

ABSTRACT

of the PhD dissertation by Saule Abaykyzy Altynbekova
entitled:

“Clinical and Immunological Features of Post-COVID Syndrome in Patients with Type 2 Diabetes Mellitus”

submitted for the degree of Doctor of Philosophy (PhD)
in the specialty 8D10103 – “Medicine”

Relevance:

The COVID-19 pandemic has led to a global healthcare crisis and continues to exert a significant impact on public health. As of December 1, 2024, more than 775 million cases of COVID-19 have been reported worldwide, with over 7 million confirmed deaths [2]. These figures highlight the exceptional severity of the pandemic, ranking it among the most devastating in human history.

Despite the end of the acute phase of the pandemic, COVID-19 continues to affect human health, leaving behind long-term consequences collectively referred to as “post-COVID syndrome” or “long COVID.” This syndrome encompasses a wide range of clinical manifestations, varying from mild fatigue to severe organ dysfunctions, which may persist for weeks or even months following the initial infection. According to meta-analytical data, approximately 80% of individuals who have recovered from SARS-CoV-2 infection experience one or more persistent symptoms over an extended period, indicating the high prevalence of post-COVID syndrome. In one of our previous publications, the most common symptoms of the post-COVID condition included fatigue and reduced physical tolerance (53.5%), exertional dyspnea (51.3%), respiratory discomfort (49.4%), and hair loss (44.1%) [5], which aligns with findings from other researchers.

Moreover, in a prospective cohort study conducted among recently recovered COVID-19 patients, cardiac MRI revealed myocardial tissue damage in 78% of examined individuals and signs of ongoing myocardial inflammation in 60%. These changes were observed regardless of pre-existing health status, disease severity, or time elapsed since diagnosis. These findings underscore the need for further investigation into the long-term cardiovascular consequences of COVID-19.

Additionally, SARS-CoV-2 has demonstrated a high capacity for evolution and adaptation, as evidenced by more than 8,000 unique mutations identified in its genome. Many of these mutations, particularly in the receptor-binding domain of the spike (S) protein (positions 452, 489, 500, 501, and 505), are associated with changes in viral infectivity and other characteristics. These findings highlight the importance of studying SARS-CoV-2 genetic variability and its impact on the clinical course of post-COVID syndrome.

Research on post-COVID syndrome is of particular importance in patients with comorbidities, especially those with type 2 diabetes mellitus, which has been proven to significantly increase the risk of severe COVID-19 outcomes. T2DM is characterized by persistent hyperglycemia, impaired innate immunity, a pro-inflammatory cytokine environment, and decreased expression of angiotensin-converting enzyme 2. Additionally, the use of renin-angiotensin-aldosterone system

antagonists in these patients may further elevate risks, worsening the prognosis and increasing the likelihood of severe complications.

Impaired immune regulation in this patient group may significantly influence the clinical trajectory of post-COVID syndrome; however, the mechanisms involved remain insufficiently studied and require further exploration.

Current research confirms the link between T2DM and the severity of COVID-19, yet data on the clinical and immunological features of post-COVID syndrome in patients with T2DM remain limited. Disease progression and outcomes may be influenced by multiple factors, including the genetic variants of SARS-CoV-2, vaccination status, gender, antidiabetic therapy, body mass index, comorbidities, and individual immune response characteristics.

In this context, further studies are needed to improve understanding of the clinical and immunological mechanisms and to develop effective patient management strategies aimed at minimizing long-term complications and improving quality of life.

This dissertation addresses an urgent issue: the investigation of the clinical and immunological characteristics of post-COVID syndrome in patients with type 2 diabetes mellitus, which is essential for the development of personalized diagnostic approaches and preventive and therapeutic interventions.

The purpose of the study:

To optimize the diagnosis and management of post-COVID syndrome in patients with type 2 diabetes mellitus by identifying the clinical and immunological characteristics of the disease and factors influencing its course and outcomes.

