

O.V. Muravlova , Z.O. Shaienko , I.L. Dvornyk , L.M. Sizova ,
V.I. Ilchenko , T.I. Purdenko , O.A. Shpetnyi 
Poltava State Medical University, Poltava, Ukraine

Diabetes mellitus and COVID-19: living with double risk

For citation: *Mižnarodnij endokrinologičnij žurnal*. 2023;19(6):448-454. doi: 10.22141/2224-0721.19.6.2023.1315

Abstract. Background. The purpose is to analyze and summarize the studies conducted to determine the impact of COVID-19 on the course of diabetes mellitus and the manifestations of chronic complications of this disease. **Materials and methods.** We did the search in PubMed and ScienceDirect databases using the following line: "SARS-CoV-2 or COVID-19 and diabetes or hyperglycemia". **Results.** It was found that in patients with diabetes, the severity of COVID-19 is increased. In particular, the number of those who needed intensive care or artificial ventilation has elevated. The same negative trend is noted for the overall mortality rate in patients with diabetes. It has been found that COVID-19 contributes to an increase in the development of diabetes, including diabetic ketoacidosis, hyperosmolar syndrome, brain stroke and mental health disorders, which can potentiate the effect of COVID-19 in enhancing the manifestations of diabetes and double risk for these patients. Along with this, the common pathways of the pathogenesis of diabetes and COVID-19 determine the bidirectionality of the interaction in their comorbidity. **Conclusions.** We have demonstrated numerous links between COVID-19 pathogenetic mechanisms and diabetes. Despite this, current research shows only modest evidence of an increased risk of metabolic, neurological, and psychiatric complications in patients with diabetes who had COVID-19. However, along with the direct impact of patients' infection, the conditions of pandemic are also affected, which complicate access to the necessary care and should be taken into account when studying the clinical consequences of COVID-19 in patients with diabetes. **Keywords:** diabetes mellitus; hyperglycemia; chronic complications; COVID-19

Introduction

At the beginning of December 2019, the first cases of pneumonia of unknown origin were detected in Wuhan, the capital of Hubei Province. The new pathogen was an enveloped RNA-beta-coronavirus-2, called coronavirus severe acute respiratory syndrome 2 (SARS-CoV-2), with phylogenetic similarity of SARS-CoV [1]. By March 11, 2020, the World Health Organization declared the status of a pandemic [2].

SARS-CoV-2 became the first virus to have global effects unknown to infectious disease for over a century. Its spread was facilitated by high contagiousness combined with a long latent period and a large number of asymptomatic carriers [3]. COVID-19 can progress from a mild respiratory infection to a generalized inflammatory state, acute respiratory distress syndrome (ARDS), associated with multiple organ failure, and has a high mortality rate [4].

In about 80 % of people, infection with SARS-CoV-2 can lead to mild or unnoticeable symptoms, but in about 20 % of

those infected with COVID-19, it can lead to serious consequences with a high risk of death. Concomitant diseases significantly increase the risk of a severe course of the disease. Chronic conditions associated with Western lifestyle: cardiovascular disease, obesity and diabetes mellitus (DM) [5] are among the most at-risk associated diseases.

Given that diabetes is one of the most important comorbidities in patients with SARS, it undoubtedly has an impact on hospitalization rates, mortality and economic consequences. Today, about half a billion people worldwide have DM, and this number will increase by 25 % in 2030 and 51 % in 2045. Prevalence is estimated at 9.3 % (463 million people), rising to 10.2 % by 2030 and 10.9 % by 2045. According to various studies, the prevalence of diabetes in patients with COVID-19 has ranged from 5 to 36 % [6].

It is well known that people with diabetes have an increased risk of infection, especially influenza and pneumonia [7, 8]. In addition, DM was previously reported as the leading cause of death among people infected with pandemic

influenza H1N1 in 2009 [9, 10]. Epidemiological studies have rapidly and consistently identified DM as one of the major comorbidities associated with COVID-19 and affecting its severity.

