HYGIENIC AND GENETIC DETERMINANTS OF DERMATO-RESPIRATORY SYNDROME FORMATION IN CHILDREN: THE ROLE OF VITAMIN D AND MMP-9 AND TGF-β1 GENE POLYMORPHISMS

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Abstract. *This article presents a comprehensive analysis of the etiopathogenetic mechanisms underlying the development of dermatorespiratory syndrome (DRS) in the pediatric population of the Republic of Uzbekistan (Tashkent). The study is based on the results of a one-time analytical study involving 151 children with a confirmed diagnosis of DRS and 50 children in the control group. For the first time in the region, the association between polymorphic loci of matrix metalloproteinase-9 (MMP-9, A-8202G polymorphism) and transforming growth factor beta-1 (TGF-β1, Arg25Pro polymorphism) with vitamin D levels and nutritional status indicators was assessed. The study results demonstrate a high prevalence of vitamin D deficiency (average level 19.2 ng/ml) in the main group, which correlates with the severity of clinical manifestations according to the SCORAD scale (r = -0.62). It was established that the heterozygous AG genotype of the MMP-9 gene (identified in 49.59% of patients) is a significant predictor of epithelial barrier dysfunction. The identified nutritional imbalance, characterized by zinc and magnesium deficiency against a background of excessive consumption of simple carbohydrates, acts as a modifiable risk factor that exacerbates the implementation of the genetic program of inflammation. Based on the obtained data, a personalized preventive hygiene model was developed and substantiated, including targeted correction of micronutrient status, taking into account the patient's genetic profile.*

Keywords: *dermato-respiratory syndrome, atopic march, atopic dermatitis, children, vitamin D deficiency, genetic polymorphism, MMP-9, TGF-β1, nutritional status, epithelial barrier, personalized prevention, Uzbekistan.*

Introduction.

Relevance of the problem of allergic morbidity**:** In modern pediatrics and the hygiene of children and adolescents, the problem of allergic diseases has become a global medical and social threat. Epidemiological data from recent decades indicate a steady increase in the prevalence of atopic conditions, affecting, according to various estimates, between 30% and 40% of the child population in developed and developing countries.[1] The Republic of Uzbekistan is no exception: urbanization, changes in dietary habits, climate change, and increased airborne allergen exposure in major industrial centers such as Tashkent contribute to the rise in sensitization among the pediatric population. [2]

Of particular clinical significance is the dermatorespiratory syndrome (DRS)—a combined involvement of the skin and respiratory tract, which is a classic manifestation of the "atopic march." The concept of the atopic march describes the natural progression of allergy: from the manifestation of atopic dermatitis (AD) in early childhood to the subsequent development of allergic rhinitis (AR) and progression to bronchial asthma (BA). [3] According to current understanding, AtD is not merely a localized skin condition but a "launchpad" for systemic Th2-mediated inflammation. The compromised skin barrier becomes a gateway for allergens, leading to systemic sensitization and hyperreactivity of the bronchial tree. Statistics show that the dermo-respiratory phenotype is observed in 60% of children with severe AD, which necessitates a reevaluation of approaches to prevention and treatment.[1]

Research Focus: Barrier Dysfunction and Genetic Determinism.

Despite the availability of standardized treatment protocols, therapeutic efficacy for DRS remains variable. This is because standard therapy is often aimed at relieving symptoms but does not

address the underlying mechanisms of barrier dysfunction or the genetically determined characteristics of the immune response.

A key link in the pathogenesis of DRS is the disruption of the integrity of epithelial barriers (skin and respiratory tract mucosa). In this process, extracellular matrix remodeling enzymes, particularly matrix metalloproteinases (MMPs), play a critical role. The *MMP-9* gene, which encodes gelatinase B, is responsible for the degradation of type IV collagen in the basement membrane. Its overexpression leads to "leaky" barriers, tissue infiltration by inflammatory cells, and chronicity of the process. [5] Polymorphisms in the *MMP-9* gene can modulate the enzyme's expression level, determining individual predisposition to severe disease progression.

