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DIABETES MELLITUS AND COVID-19: A POSSIBLE ASSOCIATION AND RISKS OF DEVELOPMENT (LITERATURE REVIEW)

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DIABETES MELLITUS AND COVID-19: A POSSIBLE ASSOCIATION AND RISKS OF DEVELOPMENT (LITERATURE REVIEW)
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Type 2 diabetes mellitus (T2DM) accounts for nearly 90–95% of all diabetes cases and has a global prevalence.
The aim of the study is to analyse the latest research on the clinical features of diabetes mellitus in patients who have recovered from COVID-19 and to assess the risks of new-onset diabetes at the post-acute phase of the disease.
Materials and methods. The latest scientific publications were studied and analysed using relevant keywords using open scientometric databases such as Scopus, Science Direct (by Elsevier), and PubMed.
Results. Patients with T2DM have an increased risk of severe COVID-19, characterized by rapid progression of inflammation, the need for admission to the intensive care unit, and frequent severe complications that affect disease prognosis. A distinctive feature of the T2DM course in patients with COVID-19 was the early development of diabetic ketoacidosis, which required change of therapy. The key pathogenic mechanisms involved in the development of diabetes during COVID-19 include β-cell damage and insulin resistance. A higher risk of new-onset T2DM was observed among critically ill COVID-19 patients who were hospitalized to intensive care units, required mechanical ventilation, and had poorly controlled hyperglycemia. The time period of follow-up of patients who have recovered from COVID-19, duration of hyperglycemia and new-onset diabetes remain debatable issues and need further research and development of screening programs for patient examination.
Key words: type 2 diabetes, risks of development, SARS-CoV-2, COVID-19.

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ЦУКРОВИЙ ДІАБЕТ ТА COVID-19: МОЖЛИВИЙ ЗВ'ЯЗОК ТА РИЗИКИ РОЗВИТКУ (ОГЛЯД ЛІТЕРАТУРИ)
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Цукровий діабет 2 типу (ЦД 2) становить майже 90–95% всіх випадків діабетів і має глобальну розповсюдженість. Пацієнти з ЦД 2 входять до групи ризику тяжкого перебігу COVID-19 зі швидким прогресуванням запального процесу, потребою госпіталізації у відділення інтенсивної терапії, частим розвитком тяжких ускладнень, які впливають на прогноз хвороби. Імовірним є зв'язок між інфікуванням вірусом SARS-CoV-2 та підвищеним ризиком виникнення нового діабету 2 типу. Дискутабельними є питання щодо термінів тривалості гіперглікемії та виникнення нового діабету у пацієнтів, які перехворіли на COVID-19, що потребує проведення подальшого спостереження та обстеження таких пацієнтів.
Ключові слова: цукровий діабет 2 типу, ризик розвитку, SARS-CoV-2, COVID-19.

Introduction. Diabetes mellitus is one of the major problems worldwide, which concerns not only medical but also economic aspects, and has a huge impact on the common health and social well-being of people [1]. In 2021, the global prevalence of diabetes among people aged 20 to 79 years was 536.6 million people (10.5% of the world's population) [2]. According to statistics, in 2021, diabetes and its complications led to the deaths of 6.7 million people [1]. By the year 2045 a significant increase is expected – up to 783.2 million people with diabetes [2]. It should be noted that 1.271 million people with diabetes were officially registered in Ukraine in 2017 [3]. In 2020 in Odesa region, more than 9.000 people aged 18 and older with type 2 diabetes (T2DM) needed insulin therapy [4].