Understanding these aspects will help to identify and understand elements that can be useful in fighting the pandemic as best they can. In addition, many have been affected by the reduction in physical activity caused by the lockdowns imposed by most governments around the world, which is especially important for those with DM. All these consequences should be considered problematic because they increase the risk of infections, hospitalization, amputations, and death in diabetic patients [11].

However, additional research is needed on how exactly COVID-19 affects the course of DM and changes the manifestation of chronic complications of this disease. This article will review and analyze the results of research conducted by scientists from different countries around the world since the beginning of this pandemic.

The purpose of the study is to analyze and summarize the data of the conducted studies regarding the influence of COVID-19 on the course of diabetes mellitus and the manifestation of chronic complications of the disease.

Materials and methods

An extensive search of the PubMed and ScienceDirect databases was performed using the following lines “SARS-CoV-2 or COVID-19 and diabetes or hyperglycemia”. A manual search was also conducted in major general and infectious disease journals. The results of both original and review studies were included in the study in order to provide the widest amount of data on the researched question.

Pathogenetic basis of the interaction between COVID-19 and diabetes mellitus

Commonality in pathology suggests that acute adverse reactions caused by COVID-19 may superimpose on pre-existing inflammation, glucose variability, and multi-tissue damage in patients with DM to worsen outcomes.

Type 2 DM (T2DM) is associated with mild chronic inflammation. The inflammatory process in the pathogenesis of T2DM associated with the IKKb/NF-kB pathway as a molecular mediator of insulin resistance and a pharmacological target for insulin sensitization [12]. The general increased susceptibility to infections is based on the secondary weakening of the immune system [13]. In patients with DM many aspects of the innate and adaptive immune systems are disturbed: inappropriate action of T cells, impaired activity of natural killer cells, dysfunction of phagocytic cells, inhibition of chemotaxis of neutrophils, and defects in complement action [14].

Excessive caloric intake leads to stimulation of insulin secretion by β -cells of the pancreas with increased oxygen consumption, leading to cellular stress and mild inflammation. Insulin contributes to the absorption of glucose and the increase of adipocytes, which, in turn, causes the activation and recruitment of macrophages into adipose tissue. Adipocytes and macrophages then secrete more of various pro-inflammatory cytokines and chemokines (including interleukin-1 (IL-1), IL-6, IL-8, monocyte chemoattractant

protein-1, C-reactive protein) and less anti-inflammatory cytokines and adipokines (including IL-4, IL-10, IL-13 and adiponectin) [15]. All these factors can then increase insulin resistance, which will lead to an increase in the release of insulin from the pancreas and the creation of a “vicious circle”. A mild chronic inflammatory state in patients with DM may enhance the inflammatory response to SARS-CoV-2 infection and precipitate a state of hypersensitivity and cytokine storm that can lead to pneumonia, ARDS, and ultimately to MODS seen in severe COVID-19 [16]. Consistent with this, patients with COVID-19 and DM had higher levels of IL-6, CRP, and fibrinogen compared to patients without it [17].

Quarantine measures have become an equally important factor affecting the health of people with DM. Forced orders to stay at home/in place during the pandemic resulted in reduced physical activity, altered diet and increased stress. In addition, a decrease in exposure to sunlight and, as a result, a decrease in vitamin D, leads to a decrease in its anti-inflammatory effect, which can also increase insulin resistance [18]. The above-mentioned factors worsen the condition of patients.

Features of the clinical course of COVID-19 in patients with diabetes mellitus

The prevalence of DM in patients with COVID-19 caused by severe acute respiratory syndrome caused by SARS-CoV-2 varies by country: from 5 to 20 % in China, 17 % in Italy and 33 % in the USA [19–21].