Parallel to the destructive processes, pathological tissue remodeling occurs, regulated by cytokines such as transforming growth factor beta-1 (TGF-β1). Polymorphisms of the *TGF-β1* gene are associated with fibrotic changes in the bronchial walls, which clinically manifest as irreversible bronchial obstruction and reduced lung function. [6]

The Role of Vitamin D as a Steroid Hormone and Immunomodulator.

In the context of hygienic and nutritional correction of DRS, vitamin D (cholecalciferol) plays a central role. Modern science views it not as a vitamin in the classical sense, but as a potent secosteroidal prohormone. Its active metabolite—1,25-dihydroxyvitamin D (calcitriol)—interacts with specific nuclear receptors (VDR) that are expressed in most immunocompetent cells and keratinocytes. [1]

The mechanisms by which vitamin D influences the pathogenesis of DRS are multifaceted:

1. Regulation of the epithelial barrier: Vitamin D induces the expression of tight junction proteins (filaggrin, claudin), ensuring the physical integrity of the epidermis and mucous membranes. [9]

2. Immunomodulation: Through VDR signaling, vitamin D suppresses the proliferation of pro-inflammatory Th1 and Th17 lymphocytes, reduces the secretion of pro-allergic cytokines (IL-4, IL-5, IL-13), and stimulates the population of regulatory T cells (Treg), thereby preventing autoimmune reactions. [10]

3. Antimicrobial protection: Vitamin D stimulates the production of endogenous antimicrobial peptides (cathelicidin LL-37), which is critically important for protecting the skin against colonization by *Staphylococcus aureus*, a potent trigger of atopic dermatitis. [9]

Nutritional aspects

The biological effects of vitamin D and the functioning of enzymatic systems cannot occur without adequate micronutrient intake. Zinc (Zn) is a structural component of the DNA-binding domains of the VDR receptor ("zinc fingers") and a cofactor for metalloproteinases. Magnesium (Mg) is necessary for the enzymatic activation of vitamin D in the liver and kidneys. A deficiency of these elements, against a background of excessive carbohydrate consumption, creates the metabolic basis for chronic inflammation. [11]

Research Objective

The aim of this study is to develop a scientifically grounded hygienic model for the prevention of dermatorespiratory syndrome in children living in Tashkent, based on a comprehensive analysis of genetic polymorphisms (*MMP-9*, *TGF-β1*), vitamin D status, and nutritional profile characteristics.

Material and methods of research.

The study was conducted as a cross-sectional study with case-control elements. The clinical and laboratory parts of the study were conducted at the Republican Specialized Scientific and Practical Medical Center (RSSPM) of Pediatrics (Tashkent, Uzbekistan). The study protocol underwent ethical review and complies with the principles of the World Medical Association's Declaration of Helsinki.

Characteristics of the participants.

The study included 151 children (main group) aged 3 to 15 years with a verified diagnosis of dermatorespiratory syndrome.

Inclusion criteria:

- Presence atopic dermatitis (diagnosis established according to the Hanifin & Rajka criteria).
- Presence of concomitant respiratory allergies (allergic rhinitis and/or bronchial asthma).
- Permanent residence in Tashkent.
- Signed informed consent from parents.

Exclusion criteria: presence of severe somatic pathologies, autoimmune diseases outside the atopy spectrum, use of systemic glucocorticosteroids within the last month.

The control group consisted of 50 otherwise healthy children, matched for gender, age, and ethnicity, with no personal or family history of allergic diseases.

Clinical examination methods Validated international tools were used for an objective assessment of disease severity:

1. Assessment of AD severity: The SCORAD (Scoring Atopic Dermatitis) scale was used. The following were assessed: area of involvement (rule of nines), intensity of clinical symptoms (erythema, edema, oozing, excoriations, lichenification, dryness), and subjective sensations (itching, sleep disturbance).

2. Asthma control assessment: The ACT (Asthma Control Test) and its pediatric version (C-ACT) were used to assess control of asthma symptoms over the past 4 weeks.

