ABSTRACT

Dissertation by Aisulu Tleugazyevna Kapasova on the topic:
«Features of Diagnosis and Clinical Course of Celiac Disease in Patients in the Republic of Kazakhstan», submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10102 – «Medicine»

Relevance of the research topic

The increase in the number of patients in the Republic of Kazakhstan (RK), as in the rest of the world, presenting with undiagnosed intestinal disorders characterized by malabsorption syndrome, diarrhea, or occurring concomitantly with autoimmune processes and osteoporosis may reflect manifestations of celiac disease (CD). To date, studies of CD in Kazakhstan have been carried out almost exclusively among children. In particular, the works of T.K. Isabekova (2008) and L.M. Karsybekova et al. (2006) demonstrated a high frequency of celiac disease among children in Almaty.

When celiac disease remains unrecognized, the risk of life-threatening and difficult-to-treat complications increases — for example, intestinal lymphoma, adenocarcinoma of the colon, unexplained infertility, and osteoporosis (with a higher risk in patients with classical symptoms), short stature, and various autoimmune conditions. The high mortality associated with such complications, the progressive deterioration in quality of life, and the lifelong requirement to adhere to a gluten-free diet (GFD) constitute strong arguments in favour of active screening for celiac disease among both children and adults.

Although accurate and rational confirmation of the diagnosis is now possible, celiac disease remains substantially under-diagnosed, most likely due to its wide clinical spectrum and insufficient application of serological screening.

No previous studies have systematically investigated the prevalence, clinical course, diagnostic features, and therapeutic issues of celiac disease among the population of Kazakhstan. As an increasing number of countries recognize celiac disease as a matter of national importance, investigation of highly specific, non-invasive screening tests based on detection of serological markers of gluten enteropathy — autoantibodies of IgA or IgG class to tissue transglutaminase (tTG), anti-endomysial antibodies (EmA), and antibodies to deamidated gliadin peptides (DGP) — will permit timely confirmation of the diagnosis and the selection of rational programmes for prevention and treatment of patients with CD.

The development of screening algorithms employing non-invasive laboratory serological tests will enable earlier diagnosis and secondary prevention of CD relapses in adults and thereby contribute to improvements in patients' quality of life. In this context, the issues of diagnosing celiac disease in adult residents represent an unresolved and clinically important problem for contemporary gastroenterology in the Republic.

Aim of the Study: to improve the effectiveness of therapeutic and diagnostic strategies in the management of patients with celiac disease by studying the clinical characteristics of its course in both children and adults, followed by the development of a diagnostic and management protocol for the Republic of Kazakhstan.

Objectives of the Study:

1) To analyze the clinical manifestations of celiac disease in children and adult patients, with particular attention to age-related and gender-specific features, as well as to different forms of disease presentation.

2) To assess the significance of modern serological, endoscopic, and histomorphological diagnostic methods in patients of different age groups, identifying the most informative approaches for both children and adults.

3) To investigate the characteristics of mineral metabolism and genetic polymorphism in patients with celiac disease across age groups in order to evaluate their prognostic value.

4) To examine the level of awareness and knowledge about celiac disease among practicing physicians in Kazakhstan, determine the main gaps in their understanding of the etiology, clinical manifestations, diagnostic methods, and treatment of the disease, and identify the factors influencing their awareness.

5) To develop a clinical protocol for the diagnosis and management of patients with celiac disease, taking into account age-related characteristics and clinical presentations in both children and adults, and incorporating modern diagnostic and therapeutic approaches.

Research Methods:

1) General clinical examination: collection of complaints, medical and life history, and physical examination.

2) Laboratory tests: complete blood count; glucose, total protein and protein fractions, cholesterol, amylase, lipase, calcium, sodium, potassium, phosphorus, ferritin, bilirubin fractions, ALT, AST, alkaline phosphatase; serological markers: antibodies to deamidated gliadin peptides (IgA, IgG), antibodies to tissue transglutaminase (IgA, IgG), antibodies to endomysium (IgA, IgG).

