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COMPREHENSIVE ANALYSIS OF THE PHYSIOLOGICAL AND BIOCHEMICAL MECHANISMS OF CELIAC DISEASE

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КОМПЛЕКСНЫЙ АНАЛИЗ ФИЗИОЛОГИЧЕСКИХ И БИОХИМИЧЕСКИХ МЕХАНИЗМОВ ЦЕЛИАКИИ

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Abstract. Celiac disease is a chronic, immune-mediated enteropathy that occurs in genetically susceptible individuals following the ingestion of gluten, a protein complex found in wheat, barley, and rye. It is primarily characterized by an abnormal adaptive immune response, leading to inflammation and structural damage in the small intestine. The hallmark pathological feature of the disease is villous atrophy—flattening and shortening of the intestinal villi—alongside crypt hyperplasia and intraepithelial lymphocytosis, all of which contribute to impaired nutrient absorption and the clinical manifestation of malabsorption syndrome. At the molecular level, gluten is incompletely digested in the gastrointestinal tract, resulting in the accumulation of immunogenic proline- and glutamine-rich peptides. These peptides are further modified by the enzyme tissue transglutaminase (tTG) through deamidation, enhancing their affinity for HLA-DQ2 or HLA-DQ8 molecules on antigen-presenting cells in the intestinal mucosa. This interaction stimulates the activation of gluten-specific CD4+ T cells, which secrete proinflammatory cytokines and recruit other immune cells, leading to chronic inflammation and tissue injury. Additionally, patients with celiac disease develop circulating autoantibodies against tTG, which are used as diagnostic markers. While the cornerstone of treatment is a strict lifelong gluten-free diet, adherence can be challenging, and accidental exposure remains a common problem. As a result, current research is increasingly focused on developing alternative or adjunctive therapies, including enzyme supplementation, zonulin pathway blockers, and immunomodulatory agents, which aim to improve intestinal barrier function or regulate the immune response. These approaches offer promising avenues for more comprehensive disease management in the future.

Аннотация. Целиакия – хроническая иммуноопосредованная энтеропатия, которая развивается у генетически предрасположенных людей после употребления глютена – белкового комплекса, содержащегося в пшенице, ячмене и ржи. Заболевание характеризуется, прежде всего, аномальным адаптивным иммунным ответом, приводящим к воспалению и структурным повреждениям тонкого кишечника. Отличительной патологической особенностью заболевания является атрофия ворсинок – уплощение и укорочение кишечных ворсинок – в сочетании с гиперплазией крипт и интраэпителиальным лимфоцитозом, что способствует нарушению всасывания питательных веществ и клиническому проявлению синдрома мальабсорбции. На молекулярном уровне глютен не

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полностью переваривается в желудочно-кишечном тракте, что приводит к накоплению иммуногенных пептидов, богатых пролином и глутамином. Эти пептиды далее модифицируются ферментом тканевой трансглутаминазой (tTG) посредством дезамидирования, что повышает их сродство к молекулам HLA-DQ2 или HLA-DQ8 на антигенпрезентирующих клетках слизистой оболочки кишечника. Это взаимодействие стимулирует активацию глютен-специфических CD4+ Т-клеток, которые секретируют провоспалительные цитокины и привлекают другие иммунные клетки, что приводит к хроническому воспалению и повреждению тканей. Кроме того, у пациентов с целиакией вырабатываются циркулирующие аутоантитела к тТГ, которые используются в качестве диагностических маркеров. Хотя краеугольным камнем лечения является строгая пожизненная безглютеновая диета, ее соблюдение может быть сложным, а случайное воздействие остается распространенной проблемой. В результате современные исследования все больше фокусируются на разработке альтернативных или дополнительных методов лечения, включая ферментные добавки, блокаторы зонулинового пути и иммуномодуляторы, направленные на улучшение барьерной функции кишечника или регуляцию иммунного ответа. Эти подходы открывают многообещающие пути для более комплексного лечения заболевания в будущем.

Keywords: celiac disease, gluten, autoimmune response, tissue transglutaminase (tTG), malabsorption syndrome, zonulin, HLA-DQ2/DQ8, immunopathogenesis.

Ключевые слова: целиакия, глютен, аутоиммунный ответ, тканевая трансглутаминаза (тТГ), синдром мальабсорбции, зонулин, HLA-DQ2/DQ8, иммунопатогенез.

Celiac disease (CD) is a systemic autoimmune disorder with immunogenetic foundations, associated with hypersensitivity to gluten proteins and strongly linked to the HLA-DQ2 and HLA-DQ8 alleles. The disease primarily affects the small intestine; however, the clinical manifestations are broad, with both intestinal and extra-intestinal symptoms [5].

