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Abstract.

Patients with diabetes have more complications and higher mortality from COVID-19. This is due to the fact that diabetes impairs the immune response. Hyperglycemia causes a violation of the immune response, which in turn cannot control the spread of pathogenic microorganisms and therefore patients with diabetes are more susceptible to infections. The purpose of the work — analysis of bibliometric databases of literature on new developments in diabetes and COVID-19 and focused on clinical recommendations for patients with diabetes infected with COVID-19. The search methods included a literature review of scientific articles that studied diabetes and COVID-19. According to the results of the analysis of the articles obtained as a result of the search in the PubMed, SCOPUS, Web of Science, MedScape databases, a combination of the terms “diabetes and SARS-CoV-2”, “diabetes and COVID-19”, “pathogenesis of diabetes in case of COVID-19”, “pancreas”, “clinical features”, “diagnosis”, “treatment”, “clinical recommendations”, we found 32 messages from 2020 to 2022. The main parameters of the study were outpatients and inpatients with diabetes and COVID-19 of middle and elderly age starting from 46 years and up to 82 years of age in France, China, the USA, Great Britain, in which a nationwide, retrospective, population-based study was conducted. The following concomitant diseases are included in the main studies: arterial hypertension, cardiovascular diseases, heart failure, chronic kidney disease, chronic obstructive pulmonary disease, myocardial infarction, cerebrovascular diseases. Issues of pathogenetic mechanisms in DM and COVID-19, as well as management of patients with DM and COVID-19 are highlighted.

Key words. Diabetes mellitus, COVID-19, SARS-CoV-2, angiotensin-converting enzyme-2, cytokines.

Introduction.

In November 2019, the epidemic that arose in China in the city of Wuhan exceeded all previous epidemics in terms of its scale [1]. The new respiratory disease was named - COVID-19 (Coronavirus Disease 2019) [2]. The causative agent is the SARS-CoV-2 coronavirus [3]. In Ukraine, for the first time, COVID-19 was registered in Chernivtsi on February 29, 2020, in a man who had visited Italy the day before [4-6].

As of March 23, 2023, there are more than 680 million confirmed cases of COVID-19 worldwide, including 6,824,670 deaths. The updated number of cases of the disease in English-language sources in the form of an interactive map with coverage of confirmed cases around the world is presented on the websites of the World Health Organization (WHO) and the European Center for Disease Prevention and Control (European Center for Disease Prevention and Control, ECDC) [7].

In most medical recommendations regarding COVID-19, it is emphasized that diabetes is one of the categories of high risk of the disease, because data from Chinese scientists showed an increased mortality rate in this category of patients [8].

Given the high prevalence of cardiovascular changes, obesity, and hypertension in patients with DM, it is not fully understood whether DM is an independent risk factor in patients with COVID-19 or whether there is a combined adverse effect of one or more diseases in addition to the primary disease.

Given the high rate of deaths in DM and COVID-19, clinical recommendations for such patients are necessary, for understanding which it is necessary to clarify the pathogenetic mechanisms of DM and COVID-19, which became the subject of our search.

Search strategy.

The search methods included a literature review of scientific articles that studied diabetes and COVID-19. According to the results of the analysis of the articles obtained as a result of the search in the PubMed, SCOPUS, Web of Science, MedScape databases, a combination of the terms “diabetes and SARS-CoV-2”, “diabetes and COVID-19”, “pathogenesis of diabetes in case of COVID-19” was used -19”, “pancreas”, “clinical features”, “diagnosis”, “treatment”, “clinical recommendations”, we found 32 messages from 2020 to 2022. The inclusion criteria for literature sources were information on changes in the body of diabetes patients infected with SARS-CoV-2 coronavirus to summarize new advances in diabetes and COVID-19 and to focus on clinical recommendations for patients with diabetes.

We also got the full text relevant cross-references by search results. In addition, we obtained access to currently available scientific literature and recommendations on the websites of the World Health Organization and the Centers for Disease Control and Prevention (CDC). Literary data related to morbidity, pathogenesis, clinical features, diagnosis, and treatment were studied and summarized.