Type 2 diabetes mellitus (T2DM) accounts for nearly 90–95% of all diabetes cases. The disease is considered to be a disorder of carbohydrate metabolism caused by insulin resistance or relative insulin insufficiency, impaired insulin secretion with or without insulin resistance. The disease is accompanied by the frequent development of complications in various organ systems – nephropathy, diabetic retinopathy, diabetic foot syndrome, polyneuropathy, and others, which leads to disability of patients with diabetes [5]. Today, the issue of the increased susceptibility of patients with T2DM to infection with various pathogens is undetermined and actual. Many scientific studies have confirmed an increased risk of infection in patients with T2DM compared to the general population. For example, patients with diabetes were more likely to have an increased risk of infection compared to patients without diabetes (OR 1.21, 95% CI 1.07–1.37) [6]. And the frequency of antibiotic use in patients with T2DM for concomitant urinary tract infection, skin infection, septicaemia, and tuberculosis

compared to patients without diabetes was 364 vs 275 per 1000 man-years (OR 1.24, 95% CI 1.23–1.25) [7].

The coronavirus disease (COVID-19) pandemic caused by the SARS-CoV-2 virus has dramatically changed the epidemiology of noncommunicable diseases [8]. In January 2024, 701.169.569 cases of COVID-19 and 6.964.576 deaths were reported worldwide [9]. All efforts of the world's scientists were aimed at improving the diagnosis, treatment, and prevention of COVID-19. However, it is very important to examine and monitor patients who have had a coronavirus infection in order to assess the possible consequences, including the development of new-onset diabetes.

The question of whether patients with diabetes are more susceptible to the SARS-CoV-2 virus infection remains controversial today. Many global studies have shown that patients with T2DM are at risk of having a more severe course of COVID-19. However, there is a lack of data on the clinical features of diabetes mellitus in patients and a possibility of new-onset diabetes in patients who have had COVID-19 in the distant past period.

The aim of the study was to analyse current research on the clinical features of diabetes mellitus in patients with COVID-19 and to assess the risk of new-onset diabetes in the post-acute period of the disease.

Materials and methods of the study. Modern scientific publications of Ukrainian and foreign scientists were studied and analysed using the scientometric open databases Scopus, Science Direct (from Elsevier) and PubMed. The literature search was conducted using the following keywords: type 2 diabetes mellitus, risk of developing diabetes mellitus, SARS-CoV-2, COVID-19. Only full texts of meta-analyses, original clinical, randomised controlled trials, and systematic reviews were considered.

Research results and discussion. Many modern works of scientists around the world state that patients with type 2 diabetes mellitus are at risk of a more severe course of COVID-19. Scientific publications have highlighted that patients with T2DM had the greatest probability to develop complications, have a higher percentage of hospital admissions to intensive care units, longer hospital stays, and mortality caused by COVID-19 [10]. The incidence of diabetes in patients with COVID-19 admitted to intensive care units was twice as high as in patients without diabetes admitted to specialised wards [11]. A systematic review and meta-analysis of 729 studies of 29.874.938 patients with COVID-19 showed that the general prevalence of diabetes was 14.7% (95% CI 12.5–16.9) among confirmed cases. The prevalence of diabetes was 10.4% (95% CI 7.6–13.6) among confirmed cases but treated on an outpatient basis; 21.4% (95% CI 20.4–22.5) among hospitalised patients; 11.9% (95% CI 10.2–13.7) among patients with a mild disease course; 28.9% (95% CI 27.0–30.8) among patients with a severe disease course; 34.6% (95% CI 32.8–36.5) among those who died [12]. One of the studies noted a higher mortality rate among patients with COVID-19 who had cardiovascular diseases (OR 3.42, 95% CI 2.86–4.09), immune and metabolic disorders (OR 2.46, 95% CI 2.03–2.85), respiratory diseases (OR 1.94, 95% CI 1.72–2.19), cerebrovascular diseases (OR 4.12, 95% CI 3.04–5.58), any types of cancer (OR 2.22, 95% CI 1.63–3.03), kidney diseases (OR 3.02, 95% CI 2.60–3.51) and liver diseases (OR 2.35, 95% CI 1.50–3.69) [13]. The mortality rate in patients with diabetes with severe COVID-19 was 81.2% [14]. In a retrospective observational study conducted by Bode B. et al. among hospitalised patients with laboratory-confirmed COVID-19, the highest mortality rate was shown in patients with diabetes and/or uncontrolled hyperglycemia compared to patients without diabetes or hyperglycemia – 28.8% vs. 6.2% ($p<0.001$) [15].

