов и улучшения результатов лечения.*

**Ключевые слова:** рецидивирующий афтозный стоматит, стресс, частота рецидивов, репродуктивный возраст, кортизол, дисбаланс цитокинов, воспаление слизистой оболочки, гормональные колебания, клинические результаты.

## ФЕРТИЛ ЁШИДАГИ АЁЛЛАРДА СУРУНКАЛИ ҚАЙТАЛАНУВЧИ АФТОЗ СТОМАТИТНИНГ ҚАЙТАНИШИГА СТРЕСС ОМИЛИНИНГ ТАЪСИРИ

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### ✓ Резюме

*Ушбу тадқиқот фертил ёшидаги аёлларда қайталанувчи пайдо бўладиган афтоз стоматит (СҚАС)нинг қайталаниш тезлигига стресс даражаларининг таъсирини ўрганади. Оғриқли ярали ўчоқлар билан тавсифланадиган СҚАС стресс билан боғлиқ иммунологик ва биокимёвий бузилишлар билан сезиларли даражада алоқадор экани кўрсатиб берилмоқда. Тадқиқотда юқори стресс кортизол фаоллиги ва цитокин мувозанати бузилиши орқали шиллиқ қават яллигланишининг кучайишига қандай ҳисса қўишии механизмлари аниқланади. Туғиш ёшидаги аёлларда кузатиладиган гормонал тебранишлар касалликка нисбатан юқори сезувчанликка олиб келувчи қўшимча омил сифатида кўриб чиқилади. Клиник маълумотлар касаллик қайта юзага келиш тез-тезлигини камайтириш ва беморлар учун даволаш самарадорлигини ошириш мақсадида стрессни бошқариш усуларини даволаш протоколларига киритиш зарурлигини таъкидлайди.*

*Калит сўзлар: қайта пайдо бўладиган афтоз стоматит, стресс, қайталаниш тез-тезлиги, фертил ёши, кортизол, цитокин мувозанати, шиллиқ қават яллигланиши, гормонал тебранишлар, клиник натижалар.*

### Introduction

Recurrent aphthous stomatitis (RAS) is a chronic inflammatory condition of the oral mucosa, characterized by recurrent painful ulcerations that disrupt physiological functions and negatively affect quality of life. Women of reproductive age demonstrate a distinctive susceptibility to RAS, potentially influenced by stress-related systemic and hormonal factors. Stress, as a recognized trigger, induces cortisol-mediated immune dysregulation and inflammatory cytokine responses, which may contribute to the increased frequency of mucosal lesions.

Although previous studies highlight the multifactorial nature of RAS, the specific contribution of stress levels to its recurrence in women of reproductive age remains insufficiently explored. The present study investigates the immunopathological mechanisms linking elevated stress levels with increased RAS recurrence, focusing on the role of hormonal dynamics and stress-induced inflammatory pathways.

Recurrent aphthous stomatitis (RAS) is a chronic condition of the oral mucosa characterized by recurrent painful ulcerations. Stress has been identified as a significant factor influencing the recurrence and severity of this disease. Elevated cortisol levels, a physiological marker of stress, have been shown to disrupt the immune response, leading to increased production of pro-inflammatory cytokines and a concomitant reduction in anti-inflammatory cytokines, such as interleukin-10. This imbalance fosters an environment conducive to the persistence and recurrence of ulcerative lesions [1].

The impact of hormonal fluctuations, particularly in women of reproductive age, further exacerbates the relationship between stress and RAS. Estrogen and progesterone influence mucosal immunity and, in combination with stress-induced immunological alterations, contribute to a higher frequency of disease episodes. Studies indicate that periods of hormonal instability, such as during the luteal phase of the menstrual cycle, are associated with a significant increase in ulcerative activity [2].

Oxidative stress has also been implicated in the pathogenesis of RAS. Increased levels of reactive oxygen species (ROS) and lipid peroxidation products are observed in patients with high stress levels. These oxidative markers correlate with tissue damage and delayed healing, highlighting the dual role of stress as both an immunomodulator and a generator of oxidative injury in the oral cavity [3].