During the first outbreak in Wuhan, it was noted that DM was associated with a higher risk of severe pneumonia, the release of enzymes associated with tissue damage, excessive uncontrolled inflammatory reactions and hypercoagulation [22]. In the report of the Center for Disease Control and Prevention in China, summarizing the results of 72,314 cases of the disease, it is noted that the overall mortality rate was 2.3 %, and for cases of DM was 7.3 % [23]. A review of the hospital records of 1,099 patients in China found that the overall prevalence of DM was 7.4 %, but among those who required intensive care or mechanical ventilation or who died, the prevalence was 26.9 %, compared with 6.1 % among those who did not have these signs of a serious illness. A review of 5,279 confirmed infections at one New York Medical Center found that a total of 22.6 % had pre-existing DM, but only 9.7 % of those who did not need hospitalization suffered from DM, compared with 34.7 % of those hospitalized [24]. An initial assessment of comorbidities among affected US cases by the Centers for Disease Control found that of 7,162 cases with complete records, a total of 10.9 % had DM, but the prevalence was only 6 % of those who did not require hospitalization, compared with 24 % of cases require hospitalization and 32% of those who were subsequently hospitalized in the intensive care unit [25].

One patient who died of COVID-19 was 73 years old and had T2DM [26]. H. Shi et al. report that comorbidities with DM are important independent risk factors predicting acute kidney injury among patients with COVID-19 [26]. 126 out of 355 patients who died had DM (35.5 %) compared to only three patients (0.8 %) among patients who died who did not have the disease [5]. Other research, which involved 242 patients, showed a higher prevalence of DM among severe pa-

tients (4/37, 10.8) than among non-serious patients (11/205, 5.4 %) [28]. L. Hu et al. reported a higher prevalence of DM outcomes, including severe (22/146, 15.1 %) compared with mild (14/151, 9.3 %), critical (11/26, 42.3 %), and favorable (28/260, 10.8 %) versus unfavorable (19/63, 30.2 %) [29]. Similarly, in the research of C. Eastin et al., the prevalence of DM was higher in patients with a severe course than with a mild course (28/173, 16.2 % vs. 53/926, 5.7 %) [30]. The mortality rate for COVID-19 among patients with DM was 7.3 %, which was higher than the overall mortality rate (2.3 %) [23]. In another study, among 52 critically ill patients, the prevalence of DM was 2/20 (10 %) in survivors and 7/32 (22 %) in nonsurvivors [31]. In 140 patients (severe — 58, mild — 82), DM was detected in 8 (13.8 %) and 9 (11 %) cases, respectively [32]. Similarly, among 191 patients, severe (137) and mild (54) course of DM were distinguished, the prevalence of DM was 19 (14 %) and 17 (31 %), respectively [33].

Several meta-analyses have documented the effects of diabetes on the severity and effects of COVID-19. Meta-analysis, including 31 studies with a total of 6,104 cases, showed that in patients with already existing DM, the development of severe form COVID-19 was more frequent than in cases without DM [34]. Another meta-analysis of 14 studies, including 4,659 cases from China and the USA with a prevalence of DM of 23.8 %, showed that the risk of death increased in diabetic patients [35]. A larger meta-analysis, including 33 studies with 16,003 cases, showed that the prevalence of DM in general is 11.2 %, but subgroup analysis found a prevalence of 10.5 % in China and 19.3 % outside China (mainly in the US) DM increased the risk of severe illness and death [36]. Further meta-analysis of 30 studies with 6,452 cases showed that DM increases the risk of severe COVID-19, ARDS and death [37].

Various studies have reported that patients with diabetes are more likely to develop COVID-19 disease and complications such as ARDS and even death than healthy individuals. DM was a predictor of adverse outcomes, and the prevalence of diabetes was higher in patients with a severe course than in patients with a mild course in studies involving 1,451 patients [29, 30, 38–40]. Furthermore, another nine studies clearly indicate that DM is a risk factor for adverse outcomes and is associated with ARDS and prolonged treatment in patients with COVID-19 [26, 27, 29, 41–43]. In a nonrelevant study of 113 patients with septic shock, a history of DM was associated with a lower risk of ARDS compared with nondiabetic patients [44]. This result requires further research.

