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Review Article

Hyperglycemia in COVID-19. Review

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Abstract

Hyperglycemia is often detected in patients with COVID-19. At the same time, persons with this disorder have longer hospitalization periods and an increased risk of an unfavorable outcome. Diabetes mellitus occupies one of the leading positions in the structure of the incidence of a new coronavirus infection. During infection with MERS-CoV-2, blood sugar control significantly worsens not only in patients with impaired carbohydrate metabolism, but also in people without previous glucose metabolism disorders. In this paper, possible mechanisms of hyperglycemia development in COVID-19 are considered.

Keywords: *COVID-19; SARS-CoV-2; Hyperglycemia; Diabetes Mellitus*

Abbreviations

AG: Arterial Hypertension; ACE-2: Angiotensin Converting Enzyme Type 2; WHO: World Health Organization; GCS: Glucocorticosteroids; BMI: Body Mass Index; DCM: Disorders of Carbohydrate Metabolism; OGTT: Oral Glucose Tolerance Test; RNA: Ribonucleic Acid; mRNA: Matrix Ribonucleic Acid; SGG: Stress Hyperglycemia; DM: Diabetes Mellitus; DM1: Type 1 Diabetes Mellitus; DM2: Type 2 Diabetes Mellitus; SIDM: Steroid-Induced Diabetes Mellitus; CVD: Cardiovascular Diseases; RF: Risk Factors; COPD: Chronic Obstructive Pulmonary Disease; COVID-19: A New Coronavirus Infection Caused by a Virus SARS-CoV2; GLUT4: Glucose Transporter Type 4; HbA1c: Glycated Hemoglobin; IL-1: Interleukin 1; SARS: Severe Acute Respiratory Syndrome; TNF-α: Tumor Necrosis Factor Alpha

Introduction

March 11, 2020. The World Health Organization (WHO) has declared a global pandemic of the new coronavirus infection COVID-19, which has so far covered about 187 countries of the world. Every day there is more and more data that allows us to identify the impact of a new coronavirus infection on the course of chronic diseases [1].

Respiratory failure and systemic inflammatory response syndrome in the severe course of the new coronavirus infection COVID-19 are accompanied by nonspecific metabolic disorders, which are manifested by impaired glucose catabolism, lactate accumulation, various disorders of the acid-base state. Hyperglycemia is a frequent disorder detected in patients with COVID-19. At the same time, it was found that patients with hyperglycemia have longer hospitalization periods and an increased risk of an unfavorable outcome [2].

Diabetes mellitus (DM) occupies one of the leading positions in the structure of the incidence of a new coronavirus infection. Thus, in one study, out of 41 hospitalized patients in Wuhan, 20% had DM [3]. In another retrospective cohort study of 191 patients, DM was present in 19% [4]. However, there is evidence that during infection with SARS-CoV-2, blood sugar control significantly worsens not only in patients with impaired carbohydrate metabolism, but also in people without previous glucose metabolism disorders [5-9].

In this paper, according to domestic and foreign literature, we decided to consider possible mechanisms of hyperglycemia development in COVID-19, taking into account the peculiarities of the pathogenesis and course of the disease and reproduction of SARS-CoV-2.

There are several possible causes of hyperglycemia in COVID-19:

1) Stress-induced disorders;
2) Damage to the pancreas by the SARS-CoV-2 virus;
3) Undiagnosed DM 2;
4) Prediabetes;
5) DM, first identified against the background of COVID-19;
6) Introduction of glucose solutions;
7) Appointment of glucocorticoids.

1. Stress hyperglycemia (SGG) in COVID-19 is a syndrome of increased blood glucose levels that develops under various stressful conditions in individuals without previous disorders of carbohydrate metabolism [10-12]. Despite the fact that SARS-CoV-2 has been little studied, the following pathogenetic mechanisms of the development of SGG and DM in COVID-19 can be assumed.

