RESEARCH JOURNAL OF TRAUMA AND DISABILITY STUDIES

Volume: 02 Issue: 11 Nov– 2023 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

Diabetes Mellitus Under the Covid-19 Viral Pandemic.

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Summary. In 2020, the world faced an unprecedented health challenge associated with the invasion of the novel coronavirus SARS COV-2. This is also a challenge for healthcare systems around the world. The most vulnerable in these conditions were patients with diabetes mellitus (DM) due to the peculiarities of their immune status and immune response to a viral attack, due to excessively high activity of the virus in conditions of hyperglycemia, due to comorbidity and obesity, which often accompany the course of DM. The severe course of the COVID-19 disease requires a mandatory review of the usual glucose-lowering therapy. It remains extremely important to maintain optimal glycemic control and prevent the development of ketoacidosis, and therefore, in most cases, insulin becomes the priority drug for glycemic control. The search for new drugs to combat coronavirus infection continues, and new randomized clinical trials of drugs are starting. Innovative antidiabetic drugs are also being tested as candidates for potentially effective drugs to combat coronavirus.[1,2,3,4]

Keywords: coronavirus; COVID-19; diabetes; angiotensin converting enzyme type 2; glucocorticoids.

A little more than 150 days have passed since the new coronavirus SARS COV-2 began its attack on our planet and gave rise to a new disease called COVID-19. In a complicated course, the disease leads to the development of acute respiratory distress syndrome due to viral pneumonia and to the death of patients from respiratory failure. The epidemic, which began in the Chinese province of Wuhan in December 2019, has spread to all countries and continents without exception. According to the World Health Organization (WHO), as of May 28, 2020, there were more than 5.7 million cases (with a laboratory confirmed diagnosis) and more than 356 thousand

Volume: 02 Issue: 11 Nov– 2023 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

people who died from the consequences of viral pneumonia.[6,7] This figure is growing every day by at least 70 thousand new confirmed cases of coronavirus infection. In Russia, as of the same date (05/28/2020), 379 thousand cases and more than 4 thousand deaths were registered. In connection with the current unfavorable epidemiological situation, the lives of people around the world are divided into “BEFORE” and “AFTER” the viral invasion! To avoid transmission of the virus by airborne droplets and contact, quarantine or self-isolation regimes have been introduced everywhere, mandatory wearing of personal protective equipment (masks, gloves), restaurants, cafes, clubs, theaters, cinemas, parks and other places of general gathering of people have been closed, and scheduled flights have been suspended. - and railway connections between countries. Currently, such measures are the only effective means of preventing the spread of viral infection. Due to the current unfavorable epidemiological situation, the lives of people all over the world are divided into “BEFORE” and “AFTER” the viral invasion! To avoid transmission of the virus by airborne droplets and contact, quarantine or self-isolation regimes have been introduced everywhere, mandatory wearing of personal protective equipment (masks, gloves), restaurants, cafes, clubs, theaters, cinemas, parks and other places of general gathering of people have been closed, and scheduled flights have been suspended. - and railway connections between countries. Currently, such measures are the only effective means of preventing the spread of viral infection.[8]

FREQUENCY OF COVID-19 AND SEVERITY OF DISEASE IN PATIENTS WITH DIABETES MELLITUS

The most vulnerable categories of people susceptible to this disease are patients with severe chronic diseases, such as heart and vascular diseases (coronary heart disease (CHD), heart failure, arterial hypertension, cerebrovascular diseases), chronic obstructive pulmonary disease (COPD), chronic disease kidneys and, of course, diabetes mellitus (DM). An analysis conducted by various groups of scientists from China, Italy and the USA showed a different incidence of confirmed SARS COV-2 infection in patients with diabetes. Thus, according to the Centers for Disease Prevention and Control, the incidence of diabetes among patients with COVID-19 was 5.3% of 20,892 patients in China, 10.9% of 7,162 patients in the USA and 35.5% of 355 patients in Italy. In Russia, these data entering the Federal Register of COVID-19 have yet to be analyzed.[9,10] The collection of information about patients with diabetes during the epidemic is carried out, among other things, by registering cases of past infection and its outcomes in the database of the Russian Register of Patients with Diabetes "(diaregistry.ru). If we compare data on the prevalence of

