Diabetes and Metabolic Syndrome – Risk Factors for Covid-19 (literature review)

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Abstract

The COVID-19 pandemic is caused by severe acute respiratory syndrome 2 (SARS-CoV-2). The epidemiological situation, which has changed the past 2 years, dictates new rules of life. The nature of modern human nutrition has become a significant factor contributing to the occurrence of chronic diseases of the endocrine and cardiovascular systems (including obesity, type 2 diabetes mellitus, metabolic syndrome), each of them has become a risk factor of severe forms of COVID-19.

The aim of the study was to review scientific data on the risk factors of COVID-19, taking into account metabolic disorders that complicate the course of a new coronavirus infection, based on publications in the databases "Pubmed", "Google Scholar" for the period 2020-2021.

Three main pathophysiological mechanisms linking metabolic disorders and COVID-19 have been identified: angiotensin converting enzyme dysregulation; liver dysfunction, chronic systemic inflammation with hypercoagulation. It has been shown that the risk observed among people with diabetes is also associated with insulin resistance, obesity, which can lead to an unfavorable outcome. It has been proven that diabetes and hyperglycemia are independent predictors of mortality and morbidity of COVID-19, and glycemic control can significantly improve the prognosis for the patient.

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Introduction

Severe acute respiratory syndrome 2 (SARS-CoV-2) was first detected in 2019 in Wuhan, Hubei Province (China), quickly spread around the world and in the shortest possible time reached the scale of a pandemic with a high mortality rate. On March 11, 2020, WHO announced the COVID-19 pandemic.[1, 2] It was revealed that the disease is caused by a new single-stranded RNA virus (ss-RNA, 29903 bp) belonging to the group of coronaviruses (CoV).[3] Typical symptoms are fever, severe respiratory distress syndrome, lymphopenia. In severe cases, sepsis and septic shock, thromboembolism, multiple organ failure (damage to the heart, liver, kidneys) were noted. [4,5]

According to the WHO monitoring center, the global number of registered cases currently exceeds 190 million, and the number of deaths exceeds 4 million. According to Rosstat, 6.03 million cases were registered in Russia, 151 thousand people died.

COVID-19 can occur in the form of acute respiratory illness (ARI), or atypical pneumonia.[5] However, there are cases of asymptomatic course.[6,7] The risk of developing severe forms increases in the elderly (the total mortality from COVID-19 is about 1.4%, most of the dead are elderly people).[8-10] More severe forms with a high risk of complications are found in people with cardiovascular diseases, arterial hypertension, metabolic syndrome (MS), diabetes mellitus (DM), chronic respiratory diseases. [4,11,12,13,14,15]

High mortality of patients with MS is probably one of the important risk factors for the development of COVID-19 complications.[16,17] MS is defined as a set of metabolic disorders, including insulin resistance, dyslipidemia, central

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obesity and arterial hypertension, which are risk factors for the development of type 2 diabetes mellitus (DM2) and cardiovascular diseases.[9,18]

The aim of the study is to review the literature for the years 2020-2021 to identify the pathogenetic relationship of metabolic syndrome, diabetes mellitus with the development of severe forms of COVID-19.

Materials and methods

PubMed and Google Scholar databases for 2020-2021 were analyzed, keywords-metabolic syndrome, CAVID-19, diabetes, obesity, liver, arterial hypertension.

Discussion

It has been clinically proven that MS and DM are an important risk factor for the development of COVID-19, but further studies are needed to identify the pathophysiological processes involved in the relationship between DM and COVID-19.

Based on the analysis of the literature data, three main pathophysiological pathways linking MS, DM and COVID-19 were identified:

1. metabolism of angiotensin converting enzyme 2 (ACE2);
2. liver diseases accompanied by increased production of alanine aminotransferase (ALT), asparaginaminotransferase (AST);
3. chronic inflammation and hypercoagulation.

ACE2 metabolism.