All representatives of SARS viruses are characterized by the introduction into target cells through the receptor - angiotensin converting enzyme type 2 (ACE-2) [13]. The life cycle of SARS-CoV-2 begins with penetration into the cell by endocytosis: the S-protein binds to the ACE-2 receptor, inhibiting its further expression, then cleaves, as a result of which the virus membranes and endosomes merge, and RNA is released. Translation results in the formation of p1a and 1ab polyproteins involved in the formation of a copy of the virus RNA, as well as eight mRNA molecules associated with the synthesis of viral proteins in the lumen between the endoplasmic reticulum and the Golgi complex. Virions are collected in the cytoplasm and exit the cell by exocytosis [5].

High expression of ACE-2 is noted not only in the mucous membranes of the upper respiratory tract, alveolar cells of type 2, but also in cardiomyocytes, proximal renal tubules, liver, colon epithelium and pancreas [14]. Such localization of ACE-2 expression can also determine the development of various extrapulmonary manifestations of the disease, in particular SGG. The explanation for this may be primarily that the expression of ACE-2 is observed in the cells of the endocrine and exocrine parts of the pancreas, and a direct cytopathic effect of the virus can be assumed. In addition, a developing systemic inflammatory reaction with a high amount of TNF-α, IL-1 can cause cell death, especially of the insular apparatus, one of the structural units of which are β-cells synthesizing and accumulating insulin. The death of -cells leads to a violation of the production of this main hypoglycemic hormone, which is a consequence of hyperglycemia [15].

Also, in the conditions of COVID-19, as well as other stressful conditions for the body, the cause of the development of SGG may be the production of counterinsular hormones associated with a stressful situation in the body - glucocorticosteroids (GCS) and catecholamines. The development of SGG, in this case, is associated with the influence of stress hormones on the activation of lipolysis. The latter, on the one hand, increases the level of free fatty acids, inhibiting the aerobic oxidation of glucose with subsequent stimulation of gluconeogenesis, on the other hand, causes oxidative stress [10-12]. Counterinsular hormones also suppress insulin secretion, stimulate gluconeogenesis and glycogenolysis in the liver, causing hyperglycemia [5].

One of the first published papers on the assessment of the relationship between the SARS coronavirus and carbohydrate metabolism is a study conducted in China in 2009 among patients with SARS (SARS syndrome). The prospective follow-up included 39 patients without DM and a history of GCS therapy who were hospitalized for laboratory-confirmed coronavirus pneumonia. 20 of them (51%) had hyperglycemia that persisted for several days. The level of glycemia normalized by the end of hospitalization in all patients [16]. A second assessment of the state of carbohydrate metabolism in these patients was carried out after 3 years. DM was detected in only 2 out of 39 people (5%), which confirms the transient nature of glycemia that developed against the background of coronavirus infection, i.e. stress hyperglycemia [17].

In the USA, out of 1,122 patients without diabetes and a history of GCS therapy hospitalized for COVID-19, 257 patients (22.9%) had SGG. Its development was confirmed by an increase in the glucose level in capillary blood above 9.9 mmol/l for several days [18,19]. The results of observation of 85 patients, also conducted in the USA, demonstrate the development of SGG in hospitalized patients [8].

2. Damage to the pancreas by the SARS-CoV-2 virus. An immunohistochemical study of biopsies of the lungs, heart, kidneys and pancreas of a 42-year-old patient who died of coronavirus pneumonia was performed [16]. At the same time, the expression of ACE-2 was observed in all the studied organs, including the pancreas. Moreover, the level of expression of ACE-2 in the cells of the endocrine part was higher than in the exocrine part [16,17].

In addition to direct cytotoxic effects on the cell due to virus replication, indirect damage to pancreatic β-cells is also possible, associated with a decrease in the expression of ACE-2 on the surface of β-cells after penetration of SARS-CoV-2 into them. The protective effect of ACE-2 on the functional state of β-cells is associated with an increase in the activity of angiotensin 1-7 and a decrease in the activity of angiotensin 2, which leads to apoptosis of β-cells, a decrease in their differentiation, the production of free radicals and local inflammation. Thus, a decrease in the expression of ACE-2 on the surface of β-cells after penetration of SARS-CoV-2 into them can lead to a decrease in the functional activity of β-cells and insulin deficiency [5].

