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MODERN UNDERSTANDING OF CELIAC DISEASE IN ADULTS

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Abstract

Celiac disease is a condition that causes inflammation and damage to the mucosa of the small intestine due to the activation of the immune system by gluten peptides in genetically susceptible individuals. It affects approximately 1% of the world's population and is characterized by symptoms such as diarrhoea, abdominal pain, and fatigue. If left untreated, it can lead to long-term complications such as malnutrition and an increased risk of developing other autoimmune diseases. The diagnosis of celiac disease requires a combination of serological tests and intestinal biopsy. This text is based on a literature review of celiac disease, which involved reviewing 35 articles from the PubMed database. The key search terms used were 'celiac disease', 'causes of celiac disease', 'diagnostic methods', and 'prevention of celiac disease'. The only known treatment for celiac disease is a lifelong gluten-free diet, which can alleviate symptoms and prevent complications. There is a lack of research on celiac disease in Kazakhstan, leaving the prevalence and burden of the disease in the country unknown. This study aims to investigate the current understanding of celiac disease in adults, including its prevalence, clinical manifestations, diagnostic methods, and potential implications for patient management. The study is relevant and evaluates various characteristics of celiac disease. Genetic factors, specifically susceptibility to DQ8 and DQ2 at the second HLA locus, are significant in the development of CD. Additionally, the use of antibiotics in early childhood may also be a contributing factor. As there is a lack of data on celiac disease in Central Asia, including Kazakhstan, a comprehensive study of this topic in Kazakhstan would provide a better understanding of the prevalence of celiac disease.

Key words: celiac disease, gluten sensitivity, gluten-free diet, diagnosis.

Introduction. Gluten is a group of proteins found in wheat, barley, oats, and rye [1]. The most harmful component is alpha gliadin. Abnormal sensitivity to gluten causes damage to the mucosa of the small intestine and an inflammatory response that ultimately leads to gradual atrophy of the villi. Celiac disease is more prevalent in Northern and Western Europe, but it is now a global issue. A systematic review of global celiac disease prevalence found a seroprevalence rate of 1.4%. Prevalence rates varied by continent, ranging from 1.3% in 11 South American studies to 1.8% in 20 Asian studies [2]. A systematic review and meta-analysis of 33 studies that measured incidence at multiple time points showed that 73% of the studies reported significant increases in diagnosis rates over time [3]. The prevalence of celiac disease in Kazakhstan is currently low, and there is a lack of data on the disease in Central Asia. One of the few available studies on celiac disease in Kazakhstan is an epidemiological screening study conducted in 2009 among children in Almaty city. The study revealed a disease frequency of 1:262, with a predominantly atypical form occurring at a frequency of 1:5 [4-9]. Celiac disease has not been extensively studied in Kazakhstan, making it difficult for the population to receive a diagnosis. CD imposes a burden on both affected individuals and their families, as those with celiac disease have an increased risk of developing coronary heart disease [10-11] and a significantly higher risk of small intestine cancer [12]. Therefore, further research on celiac disease is of utmost importance. The prevalence of the disease is highest in Europe and Oceania at

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0.8 percent, while South America has a prevalence rate of 0.4%, which is half that of Europe. Studies conducted in Asia have found a prevalence rate of 0.6%, while in Africa and North America, the rate is 0.5% of the total population [13] (refer to Figure 3). Researchers from Sweden have discovered an association between celiac disease and type 1 diabetes mellitus. The prevalence of celiac disease in type 1 diabetics was found to be 6% of the total study group of 26,605 people [14]. The highest prevalence rates are observed in Europe (6.1%), North America, and the Middle East (4.8%). Celiac disease is more prevalent in patients with Down's syndrome, with a prevalence of 6% in Europe and 5.4% in the Asia-Pacific region [15].

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Figure 1. Rates of celiac disease seroprevalence worldwide [15].

Figure 1 displays the prevalence values divided into four groups based on percentiles. The light grey percentile represents countries with a pooled national prevalence between 0.2% and 0.8%, while the dark black percentile includes countries with a pooled national prevalence between 2.1% and 8.5%. Additionally, a study was conducted in the Asia-Pacific region to determine the prevalence in high-risk and low-risk groups. According to the results, the Middle East Asia-Pacific region has the highest cumulative seroprevalence of celiac disease at 1.4%, followed by South Asia at 1.2%. The lowest seroprevalence is observed in East Asia, with only 0.06% of the total population affected [16].

