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САХАРОСНИЖАЮЩАЯ ТЕРАПИЯ И ТЕЧЕНИЕ ПОСТКОВИДНОГО СИНДРОМА, ЕСТЬ ЛИ СВЯЗЬ?

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Hypoglycemic Therapy and the Course of Post-Covid Syndrome, is There a Connection?

Резюме

Сахарный диабет (как 1, так и 2 типа) считается одним из факторов риска тяжелого течения COVID-19 и смерти от этой инфекции. Перенесенная инфекция COVID-19 приводит к ухудшению контроля уже имеющегося сахарного диабета, прогрессированию предиабета в диабет, увеличению числа новых случаев диабета и росту удельного веса глюкокортикоид-индуцированного диабета, что значительно усугубляет течение постковидного синдрома для данной категории пациентов. Сахароснижающие препараты могут влиять на патогенез COVID-19, что может иметь значение для лечения пациентов с сахарным диабетом 2 типа и постковидным синдромом. В обзоре также представлены собственные данные о влиянии на постковидный синдром различных режимов приема пероральных сахароснижающих средств у лиц с сахарным диабетом 2 типа. Наблюдение показало, что использование ингибиторов дипептидилпептидазы-4 в составе лечебной стратегии у пациентов с сахарным диабетом 2 типа с перенесенной инфекцией COVID-19 ассоциировалось с уменьшением продолжительности и выраженности проявлений постковидного синдрома.

Ключевые слова: *сахарный диабет, инфекция COVID-19, постковидный синдром, ингибиторы дипептидилпептидазы-4, метформин*

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Abstract

Diabetes mellitus (both type 1 and type 2) is considered one of the risk factors for severe COVID-19 and death from this infection. Past infection with COVID-19 leads to deterioration in the control of existing diabetes mellitus, progression of pre-diabetes to diabetes, an increase in the number of new cases of diabetes and an increase in the proportion of glucocorticoid-induced diabetes, which significantly aggravates the course of post-COVID syndrome for this category of patients. Antihyperglycemic drugs may influence the pathogenesis of COVID-19, which may be of relevance for the treatment of patients with type 2 diabetes mellitus and post-COVID syndrome. The review also presents our own data on the effect of

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various regimens of oral hypoglycemic agents on post-COVID syndrome in people with type 2 diabetes mellitus. The observation showed that the use of dipeptidyl peptidase-4 inhibitors as part of a treatment strategy in patients with type 2 diabetes mellitus with a past COVID-19 infection was associated with a decrease in the duration and severity of post-COVID symptoms.

Key words: *diabetes mellitus, COVID-19 infection, post-COVID syndrome, dipeptidyl peptidase-4 inhibitors, metformin*

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ACE2 — angiotensin converting enzyme 2, GLP-1ra — glucagon-like peptide-1 receptor agonist, VAS — visual analogue scale, DPP-4 — dipeptidyl peptidase-4, IHD — ischemic heart disease, DPP-4i — dipeptidyl peptidase-4 inhibitor, SGLT-2i — sodium-glucose linked transporter-2 inhibitor, RCS — randomised controlled study, DM — diabetes mellitus, HbA1C — glycated hemoglobin

The novel coronavirus infection (COVID-19) caused by SARS-CoV-2 was first observed in China in December 2019 and very rapidly spread over the globe.

SARS-CoV-2 which causes this infection is an RNA virus; its single-stranded RNA genome is covered with a two-layer protein lipidic cover. The main receptor for the virus to attach to and penetrate in human cells is angiotensin converting enzyme 2 (ACE2), which is abundant in alveolar, vascular endothelium, myocardiocyte and a number of other cells (including pancreatic β-cells, thyrocytes, etc.).

The main route in humans is respiratory. Usually, symptoms develop over 5–6 days after contamination (sometimes 10–14 days). Moderate respiratory and general infection symptoms (fever, fatigue, headache, myalgias, possible nausea and vomiting) last for approximately 2 weeks. However, at this stage a majority of patients will develop a significant lung damage (viral pneumonia), which is complicated with acute respiratory distress syndrome, systemic inflammation response syndrome, multi-organ involvement, shock, and leads to death. Cytokine storm (hyperimmune inflammation) and thrombosis with vasculitis have a vital role to play in these complications. Often COVID-19 infection causes destabilization and exacerbation of underlying chronic diseases [1, 2].