Volume: 02 Issue: 11 Nov– 2023 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

COVID-19 in China and the United States (5.3% and 10.9%, respectively) with the overall prevalence of diabetes in these countries (10.9% and 13.3%, respectively), it becomes obvious that the number infected patients with diabetes does not exceed the overall prevalence of diabetes in these countries. This means that the risks of developing this disease in patients with diabetes do not exceed those in the general population. However, if a person with diabetes is already infected with the new coronavirus SARS COV-2, then his disease is much more severe than in patients without diabetes, and the frequency of deaths in patients with diabetes is significantly higher. This fact has been confirmed in a number of studies by Chinese colleagues, whose experience is summarized in the review [11]. According to the studies reviewed, the incidence of severe COVID-19

GallbladderFREQUENCY OF COVID-19 AND SEVERITY OF DISEASE IN PATIENTS WITH DIABETES MELLITUS

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WHY ARE PATIENTS WITH DM SUPPOSED TO MORE SEVERE COVID-19?

The tendency of patients with diabetes to have a more severe course of the disease with a higher

Volume: 02 Issue: 11 Nov– 2023 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

frequency of deaths can be explained by the peculiarities of the interaction of the virus and its receptor under conditions of hyperglycemia, the characteristics of the immune response and the health status of patients with diabetes in general. Expression of ACE2 (receptor of the SARS COV-2 virus) in diabetes In order for the SARS COV-2 virus to invade human target cells (primarily alveolar cells of the lungs), it must come into contact with its receptor. It has been established that such a receptor for the new coronavirus is angiotensin-converting enzyme type 2 (ACE2) [8]. The expression of this enzyme is quite high in the oral mucosa, nasopharynx and in lung tissue (in type 2 alveolar cells).[14] That is why the "entry gate" for the virus is the upper respiratory tract, after which the virus easily penetrates the lungs and affects the alveoli, causing the rapid development of pneumonia and respiratory failure. ACE2 expression is also high in colon enterocyte cells, myocardial cells, proximal renal tubules, liver, and pancreas (Fig. 1). This localization of expression of the receptor for the new coronavirus may explain other manifestations of the disease, such as diarrhea, loss of smell, first-time transient hyperglycemia. After the viral spike has connected with its ACE2 receptor on the surface of target cells, transmembrane serine protease (TMPRSS2) "cuts" the ACE2 receptor, which leads to activation of the viral spike, and it, together with the receptor, is introduced into the cell, where it occurs its further replication. [15,16] In experimental studies on mice, it was shown that under conditions of hyperglycemia in a number of organs and tissues (kidneys, liver, pancreas), the expression of ACE2 increases many times. It has been proven that in the presence of hyperglycemia in the lung tissue, the process of glycosylation of the ACE2 receptor (i.e., protein binding to glucose) is activated, which increases its affinity for the SARSCOV-2 virus. Consequently, in diabetes, not only the expression of the receptor increases (in many tissues), but also its binding to the coronavirus. Both processes lead to greater sensitivity of patients with diabetes to viral attack. Hyperglycemia as a "provoker" of a cytokine "storm" WHAT CORRECTION OF GLOW-LOWING THERAPY FOR DM IS REQUIRED UNDER COVID-19?