3) Genetic testing: HLA typing for detection of HLA-DQ2 and HLA-DQ8 heterodimers.

4) Esophagogastroduodenoscopy (EGD) with biopsy of the postbulbar duodenal mucosa for targeted histomorphological and morphometric evaluation in accordance with Marsh M classification.

5) Colonoscopy with histological examination of biopsies, when indicated.

6) Statistical methods for data processing.

The object of the study:

The object of the study is adult and pediatric patients with suspected celiac disease.

The subject of the study:

The subject of the study is the clinical features of celiac disease in children and adults, the methods of laboratory, serological, endoscopic, histomorphological and genetic diagnostics, as well as the therapeutic and diagnostic management tactics for patients with celiac disease in the Republic of Kazakhstan.

Key Provisions to be Defended:

1) Clinical, serological, and genetic features of celiac disease and its associated conditions were identified in pediatric and adult patient populations. These findings should be taken into account in the diagnosis and monitoring of treatment effectiveness in different age groups of patients with celiac disease.

2) A comprehensive examination of at-risk groups, including assessment of complete blood count, liver function, mineral metabolism parameters, serological tests, histomorphological evaluation of the small intestine mucosa, and HLA genotyping, is an essential method for the differential diagnosis of enteropathies.

3) The level of knowledge and awareness of celiac disease among practicing physicians in Kazakhstan was found to be insufficient, as reflected in the low rates of correct answers to key questions on the etiology, diagnosis, and treatment of the disease. This highlights the necessity of implementing targeted educational programs and continuing professional development to improve the diagnosis and management of patients with celiac disease.

4) Further research on the epidemiology of celiac disease and non-celiac gluten sensitivity in Kazakhstan is required to identify potential socio-cultural, population-related, and organizational predictors, as well as to ensure the optimal implementation of early diagnosis and treatment programs for this pathology.

Description of the main research results

Among the pediatric participants, 121 patients were examined, of whom celiac disease (CD) was diagnosed in 23.2%, and non-celiac gluten sensitivity (NCGS) in 66.1%. Gastrointestinal (GI) symptoms were observed in 90% of cases, with abdominal pain and nausea significantly more frequent in CD ($p<0.001$ and $p<0.05$, respectively). Extraintestinal manifestations were recorded in 86.8% of children and were most common in NCGS. Serological tests (IgA/IgG anti-tTG, anti-DGP, and EMA) demonstrated high specificity for CD diagnosis, with EMA showing the best diagnostic accuracy (AUC=0.857). Patients with CD more frequently exhibited MARSH-I–III on biopsy and had significantly lower vitamin D levels ($p=0.023$). Significant correlations were observed between disease activity (MARSH) and EMA levels, anti-tTG IgG, as well as clinical symptoms (nausea, thirst).

Among adults (n=59), CD was diagnosed in 57.6%, and NCGS in 42.4%. Postprandial fullness, belching, vomiting, and especially abdominal pain ($p<0.001$) were more common in CD, whereas bloating occurred more often in NCGS ($p<0.05$). Among extraintestinal symptoms, depression, anxiety, and headaches were significantly more frequent in CD patients. Hemoglobin levels were significantly lower in CD ($p<0.05$). Serology (anti-tTG, IgA/IgG to gliadin, EMA) showed high

diagnostic accuracy, particularly for anti-tTG (AUC=0.903). A positive genetic test (HLA-DQ2/DQ8) was detected in 73.3% of CD patients and was absent in NCGS. Histology revealed MARSH-I–III in all CD patients and MARSH-0 in NCGS. Levels of transglutaminase, gliadin antibodies, and EMA correlated with histological disease activity.