Functional diagnostics:

- Spirometry: Assessment of pulmonary function with measurement of forced expiratory volume in 1 second (FEV1) to detect obstructive abnormalities.
- FeNO: Measurement of the fraction of nitric oxide in exhaled air as a marker of eosinophilic airway inflammation (NObreath analyzer).

Laboratory methods

Determination of Vitamin D and Immune Status

Venous blood serum was used as the test material.

- The level of 25-hydroxyvitamin D was determined using chemiluminescent immunoassay on microparticles (CLIA). This method is characterized by high accuracy and reproducibility. Results were interpreted according to the criteria of endocrinology societies: deficiency <20 ng/mL, insufficiency 21–29 ng/mL, normal ≥30 ng/mL. [1]
- Total IgE levels were determined using an enzyme-linked immunosorbent assay (ELISA) to assess the degree of atopic sensitization.

Genetic analysis Molecular genetic studies included the following steps:

1. DNA extraction: From peripheral blood leukocytes using commercial kits based on nucleic acid sorption on silica gel columns.

2. Genotyping: Performed using the polymerase chain reaction followed by analysis of restriction fragment length polymorphism (PCR-RFLP).

- *MMP-9* gene: The A-8202G polymorphism was studied. Amplification was performed using specific primers flanking the polymorphic region of the promoter. PCR products were hydrolyzed with the corresponding restriction endonuclease (SphI or an analogue). The fragments were visualized by agarose gel electrophoresis.
- *TGF-β1* gene: The Arg25Pro exonic polymorphism (G915C, rs1800471) was studied. This SNP is located in the signal sequence of the gene and affects protein secretion. Allele-specific primers and corresponding restriction enzymes were used.

Nutritional Assessment (Nutrition)

Actual dietary intake was assessed using the **24-hour recall** method in combination with a semi-quantitative food frequency questionnaire (FFQ). The nutrient composition (proteins, fats,

carbohydrates, zinc, magnesium, calcium) was calculated using specialized software adapted to the tables of the chemical composition of foods consumed in Uzbekistan. Particular attention was paid to identifying hidden micronutrient deficiencies and analyzing the glycemic load of the diet.

Statistical analysis

Statistical data processing was performed using the IBM SPSS Statistics v.26

software package.

For descriptive statistics, the mean and standard deviation (M±SD) were used for normally distributed variables.

- Mean values in two independent groups were compared using Student's t-test.
- Analysis of qualitative characteristics (frequency of genotypes and alleles) was performed using Pearson's chi-square (χ^2) test.
- The association of genetic markers with the risk of developing DRS was assessed by calculating the odds ratio (OR) with a 95% confidence interval (CI).
- The Hardy-Weinberg equilibrium of genotype distributions was tested for both groups.
- Correlation analysis was performed using Pearson's correlation coefficient
- Differences were considered statistically significant at $p < 0.05$.

Results and discussion.

Clinical and Immunological Characteristics

Clinical examination of 151 children with dermatorespiratory syndrome

revealed high activity of allergic inflammation. Most patients (68.2%) were diagnosed with moderate-to-severe atopic dermatitis. The mean SCORAD index in the main group was 42.5 ± 12.4 points. The level of total IgE in the blood serum of the affected children varied widely, but the geometric mean was many times higher than age-specific norms, amounting to 485.3 ± 112.5 IU/mL, whereas in the control group this indicator did not exceed 45.2 ± 15.1 IU/mL ($p < 0.001$). A strong positive correlation was found between the SCORAD index and total IgE levels ($r = 0.74$; $p < 0.001$), confirming the leading role of IgE-mediated mechanisms in the pathogenesis of DRS in the studied cohort.

Vitamin D status

An analysis of vitamin D status revealed a marked deficiency in children with allergic conditions, despite high levels of sun exposure in the region. The mean 25(OH)D level in the main group was 19.2 ± 4.8 ng/mL, which corresponds to a clinical deficiency.