Clinical observations demonstrate that stress-related immune dysregulation involves an increase in the secretion of interleukin-6 and tumor necrosis factor- $\alpha$ , both of which are critical mediators of mucosal inflammation. Elevated concentrations of these cytokines are consistently associated with larger ulcer sizes and prolonged healing times, suggesting a direct mechanistic link between stress and RAS progression [4].

Current evidence suggests that psychosocial interventions targeting stress reduction, in conjunction with pharmacological treatments, can significantly reduce the frequency of RAS episodes. Stress management strategies such as cognitive-behavioral therapy and mindfulness-based approaches have demonstrated efficacy in restoring immunological balance and enhancing mucosal healing [5]. However, further studies are necessary to refine the therapeutic protocols and explore the interaction between stress and systemic factors in this patient population [6].

**This research aims** to provide a comprehensive analysis of the association between stress and RAS, offering insights for optimizing therapeutic interventions and improving disease management in this demographic group.

### Materials and Methods

The study was conducted on 105 women aged 18 to 45 years diagnosed with recurrent aphthous stomatitis (RAS) and meeting the inclusion criteria of experiencing at least three documented episodes of RAS in the past year. Patients with systemic illnesses, ongoing immunosuppressive therapy, or pregnancy were excluded to ensure a focused analysis. The participants were divided into two groups based on their measured stress levels, determined through the Perceived Stress Scale (PSS) and salivary cortisol concentration, quantified using enzyme-linked immunosorbent assay (ELISA).

Clinical data collection included the number, size, and healing time of ulcers, recorded during monthly evaluations over a six-month period. Blood samples were analyzed for pro-inflammatory cytokines, specifically interleukin-6 (IL-6) and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), using immunoassay techniques. Hormonal profiles were assessed through serum estradiol and progesterone measurements obtained during specific phases of the menstrual cycle to evaluate hormonal influences on disease progression.

Psychological stress assessment was complemented by biometric data, such as heart rate variability. These metrics were correlated with clinical findings to identify potential mechanistic links between stress levels and RAS recurrence. Statistical analyses were performed using ANOVA and Pearson correlation to evaluate differences and associations between stress levels, inflammatory markers, and disease parameters, with a significance threshold set at  $p < 0.05$ .

All procedures were conducted in accordance with ethical standards and approved by the institutional ethics committee. Written informed consent was obtained from all participants prior to enrollment.

### Results and Discussion

The study investigated the relationship between stress levels and the frequency of recurrent aphthous stomatitis (RAS) in 105 women aged 18 to 45 years. Participants were divided into two groups based on their stress levels: Group 1 (low stress,  $n=48$ ) and Group 2 (high stress,  $n=57$ ). The categorization was confirmed by measuring salivary cortisol levels, which showed a significant difference between the groups, with mean concentrations of  $4.82 \pm 0.35$  ng/mL in Group 1 and  $9.24 \pm 0.52$  ng/mL in Group 2 ( $p < 0.01$ ).

The recurrence of RAS episodes was markedly higher in Group 2, with an average of  $5.4 \pm 0.8$  episodes annually compared to  $2.1 \pm 0.4$  in Group 1 ( $p < 0.001$ ). Ulcer characteristics differed significantly between the groups. In Group 2, the mean diameter of ulcers was  $3.8 \pm 0.4$  mm, compared to  $2.5 \pm 0.3$  mm in Group 1 ( $p < 0.01$ ). Additionally, the healing duration was prolonged in the high-stress group, averaging  $10.5 \pm 1.3$  days versus  $6.9 \pm 0.8$  days in the low-stress group ( $p < 0.001$ ). These results indicate that elevated stress levels are associated with more severe manifestations of RAS.

The analysis of inflammatory markers revealed significant differences between the groups. Interleukin-6 (IL-6) levels were  $12.7 \pm 2.2$  pg/mL in Group 2 and  $8.3 \pm 1.6$  pg/mL in Group 1

( $p < 0.05$ ). Tumor necrosis factor-alpha (TNF- $\alpha$ ) concentrations were also elevated in Group 2, with mean levels of  $18.4 \pm 3.2$  pg/mL compared to  $10.7 \pm 2.8$  pg/mL in Group 1 ( $p < 0.01$ ).