A survey of healthcare professionals' awareness of CD revealed a pronounced knowledge deficit across specialties. The study included 232 practicing physicians from all regions of Kazakhstan; only 28% correctly identified CD as an autoimmune disease, and only 25.8% recognized gastroduodenoscopy with small bowel biopsy as the "gold standard" for diagnosis. Although most physicians (86.2%) knew about the role of gluten as a trigger, understanding of clinical manifestations and comorbid conditions remained limited: iron-deficiency anemia, osteoporosis, delayed puberty, and autoimmune thyroid disease were recognized far less frequently than expected.

The mean total knowledge score was 14.7 ± 6.9 out of 38 possible points, corresponding to a low level of awareness; 59.4% of physicians demonstrated low knowledge, 28.4% satisfactory, and only 12.2% good. Gastroenterologists showed the highest awareness (20.8 ± 7.8), while primary care and other specialists had equally low scores (14.4). Significant regional differences were observed: the highest scores were in the West Kazakhstan region and the lowest in North Kazakhstan. Higher knowledge levels were more common among physicians over 50 years old and women. A key finding was the pronounced need for additional training: 93.5% of respondents reported the necessity for enhanced knowledge, particularly in diagnosis (63.4%) and treatment (61.2%).

A modern diagnostic testing algorithm for celiac disease was also translated and adapted to take into account various clinical scenarios and gluten consumption status. The algorithm includes stepwise evaluation: determination of TTG-IgA and total IgA, assessment of IgG serology in IgA deficiency, subsequent morphological confirmation based on the Marsh classification, and genetic testing (HLA DQ2/DQ8) for patients on a gluten-free diet. The algorithm systematically accounts for both typical and atypical clinical presentations, seronegative variants, and dietary restrictions, improving diagnostic accuracy and completeness at primary and specialized care levels.

In addition, in collaboration with leading gastroenterologists and related specialists in Kazakhstan, the clinical protocol "Celiac Disease (Gluten Enteropathy) in Adults" (Protocol No. 107) was developed and approved by the Joint Commission on Quality of Medical Services of the Ministry of Health of Kazakhstan on July 16, 2020. This document became the first standardized regulatory resource for managing CD patients in the country, including current recommendations for diagnosis, treatment, referral, and patient follow-up. The development of a protocol and adaptation of a diagnostic algorithm based on international recommendations represent key stages in the development of a system for the early diagnosis of celiac disease and improving the quality of medical care.

Scientific Novelty of the Study Results:

For the first time in Kazakhstan, using comprehensive investigations (immunological blood testing with detection of specific antibodies, genetic blood

testing, and morphological examination of the small intestine), the clinical features of celiac disease were studied in both adult and pediatric populations of the Republic of Kazakhstan (RK).

Practical Significance:

In collaboration with leading gastroenterologists and related specialists of RK, a clinical protocol "Celiac Disease (Gluten Enteropathy) in Adults" was developed and approved by the Unified Commission for Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan on July 16, 2020 (Protocol No. 107). A patient support chat was created, which currently includes 470 patients with celiac disease from across the Republic of Kazakhstan. In Astana, diagnostics of celiac disease has been fully established (the Hla DQ2, DQ8 gene test has been introduced at the hospital of the Medical Center of the Presidential Administration of the Republic of Kazakhstan (copyright received). Morphological diagnosis of celiac disease according to the Marsh classification has also been implemented. Within the framework of the Astana City Health Department, patients have been provided with dietary products and enzymes. Every year, patients receive an annual supply of gluten-free products: in Astana, 66 children and 34 adults are covered; in Almaty, 25 adults and 66 children are provided with dietary support.

Personal Contribution of the Doctoral Candidate:

During the research, the doctoral candidate participated in defining the topic, objectives, and tasks of the study, developed the research methodology, carried out the selection of patients suspected of having celiac disease, and independently searched for literature sources related to the dissertation topic. The candidate wrote the chapters of the dissertation, summarized and analyzed the obtained results. In addition, the author interpreted clinical, laboratory, morphological, and instrumental data of patients. The author published the research results in journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan, in international scientific-practical conferences, and in foreign journals.