Although the prevalence of celiac disease in the CIS countries has not been adequately studied, there are some results available from a group of researchers in Russia. The paper reports that the incidence of celiac disease (CD) in Russia increased from 0.02% to 0.30% between 1999 and 2010. The highest prevalence was observed in the Sverdlovsk region in 2009, while the lowest percentage was 0.02 in Chelyabinsk and St Petersburg in 2004 and 2002, respectively [17]. Further research is needed to investigate the epidemiological situation of celiac disease in Kazakhstan. **This study aims** to review the epidemiology, pathophysiology, and diagnosis of celiac disease, as well as provide an overview of the latest research findings and anticipated changes in the coming decade.

The materials and methods used in this study are based on a review of the literature on celiac disease in general. We reviewed 35 articles from the PubMed database, focusing on the keywords 'celiac disease', 'causes of celiac disease', 'diagnostic methods', and 'prevention of celiac disease'. Only English language articles published between 1999 and 2023 were included, based on their relevance to the keywords and information provided. Studies published in non-peer-reviewed sources, non-English articles, and studies before 2005 were excluded according to our criteria. The

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literature review on celiac disease utilised a systematic approach, including a comprehensive search strategy, rigorous screening process, and qualitative synthesis of extracted data. The methods aimed to ensure an unbiased and comprehensive review of the literature.

Results and Discussion. Coeliac condition is caused by two main factors: genetics and environmental factors. The genetic factor is related to the human leukocyte antigen (HLA) genes, while the environmental factor is related to gluten proteins from the diet. Coeliac disease is a well-understood HLA-linked condition that shares immunological features with inflammatory bowel disease. However, celiac disease is characterised by unique features. The criteria for diagnosing coeliac disease include the specific triggering of gluten proteins from wheat and related grains, the requirement for the presence of HLA-DQ2 or HLA-DQ8, and the production of circulating autoantibodies to the enzyme tissue transglutaminase (TG2). When TG2 deamidates gluten peptides, they gain greater affinity for HLA-DQ2 or HLA-DQ8, leading to more active CD4+ T helper 1 T cell activation. Certain genes can activate and cause inflammation of the intestinal mucosa, leading to malabsorption and various secondary symptoms and autoimmune diseases (Figure1-2) [18]. The disease develops due to the presence of haplotypes DQ8 and DQ2 in the second HLA locus in genetically predisposed individuals. The development of the disease is also influenced by the autoantigens tissue transglutaminase (TG2) and the environmental trigger (gluten). The study shows that the presence of certain genes increases the risk of developing celiac disease by 40%. Haplotypes are present in 30-35% of the general population and in 95% of people with celiac disease. However, the presence of pathological genes does not always result in the development of the disease [19-20].

The primary environmental factor associated with celiac disease is gluten, a protein found in wheat, barley, and rye. Consuming gluten triggers an immune response that damages the small intestine in people with celiac disease. Factors that may contribute to the development of celiac disease include viral infections, stress, and changes in the gut microbiome [21]. The state of the gut microbiome also plays a role in the development of CD. A population cohort study conducted in northeastern Italy found that children who were exposed to antibiotic treatment during their early years had an imbalanced immune system in their gut, which made them more vulnerable to developing celiac disease [22].

Celiac disease is an autoimmune disease that affects the mucous membrane of the intestine, causing damage to the microvilli and resulting in indigestion and malabsorption. The mechanism of the pathology is complex. Gluten is a protein present in various cereals, especially wheat. In the intestine, it breaks down into amino acids and peptides. One of these peptides is the 33-amino acid α-gliadin peptide, which is a vital part of the alcohol-soluble fraction of gluten [23]. This peptide is not easily broken down by gastrointestinal proteases. Epithelial cells induce the expression of IL-15, which activates and proliferates CD8+ intraepithelial T lymphocytes, causing them to express.

