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BIOCHEMICAL AND IMMUNOLOGICAL ORAL FLUID PROFILES IN CHILDREN PRESENTING WITH RECURRENT HERPETIC STOMATITIS AND CONCOMITANT ALLERGIC PATHOLOGY

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Abstract.

The coexistence of allergic diseases and recurrent herpetic stomatitis (RHS) in pediatric populations correlates with exacerbated clinical manifestations and profound immunobiological dysregulation. Oral fluid serves as a reservoir for diverse biomarkers possessing diagnostic and prognostic utility for inflammatory and infectious oral cavity disorders.

Objective. *This study aimed to characterize alterations in biochemical, immunological, and metabolic oral fluid parameters among children diagnosed with RHS, both as an isolated condition and in conjunction with allergic disorders, while evaluating their diagnostic potential.*

Materials and Methods. *A prospective study was conducted involving 120 children aged 1-7 years, categorized into three cohorts: a control group of healthy individuals (n = 40), a comparison group with RHS (n = 40), and a primary group with RHS comorbid with allergic diseases (n = 40). Nine oral fluid parameters were quantified employing diagnostic test strips (Qingdao Hightop Biotech Co., Ltd.). Conducted in accordance with the principles of the WMA Declaration of Helsinki (2013 revision), this investigation was approved by the Bioethics Committees of the Bukhara State Medical Institute and Samarkand State Medical University, with written informed consent obtained from the parents or legal guardians of all participants. Statistical data are expressed as M ± SEM. Intergroup differences were analyzed via Student's t-test, with $p < 0.05$ established as the threshold for statistical significance. Data processing was performed using SPSS Statistics version 26.0. This research was integrated into the Bukhara State Medical Institute research program entitled «Development of diagnostic criteria for assessing the immunobiological status of oral fluid in infectious and inflammatory oral diseases in children» (2022-2026).*

Results. *Children with RHS exhibited significant elevations of formed elements of blood (×1.24), leukocytes (×2.14), protein (×3.10), and nitrites (×2.00; $p < 0.001$) in oral fluid. These alterations were substantially more pronounced in cases of RHS comorbid with allergy, where formed elements increased 4.76-fold, leukocytes 8.32-fold, and protein 3.25-fold, accompanied by concomitant rises in ketone bodies (×1.39) and glucose (×1.28). Ascorbic acid concentrations trended downward in both pathological cohorts ($p > 0.05$).*

Conclusions. *Formed elements of blood, leukocytes, nitrites, protein, ketone bodies, and glucose represent valuable diagnostic biomarkers and potential predictors of RHS severity and prognosis, particularly in the presence of concomitant allergic pathology.*

Keywords: *Recurrent Herpetic Stomatitis; Oral Fluid; Allergic Diseases; Diagnostic Biomarkers; Leukocytes; Nitrites; Oxidative Stress; Children.*

Introduction

Pediatric oral health constitutes an integral component of systemic well-being, being inextricably linked to immune function, metabolic processes, and somatic health [1, 2]. Herpes simplex virus type 1 (HSV-1) remains a primary etiological agent of pediatric oral infectious diseases. Systematic reviews and meta-analyses indicate that HSV-1 seroprevalence among children in Asia averages 50.0% (95% CI: 41.3-58.7%), reaches 65.2% (95% CI: 53.6-76.1%) in Middle Eastern and North African nations, and stands at 57.2% (95% CI: 49.7-64.6%) across Latin America and the Caribbean [3, 4, 5]. In the United States, notwithstanding a declining trend, pooled HSV-1 seropositivity among children persists at approximately 38.0% and increases with age [6].