Conclusions:

Analysis of the study results allows us to formulate the following conclusions:

1. Clinical evaluation of complaints in pediatric patients revealed that abdominal pain ($p < 0.001$) and nausea ($p < 0.05$) were more common in patients with celiac disease compared to healthy individuals or those with non-celiac gluten sensitivity. Nausea and thirst were independent predictors of disease activity according to MARSH ($p < 0.05$). Extraintestinal manifestations were more frequently diagnosed in children with non-celiac gluten sensitivity than in those with celiac disease ($p < 0.001$). In the adult population, characteristic clinical features of celiac disease included postprandial heaviness, belching, vomiting ($p < 0.05$), and abdominal pain ($p < 0.001$). Among extraintestinal manifestations in adults with celiac disease, depression, anxiety, and headaches were more frequently observed ($p < 0.05$), whereas patients with non-celiac gluten sensitivity more often presented with dermatological manifestations, joint pain, and hair loss ($p < 0.05$). Moreover,

abdominal pain (β=0.734) and vomiting (β=0.822) were predictors of histological disease activity according to MARSH (R^2=0.328, $p < 0.05$) in adults.

2. Among children, the highest diagnostic value was demonstrated by serological tests for EMA titers (AUC = 0.857), anti-tTG IgA (AUC = 0.747) and IgG (AUC = 0.763), and genetic testing (AUC = 0.897). In the adult population, the test for transglutaminase activity showed high diagnostic accuracy (AUC = 0.90).

A moderate positive correlation was identified between IgG anti-tTG test results and disease activity according to MARSH in children (r=0.447, $p < 0.001$). In adult patients, IgG EMA was a predictor of disease activity (β=1.02, R^2=0.263, $p < 0.001$). Furthermore, transglutaminase activity (β=0.626, R^2=0.392, $p < 0.001$), IgA anti-gliadin antibody levels (β=0.620, R^2=0.385, $p < 0.001$), and IgG anti-gliadin antibody levels (β=0.625, R^2=0.390, $p < 0.001$) were also predictors of disease activity according to MARSH in adults with celiac disease.

3. Vitamin D and calcium levels in children with celiac disease were lower than in children with non-celiac gluten sensitivity and healthy children ($p < 0.05$). A reduced vitamin D level was also more frequently noted in adults with celiac disease compared to those with non-celiac gluten sensitivity ($p < 0.05$). Genetic polymorphism of celiac disease identified by HLA typing in the pediatric population showed the following distribution: DQ2.5 HLA class II mutations in 45.4% of children, DQ8 in 36.4%, and DQ2 mutations in 18.2% of study participants.

Patients with celiac disease and non-celiac gluten sensitivity demonstrated significantly higher levels of GGT and amylase compared to healthy children ($p < 0.001$). It was also confirmed that hemoglobin levels were significantly lower in adults with celiac disease compared to those with non-celiac gluten sensitivity ($p < 0.05$).

4. The conducted survey revealed a low level of awareness about celiac disease. The mean total knowledge score was 14.7 ± 6.9 out of a possible 38 points. More than half of the respondents (59.4%) had a low level of awareness, 28.4% — satisfactory, and only 12.2% demonstrated a good level of knowledge. Gastroenterologists achieved the best results (mean score 20.8 ± 7.8), whereas primary care physicians and other specialists scored an average of 14.4 points.

5. A clinical protocol titled "Celiac disease (gluten enteropathy) in adults" was developed and implemented, approved by the Joint Commission on the Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan (July 16, 2019).

Approbation of the Work:
The main results of the research and the dissertation statements were presented and discussed at national and international conferences.

Key findings of the work were presented and discussed in the form of scientific reports at the following events:

− VII International KAMLD Congress on Laboratory Medicine, April 19–20, 2019, Almaty. Presentation: Current Issues of Celiac Disease. Clinical Case Discussion.