For COVID-19 patients, diabetes mellitus (DM) is one of the most common comorbidities which is observed approximately in 20 % of patients. DM2 is known to have a negative impact on clinical outcomes [3]. Possible unfavourable outcomes include moderate and severe COVID-19 cases, higher ICU hospitalisation rates, a higher need in anti–IL-6 receptor antibodies (tocilizumab), and high mortality rates. Also, there are reports that hyperglycemia during COVID-19 is associated with poor outcomes and can be a negative predictor in patients with or without DM2. In patients with hyperglycemia, some drugs can be less efficient, especially tocilizumab, which is administered in patients with moderate to severe COVID-19 pneumonia. Thus, not only DM2, but also hyperglycemia can have negative impact on hospitalisation, clinical outcome and drug therapy, leading to poorer prognosis for COVID-19 patients [3, 4].

Prior severe viral respiratory infections (severe acute respiratory syndrome (SARS), H1N1) demonstrated possible long-term persistence of disorders which developed during the disease, including metabolic disorders. Same features are observed in COVID-19 patients. It was noted that some patients can have long-lasting (up to 12 months and longer) dislipidemia, insulin resistance, dysglycemia. Chronic post-virus syndrome associated with chronic fatigue, variable and non-specific myalgias, depression, anxiety, irritability, hyperthermia (including subfebrile hyperthermia and some episodes of febrile hyperthermia), sleep disturbances, and other manifestations (Fig. 1) are also frequent [5].

In Russian scientific literature, this set of symptoms is commonly called “post-COVID syndrome” (“post-COVID”, “long COVID” are the terms used abroad). Some authors believe that a suitable term is “chronic COVID” (taking into account the information on possible long-lasting persistence of viral particles in various tissues of the human body). The syndrome is applicable to persons who had COVID-19 infection (usually those patients whose disease started more than 28–30 days ago) and are still experiencing impaired well-being. Such patients account for at least 30–50 % in the group of COVID-19 survivors. Long-lasting symptoms can be observed not only in patients who had severe infection, but also in patients with moderate disease. Clinical manifestations can vary, sometimes they can be severe and cause disability to work. Patients with a history of COVID-19 are at a high risk of thromboembolic complications (including pulmonary artery thromboembolia, myocardial infarction, ischemic stroke) and death.

Слабость (Weakness)	95%
Одышка (Dyspnea)	78%
Миалгии (Mialgia)	68%
Сердцебиения (Palpitations)	68%
Сухой кашель (Dry cough)	65%
Тахикардия (Tachycardia)	62%
Диарея (Diarrhea)	56%
Гипертермия (Hyperthermia)	56%
Потливость (Sweating)	55%
Снижение аппетита (Reduction of appetite)	55%
Боли в грудной клетке (Chest pain)	53%
Артралгии (Arthralgia)	52%
Тошнота (Nausea)	48%
Дисменорея (Dysmenorrhea)	35%
Зуд кожи (Itching of the skin)	33%
Светобоязнь (Photophobia)	30%
Сухость глаз (Dry eyes)	27%
Кашель с мокротой (Cough with phlegm)	26%
Запор (Constipation)	20%

«Туман в голове», снижение внимания, затруднение принятия решений, когнитивные нарушения ("Fog in the head", decreased attention, difficulty making decisions, cognitive impairment)	85%
Нарушения сна (Sleep disorders)	68%
Нарушения памяти (Memory disorders)	65%
Тревожность (Anxiety)	58%
Раздражительность (Irritability)	52%
Депрессия (Depression)	48%
Головные боли (Headache)	40%
Тремор (Tremor)	40%
Апатия (Apathy)	38%
Нарушения обоняния (Olfactory disorders)	35%
Нарушения вкуса (Taste disorders)	33%
Невралгии (Neuralgia)	32%

Figure 1. *The frequency of some general somatic (left) and neuropsychiatric (right) symptoms among 3762 patients who had health problems after suffering a COVID-19 infection (adapted from Davis H.E. et al., 2021)*

At least 1/3 of subjects discharged from inpatient clinics where they were treated for COVID-19 infection, need re-admission during the next 6 months for various reasons. After COVID-19, a majority of patients require thorough multidisciplinary follow-up (Fig. 2); in some cases, adequate rehabilitation programs are useful [6].