In patients with diabetes associated with COVID-19, data on a more pronounced proinflammatory cytokine response were obtained. The results of clinical and biochemical analyses indicate a higher number of neutrophils, higher levels of C-reactive protein, fibrinogen, lactate dehydrogenase, procalcitonin, ferritin, D-dimer, N-terminal fragment of brain natriuretic peptide prohormone (NTproBNP), and levels of receptors for IL-2, IL-6, and IL-8 [14]. The patients had a higher coagulation index ($p<0.01$) [16]. In previous studies conducted in the pre-pandemic period, it was demonstrated that patients with T2DM had a higher risk of venous thromboembolism than patients without diabetes (OR 1.44, 95% CI 1.27–1.63) [17]. Also, the risk of pulmonary embolism was higher in patients with T2DM than in control patients (OR 1.52, 95% CI 1.22–1.90) [17]. A higher risk of severe pneumonia has been reported in patients with diabetes associated with COVID-19, as well as excessive inflammatory and poorly controlled processes, release of enzymes due to tissue damage, and hypercoagulability associated with dysregulation of glucose metabolism [16].

There is information that patients hospitalised with COVID-19 have a higher incidence of diabetes-related threatening conditions such as diabetic ketoacidosis (DKA), hyperosmolar hyperglycaemic state (HHS) and persistent insulin resistance [18], which require to change treatment management. In one of the retrospective studies, a group of authors demonstrated an increase in the incidence and severity of DKA in new-onset T1DM in hospitalised patients [19]. The incidence of DKA increased by 19% among hospitalised patients during the COVID-19 pandemic compared with hospitalised patients in the pre-pandemic period (55% vs 36%; $p = 0.03$). There was also a significant increase in the risk of severe DKA compared with the pre-pandemic period (severe DKA 22.5% vs. 8.4%, $p = 0.01$) [19]. At the same time, the study of Ng SM et al. conducted in the UK during the COVID-19 pandemic does not suggest an increase in the incidence of new cases of diabetes, but indicates an increase in severe DKA cases, which is likely due to delays in hospitalisation and health care delivery [20]. Heaney AI et al. reported a case of diabetic ketoacidosis in an adult patient with new-onset diabetes associated with COVID-19 [21].

Diabetic ketoacidosis, which occurs in T1DM, has been observed in patients with T2DM who had COVID-19. There are reports of 77% of patients with T2DM who had ketoacidosis during COVID-19; of these, 83% had isolated diabetic ketoacidosis and 17% had HHS [22]. The study of S. Misra et al. analysed the frequency of hospital admissions of patients with a history of type 1 and type 2 diabetes and new-onset diabetes and symptoms of DKA during the first and second waves of the COVID-19 pandemic. In the first wave, hospital admissions of patients with T2DM with DKA

increased by 41%, and those with new-onset diabetes with DKA increased by 57%. In the second wave, hospital admissions of patients with T2DM with DKA increased by 50% and for patients with new-onset diabetes – by 61% [23].