3. Undiagnosed type 2 diabetes is one of the most important concomitant diseases associated with the severity of all three known pathogenic human coronavirus infections, including COVID-19. An international group of experts in the field of diabetes and endocrinology notes that, depending on the region, 20 - 50% of patients with COVID-19 had DM2 [20].

It was revealed that persistent hyperglycemia ≥ 10.0 mmol/l is one of the fundamental factors associated with a 4-fold increase in the risk of death of patients with COVID-19 and DM and 7-fold - without previously diagnosed DM. An increase in fasting glycemia is considered as a predictor of multiple organ damage and death among patients with COVID-19. The most vulnerable to the viral pandemic were patients with older DM (> 65 years), with unsatisfactory compensation of DM (HbA1c > 8%), with obesity, especially morbid (BMI ≥ 40 kg/m^2) [21].

The pathogenetic relationship between COVID-19 and DM is widely discussed, but the data is rather scarce. It is possible that SARS-CoV-2 infection in patients with DM causes more pronounced SGG with a large release of counterinsular hormones - GCS and catecholamines, which leads to a significant increase in blood glucose levels and abnormally high glucose variability [22]. On the other hand, a retrospective study conducted in Wuhan showed that about 10% of patients with DM2 and COPD had at least one episode of hypoglycemia (less than 3.9 mmol/L) [23]. Hyperglycemia in COVID-19 has been shown to activate proinflammatory monocytes and increase platelet reactivity, contributing to higher mortality from CVD in infected patients with DM [24]. However, the question remains how exactly these patients have an inflammatory and immune response.

Since immune staining on ACE-2 is most pronounced in the pancreatic islets, it has been suggested that SARS-CoV-2 can damage the islets of Langerhans and aggravate the course of DM2 [25]. Consequently, damage to the beta cells of the pancreas can occur both in pa-

tients with COVID-19 and in patients with diabetes, which affects the deterioration of the course of both the infectious process and the course of diabetes.

4. Prediabetes. They are called early disorders of carbohydrate metabolism, which are characterized by the presence of insulin resistance and primary or secondary dysfunction of the β-cells of the pancreas, which represent a metabolic state of high risk of developing DM2. Prediabetes is characterized by plasma glucose levels exceeding normal values of glycemia, but not sufficient for the diagnosis of "diabetes mellitus" [26]. The prevalence of prediabetes is progressively increasing worldwide, and according to reports, by 2030 more than 470 million people will have prediabetes [27].

Similar disorders (as with DM2) are also present in patients with prediabetes, even against the background of milder hyperglycemia. The phenotype of prediabetes is characterized by the presence of chronic systemic inflammation of a low degree of activity (an increase in the levels of C-reactive protein, interleukin-6 was recorded), violations of the mechanisms of innate immunity and adaptive immune response in response to infection, a procoagulant state, although to a lesser extent than in DM2 [19,28].

As noted above, the development of prediabetes is associated with a state of insulin resistance and a decrease in the function of β-cells of the pancreas, which cause disorders in the regulation of glycemia levels. Intermediate indicators of blood glucose levels are maintained for a long time with the help of a number of compensatory mechanisms, with the depletion of which the patient develops DM2. According to the data available to date, the SARS-CoV-2 virus may be exactly the factor that will lead to the disruption of these compensatory mechanisms, because it can have a direct damaging effect on the β-cells of the pancreas. Cytotoxic damage of pancreatic β-cells caused by SARS-CoV-2 can lead to aggravation of the existing dysfunction and the development of high persistent hyperglycemia in patients with a history of prediabetes [28].

It has been shown that patients with prediabetes have a younger age than patients with DM2, but at the same time they are characterized by a significant prevalence of obesity and hypertension, which brings them closer to the group of people with concomitant DM2. In this study, patients with prediabetes clearly occupied an intermediate position in terms of severity between people with DM2 and people without carbohydrate metabolism disorders. Although their average age was the youngest, it was they who most often needed intensive pathogenetic therapy, including the appointment of GCS (p=0.028) and biological drugs (p=0.001), which indirectly confirms the increase in the severity of COVID-19 already at the initial manifestations of carbohydrate metabolism disorders [29].