Recurrent herpetic stomatitis (RHS) results from latent HSV infection reactivation, manifesting as recurrent episodes of herpetic eruptions and painful oral mucosal ulcerations [7]. Beyond viral-mediated damage, RHS pathogenesis involves local inflammatory response activation, proinflammatory cytokine production, oxidative stress, and mucosal barrier dysfunction [8]. Clinical observations demonstrate that children with atopic conditions – including atopic dermatitis, allergic rhinitis, and bronchial asthma – are predisposed to more frequent and severe herpetic superinfections, such as eczema herpeticum [9]. This susceptibility stems from shifted Th1/Th2 immune response equilibrium, characterized by impaired interferon production and defective cytotoxic T-lymphocyte function – both critical for controlling HSV reactivation [9].

Recent years have witnessed a sustained increase in allergic disease prevalence within pediatric populations, consequently elevating the frequency of RHS cases superimposed on allergic disorders [10, 11]. Allergic inflammation establishes a supplementary proinflammatory milieu in the oral cavity, wherein elevated IL-4, IL-13, TNF-α, and IgE concentrations alter local immune responses, exacerbate oxidative stress, and disrupt oral fluid metabolite equilibrium [10, 12].

Oral fluid constitutes a unique biological medium comprising salivary gland secretions, gingival crevicular fluid, cellular components, and metabolic byproducts. Its biochemical profile reflects both localized oral inflammatory status and systemic physiological shifts [13, 14]. As a non-invasive biofluid, oral fluid offers distinct advantages over blood – namely accessibility, collection simplicity, and the feasibility of longitudinal sampling – rendering it particularly suitable for pediatric practice [1, 15]. Diagnostically significant parameters of oral fluid in inflammatory oral diseases include leukocytes, protein, nitrites (serving as indirect nitric oxide markers), glucose, ketone bodies, and antioxidant factors including ascorbic acid [16, 17, 18].

Oral fluid nitrites merit particular attention, as nitric oxide (NO) possesses antimicrobial and signaling properties. Its synthesis is mediated by the reduction of dietary nitrates by oral microflora alongside epithelial NO synthase activity. A systematic review and meta-analysis demonstrated that oral fluid nitrite levels correlate with caries intensity and inflammatory severity in children [19]. During viral oral mucosal infections, augmented NO production may function as a component of antiviral defense; however, excessive NO and its reactive derivatives induce tissue damage and oxidative stress [20].

Despite accumulating evidence, the extent of comprehensive oral fluid biochemical profile alterations in children presenting with RHS comorbid with allergic disorders remains insufficiently characterized, with the diagnostic utility of these parameters in clinical pediatric dentistry yet to be established.

Study Objective. This investigation aimed to characterize alterations in biochemical, immunological, and metabolic oral fluid parameters among children diagnosed with RHS – both isolated and concomitant with allergic disorders – while evaluating their diagnostic and prognostic potential.

Materials and Methods

Study Design and Setting. This prospective cohort study was conducted at the clinical facilities of the Bukhara State Medical Institute (Department of Microbiology, Virology, and Immunology) and Samarkand State Medical University (Department of Pediatric Dentistry) between 2022 and 2025.

Patient Characteristics. The study population comprised 120 children aged 1-7 years, stratified into three cohorts: a control group of healthy individuals (n = 40), a comparison group of patients with RHS lacking concomitant allergies (n = 40), and a primary group presenting with RHS comorbid with allergic disorders (n = 40).

Methodology. Oral fluid collection followed a standardized protocol involving fasting participants. Nine parameters were quantified using diagnostic test strips (Qingdao Hightop Biotech Co., Ltd.): specific gravity, pH, formed elements of blood, leukocytes, protein, ketone bodies, glucose, nitrites, and ascorbic acid. Each parameter was evaluated at specific time intervals as specified by the manufacturer's instructions.

Ethical Considerations. Conducted in accordance with the principles of the WMA Declaration of Helsinki (2013 revision), this investigation was approved by the Bioethics Committees of the Bukhara State Medical Institute and Samarkand State Medical University, with written informed consent obtained from the parents or legal guardians of all participants.

Statistical Analysis. Data are expressed as M ± SEM. Intergroup differences were analyzed via Student's t-test, with statistical significance defined as $p < 0.05$. Data processing was performed using SPSS Statistics version 26.0.