Discussion.

In November 2002, in the south of China, in the village of Foshan, atypical pneumonia was first detected, which spread to 37 countries. In March 2003, the WHO defined this disease as an acute respiratory syndrome - SARS (Severe Acute Respiratory Syndrome). Since this syndrome was clinically similar to known atypical pneumonias, SARS was called atypical pneumonia. For the first time, the term "atypical pneumonia" was used in 1938 by a virologist, Hobart Rayman, describing lung inflammation caused by mycoplasmas, chlamydia, and legionella [6]. In 2002, the causative agent of the disease was the SARS-CoV virus
from the Coronaviridae family, which previously also caused the SARS epidemic in 2002 and the MERS epidemic in 2008 [2-5].

In Ukraine, for the first time, COVID-19 was registered in Chernivtsi on February 29, 2020, in a man who had visited Italy the day before [7]. The People’s Republic of China submitted information about the SARS-CoV-2 virus to the WHO at the end of December 2019 [8], and Chinese scientists published the sequence of the SARS-CoV-2 genome [9]. This made it possible to start work on diagnostics and the creation of vaccines to fight against COVID-19. Given the high prevalence of cardiovascular changes, obesity, and hypertension in patients with DM, it is not fully understood whether DM is an independent risk factor in patients with COVID-19 or whether there is a combined adverse effect of one or more diseases in addition to the primary disease.

According to the results of the Chinese Center for Disease Control and Prevention, as of February 11, 2020, among 73,215 cases of COVID-19, the number of men and women among patients was 49% to 19.51%, respectively. Therefore, men are more prone to COVID-19 [10]. COVID-19 is observed in all age groups, the average age of patients is 47-59 years, and a more severe course is observed with comorbid conditions [11,12].

COVID-19 and glucose metabolism.

Hyperglycemia increases SARS-CoV-2 replication, and glycolysis supports SARS-CoV-2 replication through production of mitochondrial reactive oxygen species and activation of hypoxia-inducible factor 1α 20. Thus, hyperglycemia supports the proliferation of the virus. DM is a predictor of morbidity and mortality in patients with SARS. In such patients, regulation of the immune response is disturbed, which leads to severe and extensive lung pathology [13]. The presence of complications of DM, CVD, HF, and CKD increases mortality from COVID-19. National and retrospective cohort studies conducted in Europe and the USA are presented in Table 1.

A nationwide cohort study conducted in France showed that the average age of patients was 69.8±13.0 years, the number of men was 2 times higher compared to women, with a glycemic status of 8.1±1.9, arterial hypertension prevailed among concomitant diseases (77%), cardiovascular diseases (41%), chronic kidney disease (33%) and death occurred on the 7th day in 29% of patients. A retrospective cohort study conducted in China showed that the mean age of patients was 64.0 years, the largest number of patients (24%) had a glycemic profile of >9.0, hypertension (57%) and cardiovascular diseases were also predominant among comorbidities (21%), 18% of patients were in the intensive care unit, while only 8% without diabetes, mortality was 20%. A retrospective cohort study conducted in the USA showed that the average age of patients to be 67.9±13.7, the number of women and men was almost the same (649/630), the glycemic profile was 7.5±2.0, among concomitant diseases hypertension prevailed (91%), cardiovascular diseases (59%) and mortality was 33%.

Summarizing the results of the conducted research, we can say that patients with a high risk of a severe form of COVID-19 are elderly, male, have hypertension and cardiovascular diseases among the concomitant diseases. National and retrospective cohort studies in Europe and the United States have shown that cardiovascular disease and diabetes are common among patients with COVID-19 who are hospitalized in the intensive care unit.

Pathogenetic mechanisms in diabetes and COVID-19.