This question currently remains open, since in such a short time (150 days from the start of the global epidemic) no convincing evidence has been obtained about the benefits or harm of certain groups of antihyperglycemic drugs. The main guidelines for prescribing or discontinuing drugs are instructions for the use of drugs, information about their side effects, as well as recommendations for the treatment of hyperglycemia in conditions of severe infectious diseases and in intensive care units. Patients with type 1 diabetes Continue insulin therapy at the same doses.[17,18] Monitor

Volume: 02 Issue: 11 Nov– 2023 ISSN: 2720-6866
http://journals.academiczone.net/index.php/rjtds

glycemia more often (at least 7-8 times a day). If FPG increases to more than 13–15 mmol/l, measure the level of ketones in the urine and increase the dose of short-acting insulin (RAI) and ultra-short-acting insulin (RAI) during scheduled injections before meals. It is not recommended to inject more than once every 3-4 hours (for ICDs) or 2-3 hours (for ICDs); you should first evaluate the effect of the previous dose. An ideal solution for maintaining glycemic control within target values would be the use of insulin pumps with feedback functions (or with the function of stopping the supply of insulin when hypoglycemia develops), which would allow achieving optimal glycemic parameters without the risks of hypoglycemic conditions. Patients with type 2 diabetes With a mild course of the disease (temperature <38.5 °C, absence of shortness of breath, sufficient blood oxygen saturation SpO2 >93%) and FPG <13 mmol/l, absence of ketonuria. Patients with T2DM continue current therapy (any class of drugs). Metformin remains the basic drug if tolerated. Several large-scale studies have been published showing that treatment of patients with chronic respiratory diseases and even obstructive pulmonary disease with metformin for several years led to a significant reduction in the risk of mortality compared with patients who did not receive this drug.The main pharmacological action of metformin is aimed at reducing blood glucose levels due to gluconeogenesis in the liver, reducing glucose absorption in the gastrointestinal tract and increasing its utilization by peripheral tissues by increasing their sensitivity to insulin. It has been proven that metformin has not only antidiabetic, but also anti-inflammatory, antiviral, antithrombotic and antiproliferative effects with a good safety profile. Metformin activates AMP-activated protein kinase (AMPK), thereby increasing peripheral glucose utilization in skeletal muscle, leading to insulin-independent regulation of glucose levels. Under the influence of AMPK, ACE2 phosphorylation occurs, that is, the conformation of the receptor changes, which prevents the virus from penetrating the body's cells. The anti-inflammatory effect of metformin is also carried out due to AMPK, which in turn activates ACE2, which has antithrombotic, anti-inflammatory and antioxidant effects. Thus, the expression of pro-inflammatory cytokines (IL-6, TNF-α) is reduced. Metformin molecules have a protective effect on the vascular endothelium, preventing excessive platelet activation. The pleiotropic properties of metformin may be useful for those who are ill or have already recovered from coronavirus infection. Anti-inflammatory, antioxidant and immunomodulatory effects of metformin include induction of autophagy, formation of M2 macrophages and CD8 memory T-regulatory cells, decreased expression of genes encoding chemokines and cytokines, and changes in catalase and superoxide dismutase activity, as

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http://journals.academiczone.net/index.php/rjtds

well as gut microbiota composition.[19,20]

Diabetes mellitus at any severity of the disease and FPG >13–15 mol/l. Initiation of insulin therapy is recommended. Schemes for transferring patients with T2DM to insulin therapy are described in detail in “Algorithms for specialized medical care for patients with diabetes mellitus.

NCurrently, insulin is actively used to control glycemia in patients with diabetes and COVID-19. In accordance with clinical guidelines 2021. This is the only drug that can be used for severe disease. One study demonstrated the effect of insulin on reducing the regulation of ACE2 receptors, which could hypothetically help reduce the risk of COVID-19 infection in patients with diabetes using it as basic therapy.

Conclusion

The COVID-19 pandemic has shown how important glycemic control and the development of a general treatment strategy for patients with diabetes are, and it should be as personalized as possible.

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Volume: 02 Issue: 11 Nov– 2023 **ISSN: 2720-6866**
http://journals.academiczone.net/index.php/rjtds

ЭФФЕКТИВНЫЕ МЕТОДЫ ДИАГНОСТИКИ //BARQARORLIK VA YETAKCHI TADQIQOTLAR ONLAYN ILMIY JURNALI. – 2023. – Т. 3. – №. 4. – С. 191-198.

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