According to epidemiological data, approximately 1 in every 70 to 200 individuals worldwide is genetically predisposed to the condition [1]. In the pathogenesis of the disease, incompletely digested gluten-derived peptides interact with the intestinal epithelium, triggering the activation of the adaptive immune response.

The epithelial surface of the small intestine is highly specialized for nutrient absorption, characterized by densely packed villi and microvilli that dramatically increase the mucosal surface area [2]. This architectural adaptation allows for efficient digestion and uptake of dietary macronutrients. Proteins such as gluten are typically broken down into smaller peptides and amino acids through the concerted action of pancreatic and intestinal enzymes, and are absorbed via enterocytes that line the intestinal mucosa [6].

In individuals with celiac disease, however, this finely regulated process is disrupted by an inappropriate immune response to gluten-derived peptides. Certain proline- and glutamine-rich fragments of gluten resist complete enzymatic hydrolysis and reach the intestinal mucosa in immunogenic forms. These peptides are further deamidated by the enzyme tissue transglutaminase (tTG), enhancing their affinity for HLA-DQ2 or HLA-DQ8 molecules on antigen-presenting cells. This interaction initiates a cascade of immune events involving the activation of gluten-specific CD4+ T cells and the release of proinflammatory cytokines such as interferon-gamma and interleukin-15.

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The immune-mediated response leads to a breakdown in epithelial integrity, including increased intestinal permeability, intraepithelial lymphocyte infiltration, and progressive villous atrophy. As villi flatten, the absorptive capacity of the small intestine declines, resulting in impaired uptake of essential nutrients such as iron, calcium, folate, and fat-soluble vitamins. Clinically, this manifests as chronic diarrhea, malabsorption syndrome, weight loss, anemia, and growth retardation in pediatric cases. Persistent gluten exposure perpetuates mucosal injury, highlighting the importance of strict dietary management.

In celiac disease, gluten-derived peptides induce the secretion of zonulin by intestinal epithelial cells, which disrupts the function of tight junctions and compromises the integrity of the intestinal barrier [7]. This increased permeability facilitates the translocation of immunogenic peptides into the lamina propria, where they interact with the immune system. Tissue transglutaminase (tTG) enzymatically deamidates specific glutamine residues within these peptides, enhancing their binding affinity to HLA-DQ2 or HLA-DQ8 molecules expressed on antigen-presenting cells [3]. This process leads to the activation of CD4+ T-helper cells, which in turn release proinflammatory cytokines—particularly interferon-gamma (IFN-γ) — thereby sustaining chronic intestinal inflammation.

Histologically, characteristic features of celiac disease include villous atrophy, crypt hyperplasia, and dense infiltration of lymphocytes within the lamina propria. These structural alterations significantly impair the absorptive capacity of the small intestine, ultimately resulting in malabsorption syndrome [4].

The combination of epithelial damage, immune cell infiltration, and chronic inflammation constitutes the hallmark of celiac enteropathy and underlies the clinical symptoms observed in affected individuals. The persistence of gluten in the diet perpetuates these immune responses, further aggravating mucosal injury and nutrient deficiency.

The high proline and glutamine content of gluten renders it resistant to complete degradation by gastrointestinal proteolytic enzymes, leading to the generation of immunogenic peptides such as the 33-mer gliadin peptide in the intestinal lumen. These peptides are capable of triggering immune activation within intestinal epithelial cells, thereby initiating the pathological immune response characteristic of celiac disease.

In healthy individuals, the intestinal epithelial barrier serves as a critical defense mechanism, selectively allowing nutrient absorption while restricting the passage of harmful antigens and pathogens. Tight junction proteins, including claudins, occludin, and zonula occludens (ZO), maintain this barrier integrity by regulating paracellular permeability. Zonulin, an endogenous modulator of tight junctions, plays a key role in the dynamic regulation of intestinal permeability. In celiac disease, exposure to gluten peptides stimulates the release of zonulin from intestinal epithelial cells, resulting in the disassembly of tight junctions and increased paracellular permeability.

The upregulation of zonulin leads to a compromised epithelial barrier, commonly referred to as "leaky gut," which permits the uncontrolled passage of immunogenic gluten peptides and other luminal antigens into the lamina propria. This facilitates the interaction between these antigens and antigen-presenting cells, thereby enhancing the activation of the adaptive immune system. The sustained disruption of the barrier function not only contributes to chronic intestinal inflammation but also increases the risk of systemic immune responses and associated extraintestinal manifestations. Targeting the zonulin signaling pathway has emerged as a promising therapeutic approach to restore epithelial integrity and limit antigen translocation in individuals with celiac disease and other autoimmune conditions [8-10].