To date, the pathogenesis of COVID-19 is unknown, but it may be similar to the pathogenesis of the SARS-CoV virus. Although the pathophysiological mechanisms have not yet been studied, it has been noted that fatal cases of COVID-19 have been observed in elderly people with concomitant diseases, in particular, in the presence of CVD, diabetes, and chronic lung diseases [13]. According to the results of the WHO, the mortality rate among patients with hypertension is 8%, among patients with diabetes - 9%.

Research published in the journal The Lancet Respiratory Medicine links this to taking drugs that change the shape of cells and make those cells more vulnerable to the SARS-CoV-2 coronavirus. The virus penetrates into such cells more easily, damages them more often, the course of the disease is more severe, and the risk of fatal consequences increases [14]. ACE blockers help lower blood pressure, but at the same time, by increasing the expression of ACE-2, they attract more new viruses. Interacting with ACE-2, the virus depletes it, developing symptoms of deficiency of this enzyme.

DM causes high morbidity and mortality worldwide. Such changes are caused by macro- and microvascular complications [15]. Influenza and pneumonia are often serious complications in elderly people with type 2 diabetes [16]. However, data on whether DM contributes to the susceptibility of the body to disease upon exposure to the virus and affects the outcome of infection or whether CVD and renal disease, which are often associated with DM, are the main causes of mortality remain controversial [17].

For SARS-CoV-2, a molecular mechanism of entry into the cells of the human body has been established. It has been studied that the coronavirus consists of 4 proteins: spike (S), membrane (M), nucleocapsid (N) and envelope protein (E). Spike protein (S) binds to receptors on the host cell membrane (Figure 1) [18].

In figure 2 shows the period of functioning of the SARS-CoV-2 virus. Upon entering the host cell, the carrier of genetic information - sense RNA is included in the translation process without the participation of additional enzymes. RNA is placed in the center and surrounded by structural proteins. S-type proteins have appendages (spikes) that look like a crown under a microscope, which is why the Coronaviridae family was so named. On the surface of the infected cell, the S-protein of the virus (acute glycoprotein trimer) binds to the ACE 2 receptor [19]. Subsequently, the stage of transformation (rearrangement) of the spike glycoprotein occurs with the help of the cell’s own proteases (TMPRSS2, cathepsins, HAT, furin). After that, the ORF1a/b gene translation process begins. As a result of translation, polyproteins of large molecular weight are formed, which are subjected to chemical reactions, as a result of which the molecules are divided into parts by viral proteases. After that, 16 non-structural proteins are formed, which are responsible for virus replication. A replication complex is formed on vesicles with a double membrane. The replication complex produces genomic RNA of the virus and subgenomic RNAs, which encode structural proteins S, E, M, N, as well as additional
### Table 1. Clinical characteristics and outcomes in patients with diabetes and COVID-19.