Research objectives:

1. To analyze the dynamics of morbidity and mortality among patients with type 2 diabetes mellitus in Almaty during the pandemic and in the post-pandemic period.
2. To conduct a comparative analysis of the post-covid period in patients with type 2 diabetes mellitus who became ill during various variant-associated periods of COVID-19.
3. To determine the clinical features of postcovid syndrome in patients with and without type 2 diabetes mellitus, taking into account the vaccination status.
4. To study the clinical and immunological characteristics of postcovid syndrome in patients with type 2 diabetes mellitus.
5. To develop recommendations on management tactics for patients with type 2 diabetes mellitus who have had a coronavirus infection.

Research methods: The study used a combined design, including information-analytical and statistical methods, a retrospective analysis of medical documentation, a sociological method (patient survey), as well as a cross-sectional (cross-sectional, one-stage) clinical trial. The study was approved by the Local Ethics Committee of the Kazakh National Medical University named after S.D. Asfendiyarov (Protocol No. 2 (125) dated 02/23/2022).

Information and analytical method. To analyze the dynamics of morbidity and mortality in type 2 diabetes mellitus, information, analytical and statistical methods were used based on data from official registers and accounting documentation.

A retrospective analysis of medical records. A comparative analysis of the features of the post-covid period was carried out by the method of a retrospective analysis of the medical documentation of patients who had suffered coronavirus infection, with an assessment of clinical, laboratory and anamnestic data.

The sociological method (questionnaire). To identify the clinical manifestations of postcovid syndrome in patients with type 2 diabetes mellitus and without impaired carbohydrate metabolism, a structured questionnaire was used to survey patients.

Cross-sectional (single-stage) clinical trial. The clinical and immunological features of postcovid syndrome were evaluated as part of a cross-sectional study using laboratory and immunological methods, including analysis of blood biochemical parameters and IgG antibody levels to SARS-CoV-2.

Statistical methods of analysis.

Statistical data processing was performed using parametric and nonparametric analysis methods, taking into account the type of distribution of variables. For quantitative indicators, an assessment of the normality of the distribution was carried out, after which the data were presented in the form of an average value and a standard deviation, or a median and an interquartile range. The Student's t-test or the Mann-Whitney U-test were used to compare the groups, and the Kraskel—Wallis criterion was used to analyze three or more independent groups. Categorical data was analyzed using Pearson's χ^2 criterion or Fisher's exact criterion. The level of statistical significance was assumed to be $p < 0.05$.

The object of research:

Patients who had recovered from coronavirus infection (COVID-19) and were residents of Almaty, including patients with type 2 diabetes and individuals without carbohydrate metabolism disorders.

The retrospective phase of the study analyzed data from 294 patients, including 134 patients with type 2 diabetes who formed the study group and 160 patients without type 2 diabetes who formed the control group.

The sociological phase of the study involved 417 patients who had recovered from COVID-19.

The cross-sectional study included 141 patients with a history of COVID-19 who were analyzed for clinical symptoms of post-COVID syndrome, laboratory parameters, and IgG antibody levels to SARS-CoV-2.

The subject of the study:

The subject of the study is the clinical, epidemiological, laboratory and immunological features of the course of postcovid syndrome in patients with type

2 diabetes mellitus, as well as the relationship of these indicators with the severity of coronavirus infection, vaccination status and metabolic control.

The main provisions to be defended.

1. The COVID-19 pandemic had a significant impact on the epidemiological indicators of type 2 diabetes in a megalopolis, contributing to an increase in the prevalence, primary morbidity and especially mortality among this category of patients.

2. The severity of the acute phase of COVID-19 and the severity of the post-covid period in patients with type 2 diabetes mellitus vary depending on the epidemiological stage of the circulation of SARS-CoV-2 viral variants: a more severe course of the disease, increased frequency of hospitalizations and complications, as well as more pronounced neurological and cardiac symptoms in the post-covid period are noted during periods of dominance the strains "Alpha" and "Delta" compared to the "Omicron"-associated wave.

3. Patients with type 2 diabetes mellitus are characterized by a more pronounced and prolonged clinical picture of post-covid syndrome, including cardiorespiratory, neurological, cognitive and psychoemotional manifestations, which necessitates systematic multidisciplinary monitoring, while vaccination against COVID-19 helps reduce the severity of post-COVID symptoms, the frequency of hospitalizations and the need for correction of hypoglycemic therapy.