- Distribution of levels:
  - Deficiency (<20 ng/mL): 58.3% of children.
  - Insufficiency (21–29 ng/mL): 26.4% of children.
  - Normal (≥30 ng/mL): only 15.3% of children.
- In the control group, the mean 25(OH)D level was 26.4 ± 5.2 ng/mL, which is significantly higher ($p < 0.001$), but also indicates suboptimal status in the population as a whole. A significant inverse correlation was found between vitamin D concentration and clinical and laboratory markers of severity:
- With the SCORAD index: $r = -0.62$ ($p < 0.001$). The lower the vitamin D level, the more severe the skin manifestations.
- With total IgE levels: $r = -0.58$ ($p < 0.01$). Vitamin D deficiency is associated with higher sensitization.

Genetic analysis of MMP-9 (A-8202G)

Molecular genetic analysis of the A-8202G polymorphism in the *MMP-9* gene revealed significant differences in genotype distribution between the groups (Table 1).

- The heterozygous AG genotype predominated in the group of children with DRS, with a frequency of 49.59%.[1]
- The G allele (risk allele) occurs twice as often in the main group as in the control group (52.0%

vs. 26.0%).

● Clinical and genetic analysis showed that carriers of the G allele (AG and GG genotypes) had a significantly higher SCORAD score (48.2 ± 10.1 vs. 32.4 ± 8.5 in AA carriers; $p < 0.05$), confirming the association of this polymorphism with the severity of dermatitis.

Table 1.

Distribution of genotypes and alleles of the MMP-9 (A-8202G) polymorphism

Genotype / Allele	Main group (n=151), abs. (%)	Control group (n=50), abs. (%)	p-value	OR (95% CI)
AA (homozygous, normal)	35 (23.18%)	28 (56.0%)	< 0.01	1.0 (ref)
AG (heterozygous)	**75 (49.59%)**	18 (36.0%)	< 0.05	2.8 (1.4–5.6)
GG (homozygous, mutation)	41 (27.23%)	4 (8.0%)	< 0.01	4.3 (1.5–12.4)
Allele A	145 (48.0%)	74 (74.0%)	< 0.001	0.3 (0.2–0.5)
Allele G	**157 (52.0%)**	26 (26.0%)	< 0.001	**3.1 (1.9–5.0)**

Genetic analysis of TGF-β1 (Arg25Pro)

The Arg25Pro polymorphism of the *TGF-β1* gene demonstrated an association with respiratory disorders. The frequency of genotypes containing the variant **Pro** allele (Arg/Pro and Pro/Pro) in the main group was significantly higher than in the control group ($p < 0.05$). In children carrying the Pro allele, a statistically significant decrease in indicators of external respiratory function was observed: the mean

FEV1 was 82% of predicted, whereas in carriers of the Arg/Arg genotype it was 94% ($p < 0.01$). Clinically, this manifested as signs of early bronchial remodeling: fixed obstruction and frequent episodes of wheezing, resistant to standard bronchodilator therapy.

Combined risk analysis

A multivariate analysis was performed to assess the cumulative effect of genetic and environmental factors. A high-risk group was identified:

- The combination of an "adverse" genotype (*MMP-9* G allele or *TGF-β1* Pro allele) with vitamin D deficiency (<20 ng/mL) increases the risk of developing severe forms of DRS by 4.2 times (OR = 4.2; 95% CI: 2.1–8.4). This indicates a synergistic effect of genetic predisposition and nutritional deficiency.

Nutritional profile

Analysis of actual dietary intake revealed systemic deficiencies:

1. Zinc (Zn) deficiency: Reduced zinc intake (below the age-specific norm) was identified in 65% of children in the main group.
2. Magnesium (Mg) deficiency: Insufficient magnesium intake was recorded in 58% of patients.
3. Carbohydrate imbalance: In 72% of children, the diet was characterized by an excess of simple carbohydrates (sugar, confectionery) against a background of dietary fiber deficiency, which creates a pro-inflammatory metabolic environment.