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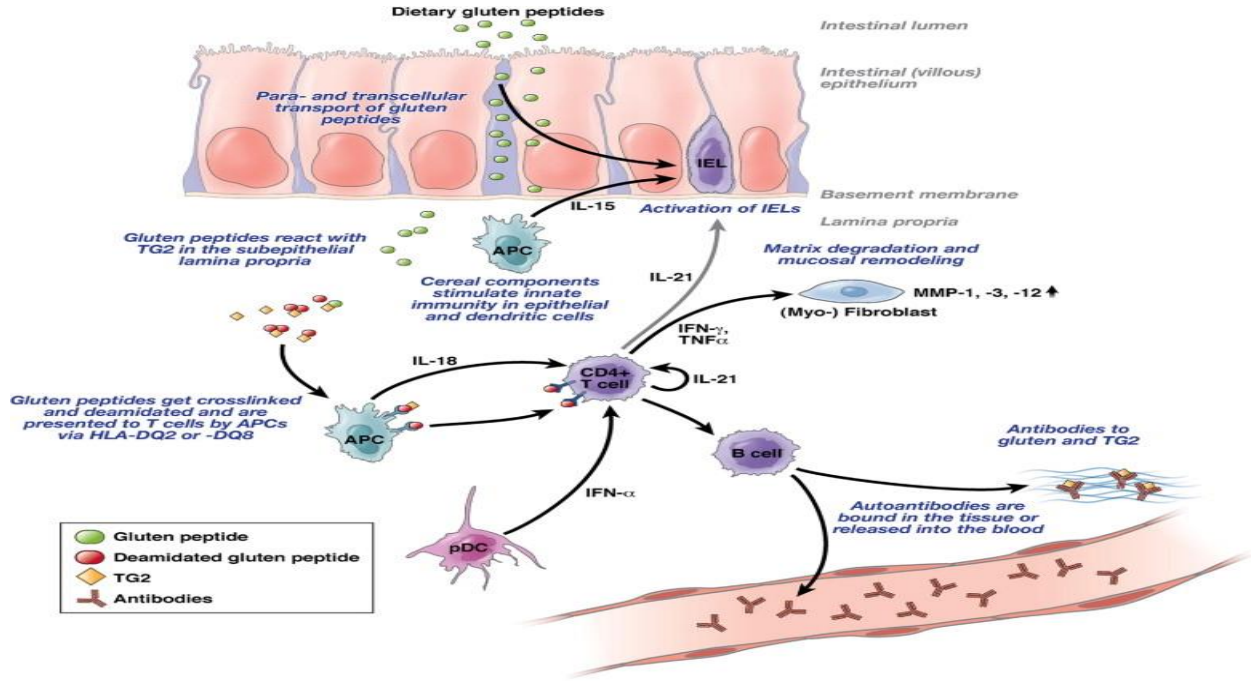

Figure 2. Pathophysiological mechanism of celiac disease.

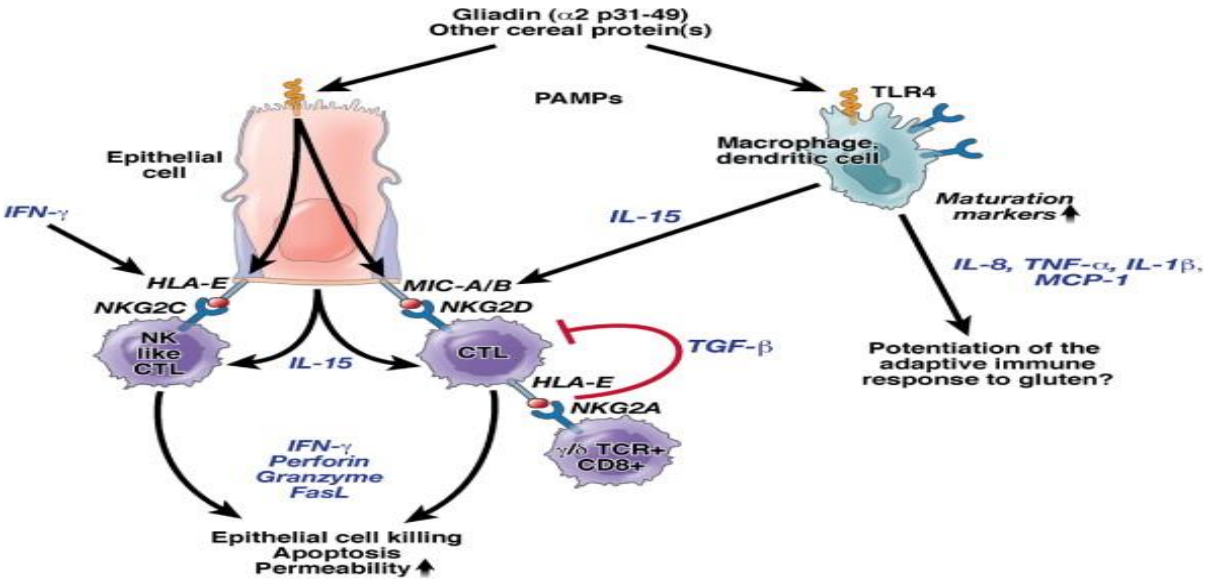

Figure 3. Innate immune responses in celiac disease.