<table>
<thead>
<tr>
<th>Region</th>
<th>Research design</th>
<th>Age (years; mean or median)</th>
<th>Number (women/men)</th>
<th>Glycaemic status, HbA1c (%) (proportion)</th>
<th>Comorbidities (%)</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td>France</td>
<td>Nationwide observational cohort study</td>
<td>68.9±13.0</td>
<td>1317 (462/855)</td>
<td>8.1±1.9</td>
<td>HTN (77) CVD (41) HF (12) CKD (33) COPD (10)</td>
<td>Primary outcome (MV, death on day 7): 29% Risk factors for primary outcome: BMI Risk factors for mortality: older age, microvascular and macrovascular complications</td>
</tr>
<tr>
<td>China</td>
<td>Retrospective cohort study</td>
<td>64.0 (56.2-72.0)</td>
<td>153</td>
<td>&lt;7.0 (16%) 7.0-8.0 (13%) 8.0-9.0 (12%) &gt;9.0 (24%)</td>
<td>HTN (57) CVD (21) CKD (4) COPD (5)</td>
<td>ICU admission: 18% (non-DM 8%) In-hospital death: 20% (non-DM 11%) Risk factors for mortality: age ≥70 years, HTN</td>
</tr>
<tr>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>67.9±13.7</td>
<td>1276 (649/630)</td>
<td>7.5±2.0</td>
<td>HTN (91) CVD (59) CKD (43) COPD (14)</td>
<td>Death: 33% Risk factors for mortality: insulin treatment before admission, COPD, male sex, older age, higher BMI</td>
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<td><strong>T1DM</strong></td>
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<tr>
<td>UK (England)</td>
<td>Population-based cohort study</td>
<td>46.6±19.6</td>
<td>264390 (114710/149 680)</td>
<td>&lt;6.5 (7%) 6.5-7.0 (8%) 7.1-9.9 (50%) &gt;10.0 (12%)</td>
<td>HTN (SBP &gt;140 mmHg (17); antihypertensive agents (44)) CKD (10) MI (1) Stroke (1) HF (3)</td>
<td>COVID-19-related deaths: 464 Risk factors for mortality: male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, previous stroke, previous HF, HbA1c ≥10.0% (reference range 6.5–7.0%) BMI (U-shaped, reference range 25.0–29.9 kg/m²)</td>
</tr>
<tr>
<td>France</td>
<td>Nationwide observational cohort study</td>
<td>56.0±16.4</td>
<td>56 (25/31)</td>
<td>8.4 (7.6 - 9.5)</td>
<td>Microvascular complications (49) Macrovascular complications (33) CKD (29) COPD (4)</td>
<td>Primary outcome (MV, death on day 7): 23% (age &lt;55 years 12%; 55–74 years 24%; ≥75 years 50%)</td>
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<td><strong>T2DM</strong></td>
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<tr>
<td>China</td>
<td>Retrospective cohort study</td>
<td>62 (55.68)</td>
<td>952 (442/510)</td>
<td>Glucose 8.3 mmol/l (6.2–12.4 mmol/l)</td>
<td>HTN (53) CHD (14) CeVD (6) CKD (5) COPD (1)</td>
<td>Well-controlled versus poorly controlled T2DM</td>
</tr>
<tr>
<td>UK (England)</td>
<td>Population-based cohort study</td>
<td>67.5±13.4</td>
<td>2874 020 (1267590/1606430)</td>
<td>&lt;6.5 (25%) 6.5-7.0 (21%) 7.1-7.5 (13%) 7.6-9.9 (25%) ≥10.0 (11%)</td>
<td>HTN (SBP &gt;140 mmHg (67); antihypertensive agents (76)) CKD (18) MI (2) stroke (2) HF (5)</td>
<td>COVID-19-related deaths: 10,525 Risk factors for mortality: male sex, older age, renal impairment, non-white ethnicity, socioeconomic deprivation, previous stroke, previous HF, HbA1c ≥7.5% or &lt;6.5% (reference range 6.5–7.0%), BMI (U-shaped, reference range 25.0–29.9 kg/m²)</td>
</tr>
</tbody>
</table>
Figure 1. Photomicrograph of the SARS-CoV-2 coronavirus and Model of the structure of vibrio coronaviruses.

Figure 2. Term of functioning of the SARS-CoV 2 virus.

Figure 3. Functioning of the SARS-CoV 2 virus in the host's body.
ORF genes that play the role of modulators of the immune response. New viral particles are collected on the membranes of the endoplasmic reticulum and the Golgi apparatus, after which they are pushed out of the cell as its secretory products.

The SARS-CoV 2 virus penetrates and multiplies in the cells of the respiratory epithelium. The variety of clinical manifestations varies from an asymptomatic infection to the development of severe lung damage and acute respiratory distress syndrome (ARDS), requiring mechanical ventilation [20]. The severity of the disease is determined both by the direct damaging effect of the virus and by the nature of the host's immune response [21].

The functioning of the SARS-CoV 2 virus in the host's body is presented in figure 3. When S-glycoproteins bind to ACE 2 receptors, the virus causes a decrease in receptor function, which leads to an imbalance of the renin-angiotensin system and causes the development of diffuse alveolar damage.