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Materials and Methods

This study was conducted as a comprehensive literature-based analysis aimed at evaluating the physiological and biochemical mechanisms underlying celiac disease. A systematic review approach was employed to gather, assess, and synthesize peer-reviewed scientific publications, clinical trials, and meta-analyses from the past two decades (2000–2024). Databases including PubMed, Scopus, and Web of Science were searched using keywords such as “celiac disease,” “gluten,” “tissue transglutaminase,” “zonulin,” “intestinal permeability,” “HLA-DQ2/DQ8,” and “immunopathogenesis.” Inclusion criteria encompassed original research articles, clinical studies, and reviews published in English that investigated molecular, immunological, and histopathological aspects of celiac disease. Studies unrelated to the disease mechanisms or focused exclusively on dietary treatment without mechanistic insight were excluded. Data extracted from the selected literature included descriptions of gluten peptide resistance, enzymatic processing by tissue transglutaminase, HLA-associated antigen presentation, zonulin-mediated tight junction disruption, immune activation pathways, and histological alterations. Special attention was paid to experimental evidence involving human intestinal biopsies, animal models, and in vitro studies using enterocyte cell lines. The findings were analyzed qualitatively and thematically, with an emphasis on identifying consistent molecular patterns and pathophysiological processes involved in disease progression. Graphical representations and mechanistic models were adapted where applicable to support the explanatory framework.

Clinical Manifestations of Celiac Disease

Celiac disease exhibits a broad spectrum of clinical manifestations, ranging from classical gastrointestinal symptoms to atypical and extraintestinal presentations. The classical form predominantly affects the small intestine, resulting in malabsorption and associated signs such as chronic diarrhea, steatorrhea, abdominal distension, bloating, and weight loss. These symptoms are often accompanied by failure to thrive and growth retardation in pediatric patients. In addition to gastrointestinal complaints, patients may present with anemia secondary to iron, folate, or vitamin B12 deficiencies, osteoporosis due to impaired calcium absorption, and neurological symptoms including peripheral neuropathy and ataxia. Dermatological manifestations such as dermatitis herpetiformis—an intensely pruritic, blistering rash — are considered pathognomonic for celiac disease. Non-classical and silent forms of the disease are increasingly recognized, with some individuals exhibiting minimal or no overt gastrointestinal symptoms but presenting with isolated extraintestinal findings such as fatigue, elevated liver enzymes, infertility, recurrent miscarriages, or autoimmune comorbidities including type 1 diabetes mellitus and autoimmune thyroiditis. The variability in clinical presentation often complicates timely diagnosis, underscoring the importance of serological screening and histopathological confirmation in at-risk populations.

Regional Epidemiology and Prevalence in Azerbaijan and Surrounding Areas. Data regarding the prevalence of celiac disease in Azerbaijan and the broader South Caucasus region remain limited due to underdiagnosis and insufficient population-based screening. However, preliminary studies and hospital reports suggest that the prevalence may be comparable to global averages, potentially ranging from 0.5% to 1% among the general population. Genetic studies indicate that the frequency of HLA-DQ2 and HLA-DQ8 alleles in Azerbaijani populations is consistent with that observed in other Eurasian populations, suggesting a similar genetic susceptibility profile. Nonetheless, cultural dietary habits, such as high consumption of wheat-based products, may influence disease expression and presentation. Recent efforts by regional medical centers have focused on increasing awareness and improving diagnostic capabilities, leading to a gradual rise in reported cases.

Nonetheless, further epidemiological research, including large-scale seroprevalence surveys and genetic screenings, is essential to accurately define the burden of celiac disease in Azerbaijan and tailor public health interventions accordingly.

Conclusion

Celiac disease is a multifactorial autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals. The interplay between resistant gluten peptides, tissue transglutaminase-mediated modification, and HLA-DQ2/DQ8-restricted immune activation leads to chronic intestinal inflammation and villous atrophy, resulting in malabsorption and diverse clinical manifestations. Disruption of the intestinal barrier, mediated by zonulin-induced tight junction dysfunction, further facilitates antigen translocation and perpetuates immune responses. Despite the availability of effective serological markers and histopathological criteria for diagnosis, the heterogeneity of clinical presentations continues to challenge timely identification and management. Currently, adherence to a strict gluten-free diet remains the cornerstone of therapy, although emerging immunomodulatory treatments show promise. Further research into the molecular mechanisms and regional epidemiology of celiac disease, particularly in understudied populations such as Azerbaijan, is essential to improve diagnostic accuracy, tailor therapeutic strategies, and ultimately enhance patient outcomes.

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