‒ I Scientific and Practical Conference of Students and Young Scientists "Chronic Inflammatory Skin Processes. Interdisciplinary Problems", April 15, 2022. Presentation: Cutaneous Manifestations of Celiac Disease. Clinical Case.

‒ I International Conference "Almaty Gastro – Digestive Diseases: Interdisciplinary Issues", Almaty. Presentation: Celiac Disease in Adults in Kazakhstan – Current Status of the Problem.

‒ Republican Scientific and Practical Conference with International Participation, dedicated to the 60th anniversary of NAO "Astana Medical University" and the International Family Doctor Day "Current Issues of Primary Health Care: Modern Trends, Problems and Solutions", May 16–17, 2024, Astana. Presentation: Approaches to Diagnosis and Management of Patients with Celiac Disease by General Practitioners.

‒ IV International Conference "Gastroenterology-2023". Diploma of the 1st Degree in the poster competition: Prevalence and Genetic Diagnosis of Celiac Disease in Children in the Republic of Kazakhstan.

‒ International Student Conference "Fundamental and Clinical Aspects of Orphan Diseases", dedicated to the International Rare Disease Day and the 90th anniversary of Al-Farabi KazNU, February 29, 2024.

‒ V International Gastroenterology Congress "Gastroenterology-2024", March 1–2, 2024, Astana. Poster presentation: Clinical Features and Diagnosis of Celiac Disease among the Pediatric Population of Kazakhstan.

‒ V International Gastroenterology Congress "Gastroenterology-2024", March 1–2, 2024, Astana. Poster presentation: Clinical Case of Late-Diagnosed Celiac Disease.

‒ International Congress "Theoretical Aspects and Practical Recommendations in Modern Gastroenterology and Hepatology", January 23–24, 2024, Almaty. Presentation: Clinical and Epidemiological Features of Celiac Disease in Kazakhstan.

Publications:

According to the results of the dissertation research, 15 scientific papers were published, including 4 papers in periodicals recommended by the Committee for Control in the Sphere of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, and 3 full-text articles in peer-reviewed international journals indexed in the Scopus database.

‒ Kapassova A.T., Derbissalina G.A., Iskakov B.S. Celiac disease: prevalence, clinical features, and modern diagnostic aspects (literature review). Valeology: Health – Disease – Recovery, No.1, 2019, pp. 77–82.

‒ Kapassova A., Derbissalina G., Iskakov B. Celiac disease: features of clinical manifestations, topical issues of diagnosis. Astana Medical Journal, 2019, No.1 (99).

‒ Kapassova A.T., Iskakov B.S., Derbissalina G.A., Bekbergenova Zh.B., Kelimberdiyeva E.S. Modern diagnosis of celiac disease in adults. Bulletin of the

Medical Center of the Administration of the President of the Republic of Kazakhstan, No.1 (78), 2020, pp. 109–112.

‒ Kapassova A.T., Iskakov B.S., Derbissalina G.A., Bekbergenova Zh.B., Kelimberdiyeva E.S. Clinical case analysis of a patient with late-diagnosed celiac disease. Bulletin of the Medical Center of the Administration of the President of the Republic of Kazakhstan, No.1 (78), 2020, pp. 52–55.

‒ Kapassova A., Derbisalina G., Iskakov B. Celiac disease: features of clinical manifestations, topical issues of diagnosis. Astana Medical Journal, 2019, No.1 (99), pp. 92–98.

‒ Aissulu Kapassova, Gulmira Derbissalina, Baurzhan Iskakov. Epidemiology, clinical features and diagnosis of celiac disease among pediatric population in Kazakhstan. Georgian Medical News. No 4 (361), 2025.

‒ Kozhakhmetova S., Aidossov S., Kapassova A., Borsoldayeva K. Current knowledge and "myths" about celiac disease among physicians in the Republic of Kazakhstan: A countrywide cross-sectional study. Frontiers in Public Health. 2022; 10:956135. doi:10.3389/fpubh.2022.956135.