4. An analysis of the immune response indicators demonstrated that patients with T2DM and signs of cystic fibrosis are characterized by a more pronounced increase in IgG titers to SARS-CoV-2, which may reflect a pronounced immune response to the infection. The higher level of specific IgG antibodies in patients with type 2 diabetes mellitus reflects both the severity of the infection and the expediency of timely vaccination of this group of patients.

5. The need for personalized and step-by-step clinical and diagnostic management of patients with type 2 diabetes mellitus who have undergone COVID-19 is substantiated, including risk stratification, therapy correction, vaccination, and follow-up to prevent decompensation and vascular complications.

Description of the main research results

As part of the dissertation work, a comprehensive epidemiological, clinical and immunological study was conducted aimed at studying the postcovid syndrome in patients with type 2 diabetes mellitus. An analysis of official statistical data for 2019-2023 made it possible to characterize the dynamics of the main epidemiological indicators of the disease in a megalopolis and assess the impact of the COVID-19 pandemic on the condition of this group of patients.

The clinical part of the study was devoted to a comparative assessment of the course of COVID-19 in patients infected during various epidemiological periods associated with the circulation of various variants of SARS-CoV-2. The data obtained indicate marked differences in the severity of the disease, the structure of comorbid pathology, the frequency of hospitalizations and the nature of

complications, which emphasizes the importance of the epidemiological context in analyzing the clinical course of infection.

Special attention is paid to the study of postcovid syndrome in patients with type 2 diabetes mellitus. The analysis of clinical manifestations showed that in this category of patients, symptoms persist for a longer time and are more pronounced than in people without impaired carbohydrate metabolism. At the same time, the dependence of the nature and intensity of postcovid manifestations on gender, age and vaccination status was revealed, which indicates the multifactorial nature of the formation of postcovid syndrome.

Laboratory studies performed in the long-term postinfectious period made it possible to assess the features of the metabolic and immune status of patients. The results obtained indicate the persistence of carbohydrate metabolism disorders in patients with type 2 diabetes mellitus, as well as differences in the level of specific IgG antibodies to SARS-CoV-2, which may reflect the characteristics and duration of the humoral immune response in patients with metabolic disorders.

The combination of clinical, epidemiological and laboratory data served as the basis for the development of a practice-oriented algorithm for the management of patients with type 2 diabetes mellitus in the post-covid period. The algorithm is focused on a step-by-step and personalized approach aimed at optimizing outpatient follow-up, correcting therapy and preventing complications in outpatient settings.

Justification of scientific novelty

1. For the first time at the regional level (Almaty), a comprehensive analysis of the dynamics of morbidity, prevalence and mortality among patients with type 2 diabetes during the pandemic and post-pandemic recovery (2019-2023) was conducted. It was found that the prevalence of the disease showed a gradual increase while maintaining a steady trend, while the indicators of primary morbidity and mortality reached peak values in In 2021, reflecting the combined impact of pandemic factors and the metabolic consequences of SARS-CoV-2 infection.

2. The clinical features of the post-cystic period in patients with type 2 diabetes mellitus who were infected during various epidemiological periods were determined. It was shown that in the early phases of the pandemic (periods corresponding to the circulation of the Alpha and Delta variants), the disease was more severe, accompanied by a higher frequency of hospitalizations, cardiovascular and musculoskeletal complications, as well as more pronounced neurological and cardiac symptoms compared with the period corresponding to the Omicron-associated wave.

3. The features of the clinical course of postcovid syndrome in patients with type 2 diabetes mellitus, characterized by a higher frequency of respiratory, neurological, cardiovascular and urogenital symptoms compared with people without diabetes, were revealed. It has been shown that vaccination against COVID-19 is associated with a decrease in the severity of post-covid symptoms, the risks of hospitalization and the need for correction of hypoglycemic therapy.