In terms of pathophysiology, post-COVID syndrome is not a single clinical unit, but a set of symptoms and syndromes depending on a number of biological factors that require additional examinations.

Generally accepted factors include organ damage, persistent impairment in the regulation of inflammatory and immune response, as well as undiagnosed microvascular thrombosis and endothelitis. An assumption was made on the impact from some other causes: permanent tissue sources of SARS-CoV-2, reactivation of other viruses, dysfunction of the brain stem and/or nervus vagus, as well as autoimmunity activation due to molecular mimicry between pathogen and host proteins. Also, development of this condition can be facilitated by secondary infections (both bacterial or mycotic infections), sequelae of long-lasting hospitalisation, critical condition and intensive care, drug side effects (e. g., side effects of corticosteroids), social, economic, and psychological aspects. Besides, protein and micronutrient deficiency resulting from long-lasting hospitalisation and poor oral alimentation lead to nutritional deficiency in patients with severe COVID-19 [4, 6, 7].

A history of COVID-19 infection causes aggravation of pre-existing DM, pre-diabetes progression to diabetes, rise in the number of newly diagnosed DM cases and increase in the relative weight of glucocorticoid-induced diabetes, thus significantly worsening post-COVID syndrome in this patient group. Therefore, it is essential to use various hypoglycemic medications not only during COVID-19, but also during the post-infection period [3].