Research Integration. This investigation was conducted as part of the Bukhara State Medical Institute research program entitled «Development of diagnostic criteria for assessing the immunobiological status of oral fluid in infectious and inflammatory oral diseases in children» (2022-2026).

Results

1. Oral Fluid Parameters in Healthy Children

Baseline oral fluid parameters for healthy children, utilized as reference values, are detailed in Table 1.

Table 1

Oral fluid biochemical parameters in clinically healthy children

Indicators	Control group, n=40
Density, unit	1.03 ± 0.01
pH	6.29 ± 0.04
Blood formed elements (μL)	78.90 ± 4.20
Leukocytes, μL	19.40 ± 4.11
Protein, g/L	0.20 ± 0.04
Ketones, mmol/L	0.54 ± 0.04
Glucose, mmol/L	1.12 ± 0.10
Nitrite, mg/L	20.0 ± 1.54
Vitamin C, mmol/L	0.71 ± 0.13

Note: Data are presented as M ± SEM.

Formed elements of blood in the oral fluid of healthy children were 78.90 ± 4.20 μL, reflecting the physiological influx of blood cells from the gingival crevicular fluid. Leukocyte counts (19.40 ± 4.11 μL) indicate the activity of local immune defense mechanisms, whereas protein concentrations (0.20 ± 0.04 g/L) correspond to physiological serum and secretory immunoglobulin levels. Nitrite concentrations (20.0 ± 1.54 mg/L) represent basal oral microflora activity in dietary nitrate reduction, complemented by ascorbic acid (0.71 ± 0.13 mmol/L) providing antioxidant protection for the oral mucosa.

2 2. Oral Fluid Parameters in Children with Isolated RHS.

Comparative analysis of oral fluid parameters within the RHS cohort is detailed in Table 2.

Among the nine parameters evaluated, four – formed elements of blood, leukocytes, protein, and nitrites – differed significantly from control values ($p < 0.05$-0.001). Protein concentration exhibited the most substantial elevation, increasing 3.10-fold ($p < 0.001$) and reflecting augmented serum immunoglobulin synthesis in response to herpetic infection. Nitrite levels doubled ($p < 0.001$), evidencing intensified nitric oxide-mediated inflammatory pathway activity. Oral fluid leukocytosis (×2.14; $p < 0.001$) demonstrates local cellular immune response activation following viral mucosal injury (Figure 1). No significant intergroup differences were observed for the remaining five parameters, including specific gravity, pH, ketone bodies, glucose, and ascorbic acid ($p > 0.05$).

Table 2

Comparative oral fluid parameters in children with recurrent herpetic stomatitis

Indicators	Control group, n=40	Comparison group, n=40
Density, unit	1.03 ± 0.01	1.03 ± 0.01 ↔
pH	6.29 ± 0.04	6.37 ± 0.06 ↔
Blood formed elements (μL)	78.90 ± 4.20	97.83 ± 8.58* ↑
Leukocytes, μL	19.40 ± 4.11	41.43 ± 7.85* ↑
Protein, g/L	0.20 ± 0.04	0.62 ± 0.33* ↑
Ketones, mmol/L	0.54 ± 0.04	0.55 ± 0.03 ↔
Glucose, mmol/L	1.12 ± 0.10	1.29 ± 0.23 ↔
Nitrite, mg/L	20.0 ± 1.54	40.0 ± 1.69* ↑
Vitamin C, mmol/L	0.71 ± 0.13	0.62 ± 0.06 ↔

Note: ** denotes statistically significant differences relative to the control group; ↑ indicates the direction of change; ↔ signifies no significant differences.*