4. For the first time, a comparative analysis of clinical and laboratory parameters in patients who suffered from COVID-19 in the long-term post-infection period was carried out. It was found that the structure of kidney-shaped symptoms and biochemical parameters is generally comparable in patients with and without diabetes, however, patients with type 2 diabetes have higher levels of specific IgG antibodies to SARS-CoV-2, which may reflect enhanced and prolonged activation of the humoral immune response.

5. An algorithm for managing patients with type 2 diabetes mellitus in the post-covid period has been developed, including risk stratification, recommendations for therapy, vaccination, follow-up and medical rehabilitation, which allows for a personalized approach to managing the condition of this category of patients.

Practical significance of the results obtained

The results of the dissertation research are of practical importance for outpatient and specialized healthcare units and can be used in the daily clinical practice of endocrinologists, internists and general practitioners.

The data obtained on the clinical features of the course of postcovid syndrome in patients with type 2 diabetes mellitus make it possible to increase the alertness of doctors regarding prolonged cardiorespiratory, neurological and psychoemotional disorders, which contributes to earlier detection of complications and timely correction of therapeutic tactics.

The use of the proposed algorithm contributes to a systematic approach to assessing the condition of patients, risk stratification, correction of hypoglycemic therapy and prevention of vascular complications, as well as optimizing patient routing, reducing the frequency of decompensation of carbohydrate metabolism and reducing the need for emergency hospitalizations, which increases the effectiveness of outpatient care and promotes the rational use of healthcare resources.

The materials of the dissertation research can be used in the development of local clinical protocols, methodological recommendations, as well as in the educational process during the training of interns, residents and students of advanced training courses in the specialties of Endocrinology and General Medical Practice.

Personal contribution of the doctoral student

The personal contribution of the dissertation researcher consists in the independent choice of a topic and the justification of its scientific and practical significance, the formation of the purpose and objectives of the research, the development of its design, as well as in the organization and phased implementation of all stages of the work. The author personally collected clinical and laboratory data from all included patients, was directly involved in the implementation of special research methods, the formation of a register of observations and statistical analysis. The dissertator also independently formulated key conclusions, conclusions and suggestions for the practical application of the results.

Conclusions

1. An analysis of epidemiological indicators in Almaty for 2019-2023 showed an increase in the prevalence of type 2 diabetes mellitus from 2,152.7 to 2,367.8 cases per 100,000 population (an increase of 4.6%), while the maximum rates of primary morbidity were recorded in 2021 - 254.1 per 100,000 population (an increase of 28.3%). The peak in mortality also occurred in 2021, amounting to 143.2 per 100,000 population, which corresponds to an increase of 42.3%, followed by a decrease in 2023, reflecting the increased vulnerability of patients with type 2 diabetes to COVID-19.

2. A comparative analysis of the clinical and laboratory characteristics of patients with COVID-19 who became ill during various variant-associated periods showed that the course of infection in the circulating phases of the Alpha and Delta strains was characterized by greater severity and frequency of hospitalizations (59.8% and 63.0% versus 8.6% for Omicron, $p < 0.001$), higher level of comorbidity (type 2 diabetes - 55.7–57.6% vs. 25.7%, $p < 0.001$; HYPERTENSION was 62.9–73.9% versus 45.7%, $p < 0.001$) and was accompanied by a higher incidence of cardiovascular and musculoskeletal complications, as well as more pronounced neurological and cardiac symptoms compared with the period corresponding to the Omicron-associated wave ($p < 0.05$).

3. Postcovid syndrome in patients with type 2 diabetes mellitus is characterized by a higher frequency and duration of symptoms compared with people without diabetes, especially shortness of breath (61.8% vs. 47.2%), fatigue (65.2% vs. 46.3%), neurological and musculoskeletal disorders ($p < 0.001$). Unvaccinated patients, as well as women and people over 45 years of age, demonstrated a 2-3-fold higher incidence of respiratory, cognitive, and asthenic symptoms compared with vaccinated patients ($p < 0.001$).