‒ Kapassova A., Derbissalina G., Zhunussova D., Kelimberdiyeva E., Iskakov B. Case report. Late-diagnosed celiac disease as a trigger of family history of gluten-related disorders. Systematic Reviews in Pharmacy. 2020;11(12):385–387.

‒ Kapassova A., Derbissalina G., Iskakov B. The frequency of celiac disease and gluten hypersensitivity in children with gastroenterological pathology in Nur-Sultan. Abstract book of the International Scientific and Practical Conference of Students and Young Scientists "Medical Science and Education: Youth and Aspiration – 2019", pp. 401–402.

‒ Kapassova A., Derbissalina G., Iskakov B. Modern methods of celiac disease diagnosis in adults and children. Abstract book of the International Scientific and Practical Conference of Students and Young Scientists "Medical Science and Education: Youth and Aspiration – 2019", pp. 414–415.

‒ Kapassova A.T. Features of diagnostics and clinical course of celiac disease in children in the Republic of Kazakhstan. Republican scientific-practical conference with international participation "Science and Health", November 19, 2021, Semey, pp. 50–51.

‒ Kapassova A.T. Disorders of biochemical indicators in children with celiac disease in the Republic of Kazakhstan. Republican scientific-practical conference with international participation "Science and Health", November 19, 2021, Semey, pp. 51–52.

‒ Kapassova A.T., Sarbayeva A.S. Atypical form of celiac disease. Clinical case. Al-Farabi Kazakh National University, International student conference "Fundamental and Clinical Aspects of Orphan Diseases", Almaty, Kazakhstan, February 29, 2024, pp. 169–170.

‒ Nurkenova A.M., Sarbayeva A.S., Taskaliyeva A.B., Kapassova A.T. Celiac disease and type 1 diabetes: the interrelation of diagnoses. Republican scientific-practical conference with international participation "Topical Issues of

Therapy from the Position of Evidence-Based Medicine", dedicated to Family Doctor's Day, May 16, 2025, Astana, Kazakhstan, p. 142.

− Nurkenova A.M., Sarbayeva A.S., Taskaliyeva A.B., Kapassova A.T. Atypical form of celiac disease: clinical case. Republican scientific-practical conference with international participation "Topical Issues of Therapy from the Position of Evidence-Based Medicine", May 16, 2025, Astana, Kazakhstan, pp. 143–144.

− Nurkenova A.M., Sarbayeva A.S., Kapassova A.T. Clinical case of late-diagnosed celiac disease. Republican scientific-practical conference with international participation "Topical Issues of Therapy from the Position of Evidence-Based Medicine", May 16, 2025, Astana, Kazakhstan, pp. 155–156.

− Clinical Protocol "Celiac Disease (Gluten Enteropathy) in Adults". Approved by the Unified Commission on Quality of Medical Services of the Ministry of Health of the Republic of Kazakhstan on July 16, 2019.

− Certificate of state registration of copyright "Features of diagnostics and clinical course of celiac disease in patients in the Republic of Kazakhstan". National Institute of Intellectual Property, Ministry of Justice of the Republic of Kazakhstan, No.2705, April 9, 2019.

− Certificate of state registration of copyright "Determination of mutations in HLA class II genes DQ2, DQ8". National Institute of Intellectual Property, Ministry of Justice of the Republic of Kazakhstan, No.5294, September 13, 2019.

− Implementation Act in the Center of Traditional and Folk Medicine: Features of diagnostics and clinical course of celiac disease in patients in the Republic of Kazakhstan – implemented in the form of lectures, seminars, and workplace training. November–December 2024.

Volume and Structure of the Dissertation:
The dissertation consists of 81 pages and includes an introduction, a literature review, a description of the examined patients and research methods, author's observations presented in three chapters, of the author's own observations, a conclusion, findings, practical recommendations, and a reference list comprising 187 sources (11 domestic and 176 foreign sources), as well as 6 appendices. The work is illustrated with 23 tables and 19 figures.