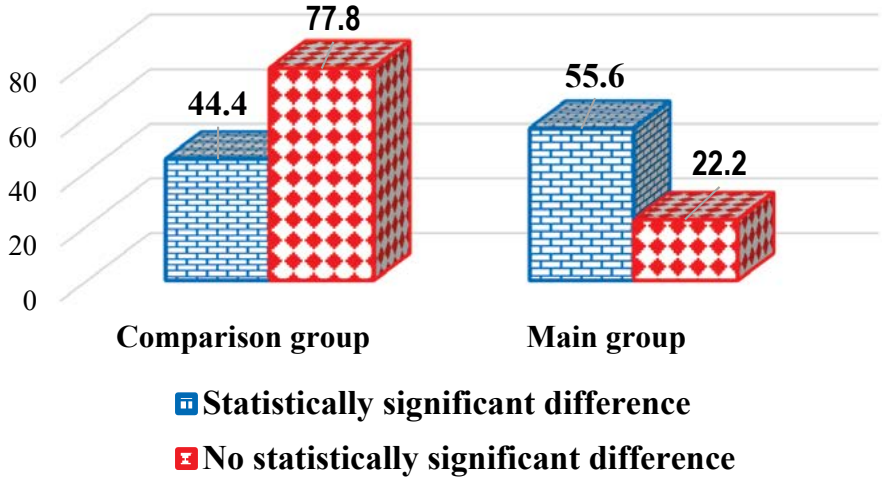

Figure 1. Differences of the comparison and main groups' indicators relative to the control group parameters, %.

3. Oral Fluid Parameters in Children Presenting with RHS and Concomitant Allergic Disorders.

Oral fluid profiles within the primary cohort (RHS + allergy) relative to both control and comparison groups are detailed in Table 3.

Within the primary cohort, seven of the nine evaluated parameters (77.8%) exhibited statistically significant deviations from control values. The most pronounced elevations occurred in leukocyte counts (8.32-fold) and formed elements of blood levels (4.76-fold; $p <$ 0.001), substantially exceeding the values recorded in the comparison group. A summary of fold changes relative to baseline is provided in Table 4.

Table 3

Comparative oral fluid parameters in children with RHS comorbid with allergic disorders

Indicators	Control, n=40	Comparison, n=40	Main group, n=40
Density, unit	1.03 ± 0.01	1.03 ± 0.01 ↔	1.04 ± 0.01 ↔
pH	6.29 ± 0.04	6.37 ± 0.06 ↔	6.49 ± 0.08* ↑
Blood formed elements (μL)	78.90 ± 4.20	97.83 ± 8.58* ↑	375.88 ± 33.41*↑^
Leukocytes, μL	19.40 ± 4.11	41.43 ± 7.85* ↑	161.43 ± 25.62*↑^
Protein, g/L	0.20 ± 0.04	0.62 ± 0.33* ↑	0.65 ± 0.04* ↑
Ketones, mmol/L	0.54 ± 0.04	0.55 ± 0.03 ↔	0.75 ± 0.07*↑^
Glucose, mmol/L	1.12 ± 0.10	1.29 ± 0.23 ↔	1.43 ± 0.22* ↑
Nitrite, mg/L	20.0 ± 1.54	40.0 ± 1.69* ↑	40.0 ± 1.72* ↑
Vitamin C, mmol/L	0.71 ± 0.13	0.62 ± 0.06 ↔	0.65 ± 0.05 ↔

*Note: * indicates significant differences relative to the control group; ^ denotes significant differences between the comparison and primary cohorts; ↑ indicates an increase; ↔ signifies no significant differences.*

Table 4

Fold changes in oral fluid parameters relative to the control group

Indicators	RGS vs Control (fold change)	RGS+Allergy vs Control (fold change)
Blood formed elements	1.24* ↑	4.76* ↑
Leukocytes	2.14* ↑	8.32* ↑
Protein	3.10* ↑	3.25* ↑
Nitrite	2.00* ↑	2.00* ↑
Ketones	1.02 ↔	1.39* ↑
Glucose	1.15 ↔	1.28* ↑
Vitamin C	–1.15 ↔	–1.09 ↔

*Note: * denotes statistically significant differences; ↑ indicates an elevation; ↔ signifies no significant differences; negative values represent a decrease.*

The exacerbation of oral fluid leukocytosis concomitant with allergic pathology aligns with intensified chronic inflammation. Patients with allergic disorders exhibit dysregulated Th1/Th2 equilibrium, establishing an immunosuppressive milieu that facilitates more frequent and severe HSV reactivations [9]. Elevated ketone body concentrations within the primary cohort (×1.39; $p < 0.05$) reflect augmented hepatic lipid catabolism responding to increased metabolic demands amidst systemic inflammation. Similarly, the rise in glucose levels (×1.28; $p < 0.05$) corresponds to the heightened energy consumption of inflamed tissues.