Growing evidence also suggests that COVID-19 in diabetic patients is more likely to be associated with severe or critical illness, with rates ranging from 14 to 32 % in different studies [25, 32, 42, 45, 46]. According to A. Brufsky, potentially in uncontrolled hyperglycemia, high and abnormally glycosylated ACE2r in the lung, nasal airways, tongue, and oropharynx may also serve as an enhanced binding site for SARS-CoV-2, resulting in a higher susceptibility to COVID-19 [47]. This indicates the presence of stress hyperglycemia (i.e., transient elevation of glycemia in patients with glycosylated hemoglobin < 6.5 % after acute illness or surgery) [48], which may have a worse outcome in acute illness compared with previously diagnosed DM. Taking into

account that patients with stress hyperglycemia had similar worse outcomes in a previous meta-analysis, this finding is not surprising [49, 50]. Stress hyperglycemia was one of the bad prognostic factors and was associated with a significant increase in the frequency of respiratory failure and death in subjects of SARS [9].

Nevertheless, hyperglycemia is still a strong predictor of prognosis in hospitalized patients with COVID-19. In addition, hyperglycemic COVID-19 patients, compared with normoglycemic subjects, showed a higher cumulative incidence of serious disease. Besides, optimal blood glucose control with insulin infusion may improve the prognosis of hospitalized patients with COVID-19 and patients with hyperglycemia [51]. Patients with mild infections and usual oral doses can continue to take the usual hypoglycemic drugs. However, the treatment of DM causes difficulties.

Despite many uncertainties, the guidelines for the COVID-19 pandemic in most countries include people with DM as being at risk. However, reports from pediatric endocrinologists in China and Italy state that they have had no cases of COVID-19 in children, adolescents, or young adults under 25 years of age with DM requiring hospitalization. It is also reported that children with DM did not have a different disease pattern compared to children without DM [52]. In contrast, older people, especially men and/or people with DM, hypertension, and/or obesity, are prone to severe COVID-19 [53].

Complications of diabetes in patients with COVID-19

Current studies have shown that diabetes affects clinical results, but these reports are not final and require further study. DM is a predictor of adverse clinical consequences [29]. DM is one of the most common diseases and the main cause of many expensive complications; if this occurs in young patients, it may exclude them from the workforce. Although the inflammatory response, hyperglycemia, and tissue damage are very acute in COVID-19 infection, they are mirrored in the pathology of DM, which is characterized by chronic low-grade inflammation, impaired glycemic control, and slowly progressive damage to many tissues, such as diabetic microvascular and macrovascular complications.

It has been reported that COVID-19 may increase the risk of developing diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome, even in people without previously diagnosed DM. Along with this, there is a tendency to hypocoagulation protrombotic condition in patients with DM against the background of COVID-19 [54]. Insulin resistance and DM contribute to atherothrombotic conditions as a result of imbalance of factors that regulate coagulation and fibrinolysis. Many coagulation factors (tissue factor and fibrinogen) and adhesion molecules (P-selectin) increase, anticoagulant proteins (antithrombin) decrease, and fibrinolysis decreases due to an increase in plasminogen activator inhibitor type 1. All of this leads to an increased probability of endothelial dysfunction and platelet aggregation, which contributes to the formation of occlusive thrombus in the heart and lungs in patients with COVID-19 and DM. Patients with COVID-19 have elevated levels of fibrinogen, CRP and D-dimer, indicating an increase not only in coagulation but also in fibrinolysis. The imbalance between coagulation and

fibrinolysis is responsible for most of the pathology observed in COVID-19 [55]. Lung, heart, and brain damage is a common pathology in COVID-19, which is associated with fibrous clots and disseminated intravascular coagulation [56].