Celiac disease presents a heterogeneous clinical picture. In addition to intestinal symptoms such as signs of malabsorption, abdominal discomfort, and motility disorders, extraintestinal symptoms or complications may also occur, which can be mild or exclusive. Malabsorption can result in weight loss, stunted growth in children, osteomalacia, osteoporosis, and changes in dental enamel. Peripheral (poly)neuropathy, tetany, muscle weakness, night blindness, haematoma, oedema and recurrent oral aphthae have been reported in patients with celiac disease. Additionally, up to 25% of patients with celiac disease may experience blistering dermatitis herpetiformis (Duhring's disease) [26].

Celiac disease can be diagnosed at any age, including in older individuals, and has a polymorphous clinical presentation. The CD is a characteristic finding for clinicians. The clinical

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spectrum of CD includes a range of symptoms that can affect both the intestines and other parts of the body, as well as specific markers that can be detected through serological screening. Common symptoms of CD include diarrhea, weight loss, abdominal distension, and constipation. The distinction between classic and atypical CD based on manifestation has been removed. This is because atypical indications and manifestations, such as anaemia, low bone density, and neuropathy, may be more common than typical manifestations like abdominal pain and prolonged diarrhea [27]. Extra-intestinal manifestations may be indicative of the systemic nature of the disease and include long-standing fatigue, anaemia, low bone mineral density, aphthous stomatitis, high-risk transaminase levels, joint/muscle pain, oral abortions, epilepsy, and peripheral neuropathy [28-29].

Several serological markers are used in the diagnosis of celiac disease, including anti-gliadin antibodies, antibodies to endomysium, antibodies to tissue transglutaminase, and antibodies to deamidated gliadin peptides [30]. It is important to note that no single serological marker has perfect sensitivity and specificity, and this conclusion is confirmed by a biopsy of the small intestine. Therefore, all considerations should be based on a gluten-containing diet. In some cases, if the serological test is negative, it is recommended to perform an endoscopic examination and biopsy of the small intestine. It is important to note that when biopsy samples contain three to four progressive villus-crypt squares, a morphological study of the small intestine should be conducted, the number of intraepithelial lymphocytes should be counted, and an immunohistochemical study should be performed in uncertain cases [31]. Patients with several diseases that cause villous decay and lead to histological mimicry should be prohibited from consuming gluten.

Treatment options include a gluten-free diet, dietary supplements, pharmacological therapy, and psychological support.

Furthermore, individuals with celiac disease may experience deficiencies in crucial nutrients such as iron, calcium, and vitamin D, even when adhering to a gluten-free diet, due to malabsorption in the small intestine. To address these nutritional deficiencies and enhance the overall health of those with celiac disease, dietary supplements containing a variety of vitamins and minerals, including iron, calcium, vitamin D, and B vitamins, may be recommended. In addition, probiotics may be recommended to restore a healthy gut microbiome, which can be disrupted in people with celiac disease. Treating macro- and micronutrient deficiencies with oral or enteral supplements is now considered best practice. Parenteral nutrition may be considered for patients with severe malnutrition due to malabsorption. Celiac disease may result in deficiencies of both macro- and micronutrients, and malnutrition should be evaluated through a combination of history, physical examination, and objective testing of micronutrient levels. It is crucial for individuals with celiac disease to collaborate closely with a registered dietitian or other healthcare professional to ensure that their nutritional requirements are met and that any supplements are safe and appropriate for their condition. Proper management, including the use of dietary supplements, can help people with celiac disease achieve good health outcomes and improve their overall quality of life [39-42].

While a gluten-free diet remains the primary treatment for celiac disease, researchers worldwide are developing drug treatments for the condition. Gliadin peptides undergo deamination by tissue transglutaminases. The resulting degraded amino acids affect the activation of various processes that harm the intestinal mucosa, particularly the intestinal villi. Consequently, drugs have been developed to inhibit transglutaminase activity, thereby preventing the modification of the intestinal villi. A randomized trial was conducted using the oral transglutaminase 2 inhibitor ZED1227 [43]. During the trial, participants with celiac disease were divided into four groups. Each group, except the fourth placebo group, received a specific dose of the drug and 3 g of gluten daily for six weeks. The results showed that treatment with the highly specific transglutaminase-2 inhibitor ZED1227 reduced gluten-induced damage to the duodenal mucosa. The most significant effect of the drug was observed in patients taking 50 mg and 100 mg of the drug [43]. This study presents evidence of BL-7010's efficacy in reversing gluten-associated pathology in a model of chronic gliadin

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sensitisation using NOD-DQ8 mice. BL-7010, which contains hydroxyethyl methacrylate, can prevent digestive enzymes from degrading gliadin by binding to it [44]. Probiotics may be beneficial for patients with a poor response to a gluten-free diet. For instance, the addition of Bifidobacterium lactis may hasten mucosal recovery following a switch to a gluten-free diet or offer mucosal protection against damage.