Discussion

The present study's findings demonstrate that the oral fluid biochemical and immunological profile undergoes substantial changes in RHS, with concomitant allergic pathology leading to significantly more pronounced and multifaceted alterations. This aligns with contemporary data highlighting saliva's value as a non-invasive diagnostic biofluid [1, 14].

A prominent change observed in both pathological groups was an increase in oral fluid leukocytes, notably an 8.32-fold elevation in children with RHS and allergy. This observation corroborates the significance of oral fluid leukocytosis as a sensitive marker of inflammatory processes. Recent investigations into proinflammatory cytokines and antioxidant enzymes in the oral fluid of children with dentofacial infections revealed analogous patterns: elevated inflammatory markers correlated with clinical manifestation severity, and comprehensive biochemical parameter assessment provided greater diagnostic utility than isolated indicators [21].

A threefold increase in protein concentration in both the comparison and primary groups is associated with enhanced immunoglobulin synthesis, predominantly secretory IgA, whose role as the first line of local antiviral defense in the oral cavity is well-established [22]. Similar protein elevations in infectious and inflammatory diseases have been documented in studies examining oral fluid biomarkers across various oral pathologies [2].

The twofold increase in nitrites, consistent across both pathological groups, affirms nitric oxide's role as a pivotal inflammatory mediator in viral mucosal infections. Systematic analysis has established oral fluid nitrites as a reliable indicator of NO-dependent mechanisms involved in both antimicrobial defense and inflammatory damage [19, 20]. A two-stage mechanism – bacterial reduction of dietary nitrates coupled with epithelial NO synthase activation during inflammation – explains the persistently elevated nitrite levels irrespective of an allergic component [20].

The additional elevations in ketone bodies and glucose, specifically characteristic of the primary group, reflect metabolic stress induced by a dual inflammatory signal: viral and allergic. Both changes correspond to augmented

catabolism and increased energy expenditure during chronic combined inflammation Analogous metabolic shifts have been identified in systematic analyses of salivary biomarkers in children with caries undergoing comprehensive treatment [23].

Although not reaching statistical significance, the trend toward decreased ascorbic acid in both pathological groups holds clinical importance: a reduction in the oral fluid's antioxidant reserve compromises mucosal protection against oxidative damage. Impaired oral fluid antioxidant status in infectious and inflammatory diseases is a consistent finding, well-described in reviews on oxidative stress markers in saliva [24, 25].

The higher proportion of statistically significant parameters in the primary group (77.8%) compared to the comparison group (44.4%) aligns with the concept of an allergic background acting as a factor that potentiates systemic and local inflammatory responses. The observed changes are consistent with the contemporary paradigm viewing oral fluid as an informative «mirror» of the body's inflammatory status, while its comprehensive biochemical analysis represents a promising tool for non-invasive monitoring in children [26].

Study Limitations. Absolute value precision is constrained by the application of semi-quantitative test strips. The absence of an immunoglobulin profile (IgA, IgG, IgM, sIgA) further precludes detailed characterization of protein fraction alterations, necessitating future expanded investigations incorporating cytokine parameters and immunophenotyping.

Conclusions

1. Among children with RHS, 44.4% of oral fluid parameters differed significantly from control values, specifically formed elements of blood, leukocytes, protein, and nitrites ($p < 0.001$). These elevations are attributed to viral mucosal damage, local immune response activation, and NO-mediated inflammatory pathways.