Multiple metabolic and vascular disorders occur in diabetes, which delay the reaction to pathogenic microorganisms [22]. Hyperglycemia suppresses the immune system [23,24]. SARS-CoV-2 infects circulating cells of the immune system and increases the programmed cell death of lymphocytes (CD3, CD4 and CD8 T cells), which causes lymphocytopenia [25]. Decreased T-cell function and hyperfunction of neutrophils lead to hyperproduction of a number of pro-inflammatory cytokines (IL1β, IL-2, IL-6, IL-7, IL-8, IL-17, MCP1, TNFα, etc.), which is called the "cytokine storm" syndrome [26].

The presence of spike-like protein in patients with DM causes hypercytokinemia, a "cytokine storm" [27]. Hyperglycemia and insulin resistance increase the secretion of pro-inflammatory cytokines [28]. WHO identifies three main conditions that put people at higher risk of complications and death - heart disease, lung disease, and diabetes.

Infection with the SARS-CoV 2 virus leads to an increase in the level of inflammatory mediators in the blood, including lipopolysaccharides, inflammatory cytokines, toxic metabolites. Alteration of natural killer cell activity and IFNγ production increases interstitial and/or vascular permeability to proinflammatory products, increases reactive oxygen species (ROS) production, leading to pulmonary fibrosis, acute lung injury, and acute respiratory distress syndrome (ARDS). Increased expression of angiotensin II leads to activation of the renin-angiotensin-aldosterone system by the virus. In turn, reactive oxygen species and the renin-angiotensin-aldosterone system activated by the virus cause insulin resistance, hyperglycemia, damage to the vascular endothelium, which leads to the development of cardiovascular complications, thromboembolism, and disseminated intravascular coagulation (DIC). Infection also causes an increase in fibrinogen and D-dimer, which leads to an increase in blood viscosity, damage to the endothelium of vessels, cardiovascular complications, thromboembolism and disseminated intravascular coagulation (DIC) (Figure 4).

Recently, there have been reports of caution in patients with CVD when taking ACE inhibitors. Since ACE-2 receptors are the "entrance gate" for the coronavirus, taking ACE inhibitors and ARBs increases the risk of contracting a coronavirus infection.

Many elderly people use ACE inhibitors and ARBs to lower blood pressure, which causes an increase in the number of ACE-2 receptors, so such people are much more susceptible to the virus. This explains the high infection and mortality rates in the elderly with concomitant hypertension who use ACE inhibitors, which cause the proliferation of ACE-2 receptors, which are targets for COVID-19. In addition, the elderly often have

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**Figure 4. Pathogenetic mechanisms in diabetes and COVID-19.**
chronic diseases: heart, blood vessels, liver, kidneys, often in combination with diabetes. Accordingly, a significant increase in the load on them in the presence of a viral infection causes negative consequences.

Management of DM.

An extremely important element of development is ACE-2, which plays the role of the SARS-CoV-2 receptor [29,30]. There is an assumption that insulin can cause excessive expression of ACE receptors [31,32], which increases the risk of developing complications during infection in patients with diabetes (Figure 5).

Acute hyperglycemia is possible in patients with DM when combined with COVID-19, which may be exacerbated by insulin resistance associated with inflammation, thus prompt and effective provision of appropriate glycemic control is necessary [26]. According to Drucker's review, analogs of dipeptidyl peptidase DPP4 and glucagon-like peptide GLP1 are recommended for patients with mild and moderate symptoms, as these drugs have proven glucose-lowering effectiveness in hospital settings, as well as in outpatient clinics [27]. However, there are insufficient data to support the use of these drugs instead of insulin in critically ill patients with diabetes and COVID-19 [28].

Thiazolidinediones are agonists of the γ receptor, which regulates the transcription of genes involved in glucose and lipid metabolism. In animal studies, thiazolidinediones have been found to reduce insulin resistance. In a review of randomized controlled trials comparing thiazolidinediones with placebo for the prevention of stroke and vascular disease in stroke survivors, treatment with thiazolidinediones reduced the incidence of recurrent stroke compared with placebo [29].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors work on the kidneys to lower blood glucose levels and are used to treat type 2 diabetes. SGLT2 reduces the infiltration of inflammatory cells into arterial plaques and decreases the mRNA expression of some cytokines and chemokines, such as TNF, IL-6, and monocyte chemoattractant protein 1 (MCP1) [24].