Recently, there have been increasing reports of symptoms persisting in the post-COVID period. In particular, according to previous studies, SARS-CoV-2 penetrates the blood-brain barrier and can directly affect nervous tissue, causing the development of neurological and psychiatric symptoms [57]. Thus, for patients with DM, the risk of neurological complications in the post-covid period may increase.

Patients with COVID-19 are at high risk of developing a stroke, especially patients with comorbid pathology. There are no significant reserves of oxygen and glucose in the cells of the human brain, so a decrease in blood flow in the cerebral vessels is accompanied by diffuse ischemia of the brain, which is clinically manifested by syncopal states and the development of cerebral stroke [58]. The development of stroke in patients with COVID-19 increases the risk of mortality. Mortality risk factors: advanced age, diabetes, hypertension, smoking, dyslipidemia [59].

In addition, it is known that patients with DM are more susceptible to the development of psychological stress, anxiety and depression [60]. These manifestations may be intensified in patients suffering from acute myocardial infarction [61]. This is explained by the fact that stress-related conditions and affective disorders, as well as COVID-19 and DM, have a link related to pro-inflammatory cytokines in their pathogenesis, in particular, by activating the NF- κ B factor, which in turn leads to potentiation of the development of complications and increased severity of comorbid conditions [62]. Stress in patients with DM is associated with poorer metabolic control, including higher levels of glycated hemoglobin, higher body mass index, and increased blood pressure. Thus, the current pandemic scenario, even in uninfected subjects, may contribute to impaired metabolic control due to difficulties in accessing the health care system, lack of physical activity, and increased stress associated with prolonged isolation.

Discussion

The analysis of the studies shows that the acute COVID-19 pandemic was superimposed on a slow metabolic disease pandemic, one of which is DM. As a result, the severity of the course of COVID-19 increased in these patients. In particular, the number of those who needed intensive therapy or artificial ventilation increased. The same negative trend is noted for the indicator of the overall mortality rate for patients with DM. Thus, diabetes mellitus is considered as a risk factor for COVID-19 severity.

In addition, the common pathway of the pathogenesis of DM and COVID-19 cause two-way interaction at this morbidity. We found that despite the detailed study of the impact of DM on the course of COVID-19, insufficient attention is paid by modern researchers to feedback. It has been determined that COVID-19 contributes to the development of complications of DM, including diabetic ketoacidosis, hyperosmolar syndrome, stroke and mental health disorders, which may potentiate the effect of COVID-19 in increasing the manifestations of DM, thus closing the vicious circle

double risk for these patients. Further research should be directed at determining the impact of transmitted COVID-19 on the manifestations and complications of DM and the factors that enhance these interactions.

Health care systems should develop programs aimed at reducing the impact and risk of disease in patients with DM, namely: the organization of distance counseling and distance education systems (on medication and diet therapy issues), which will significantly help to adhere to the target level of glycemia for patients in isolation and reduce the number of unnecessary hospitalizations and visits to an endocrinologist. All these measures will help to significantly reduce the burden on the health care system in the conditions of a pandemic, because remote measures reduce the physical load on inpatient and polyclinic departments of hospitals. Therefore, it is necessary to develop and test remote monitoring systems for diabetes patients in conditions of isolation and infection during a pandemic.

Conclusions

Despite the great attention paid to the common pathogenic mechanisms of COVID-19 and DM, current studies show only modest evidence of an increased risk of metabolic, neurological, and psychiatric complications in patients with DM after experiencing COVID-19. However, along with the direct impact of infection on the condition of patients, the conditions of the pandemic also affect access to the necessary care and should be taken into account when studying the clinical consequences of transferred COVID-19 on patients with DM.

Ethics approval and consent to participate. Not applicable.