4. In patients with cystic syndrome and type 2 diabetes mellitus, examined more than a year after the coronavirus infection, clinical manifestations, including respiratory, asthenic, neurological and musculoskeletal symptoms, as well as indicators of general and biochemical blood analysis (total protein, ALT, AsT, total bilirubin, urea, creatinine, total cholesterol, CK, LDH)) were generally comparable to those in the control group ($p > 0.05$), with the exception of glucose and glycated hemoglobin levels ($p < 0.05$). The level of specific IgG antibodies to SARS-CoV-2 significantly differed between the groups ($p = 0.028$), and there was a tendency to higher values in patients with metabolic disorders, which may reflect a more pronounced and long-lasting humoral reaction.

5. A comprehensive algorithm for the management and follow-up of patients with type 2 diabetes mellitus has been developed. COVID-19 survivors, which provides for step-by-step tactics in the acute and post-covid periods, correction of therapy and preventive measures aimed at stabilizing metabolic status and reducing the risk of complications.

Approbation of the dissertation results

The main provisions and results of the dissertation work were reported

at conferences:

1. International Conference "Comorbidity of endocrinopathy", 04/29/2022, Almaty — "Life after COVID-19: features of the course in patients with type 2 diabetes".

2. International Conference, 11/11/2022, Almaty — "Diabetes mellitus and COVID-19: lessons of the pandemic".

3. World Diabetes Day Conference, 11/14/2022, Almaty — "Long-term consequences of the COVID-19 pandemic in patients with type 2 diabetes."

4. Conference on World Diabetes Day, 11/14/2023, Almaty — "Clinical and laboratory features of postcovid syndrome in patients with type 2 diabetes in different periods of infection."

Publications

As part of the dissertation research, 5 articles were published, including 2 in journals included in Scopus/WoS, as well as a utility model patent and an author's certificate.:

- Altynbekova S. et al. Post-COVID syndrome and type 2 diabetes mellitus in Kazakhstan: clinical manifestations and vaccine efficacy // *Ann. Pediatr. Endocrinol. Metab.* 2024. Vol. 29, № 5. P. 325–336;

- Altynbekova S.A. et al. Retrospective analysis of the characteristics of the post-COVID period in patients with type 2 diabetes, infected during different variant-associated periods of COVID-19 // *Diabetes Mellit.* 2024. Vol. 27, № 5. P. 441–450;

- J. Abylayuly, S.V. Bolshakova, S.A. Altynbekova. Post-COVID-19 syndrome and diabetes mellitus: an overview. *Pharmacy of Kazakhstan.* 2022 No.3. 70-77 pages;

- Altynbekova S., Abylayuly Zh., Bolshakova S. Current concepts and challenges of COVID-19 vaccine prophylaxis in patients with type 2 diabetes mellitus. *SCIENCE & HEALTHCARE.* No. 1, 2024. 132-139str.

- J. Abylayuly, S.V. Bolshakova, S.A. Altynbekova. The effect of new classes of sugar-lowering drugs on clinical and laboratory changes in patients with type 2 diabetes mellitus in the post-covid period. *Pharmacy of Kazakhstan, December No.6 (257) 2024, 155-160 pages.*

- Utility model patent, No. 10203 dated 08/15/2024

S.A. Altynbekova Zh. Abylayuli, S.V. Bolshakova A system for monitoring glucose levels in patients with diabetes mellitus and post-covid syndrome; .

- Copyright, No. 52416 dated 12/10/2024.

S.A. Altynbekova Zh. Abylayuli, S.V. Bolshakova. Characteristics of clinical manifestations of post-covid syndrome in patients with type 2 diabetes mellitus.

- Copyright, No. 64301 dated 11/18/2025.

S.A. Altynbekova Zh. Abylayuli, S.V. Bolshakova. An algorithm for the management of patients with type 2 diabetes mellitus in the acute and post-COVID-19 period.

Information about implementations:

An act of implementation of the results of scientific research work on the bases of the KGP at the Municipal Polyclinic No. 4, Almaty, has been developed.

Scope and structure of the dissertation

The thesis is presented on 135 pages and includes structurally completed sections: introduction, literature review, description of materials and methods, results of own observations, discussion, conclusion, conclusions and practical recommendations. Additional materials are provided in the appendices. The illustrative series includes 23 tables and 22 figures. The bibliographic list covers 181 sources of domestic and foreign publications.