The data obtained still need to be studied in large-scale studies, but now it is necessary to pay close attention to patients with prediabetes and consider early disorders of carbohydrate metabolism as a potential risk factor for a more severe course of COVID-19.

5. Newly detected DM on the background of COVID-19. As we mentioned above, hyperglycemia detected for the first time in a patient with COVID-19 may result from direct damage to β-cells by the SARS-CoV-2 virus or be a consequence of an inflammatory reaction to the virus, but it may also turn out to be an independent debut of DM.

Indeed, to date, it has not yet been precisely established whether the cases of the onset of DM2 in patients who have undergone COVID-19 are a transformation of previously existing disorders of carbohydrate metabolism or a completely new type of diabetes. However, taking into account the associations described above, it can be concluded that patients with prediabetes who have contracted COVID-19 should be assigned to a high-risk group not only for the development of DM2, but also for a more severe course of COVID-19 [19].

More frequent cases of fasting glycemic disorders and the occurrence of diabetes with an acute onset were previously noted among patients with SARS-CoV-2-associated pneumonia than with pneumonia caused by another pathogen [16]. In general, these observations confirm the hypothesis of a potential diabetogenic effect of COVID-19, in addition to the already known mechanisms of the stress response

of the body associated with a severe course of diseases. However, it is unclear whether such changes in glucose metabolism that suddenly occur during severe COVID-19 persist or disappear after infection. How common is the phenomenon of newly diagnosed DM, and is it a classic DM1 or DM2 or a new type of diabetes?

Thus, it can be said that COVID-19 may become a new risk factor for developing DM2 along with other already well-known RF.

6. Introduction of glucose solutions. The most common metabolic disorders are associated with the introduction of carbohydrate solutions. Hypoglycemic syndrome develops as a result of excessive infusion rate of glucose solutions (especially highly concentrated ones) with concomitant pronounced glycogenolysis [30]. According to K. Jeejeebhoy., *et al*. (2001) the occurrence of hyperglycemia is characteristic of at least 50% of all cases of parenteral nutrition [31].

It has long been known that the use of glucose solutions, especially in the intensive care of critical conditions, is by no means a completely safe measure. Its excessive administration or insufficient correction with insulin can quickly lead to hyperglycemia and glucosuria with the development of hyperosmolar syndrome. Hyperglycemia may also be the earliest sign of sepsis, including catheter-associated. Excess glucose causes osmotic diuresis, stimulates the secretion of insulin, which, in turn, promotes the transfer of potassium and phosphorus from the extracellular fluid into the cell. In emaciated patients with reduced potassium and phosphorus reserves, this is especially dangerous due to the risk of arrhythmia and other cardiovascular disorders, as well as respiratory and neurological disorders [30].

7. Steroid-induced hyperglycemia in COVID-19. GCS are widely used in almost all fields of medicine, in particular in autoimmune diseases in transplantology [32], in exacerbation of COPD, acute gout, chemotherapy protocols, bacterial meningitis, cytokine storm observed in diseases with an immuno-inflammatory component, including COVID-19 [32-34].

The use of GCS in the framework of pathogenetic treatment, in addition to the main immunosuppressive and anti-inflammatory effects, is associated with the development of a number of adverse effects. Their most common manifestations include arterial hypertension (AG), carbohydrate metabolism disorders (DCM), dyslipidemia, osteoporosis, and mental disorders [18]. GCS is usually prescribed for a long time (in 22% of cases - more than 6 months, in 4% - more than 5 years). Hyperglycemia and diabetes mellitus are frequent undesirable effects of GCS, which can be observed both in patients who do not suffer from diabetes and in patients with pre-existing diabetes. GCS therapy can provoke the development of DM (the so-called steroid-induced DM) and increase the level of hyperglycemia in patients with previously established DM [35].

Steroid-induced diabetes mellitus (SIDM) is defined as an abnormal increase in blood glucose levels associated with the use of GCS in patients with/without a previous history of DM. The criteria for its diagnosis, according to the clinical recommendations of the American Diabetes Association are: fasting blood glucose (8 hours after meals) ≥ 7.0 mmol/l (126 mg/dl); 2 hours after an oral glucose tolerance test (75 g glucose) ≥ 11.1 mmol/l (200 mg/dl); HbA 1c ≥ 6.5% or accidental detection of plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dl) in patients with symptoms of hyperglycemia [36].