We analyzed studies observing the correlation between DM and SARS-CoV-2, with the participation of ACE2 as a cellular mechanism for the introduction of the virus into human cells.[19-23] Maintaining the regulation of ACE2 in DM, on the one hand, plays an important anti-inflammatory and antioxidant role, protecting the lungs from acute respiratory diseases.[3,16,24] On the other hand, the expression of ACE2 is significantly increased in patients with DM and arterial hypertension treated with angiotensin converting enzyme (ACE) inhibitors as an adaptive response to counteraction to elevated levels of Ang-II and Ang-I.[25, 26] A number of studies have shown that the use of ACE inhibitors promotes the penetration of SARS-CoV-2 into pneumocytes and other tissue cells rich in ACE2, increases the infectious load and leads to a more severe course of COVID-19 due to a significant increase in the expression of ACE2 receptors.[25,27]

On the other hand, an increase in the expression of ACE2 receptors is directly related to bradykinin (they are involved in its cleavage). As a result, there is a significant shift in the work of the renin-angiotensin-aldosterone system, leading to a significant increase in the concentration of bradykinin. A high concentration of bradykinin causes vasodilation with subsequent hypotension, as well as increased endothelial permeability. Bradykinin enhances the synthesis of hyaluronic acid (including in the lungs). Tissue fluid with hyaluronic acid forms a hydrogel in the lumen of the alveoli, causing respiratory failure and causing the ineffectiveness of artificial lung ventilation.[18]

Arterial hypertension has a significant impact on the DM-ACE2-COVID-19 triangle and, along with DM, can be considered as a leading risk factor for complications and deaths of COVID-19.[27] The mechanism of damage to the heart muscle may be associated with a high concentration of ACE2 in the myocardium, since this enzyme is used by SARS-CoV-2 to enter the cell, making the heart a favorable place for viral colonization. Hypoxia stimulated by COVID-19 can cause myocardial damage and have severe consequences for the patient.[19]

Liver dysfunction.

The liver is also an important organ for the implementation of metabolic functions of the body. Like other organs, liver cells, especially bile duct cells, contain the ACE2 enzyme on their surface, so liver tissue is also affected by the virus.[28] An analysis of the literature data showed that a moderately elevated level of the liver enzyme ALT is an important diagnostic criterion in newly infected patients with SARS CoV-2 for the subsequent development of acute respiratory distress syndrome (ARDS).[19,29] Therefore, the severity of the course of SARS CoV-2 can be affected by chronic liver diseases, including chronic viral hepatitis, non-alcoholic fatty liver disease and other metabolic disorders, including MS and DM.[30,31]

Today, it is still not completely clear whether the liver damage is primary, caused directly by the SARS CoV-2 virus and an inflammatory reaction, or secondary, caused by

drugs used in the treatment of COVID-19, or hypoxia caused by pneumonia. In this context, non-alcoholic fatty liver disease, as a hepatic manifestation of MS, is considered in the literature as a concomitant pathology subject to detailed observation.[32]

Chronic inflammation and hypercoagulation.

It is known that adipose tissue is considered a biologically active endocrine and paracrine organ. In obese individuals, the concentration of pro-inflammatory cytokines increases-interleukin-6 (IL-6)[3,9], tumor necrosis factor alpha (TNF-α)[33,34], plasminogen activator inhibitor – 1 (PAI-1).[18,32] The mechanism by which adipocyte dysregulation occurs has not been fully studied, but a positive correlation has been found between fat accumulation and oxidative stress, with the production of reactive oxygen species and increased expression of NADPH oxidase with a concomitant decrease in the expression of antioxidant enzymes.[34,35]

SARS-CoV-2 affects not only cells of the upper respiratory tract and epithelial cells of the lung alveoli, but also circulating immune cells that induce apoptosis of lymphocytes.[36,37] Since T-cells of the immune system suppress the activation of innate immunity, as a result, lymphocytopenia can suppress innate immunity and increase the secretion of cytokines.[29,38] Excessive production of proinflammatory cytokines (TNF-α, IL-6, IL-1β and CXC-chemokine ligand) leads to a so-called cytokine storm, which leads to a high risk of vascular hyperpermeability, multiple organ failure and death.[8] Cytokine storm is more likely in patients with diabetes mellitus, since diabetes mellitus is already characterized by low-grade chronic inflammation. Moreover, in the case of a high viral load, the ability to cause an acute immune response may be impaired in patients with diabetes, exposing them to more serious adverse consequences. A high concentration of inflammatory markers in the blood (C-reactive protein, procalcitonin and ferritin), the predominance of neutrophils over lymphocytes and an increased concentration of inflammatory cytokines and chemokines in the blood were associated with the severity of COVID-19 (inflammatory infiltration was detected in the lungs, heart, spleen, lymph nodes and kidneys).[8,36]