Among the most frequent factors that can provoke DKA are the discontinuation of insulin or the impact of infection on the organism. One study showed that 40.1% of the DKA cases were caused by infection, 16.8% – by discontinuation of insulin, and 36.99% – by unclear factors [24]. There are reports on the use of drugs that can cause DKA by affecting carbohydrate metabolism. These include corticosteroids, thiazides, sympathomimetics, pentamidine, and antipsychotic drugs [24]. It is assumed that the development of DKA occurs in patients with new-onset diabetes associated with COVID-19, which may have been undiagnosed previously and is caused by significant metabolic disorders due to the influence of The SARS-CoV-2 virus or the direct effect of the virus on β-cells with a decrease in insulin secretion [25]. During the course of COVID-19, patients may develop ketosis or ketoacidosis, or diabetic ketoacidosis in those with a history of diabetes [26]. However, 64% of patients with diagnosed COVID-19 and signs of ketoacidosis did not have a history of diabetes [26]. DKA and HHS are two of the most serious acute complications of diabetes that require emergency care. DKA has a typical triad of clinical signs: uncontrolled hyperglycemia, metabolic acidosis and increased total ketone concentration in the organism. HHS is characterised by the development of severe hyperglycemia, hyperosmolarity and dehydration in the absence of significant ketoacidosis [27]. Three stages of ketoacidosis severity have been identified, namely: mild stage with pH less than 7.3 or bicarbonate less than 18 mmol/L, moderate stage with pH less than 7.2 or bicarbonate less than 10 mmol/L, and severe stage with pH less than 7.1 or bicarbonate less than 5 mmol/L [28]. The studies of F. Rubino et al. have reported new-onset diabetes with ketosis symptoms in patients with COVID-19. There is a suggestion that the development of DKA in patients with COVID-19 who did not have diabetes may be a precursor to new-onset diabetes [29]. In addition, clinical trials have shown a high need in insulin and a high degree of insulin resistance in critically ill patients with COVID-19 and diabetes [30]. Some publications describe the peculiarities of clinical and biochemical parameters in patients with diabetes or hyperglycemia hospitalised with COVID-19. For example, the number of neutrophils was higher (5.8×10^9/L [3.7–8.7]; $p<0.05$) and lymphocytes were lower (0.7×10^9/L [0.5–1.2]; $p<0.05$) in patients with hyperglycemia. D-dimer level was higher in patients with hyperglycemia and diabetes compared with patients with normoglycemia. There were no differences in lipid level and blood pressure between patients with hyperglycemia, diabetes and normoglycemia. The glomerular filtration rate was slightly lower in patients with diabetes compared with patients with normoglycemia and hyperglycemia (65.1 ml/min/1.73 m^2 [34.6–81.7]; $p<0.01$ [31]). Hyperglycemia was also detected in patients without a history of diabetes [15].

The study of H. Li et al. showed that patients with a history of diabetes mellitus and new-onset diabetes were more likely to have acute respiratory distress syndrome (3.1%–10.5% vs. 0.8%–3.1%), acute renal dysfunction (15.3%–17.0% vs. 1.5%–3.1%), and hypoalbuminemia (36.7%–39.4% vs. 10.8%–19.4%) during hospitalisation compared with patients with normoglycemia or hyperglycemia. Antihypertensive ($p<0.003$), hypoglycaemic ($p<0.001$), hypolipidemic ($p<0.051$), corticosteroids ($p<0.001$), oxygen support ($p<0.001$) were used more often in the treatment of such patients compared to patients with normoglycemia [32].

A number of studies have revealed peculiarities of glucose metabolism and insulin resistance in patients with COVID-19 without a history of diabetes. In one of his studies, M.P. Plummer et al. (2016) assessed probability of an association between stress hyperglycemia and new-onset diabetes in patients with a critical disease course. Stress hyperglycemia was detected in 17% of patients with no history of diabetes. At the same time, the risk of developing diabetes in these patients was almost twice as high as in patients without hyperglycemia (OR 1.91, 95% CI 1.62–2.26, at $p<0.001$) [33]. The interesting data were obtained from the study of the SARS-CoV-1 outbreak that occurred in 2002–2004. They showed that 10% of patients who had new-onset hyperglycemia after virus infection were diagnosed diabetes during a 3-year follow-up period. The risk of developing diabetes in patients with detected hyperglycemia was almost 2 times higher compared to patients without hyperglycemia (OR 1.91, 95% CI 1.62–2.26 at $p<0.001$) [33]. The results of retrospective cohort studies and patient follow-up revealed an incidence of new cases of diabetes – 29 per 1000 man-years during 4.6 months and after COVID-19 [34]. Hyperglycemia was detected in almost 35% of patients with a history of COVID-19 and was observed for 6 months after the discharge. In the meta-analysis of T. Sathish et al., which was conducted to determine the percentage of newly diagnosed diabetes in patients in COVID-19, 14.4% (95% CI 5.9%–25.8%) was reported [35]. In the study of D.B. Shrestha et al., 19.70% of patients with COVID-19 (95% CI 10.93–32.91) had new-onset diabetes, and 25.23% (95% CI 19.07–32.58) had associated hyperglycemia [36].