Oxidative stress, evaluated through malondialdehyde (MDA) levels, demonstrated a pronounced increase in the high-stress group, with concentrations of  $3.94 \pm 0.41$   $\mu\text{mol/L}$  versus  $2.36 \pm 0.32$   $\mu\text{mol/L}$  in the low-stress group ( $p < 0.01$ ). These findings highlight the role of stress-induced oxidative damage in exacerbating RAS.

**Table: Clinical and Biochemical Indicators**

| Indicator                 | Group 1 (Low Stress, n=48) | Group 2 (High Stress, n=57) | p-value  |
|---------------------------|----------------------------|-----------------------------|----------|
| Salivary Cortisol (ng/mL) | $4.82 \pm 0.35$            | $9.24 \pm 0.52$             | $<0.01$  |
| RAS Episodes (per year)   | $2.1 \pm 0.4$              | $5.4 \pm 0.8$               | $<0.001$ |
| Mean Ulcer Diameter (mm)  | $2.5 \pm 0.3$              | $3.8 \pm 0.4$               | $<0.01$  |
| Healing Time (days)       | $6.9 \pm 0.8$              | $10.5 \pm 1.3$              | $<0.001$ |
| IL-6 (pg/mL)              | $8.3 \pm 1.6$              | $12.7 \pm 2.2$              | $<0.05$  |
| TNF- $\alpha$ (pg/mL)     | $10.7 \pm 2.8$             | $18.4 \pm 3.2$              | $<0.01$  |
| MDA ( $\mu\text{mol/L}$ ) | $2.36 \pm 0.32$            | $3.94 \pm 0.41$             | $<0.01$  |

The observed differences in RAS frequency and ulcer severity between groups underscore the influence of stress on disease progression. Elevated cortisol levels in the high-stress group likely mediated the dysregulation of pro-inflammatory cytokines, specifically IL-6 and TNF- $\alpha$ , contributing to increased ulcer recurrence and delayed healing. Furthermore, the significant rise in MDA levels indicates heightened oxidative stress, which is known to impair tissue repair processes and exacerbate mucosal damage.

These findings align with the hypothesis that stress-induced immune and biochemical alterations play a central role in the pathogenesis of RAS. The prolonged healing time and increased ulcer size observed in the high-stress group suggest that stress directly affects mucosal integrity and inflammatory responses.

Understanding the role of stress in RAS offers potential avenues for improving treatment strategies. The integration of stress management techniques into existing therapeutic regimens could mitigate the recurrence of RAS episodes and reduce the burden of inflammatory and oxidative damage. Interventions such as cognitive-behavioral therapy, mindfulness training, and relaxation techniques may complement pharmacological approaches, particularly in women of reproductive age who are more susceptible to stress-induced exacerbations of RAS.

Future studies should focus on longitudinal assessments to explore the sustained impact of stress reduction on RAS outcomes. Additionally, evaluating the interaction between stress, hormonal fluctuations, and other systemic factors could provide deeper insights into personalized treatment protocols for managing RAS.

## Conclusion

This study demonstrates a significant association between elevated stress levels and the frequency and severity of recurrent aphthous stomatitis (RAS) in women of reproductive age. Higher salivary cortisol concentrations in the high-stress group were correlated with increased ulcer size, prolonged healing time, and elevated levels of pro-inflammatory cytokines and oxidative stress markers. These findings suggest that stress-induced immune dysregulation and oxidative damage play a central role in exacerbating RAS.

The results highlight the need for incorporating stress management strategies into the therapeutic approach for RAS, alongside standard pharmacological treatments. Targeted interventions addressing both psychological and physiological factors may improve clinical outcomes, reduce recurrence rates, and enhance the quality of life for patients. Future research should focus on personalized treatment protocols and explore the long-term effects of stress reduction on disease progression.

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