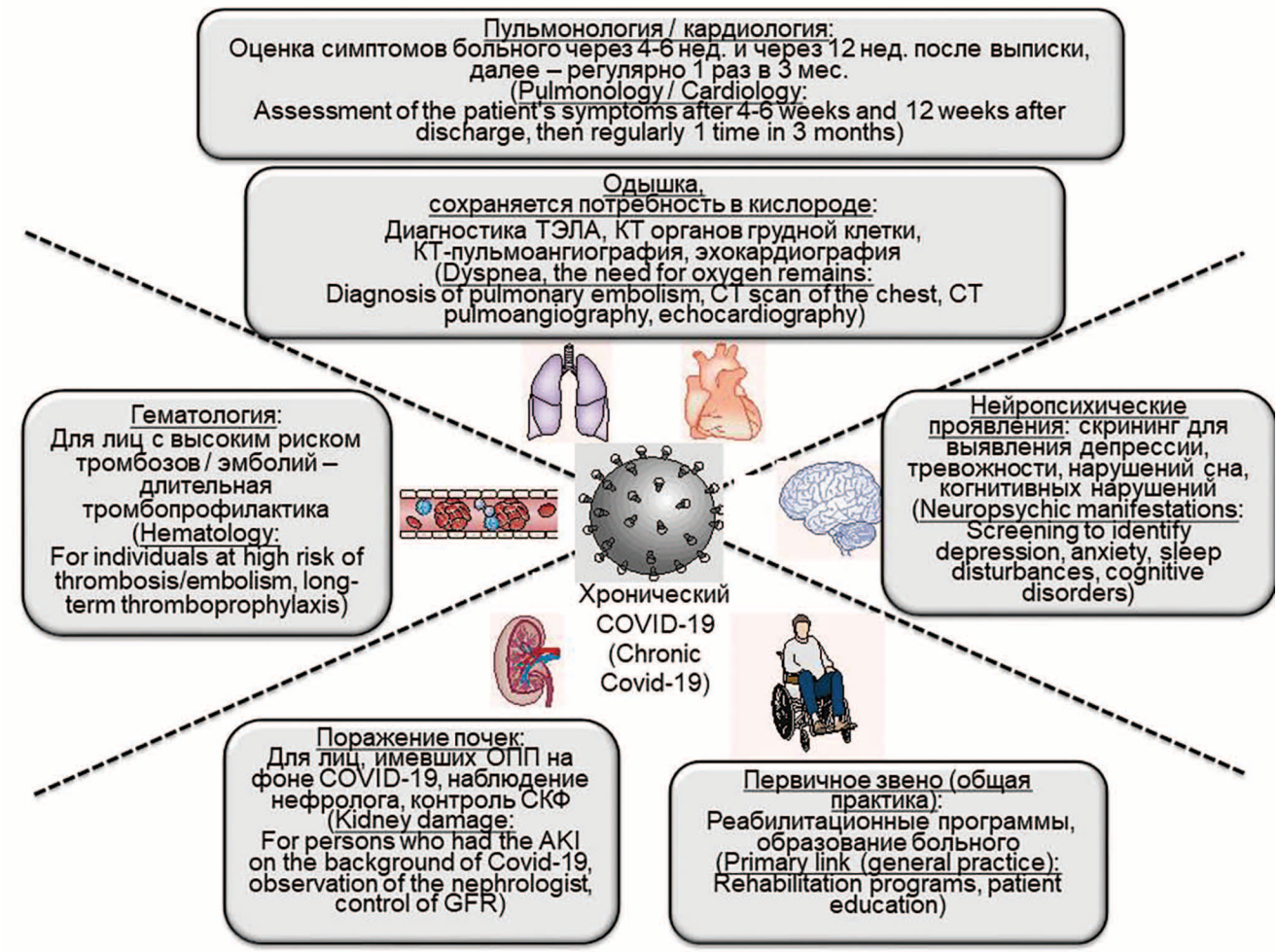

Figure 2. *Multidisciplinary approach to the COVID-19 survivor (adapted from Nalbandian A. et al., 2021)*
Note: PE — pulmonary embolism; CT — computed tomography; AKI — acute kidney injury; GFR — glomerular filtration rate

Antihyperglycemic drugs can affect COVID-19 pathogenesis, and these effects can be essential for the treatment of DM2 patients with the post-COVID syndrome. Currently, there are no results of large randomized controlled studies (RCS) evaluating the role of various classes of hypoglycemic agents in this patient group.

Available data on the use of hypoglycemic drugs relate to the COVID-19 period itself and not to the post-COVID syndrome. However, the data on the use of hypoglycemic agents during the acute period allow assuming that their effect in subjects with "chronic COVID" is similar; and further studies are needed.

At the moment, RCS DARE-19 is a topic that has been debated a lot; the study evaluates the effect of dapagliflozin, a sodium-glucose linked transporter-2 inhibitor (SGLT-2i), on the progress of COVID-19, but not post-COVID syndrome [8]. The study enrolled 1250 patients (mean age: 61 years) hospitalised with this infection (subjects in critical condition and those with marked respiratory distress were excluded). All subjects had at least 1 cardiac and metabolic risk factor (DM was observed in 51 % of patients, arterial hypertension — in 85 %). Subjects were randomized to take either dapagliflozin 10 mg/day or placebo. The study results did not demonstrate any reduction in the risk of respiratory, cardiovascular or renal dysfunction and mortality with dapagliflozin therapy; however, its satisfactory tolerability was verified. The DARE-19 data allow for reliable administration of SGLT-2i in mild to moderate COVID-19, while patients with severe disease should take these drugs with caution. Due to the risk of dehydration, diabetic ketoacidosis and acute kidney injury, SGLT-2i drugs are not indicated for severe coronavirus infection [8].

Available new data indicate that SGLT-2i have the same anti-inflammatory effect, including macrophage polarisation and reduction in proinflammatory cytokines levels [9-11]. A study of empagliflozin demonstrated that this drug inhibits acetylcholinesterase, reduces oxidative stress and positively modulates neurotransmission

and neuronal plasticity with a marked neuroprotective effect, which is an important factor in the management of patients with post-COVID syndrome [9, 11, 12].

Currently, there are reliable data on the adequate safety and satisfactory tolerability of dipeptidyl peptidase-4 inhibitors (DPP-4i) and insulin [13].

A number of experimental and epidemiological studies demonstrated positive potential biological effects of DPP-4i in COVID-19 infection; however, a favourable impact on disease prognosis was not proven. This class of drugs is well-tolerated even in severe infection cases. Therefore, DPP-4i can be continuously used in COVID-19 of various severity [13].