According to various authors, the development of steroid-induced disorders of carbohydrate metabolism is 13.0 - 32.5% [35]. However, hyperglycemia or DM does not develop in all patients taking GCS. It is assumed that DM is more common in patients with additional risk factors, such as taking GCS in high doses (prednisone >20 mg, hydrocortisone >50 mg, dexamethasone > 4 mg) or for a long time, old age, increased body mass index, pre-existing fasting hyperglycemia and/or impaired tolerance glucose, gestational diabetes or steroid-induced diabetes in the anamnesis, diabetes in close relatives, HbA 1c level ≥ 6% [7].

GCS have quite a lot of side effects. Among the main medium- and long–term undesirable effects of this group of drugs are an increase in insulin resistance, an increase in cardiovascular risk and the risk of bacterial infections [6]. The mechanisms of hyperglycemia and DM development under the action of GCS are very diverse and have not been fully studied [35].

Mechanisms of hyperglycemia development when taking GCS:

1) Insulin resistance. GCS reduce peripheral glucose uptake at the level of muscle and adipose tissue. Skeletal muscles are primarily responsible for insulin-mediated glucose uptake after meals, and GCS can cause insulin resistance by directly interfering with various components of the insulin signaling cascade: GCS reduce the number of GLUT4 carriers on the surface of skeletal muscle cells. Glucose penetrates into the cells of the striated musculature through a mechanism of facilitated diffusion. The potential of glucose uptake per unit time by skeletal muscle cells is directly proportional to the number of GLUT4 carriers on the cell surface and the glucose concentration gradient between the extracellular and intracellular fluid. Considering that skeletal muscles are responsible for the absorption of 80% of postprandial glucose, this proportion decreases due to a decrease in the potential for glucose absorption, which leads to hyperglycemia [36].
2) Increased appetite. GCS, acting on the cells of the hypothalamus, activate neuropeptide Y [34], whose receptors are involved in various functions of the nervous system, including the regulation of saturation, emotional state, vascular tone, secretion of the gastrointestinal glands [37]. This effect of GCS leads to an increase in appetite and aggravation of hyperglycemia [34].
3) Stimulation of differentiation of preadipocytes into adipocytes. The effect of GCS on the receptors of preadipocytes increases the differentiation of the latter into adipocytes, which determines the increase in the amount of adipose tissue. However, GCS has different effects on peripheral and visceral adipose tissue, determining the typical picture of visceral obesity in essential AG. An increase in the level of free fatty acids produced in excess by visceral fat provides potentiation of insulin resistance, lipotoxicity, slowing down of insulin metabolism and strengthening of catabolic processes (proteolysis and lipolysis) in peripheral tissues. And activation of gluconeogenesis enzymes and increased glucagon secretion lead to increased gluconeogenesis and glycogen cleavage. This together provides an increase in glucose production by the liver [29].
4) An increase in the rate of gluconeogenesis in the liver and an increase in the production of glucagon. The liver plays an important role in controlling glucose metabolism by maintaining fasting glycemia. GCS increase the production of endogenous glucose directly due to the activation of numerous genes involved in carbohydrate metabolism in the liver, which leads to increased gluconeogenesis [36].
5) Reduction of insulin synthesis by pancreatic cells. The suppression of insulin synthesis may be due to both the direct damaging effect of GCS on pancreatic β-cells and due to a decrease in the activity of glucagon-like peptide-1 [34], which normally increases insulin secretion, causes proliferation and neogenesis of beta cells and increases the reaction of beta cells to glucose [38].
6) The formation of a vicious circle. A greater increase in plasma glucose increases insulin resistance [35].

The severity and progression of these changes depend on several parameters, including the dose of drugs, the period of administration and individual tolerability. For example, it was shown that high doses of prednisolone (75 mg) administered once suppressed insulin secretion, while prolonged use of prednisolone 30 mg for 15 days led to an increase in insulin resistance without damaging the secretory ability of β-cells [39]. In another study conducted in 2011. Hansen., *et al*. showed that the level of glucagon increases against the background of the introduction of GCS, while there are no changes in glucose elimination and insulin secretion [40].