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Received 08.06.2023

Revised 28.08.2023

Accepted 11.09.2023 ■

Information about authors

Oksana Muravlova, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: o.muravlova@pdmu.edu.ua; <https://orcid.org/0000-0002-5319-7092>

Zlatozlava Shaienko, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: z.shaienko@pdmu.edu.ua; <https://orcid.org/0000-0002-8718-7589>

Iryna Dvornyk, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: i.dvornyk@pdmu.edu.ua; <https://orcid.org/0000-0002-3809-8272>

Ljudmila Sizova, MD, PhD, Associate Professor at the Department of Infectious Diseases with Epidemiology, Poltava State Medical University, Poltava, Ukraine; e-mail: isizof@gmail.com; <https://orcid.org/0000-0002-8335-3295>

Valentina Ilchenko, MD, PhD, Associate Professor at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: v.ilchenko@pdmu.edu.ua; <https://orcid.org/0000-0002-1945-0250>

Tatiana Purdenko, MD, PhD, Associate Professor at the Department of Nervous Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: t.purdenko@pdmu.edu.ua; <https://orcid.org/0000-0002-3561-4331>

Oleksandr Shpetnyi, Assistant at the Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University, Poltava, Ukraine; e-mail: o.shpetnyi@pdmu.edu.ua; <https://orcid.org/0000-0002-8320-3326>

Conflicts of interests. Authors declare the absence of any conflicts of interests and own financial interest that might be construed to influence the results or interpretation of the manuscript.

Information about funding. This work is a part of a research project No. 0121U108263 of Department of Endocrinology with Pediatric Infectious Diseases, Poltava State Medical University.

Муравльова О.В., Шаєнко З.О., Дворник І.Л., Сізова Л.М., Ільченко В.І., Пурденко Т.І., Шпетний О.А.
Полтавський державний медичний університет, м. Полтава, Україна

Цукровий діабет і COVID-19: життя з подвійним ризиком

Резюме. Мета: проаналізувати та узагальнити дослідження, проведені для визначення впливу COVID-19 на перебіг цукрового діабету та прояви хронічних ускладнень цього захворювання. **Матеріали та методи.** Ми здійснили пошук у базах даних PubMed і ScienceDirect, використовуючи наступний рядок: «SARS-CoV-2 або COVID-19 і діабет або гіперглікемія». **Результати.** Виявлено, що у хворих на цукровий діабет посилюється тяжкість перебігу COVID-19. Зокрема, зросла кількість тих, хто потребує інтенсивної терапії або штучної вентиляції легень. Така ж негативна динаміка спостерігається і за показником загальної смертності хворих на цукровий діабет. Було встановлено, що COVID-19 збільшує частоту розвитку діабету, включаючи діабетичний кетоацидоз, гіперосмолярний синдром, мозкового інсульту і розладів психічного здоров'я, що може потенціювати вплив COVID-19 на посилення проявів цукрового діабету і мати подвійний ризик для пацієнтів. Разом із цим спільність шляхів патогенезу цукрового діабету та COVID-19 зумовлює

двонаправленість взаємодії при їх коморбідності. Аналіз досліджень показує, що гостра пандемія COVID-19 наклалася на пандемію уповільнених метаболічних захворювань, одним з яких є цукровий діабет. Як наслідок, у цих пацієнтів посилилася тяжкість перебігу COVID-19. Таким чином, цукровий діабет розглядається як фактор ризику тяжкості COVID-19. **Висновки.** Продемонстровано численні зв'язки між патогенетичними механізмами COVID-19 і цукровим діабетом. Незважаючи на це, у поточних дослідженнях показано лише скромні докази підвищеного ризику метаболічних, неврологічних і психіатричних ускладнень у пацієнтів із діабетом, які перенесли COVID-19. Однак поряд із прямим впливом інфікування пацієнтів змінюються і умови пандемії, що ускладнює доступ до необхідної допомоги та повинно враховуватися при вивченні клінічних наслідків COVID-19 у хворих на цукровий діабет.

Ключові слова: цукровий діабет; гіперглікемія; хронічні ускладнення; COVID-19