Dipeptidyl peptidase-4 (DPP-4), a membrane enzyme, plays an essential role in the immune system as an activated T lymphocyte marker and an expression regulator for numerous chemokines, including chemokine ligand 5 (motif C–C, CCL5), stromal cell factor 1 (also known as chemokine 12 of motif C-X-C — CXCL12), ligand 2 chemokine (CXCL2, also known as beta-regulated growth protein —GRO-b), and motif C-X-C of chemokine 11 (CXCL11). Earlier on some concerns were voiced as to an increased risk of viral infections when DPP-4 is inhibited; however, the data from clinical trials investigating the relations between DPP-4i and the risk of community-acquired pneumonia in DM2 patients do not support this assumption. Despite the fact that ACE-2 is the main SARS-CoV-2 receptor, DPP-4 can also bind to the virus (since DPP-4 molecule was previously identified as a receptor for Middle East respiratory syndrome (MERS) virus, taking into account the similarity of the causative agent, SARS-CoV-2 can also interact with this molecule). Theoretically, DPP-4 modulation can help in compensating cytokine-mediated COVID-19 complications [14]. Whether DPP-4i can affect the function of DPP-4 as a virus receptor is a matter of debate. In an in vitro study, the use of DPP-4i sitagliptin, vildagliptin or saxagliptin did not block coronavirus penetration into the cells; in an experiment with peripheral human blood the use of these drugs inhibited immute T killer response to the virus [15].

The studies of the use of DPP-4i in DM2 patients and COVID-19 are currently limited. In a retrospective case control study in Northern Italy, the use of sitagliptin during hospitalisation was associated with reduced mortality and improved clinical outcomes [16]. Another case series in Italy described the relations between DPP-4i therapy and statistically significant reduction in mortality rates; however, this result was obtained from 11 patients only (including one patient who died) [17]. In another study, DPP-4i therapy was associated with poorer results (mortality rates are not shown) in 27 DM2 patients who were treated with these drugs vs. 49 patients who were taking other antihyperglycemic agents [18].

The impact of DPP-4 inhibition on the T-cell function and T-cell-mediated inflammatory and immune reactions in COVID-19 patients require further investigation. More detailed studies are essential for characterisation of the role of DPP-4 inhibitors in patients with COVID-19 / post-COVID syndrome and DM2.

Insulin drugs are a main antihyperglycemic drug class to be used in severe COVID-19 (specifically for IV administration) for adequate glycemia control and reduction of the risk of acidosis. In a majority of cases, the need in insulin can be extremely high due to a negative impact from hyperinflammation on insulin resistance. Besides, insulin drugs have anti-inflammatory effect and reduce oxidative and inflammatory stress. During the acute phase of COVID-19 a lot of patients who took oral antihyperglycemic drugs need to transition to insulin, which should be administered subcutaneously also in outpatient settings. It will then be important to choose an adequate dose of insulin, to reduce the risk of hypoglycaemia, and possibly to retreat to oral antihyperglycemic drugs [2, 13].

In epidemiological studies of glucagon-like peptide-1 receptor agonists (GLP-1ra), drugs from this class demonstrated just neutral mortality effects in patients with DM and COVID-19. In severe COVID-19, reduced uptake of these drugs can be a result of loss of appetite and GIT side effects. At the same time, their possible anti-inflammatory effects are discussed [2, 3].

Metformin demonstrated a number of possible favourable effects in COVID-19 in epidemiological studies. This drug is considered relatively safe for outpatient patients with mild infection. Due to the risk of dehydration and lactic acidosis in hospitalised COVID-19 patients, it should be administered with caution; administration to ICU patients is not acceptable (this drug needs to be replaced with insulin). Continuous blood creatinine monitoring is required if this drug is prescribed.

Sulfonylurea medications for the use in DM patients with COVID-19 are the least studied drugs. Due to the risk of hypoglycaemia, special care should be taken even in mild COVID-19 cases. In moderate and severe infection, sulfonylurea medications should be avoided [2, 19].