In patients with type 2 diabetes without clinical signs of vascular pathology, various mechanisms of coagulation activation were revealed (increased fVII, fibrinogen, PAI-1, etc.), which are leveled when euglycemia is reached, but are realized in the form of thrombosis in critical imbalance with the addition of concomitant factors, which becomes COVID-19.[39] In patients with diabetes mellitus, platelet hyperagregation is observed in microvascular angiopathy regardless of glycemic control, which suggests that factors other than hyperglycemia may contribute to platelet dysfunction.[40]

It has been proven that COVID-19 also leads to increased coagulation activity in healthy individuals, primarily due to endothelial dysfunction associated with hypoxia. The latter accompanies inflammatory and autoimmune damage to the pulmonary vessels, massive pulmonary interstitial fibrosis, but against the background of DM, hypercoagulation leads to the development of acute DIC syndrome, which leads to the formation of hemorrhagic pulmonary infarction, severe endothelial damage, disseminated vascular thrombosis with almost complete occlusion of the alveolar capillaries, and their deformation.[41,42] Here there is a "vicious circle" when chronic inflammation increases hypercoagulation, and the latter, due to the formation of microthrombs and hypoxia, increases the activity of the inflammatory process. The inclusion of COVID-19 in the pathological system automatically programs the development of DIC syndrome.

Based on the above, there is no doubt that ensuring adequate glycemic control in patients with diabetes mellitus and COVID-19 can significantly increase the number of favorable outcomes.

The peculiarities of the course of COVID-19 in patients with metabolic syndrome and diabetes mellitus should be taken into account in the treatment regimen. For example, treatment with chloroquine or hydroxychloroquine can cause hypoglycemia, especially in patients receiving insulin, due to their effect on its secretion, degradation and action.[17] Conversely, antiviral drugs such as lopinavir and ritonavir lead to hyperglycemia. Pharmacokinetic interactions with antidiabetic drugs are also common, causing excessive or insufficient exposure to antiviral or antidiabetic drugs.[17,25]

Glucocorticoids used to treat patients with COVID-19 complicated by severe acute

respiratory distress syndrome as a powerful pathogenetic, anti-inflammatory treatment, stimulate gluconeogenesis, increase insulin resistance, and cause severe hyperglycemia.[43]

The most significant factor determining the level of glucose in the blood is the consumption of simple carbohydrates.[44] However, the official dietary guidelines of most Western countries recommend a diet low in fat and high in carbohydrates, which can worsen hyperglycemia. These dietary recommendations form the basis of the menu in medical institutions.[45] The problem is not limited only to the care of patients in hospitals. As people try to isolate themselves at home, many accumulate stocks of non-perishable basic foods that are cheap (carbohydrate-rich pasta, bread, rice and cereals).9 Food and beverages such as pizza, donuts, fruit juices and other sugary drinks are likely to cause hyperinsulinemia and inflammation, especially in people with metabolic syndrome.[44,45]

As the world faces rapid transmission of the new virus, there has been little scope for testing whether patients with COVID-19 can better tolerate low-carb diets compared to other diets. Nevertheless, there is strong evidence that limiting carbohydrate hydrate in the diet is a safe and effective way to achieve good glycemic control and weight loss, as well as reduce the need for medications in the treatment of type 2 diabetes.[12, 30]

Conclusions

COVID-19 therapy in patients with diabetes is a serious clinical problem. The doctor should take into account not only the statuspresent in a patient with diabetes, but also carefully balance hypoglycemic procedures with specific methods of treating a viral infection. A thorough assessment of the risk factors that contribute to the unfavorable prognosis of CAVID-19 in patients with diabetes may be the best, if not the only way to overcome this problem. The data presented in the literature are necessary to predict an unfavorable outcome of COVID-19 against the background of metabolic disorders, which can help infectious disease specialists and general practitioners to prevent and correct treatment regimens in patients with diabetes, as well as in people with metabolic disorders and prediabetic condition, when concomitant disorders have already been diagnosed - hypertension, increased ALT concentration, IL-6, lymphopenia.

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Declaration of Interest

The authors report no conflicts of interest pertaining to any of the products or companies discussed in this article.

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