In this study, no significant difference was found in depression and hopelessness between patients diagnosed with celiac disease and women in the healthy control group. However, celiac disease does have a negative impact on women's wellbeing, which may be attributed to the restrictive diet therapy. Several articles have discussed the challenges of living with CD in adults, particularly in relation to how this disease affects physical, social, and emotional aspects of life [49]. Stress is the body's response to strain, anxiety, and everyday pressures. Excessive stress can lead to a deterioration in mood and the appearance of other symptoms. The term 'stress' describes the body's state as it attempts to adapt to life's challenging conditions. When an individual experiences severe physical and psychological pressure, the body initially attempts to protect itself. However, it eventually adapts, and the response to high pressure remains optimal. This situation is known as positive stress. Proper mental development and adaptation to the environment are essential. However, the body may not always be able to support the weight or physical load on the brain [50]. In such situations, additional stress can adversely affect a person's health and cause illness. Although celiac disease and not following the diet can cause psychiatric symptoms, a regular gluten-free diet is believed to reduce inflammation and the autoimmune response, thereby preventing potential psychiatric issues in some patients. Therefore, it is crucial for patients to be vigilant about their diet, monitor themselves for psychiatric symptoms, seek medical attention for any complaints, and disclose their coeliac condition during examinations.

Unfortunately, there is no known method to entirely prevent celiac disease. Nevertheless, certain strategies may help lower the risk of developing the condition. Observational studies over the past few decades have suggested that breastfeeding, particularly during the introduction of gluten into a child's diet, as well as the timing and method of initial gluten intake, could potentially delay or prevent the onset of celiac disease. Therefore, guidelines recommend introducing gluten gradually while the infant is still breastfed, avoiding introduction before 4 months or after 7 months. This approach may lower the risk of developing celiac disease, type 1 diabetes mellitus, and wheat allergy [51].

Two recent prospective studies of infants with a first-degree family member with CD have shown that CD can develop early in life in this high-risk group. This suggests that early environmental factors may play a crucial role in the development of CD. However, these studies have not identified any potential targets for the prevention of CD. Therefore, the gut microbiota has become a focus for innovative preventive strategies. Some researchers have suggested that viral gastrointestinal infections may play a role in the development of CD.

A recently discovered gene, ω-secalin, has been cloned and encodes a protein that contains a decapeptide sequence, QQPQRPQQPF. This peptide has been found to prevent the cellular response associated with celiac disease. In the presence of toxic gliadins, QQPQRPQQPF can prevent the agglutination of K562(S) cells. Additionally, QQPQRPQQPF can prevent immune activation induced by toxic gliadins in biopsies from celiac patients in the celiac mucosa. The identification of protective sequences, such as QQPQRPQQPF, in cereals that are considered 'toxic', could potentially lead to new strategies to reduce gluten toxicity [54]. It is important to note that these strategies are not guaranteed to prevent celiac disease and should not be used as a substitute for proper medical care and treatment.

This section concludes with a discussion. The objective of this study is to investigate the current understanding of celiac disease in adults, including its prevalence, clinical manifestations, diagnostic methods, and potential implications for patient management. The study is relevant as it

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provides a comprehensive assessment of the various aspects of celiac disease. Pathogenic factors, such as the predisposition of DQ8 and DQ2 in the second HLA locus, are crucial in the development of CD. Additionally, the use of antibiotics during early childhood may act as a triggering factor. Diagnostic methods have limited sensitivity, therefore a combination of diagnostic methods should be employed. Differential diagnosis of other conditions that cause villous atrophy can be challenging, hence additional tests are necessary to exclude other conditions. Strategies to prevent celiac disease cannot be guaranteed. However, the discovery of additional or alternative strategies for patients with CD offers hope.

As there is a lack of data on celiac disease research in Central Asia, including Kazakhstan, a consistent study of this topic in Kazakhstan will provide a complete picture of the prevalence of CD.