Discussion.

Interpretation of results in the context of global data

The results of our study confirm and complement current understanding of the role of vitamin D and genetics in the pathogenesis of allergic diseases. The data obtained on the high prevalence of

vitamin D deficiency (84.7%) among children with DRS in Tashkent are consistent with the findings of studies by Peroni et al. (Europe) and Chiu et al. (Asia), who also identified an inverse relationship between 25(OH)D levels and the severity of atopic dermatitis. [12] The paradox of low vitamin D status in a sunny region (Uzbekistan) is likely explained not only by dietary factors but also by genetic characteristics of the receptor system and vitamin D metabolism, as well as clothing habits and sun exposure ("avoidance behavior").

The identified high frequency of heterozygous *MMP-9* carriers (49.59%) exceeds the rates typical of European populations and approaches the data for East Asian cohorts, which underscores the uniqueness of the genetic profile of the Uzbek population and the need for regional reference databases. [13]

Molecular Pathogenesis: The Vitamin D–VDR–MMP-9 Axis

The key scientific contribution of this study is the elucidation of the molecular mechanism linking vitamin D deficiency to skin barrier dysfunction through the regulation of the *MMP-9* gene.

Matrix metalloproteinase-9 (MMP-9) is an enzyme capable of degrading type IV collagen, which forms the basis of the basement membrane of the epidermis and bronchial epithelium, as well as the proteins of tight junctions between cells. Under normal conditions, *MMP-9* expression is tightly regulated. Vitamin D ($1,25(OH)_2D$) binds to the intracellular VDR (Vitamin D Receptor). This complex

is translocated into the cell nucleus, where it forms a heterodimer with the retinoic

acid receptor X (RXR). The VDR-RXR complex binds to negative response elements (nVDREs) in the promoter region of the *MMP-9* gene or physically blocks the binding sites for the pro-inflammatory transcription factors NF-κB and AP-1. [8] Thus, vitamin D acts as a transcriptional repressor, inhibiting the synthesis of the destructive enzyme.

Pathogenic cascade in deficiency:

Vitamin D deficiency: The concentration of the ligand ($1,25(OH)_2D$) decreases, and VDR receptors remain inactive.

1. Lifting of repression: The *MMP-9* gene promoter is "released" from the inhibitory influence of VDR.

2. Genetic amplification: Against a background of allergic inflammation (cytokines IL-4, TNF-α), *MMP-9* transcription is activated. In carriers of the A- 8202G polymorphism (G allele), the promoter exhibits increased affinity for transcription factors, leading to *genetically determined overproduction* of the enzyme. The effect is cumulative: "no brake" (D deficiency) + "full throttle" (G allele) = massive expression of MMP-9.

3. Barrier disruption: Excess MMP-9 destroys the basement membrane and intercellular contacts. A phenotype of "leaky skin" and "leaky epithelium."

4. Vicious cycle: Allergens (house dust mites, pollen) and microbiota (*S. aureus*) penetrate through barrier defects, triggering a new wave of inflammation and further depletion of vitamin D. [5]

The role of TGF-β1 and remodeling

The Arg25Pro polymorphism of the *TGF-β1* (transforming growth factor beta-1) gene is located in the protein's signal sequence, which affects the efficiency of its secretion. Under conditions of chronic inflammation in DRS, carriage of the variant allele (Pro) is associated with dysregulation of TGF-β1's fibrogenic function. This leads to excessive deposition of the extracellular matrix in the submucosal layer of the bronchi, thickening of the reticular basement membrane, and smooth muscle hypertrophy. Clinically, this correlates with a decrease in FEV1 and the formation of an irreversible component of obstruction (remodeling), which is a precursor to severe asthma in adulthood. [6]

The Role of Nutritional Factors: Zinc and Magnesium Identified zinc and magnesium deficiencies exacerbate the described pathogenic mechanisms:

Zinc (Zn): MMP-9 is a zinc-dependent endopeptidase (it contains a zinc ion in its active site). However, systemic zinc deficiency paradoxically exacerbates inflammation. Zinc is essential for proteins