Some scientists attribute the emergence of new-onset diabetes in patients with COVID-19 to stress, or severe infection, or hormone treatment, but attention is drawn to the diabetogenic effect of the SARS-CoV-2 virus [37].

Scientists have shown the effect of the SARS-CoV-2 virus on both the exocrine part of the pancreas (32.5% of patients with severe COVID-19 have acute pancreatitis) and the β-cells of the islet of Langerhans [38]. In the exam of autopsy tissue samples from patients with COVID-19, the SARS-CoV-2 virus antigen was found in the pancreatic β-cells [39]. There is also evidence of the development of morphological, functional, and transcriptional abnormalities in β-cells, which leads to a decrease in insulin-secreting granules and impaired insulin production [39]. Besides, during clinical examination of patients with COVID-19, elevated levels of amylase and lipase were observed: in 1.85% of patients with mild COVID-19, in 17.7% of patients with severe disease, indicating a possible direct damage to the pancreas under the influence of the SARS-CoV-2 virus [39].

The development of insulin resistance is attributed to the direct effect of the SARS-CoV-2 virus on fat cells and

increased production of inflammatory adipokines. The development of insulin resistance has been described in patients with COVID-19 and a body mass index of 20.5–24.6 [40]. There are published works that consider the development of insulin resistance as a downregulation of insulin receptors in the skeletal muscles under the influence of γ-interferon induced by the SARS-CoV-2 virus; activation of serine kinases (PKR and PERK) as a result of an integrated organism response to stress under the influence of the virus [41].

Some publications have described the risks and incidence of new-onset diabetes in patients with COVID-19 and prediabetes history. A higher incidence of diabetes was found in patients with COVID-19 during hospitalisation and inpatient treatment (21.19% vs. 6.02% at p<0.001). A higher incidence of diabetes was also found after COVID-19 in patients after discharge during a 5-month follow-up (14.75% vs. 7.51% at p<0.001) [42].

Analysis of risks of new T2DM in patients with COVID-19 of varying severity showed the following. The risk of developing new-onset T2DM from day 1 to 180 after the moment of diagnosed COVID-19 was 1.1% (3510/313.924 patients with mild disease) and 4.1% (424/10.436 patients with moderate or severe disease), respectively, respectively [43]. In the other study, the risk of developing new-onset T2DM was 1.54 times higher (95% CI 1.46–1.62) in patients with mild COVID-19 compared to patients with mild influenza. At the same time, patients with moderate/severe COVID-19 had a 1.46-fold higher risk of developing diabetes compared to patients with moderate/severe influenza (95% CI 1.26–1.69) [44]. The national cohort study assessed the incidence of new-onset T2DM in the post-acute phase of COVID-19 over 11.1 months. It was found that patients with confirmed COVID-19 in the post-acute phase had an increased risk of developing T2DM compared to patients without COVID-19: 2.95 per 100 man-years (95% CI 2.90–3.01) vs 2.07 per 100 man-years (95% CI 2.05–2.10). Besides, patients with COVID-19 had an increased risk of new-onset T2DM compared with patients without COVID-19 (OR 1.42, 95% CI 1.39–1.46). The adjusted ratio for hypertension and dyslipidaemia was OR 1.30 (95% CI 1.27–1.33), which also indicates an increased risk of new T2DM in patients with COVID-19 [45]. There was an increased risk of type 2 diabetes in patients with COVID-19 who did not receive hormone therapy (OR 1.29, 95% CI 1.25–1.32) [45]. Correlations have been found between the severity of COVID-19 in the acute period and the risk of developing new-onset diabetes. The risk of diagnosing new diabetes increased depending on the severity of COVID-19 in the acute phase: non-hospitalised patients (OR 1.14, 95% CI 1.08–1.19), hospitalised patients (OR 1.34, 95% CI 1.30–1.38), patients admitted to intensive care units (OR 1.78, 95% CI 1.59–1.99) [45]. Meta-analysis of 5.787.027 patients assessed the risk of developing new-onset diabetes within the first 28 days after COVID-19 diagnosis and verification. Compared to the control group, an increased risk of developing new diabetes in the post-acute phase of COVID-19 was calculated by 59% (OR 1.59, 95% CI 1.40–1.81 at p<0.001) [46].