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ЕРЕСЕКТЕРДЕГІ ЦЕЛИАК АУРУЫ ТУРАЛЫ ЗАМАНАУИ ТҮСІНІК

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Түйіндеме

Целиак ауруы - генетикалық сезімтал адамдарда глютен пептидтерінің иммундық жүйені белсендіруіне байланысты аш ішектің шырышты қабығының қабынуы мен зақымдалуын тудыратын ауру. Бұл ауру планета халқының шамамен 1% -. әсер етеді және диарея, іштің ауыруы және шаршау сияқты белгілермен сипатталады. Егер ауру емделмеген болса, ол ұзақ мерзімді асқынуларға әкелуі мүмкін, мысалы, дұрыс тамақтанбау және басқа аутоиммунды аурулардың даму қаупінің жоғарылауы. Целиак ауруын диагностикалау үшін серологиялық сынақтар мен ішек биопсиясының комбинациясы қажет. Бұл мәтін целиак ауруы туралы әдебиеттерге шолуға негізделген, оның барысында PubMed дерекқорынан 35 мақала талданған. Негізгі іздеу терминдері ретінде "целиак ауруы", "целиак ауруының себептері", "диагностикалық әдістер" және "целиак ауруының алдын алу"қолданылды. Целиак ауруын емдеудің жалғыз белгілі әдісі-симптомдарды жеңілдететін және асқынулардың алдын алатын өмір бойы глютенсіз диета. Қазақстанда целиак ауруы бойынша зерттеулер жетіспейді, сондықтан елде аурудың таралуы мен ауыртпалығы белгісіз.

Бұл зерттеудің мақсаты-ересектердегі целиак ауруы туралы заманауи идеяны, оның таралуын, клиникалық көріністерін, диагностикалық әдістерін және пациенттерді басқарудың ықтимал салдарын зерттеу. Зерттеу өзекті болып табылады және целиак ауруының әртүрлі сипаттамаларын бағалайды. Генетикалық факторлар, атап айтқанда HLA-ның екінші локусындағы DQ8 және DQ2 сезімталдығы целиак ауруының дамуында маңызды рөл атқарады. Сонымен қатар, ерте балалық шақта антибиотиктерді қолдану аурудың дамуына ықпал ететін фактор болуы мүмкін.

Орталық Азияда, соның ішінде Қазақстанда целиак ауруы туралы деректер болмағандықтан, Қазақстанда бұл тақырыпты кешенді зерттеу целиак ауруының таралуын жақсы түсінуге мүмкіндік береді.

Түйін сөздер: целиак ауруы, глютенге сезімталдық, глютенсіз диета, диагностика.

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СОВРЕМЕННОЕ ПРЕДСТАВЛЕНИЕ О ЦЕЛИАКИИ У ВЗРОСЛЫХ

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Аннотация

Целиакия - это заболевание, вызывающее воспаление и повреждение слизистой оболочки тонкой кишки вследствие активации иммунной системы пептидами глютена у генетически восприимчивых людей. Это заболевание поражает около 1 % населения планеты и характеризуется такими симптомами, как диарея, боль в животе и усталость. Если не лечить заболевание, оно может привести к долгосрочным осложнениям, таким как недоедание и повышенный риск развития других аутоиммунных заболеваний. Для диагностики целиакии необходимо сочетание серологических тестов и биопсии кишечника. Данный текст основан на обзоре литературы по целиакии, в ходе которого было проанализировано 35 статей из базы данных PubMed. В качестве ключевых поисковых терминов использовались "целиакия", "причины целиакии", "методы диагностики" и "профилактика целиакии". Единственным известным методом лечения целиакии является пожизненная безглютеновая диета, которая может облегчить симптомы и предотвратить осложнения. В Казахстане не хватает исследований по целиакии, поэтому распространенность и бремя заболевания в стране неизвестны.

Цель данного исследования - изучить современное представление о целиакии у взрослых, включая ее распространенность, клинические проявления, методы диагностики и потенциальные последствия для ведения пациентов. Исследование является актуальным и оценивает различные характеристики целиакии. Генетические факторы, в частности восприимчивость к DQ8 и DQ2 во втором локусе HLA, играют важную роль в развитии Ц. Кроме того, использование антибиотиков в раннем детстве также может быть фактором, способствующим развитию заболевания.

Поскольку данные о целиакии в Центральной Азии, включая Казахстан, отсутствуют, комплексное исследование этой темы в Казахстане позволило бы лучше понять распространенность целиакии.

Ключевые слова: целиакия, чувствительность к глютену, безглютеновая диета, диагностика.