The information on the use of thiazolidinediones in COVID-19 is very limited. Despite their possible organ protective effects, they are prescribed with care in patients with mild COVID-19 and are not used in moderate and severe infection [2, 19].

We would like to present our own case study of a DM2 patient with post-COVID syndrome. 53 DM2 patients (29 men and 24 women aged 64.6 ± 9.4 years) were followd up in Central City Clinical Hospital No.1 of Donetsk and the Railway Clinical Hospital of Donetsk (disease duration: 7.6 ± 1.8 years

with concomitant ischemic heart disease (IHD) in 58.6 % of cases). All patients had a history of COVID-19; 31 (58.5 %) patients had multisegmental pneumonia and were hospitalised (including 22 patients who were admitted to ICU); the mean duration of hospitalisation was 32 days. 20 (37.7 %) COVID-19 cases did not require hospitalisation. Prior to the infection, all patients were taking oral antihyperglycemic drugs. During hospitalisation, 29 (54.7 %) patients were transferred to insulin therapy, and their usual oral therapy was resumed later on. At the same time, patients were recommended to correct their lifestyle, to take appropriate organ protective and antithrombotic medications. 1 month after discharge from the clinic or inpatient therapy completion, all patients still had clinical manifestations of post-COVID syndrome, including lack of energy (91.8 %), shortness of breath (79.4 %), myalgias (72.8 %), dry cough (65.7 %), productive cough (27.3 %), hyperthermia (56.1 %), arthralgia (54.3 %), sleep/ memory/ attention disorders (70.9 %), irritability (52.2 %), depression (47.8 %), smell disorders (35.6 %). The intensity of clinical manifestations of post-COVID syndrome was assessed using a visual analogue scale (VAS).

There were 2 groups of patients depending on the antihyperglycemic drug regimen: group A (28 patients, metformin 1000–2000 mg daily + DPP-4i saxagliptin 5 mg daily, or sitagliptin 50–100 mg daily, or vildagliptin 50–100 mg daily) and group B (25 patients, same dose of metformin + sulfonylurea medications gliclazide 60–120 mg daily, or glimepiride 2–4 mg daily, or glibenclamide 5-–10 mg daily). There were no contraindications for these drugs. The groups were similar in demographics, baseline fasting glycemia, glycated hemoglobin (HbA_{1C}), COVID-19 severity, and post-COVID syndrome characteristics. The target HbA_{1C} was 6.5–7.0 %. Patients were followed up at least once every 1–2 months, with the average follow-up duration of 8 months.

Both groups tolerated the therapy well; there were no cases of therapy discontinuation due to side effects. The target HbA_{1C} was achieved in 21 patients (84 % of cases) in group A and 20 patients (80 % of cases) in group B, p = 0.7. During the follow-up period, post-COVID syndrome manifestations resolved or significantly improved (by 40.1 ± 1.5 % according to the VAS) was observed in 75 % (21 patients) in group A and 48 % (12 patients) in group B, p = 0.05. Hospitalisations due to any reason in group A were significantly less frequent than in group B (21.4 % vs. 48 %, 6 patients and 12 patients, respectfully); there were fewer tromboembolic episodes (3.6 % vs. 24 %, 1 patient vs. 6 patients, respectively), p = 0.05. The overall post-COVID syndrome duration in group A was 5.6 ± 0.9 months vs. 6.2 ± 1.2 months in group B, p = 0.04. The positive effect from DPP-4i on the progress of post-COVID syndrome did not depend on COVID-19 severity or presence/absence of IHD.

Therefore, in our observation the use of DPP-4i in the management of DM2 patients with prior COVID-19 infection was associated with reduced duration and lower severity of post-COVID syndrome.

Conclusion. For DM2 patients who suffer from post-COVID syndrome, it is essential to select adequate antihyperglycemic drugs. One of the promising antihyperglycemic class is DPP-4i, that can improve long-term prognosis in this patient category. Prospective RCSs in various populations of DM2 patients with post-COVID syndrome are required in order to assess potential improvement in the survival rates due to DPP-4 inhibition in subjects with COVID-19, which can apply to patients without DM as well.

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Author Contribution

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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