Currently, many scientists are reviewing the prescription of drugs that reduce sugar levels in patients with diabetes and COVID-19. Insulin remains the only therapy for people with diabetes [25]. Metformin and sulfonylurea drugs do not interact with ACE-2, ADAM17, so they can be safely used in mild cases of COVID-19 [26]. The use of GLP-1 receptor agonists should be discontinued in patients with hemodynamic instability, renal and gastrointestinal dysfunction. Such therapy can cause hypovolemia and regurgitation [27]. With a severe course of COVID-19, the use of sulfonylurea drugs requires control of the level of glucose in the blood. Therefore, sulfonylurea drugs are replaced by insulin [28]. Thiazolidinediones cause fluid retention and increasing systemic edema. They are contraindicated in patients with high/low blood pressure, high/low heart rate (pulse), loss of consciousness/confusion, impaired liver, or heart function [29].

To date, the risks associated with taking aspirin have not been described. However, myocardial damage is a serious manifestation of COVID-19, acute myocardial ischemia has not been clearly described [25].

Currently, there is no direct evidence regarding the use of statins in patients with diabetes and COVID-19 [26]. There is information about increased liver and muscle enzymes associated with COVID-19 [27]. Therefore, individual therapy of patients with diabetes mellitus and COVID-19 is currently being used, considering indications for the appointment of statins, interactions with antiviral drugs [28].

Over the past 2 years, new information has emerged regarding the use of dexamethasone in critically ill patients.
with COVID-19 who are on mechanical ventilation, which has shown good results in reducing mortality in such patients [29].

According to a published report in the journal Nature, remdesivir prevents the infection of human cells by SARS-CoV-2 in vitro [30]. Previously, the US Food and Drug Administration (FDA) approved the use of remdesivir only for use in patients with severe COVID-19 to improve quality of life. Currently, the FDA has approved the emergency use of remdesivir, which shortens the course of the disease in patients with less severe forms of the disease. Remdesivir, a nucleotide analog inhibitor of RNA-dependent RNA polymerase, increased glycemia and increased insulin resistance in mice fed a high-fat diet [31]. In contrast, the increase in blood glucose levels was similar between the remdesivir and placebo groups in two randomized clinical trials with multiethnic groups and Chinese patients [31]. Thus, more evidence is needed to clarify its effects on glucose metabolism.

The antiviral drug favipiravir, developed by Fujifilm Toyama Chemical in Japan, has shown results in treating mild-to-moderate COVID-19. It has been used in Japan to treat influenza and has been approved as an experimental treatment for COVID-19. The drug likely shortens the duration of the virus and also improves the condition of the lungs in patients with COVID-19. The clinical effectiveness of this drug continues to be investigated [32]. However, the search for drugs to treat COVID-19 is ongoing, and these drugs may affect glucose metabolism in diabetes.

Conclusion.

1. Patients with DM and comorbid conditions are at high risk of progression and severe course of COVID-19.
2. SARS-CoV 2 increases the level of inflammatory mediators in the blood, increases the production of reactive oxygen species, which leads to acute lung damage and acute respiratory distress syndrome.
3. In severe cases of COVID-19, insulin, and dipeptidyl peptidase 4 inhibitors are recommended; metformin and sodium-glucose cotransporter 2 inhibitors should be discontinued.
4. Patients with diabetes and COVID-19 should follow general prevention rules, monitor glucose levels more often, eat well, and control other risk factors.

REFERENCES

combination on the serum levels of adiponectin, leptin, IL-6, IL-18, MCP-1, RANTES and sICAM-1 in rats. J Int Acad Periodontol. 2020;22:1-10.