A comparative study of GCS on the glycemic level of 193 patients diagnosed with systemic lupus erythematosus, systemic vasculitis and chronic glomerulonephritis was carried out. Of these, 98 people received pulse therapy with GCS (intravenous administration of 10 - 15 mg/kg of prednisone per day per 250 ml of 0.9% NaCl solution, 3 days in a row (1 series in 3 sessions); the course dose was 1800 - 3000 mg. Another group of 95 people received GCS per os therapy at a dosage of 7.5 - 25 mg/day. All patients underwent an oral glucose tolerance test (OGTT): patients receiving pulse therapy of GCS - 72 hours after completion of the course and patients receiving therapy of GCS per os - on an empty stomach during hospital stay. It was shown that in the group of patients receiving pulse therapy of GCS, the incidence of carbohydrate metabolism disorders was statistically significantly less frequent than with long-term use of GCS per os (p =

0.035). It is the long-term use of GCS in medium doses (15 - 25 mg/day), and not pulse therapy with overdoses of GCS, that contributes to a greater frequency of development of carbohydrate metabolism disorders. With prolonged oral therapy of GCS, the main mechanism of carbohydrate metabolism disorders is insulin resistance, which is determined by a significant increase in the calculated HOMA-IR index before and after OGTT [41].

In the study of A Donini., *et al*. 54% of hospitalized patients who, for various reasons, received prednisone at a dose of 40 mg for at least two days, hyperglycemia was registered in only two cases [42]. In a retrospective cohort study conducted using the Medicard database, about 12,000 patients with newly diagnosed DM and 12,000 patients without DM matched by gender and age were compared. Treatment with GCS was associated with a significant increase in the relative risk (2.2 times) of developing DM. The increase in risk depended on the dose, the duration of taking GCS, the choice of a specific drug and the ways of its administration [43].

Disorders of carbohydrate metabolism (DCM) against the background of GCS therapy are manifested, first of all, by an increase in postprandial glycemia, while fasting glucose levels, as a rule, remain unchanged. For example, in a study of the effect of GCS therapy on the daily rhythm of glycemia in patients with chronic obstructive pulmonary diseases, it was found that 8 hours after the morning administration of 20 mg of prednisone, glucose levels increase both in people with normoglycemia and in patients with DM2 [34].

Due to the fact that GCS can be administered in various modes, doses and forms, the time of hyperglycemia may vary. For example, the administration of prednisone once in the morning will lead to an increase in the level of glycemia at noon and in the evening, while during the night and in the morning the blood glucose level will be normal. In this regard, for this method of treatment, it is recommended to study glucose levels before lunch and before dinner, and therapy should not cause a hypoglycemic effect at night and in the morning in order to prevent hypoglycemia [34].

Taking into account the presence of predominantly postprandial hyperglycemia in the afternoon in patients with impaired carbohydrate metabolism receiving GCS, hypoglycemic therapy should be concentrated precisely for this period of time, while not affecting glycemia at night and on an empty stomach [18].

Conclusion

As we can see, hyperglycemia recorded for the first time in patients with COVID-19 is quite common.

The effect of COVID-19 on carbohydrate metabolism is determined by several possible factors. These are direct cytotoxic effects on β-cells due to the replication of the SARS-CoV-2 virus, indirect damage to pancreatic β-cells associated with a decrease in the expression of ACE-2 on their surface, the patient's comorbid background (concomitant prediabetes and type 2 diabetes mellitus), increasing the level of dysglycemia, as well as the effect of drugs: glucose and GCS used in the treatment of a new coronavirus infection.

In this regard, early screening of carbohydrate metabolism disorders and active management of patients with prediabetes are becoming an extremely important clinical task, which is primarily faced by primary care physicians. Specialists working with patients with any of the disorders of carbohydrate metabolism should abandon clinical inertia and not be limited to standard recommendations for lifestyle changes. Patients should be informed about the real risks of their condition and motivated to work together to prevent adverse outcomes.

Conflict of Interest

There is no financial interest or conflict of interest.

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