Other publications have investigated the incidence of new-onset diabetes in patients with COVID-19 compared to control group without COVID-19. The 10.9-month follow-up revealed 0.72% of newly diagnosed diabetes in patients with COVID-19 compared to 0.64% of new-onset diabetes in patients without COVID-19. Also, patients with COVID-19 who were hospitalised had an increased risk of developing new-onset diabetes compared to patients who did not have COVID-19, and the highest risk of developing diabetes was found among hospitalised patients with a severe disease course (OR 3.33, 95% CI 1.94–5.72) [47]. In the other cohort study of 181.280 patients with COVID-19, a higher risk of developing new-onset diabetes was shown in the post-acute phase of COVID-19 (OR 1.40, 95% CI 1.36–1.44) compared to the control group (a follow-up period was 352 days) [48]. Other data presented in the study of J. Zhang et al. showed that 8.6% of patients after COVID-19 developed new-onset diabetes one year after hospital discharge. In addition, it was shown that the risk of developing new-onset diabetes was higher in patients with more severe course of COVID-19 (OR 2.90, 95% CI 1.07–7.88) [49].

One more important question is the duration of diabetes that has arisen after COVID-19: whether it remains permanent. In one study of 1902 hospitalised patients with COVID-19, 31.2% of patients with a history of diabetes and 13% of patients with new-onset diabetes were identified. Follow-up of patients with new-onset diabetes for 323 days after hospital discharge showed that 56.3% of patients continued to have diabetes, and 40.6% of patients had normoglycemia or prediabetes [50]. The authors suggest that stress hyperglycemia, rather than β-cell destruction, may be the main mechanism for the development of new-onset diabetes during COVID-19 [50]. The other long-term follow-up study of patients who developed diabetes triggered by COVID-19 found that 79% of patients stopped insulin administration after six months and concluded that β-cells may be restored [51].

As a result, these studies show that diabetes increases the risk of severe COVID-19. However, there is no convincing evidence that diabetes contributes to the SARS-CoV-2 infection. And there are insufficient data on diabetes course peculiarities in patients with COVID-19.

Conclusions. Patients with type 2 diabetes mellitus have a risk of severe COVID-19, with rapid progression of the inflammatory process, the need for hospitalisation to the intensive care unit, and frequent development of severe complications that affect the prognosis of the disease. The peculiar sign of the type 2 diabetes course in patients with COVID-19 was early development of diabetic ketoacidosis, which required a change of therapy. The mechanisms of SARS-CoV-2-induced diabetes have been analysed in many studies, but β-cell damage and insulin resistance are considered to be two key links in the pathogenesis. Many studies have examined a possible link between SARS-CoV-2 infection and an increased risk of type 2 diabetes. It has been shown that a higher risk of type 2 diabetes was found among critical patients with COVID-19 hospitalised to intensive care units, requiring mechanical ventilation, and poorly controlled hyperglycemia.

However, the questions about the follow-up period of patients with COVID-19, duration of hyperglycemia and the onset of diabetes are still debatable and open, which requires further research and development of screening programmes for patients' exams.

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