2. RHS combined with allergic disorders substantially intensified oral fluid biochemical alterations, with 77.8% of parameters exhibiting significant deviations from the control. Formed elements of blood levels increased 4.76-fold and leukocytes 8.32-fold, while ketone bodies (×1.39) and glucose (×1.28) rose in response to systemic metabolic stress.

3. Comprehensive evaluation of formed elements of blood, leukocytes, protein, nitrites, ketone bodies, and glucose in the oral fluid may serve as a non-invasive diagnostic tool for stratifying RHS severity and predicting clinical outcomes in pediatric patients with concomitant allergies.

4. The trend toward decreased ascorbic acid in pathological cohorts indicates antioxidant reserve depletion, justifying its inclusion in the comprehensive monitoring of RHS patients.

Perspectives for Further Research. Future research directions involve developing a multiparametric oral fluid diagnostic profile incorporating cytokine analysis (IL-6, TNF-α, IL-10) and immunoglobulin quantification (sIgA, IgG) to further elucidate RHS immune response mechanisms. Investigating oral fluid biomarker dynamics during antiviral therapy (acyclovir) is likewise warranted to evaluate treatment efficacy. Comparative analysis of oral fluid biochemical parameters across diverse clinical forms and severities of allergic diseases remains of particular interest for establishing personalized patient management protocols.

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БІОХІМІЧНІ ТА ІМУНОЛОГІЧНІ ПОКАЗНИКИ РОТОВОЇ РІДИНИ У ДІТЕЙ З РЕЦИДИВУЮЧИМ ГЕРПЕТИЧНИМ СТОМАТИТОМ ТА СУПУТНЬОЮ АЛЕРГІЧНОЮ ПАТОЛОГІЄЮ

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Резюме.

Поєднання алергічних захворювань та рецидивуючого герпетичного стоматиту (РГС) у дітей супроводжується посиленням клінічних проявів та вираженими імунобіологічними порушеннями.

Мета. Вивчити зміни біохімічних, імунологічних та метаболічних параметрів ротової рідини у дітей з РГС у вигляді ізольованого захворювання та в поєднанні з алергічними хворобами, а також оцінити їх діагностичний потенціал.

Матеріали та методи. Проспективне дослідження 120 дітей віком 1-7 років: контрольна група (n=40), група порівняння – РГС (n=40), основна – РГС + алергія (n=40). Оцінювались 9 параметрів ротової рідини (тест-смужки Qingdao Hightop). Статистика: t-критерій Стьюдента, $p<0,05$. Дослідження проводилося відповідно до принципів Гельсінської декларації ВМА (редакція 2013 року). Протокол схвалено комітетами з біоетики БухГМІ та СамГМ У. Інформовану згоду отримано від батьків (законних представників) усіх учасників. Статистичні дані представлені як M ± SEM. Міжгрупові відмінності оцінювалися за допомогою t-критерію Стьюдента; $p<0,05$ вважалося статистично значущим. Статистична обробка – SPSS Statistics версії 26.0. Робота виконана в рамках плану НДР Бухарського державного медичного інституту за темою «Розробка діагностичних

критеріїв оцінки імунобіологічного статусу ротової рідини при інфекційно-запальних захворюваннях порожнини рота у дітей» (2022-2026 рр.).

Результати. У групі порівняння достовірно підвищені формені елементи крові (×1,24), лейкоцити (×2,14), білок (×3,10) та нітрити (×2,00). В основній групі зміни значно виражені: лейкоцити зросли в 8,32 рази, формені елементи – в 4,76 рази; додатково підвищились кетонові тіла (×1,39) та глюкоза (×1,28).

Висновки. Формені елементи крові, лейкоцити, нітрити, білок, кетонові тіла та глюкоза ротової рідини є цінними діагностичними біомаркерами та предикторами тяжкості РГС, особливо за наявності алергічного фону.

Ключові слова: рецидивуючий герпетичний стоматит; ротова рідина; алергічні захворювання; діагностичні біомаркери; лейкоцити; нітрити; окисний стрес; діти.

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