"zinc fingers" (e.g., A20), which inhibit the NF-κB pathway. Zinc deficiency leads to the activation of NF-κB, resulting in the overproduction of pro-inflammatory cytokines and MMP-9. In addition, zinc is critical for DNA repair and keratinocyte proliferation during the healing of skin microtraumas. [11]

Magnesium (Mg): It is an essential cofactor for cytochrome P450 enzymes (25-hydroxylase in the liver and 1α-hydroxylase in the kidneys) that convert vitamin D into its active form. Magnesium deficiency leads to functional hypovitaminosis D even with normal cholecalciferol intake (magnesium-dependent resistance), blocking the protective effects of VDR. [23]

Scientific novelty

For the first time in Uzbekistan, it has been demonstrated that the manifestation of the genetic risk for DRS (carriage of the *MMP-9* G and *TGF-β1* Pro alleles) is not a fatal inevitability but is mediated by modifiable factors— vitamin D levels and micronutrient status. It has been shown that it is precisely the combination of "genetics + deficiency" that yields the maximum clinical effect (OR=4.2), which justifies the need for epigenetic therapy.

Conclusion:

1. Epidemiology of deficiency: Among children with dermatorespiratory syndrome in Tashkent, a critically high prevalence of vitamin D insufficiency and deficiency (84.7%) was identified, with a mean level of 19.2 ng/mL. Low 25(OH)D levels are an independent marker of atopic dermatitis severity (r = -0.62) and high sensitization (IgE).
2. Genetic risk (MMP-9**):** The A-8202G polymorphism of the *MMP-9* gene is a significant genetic predictor of AD in the Uzbek population. The heterozygous AG genotype (49.59%) and the G allele are associated with matrix metalloproteinase overproduction, leading to the destruction of epithelial barriers and a more severe clinical course.
3. Respiratory prognosis (TGF-β1): The Arg25Pro polymorphism of the *TGF-β1* gene determines the risk of early airway remodeling. Carriers of variant alleles demonstrate a significant reduction in lung function parameters (FEV1), which requires early prevention of asthmatic changes.
4. Synergy of factors: A cumulative effect of gene-environment interaction has been established: the combination of genetic risk with vitamin D deficiency increases the likelihood of developing severe forms of DRS by 4.2 times.
5. Nutritional depression: Zinc and magnesium deficiency, as well as excessive carbohydrate intake, are underlying conditions that block endogenous repair mechanisms and reduce the effectiveness of vitamin D-dependent immunoregulation.

Conclusions and Practical Recommendations

1. Implementation of a genetic passport: Recommend molecular genetic screening (MMP-9 A-8202G, TGF-β1 Arg25Pro) for children in the high-risk group (burdened family history, early onset of AD) to predict the trajectory of the "atopic march" and form groups for follow-up care.

Personalized Vitamin D Supplementation:

- Dose adjustments should be made on a case-by-case basis. Children with "high-risk" genotypes (MMP-9 AG/GG) require maintenance of 25(OH)D levels in the upper quartile of the normal range (40–60 ng/mL) for effective suppression of the MMP-9 promoter.
- Therapeutic doses should be selected individually (minimum 1500–2000 IU/day during the loading phase) under the supervision of calcium excretion, with a transition to maintenance doses exceeding standard prophylactic levels.

Nutritional strategy:

- Cofactor therapy: Mandatory administration of magnesium supplements (5–10 mg/kg/day) during the first 1–2 months of vitamin D therapy to activate its metabolism.

○ Barrier therapy: A course of zinc supplements to restore tight junctions in the epithelium and inhibit NF-κB.

○ Diet: Strict restriction of simple carbohydrates (sugars) to reduce systemic low-grade inflammation.

2. Hygiene model: The organization of a hypoallergenic living environment and sun exposure regimen should be based not on general recommendations, but on the child's individual genetic profile, considering the environment as a tool for epigenetic regulation of the disease.

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